Transitional Care in Osteogenesis Imperfecta

Advances in Biology, Technology and Clinical Practice

Peter A. Smith, M.D.
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Edited by
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DEDICATION

This book is dedicated to

The Osteogenesis Imperfecta Foundation (OIF), Gaithersburg, MD

and

Mercy Home for Boys and Girls, Chicago, IL

Preface

Osteogenesis imperfecta (OI) is a genetic disorder characterized by fragile bones that break easily. It is also known as "brittle bone disease (BBD)." The cause of OI is a genetic mutation that affects the body's production of collagen or other collagen-related proteins. Over the past decade, our understanding about the genetic and clinical heterogeneity of OI has expanded significantly to include over 13 disorders defined by distinct genotypes. These disorders involve diverse mechanisms of disease ranging from changes in the amount and structure of type I collagen to post-translational modifications and alterations in signaling proteins. Persons with OI have in common brittle bones but also experience distinct histopathological and extra-skeletal features. Among the many challenges faced by individuals with OI is the process of transition from pediatric to adult care. This tumultuous period includes physical, physiological and developmental changes that are not clearly demarcated by a single event, but rather occur over a period of time. The process is complex and multidimensional, yet is rarely addressed in current literature. The purpose of this work is to initiate a better understanding of the transitional challenges faced by persons with OI and to identify new opportunities for problem solution.

This text began with a one-day workshop on Transitional Care in OI sponsored by Shriners Hospitals for Children, the OI Foundation, the Ralph and Marion Falk Medical Research Trust, and the Orthopaedic and Rehabilitation Engineering Center (OREC – sponsored by Marquette University and the Medical College of Wisconsin). The workshop was conducted on September 10th, 2010 at Shriners Hospital, Chicago and included national and international researchers from scientific, clinical and technical fields. It focused on clinical needs, biology and technical advances with an emphasis on applications, limitations, and problems to be solved. Through the generous support of Shriners Hospitals, the Falk Foundation, NIDRR, NIH, a host of contributors, and collaboration of the keynote speakers, this work was planned for publication.

The purpose of the book is to: 1) identify relevant needs for transitional care in OI that can be served by existing and emerging technologies, and 2) educate readers on current concepts, recent findings and anticipated advances within the biological, clinical and technical communities.

Section 1 of the text presents an overview of advances in transitional care. This section includes a national program example, as well as details on the establishment of a network of regional linked clinical research centers (LCRCs) by the OI Foundation (OIF). A summary of current concepts and emerging horizons in biomechanics, modeling and fracture prediction completes the section.

Section 2 of the text addresses biological developments and current challenges. It includes an examination of genotype-phenotype correlations in autosomal dominant OI and examines the challenges of stem cell therapies. A review of murine models of OI is included as well as an examination of recessive OI. The section concludes with a tissue level review of OI bone.

Section 3 of the text examines technology as applied to OI and identifies emerging opportunities for advances in modeling, quantitative assessment, motion analysis, dynamic imaging, mobility, and whole-body vibration. Opportunities for future research and development are also described and discussed in this section.

Section 4 is the final section and addresses clinical aspects of OI from an assessment and treatment standpoint. The section offers a clinical overview from medical and orthopaedic perspectives, and examines quality of life, pain, spinal deformity, craniofacial care, and oral health. Rehabilitation in OI receives a special focus with chapters on upper extremity considerations, driving, positioning, and mobility.

While OI remains a challenging condition, it is hoped that this work will contribute to an improved understanding of the condition as we all work to provide better transitional care from the pediatric to adult environment.

Editors

Peter A. Smith, M.D., received a B.S. degree from Stanford University in 1980 and an M.D. degree from New York University in 1984. He completed a residency in orthopaedic surgery at the University of Chicago in 1989 and a fellowship in pediatric orthopaedics at Newington Children's Hospital in 1990. He has served as an attending orthopaedic surgeon at Shriners Hospital for Children, Chicago, since 1990, where he is Director of the Osteogenesis Imperfecta Clinic and Clinical Director of the Motion Analysis Laboratory. He is a Professor in the Department of Orthopaedic Surgery at Rush University Medical Center, and an Adjunct Professor of Biomedical Engineering in the Orthopaedic and Rehabilitation Engineering Center (OREC) at Marquette University and the Medical College of Wisconsin. He actively contributes to the teaching programs in orthopaedic residency at these institutions and at the University of Illinois – Chicago, Loyola University, and Midwestern University. Dr. Smith's chief clinical interests are in orthopaedic care of children with neuromuscular disorders such as cerebral palsy and skeletal disorders such as osteogenesis imperfecta.

Frank Rauch, M.D., received an M.D. degree from the Technical University of Munich, Germany, and trained as a pediatrician at the Children's Hospital of Cologne University, Germany. Since 2001 Dr. Rauch has been a clinician-scientist at the Shriners Hospital for Children, and he is currently a Professor of Pediatrics at McGill University, Montreal, Canada. His clinical and scientific work focuses on heritable bone diseases in children and adolescents, in particular osteogenesis imperfecta. He is the Director of Clinical Laboratories at Shriners Hospital in Montreal, comprising laboratories for biochemistry, bone histomorphometry and molecular diagnostics. Dr. Rauch has published more than 180 original articles in peer-reviewed scientific journals. Since 2009, he has been Editor-in-Chief of the Journal of Musculoskeletal and Neuronal Interactions.

Gerald F. Harris, Ph.D., P.E., received a B.S.M.E. degree from the U.S. Naval Academy in 1971 and a Ph.D. degree in Biomedical Engineering from Marquette University, Milwaukee, WI, in 1981. From 1981 to 1987, he was Director of the Biomechanics Research Laboratory at Shriners Hospital, Chicago, IL. In 1987, he joined the Biomedical Engineering faculty at Marquette University, and in 1989 was appointed Director of Research in the Department of Orthopaedic Surgery at the Medical College of Wisconsin. He currently serves as the Director of the Orthopaedic and Rehabilitation Engineering Center (OREC) at Marquette University and the Medical College of Wisconsin. His research interests include rehabilitation engineering, orthopaedic biomechanics (pediatric and adult), and human motion analysis.

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SECTION 1

Advances in Transitional Care

1 TRANSITIONAL CARE AND OUTCOMES: A NATIONAL PROGRAM EXAMPLE

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INTRODUCTION

One of the most tumultuous developmental periods is the transition from early adolescence into adulthood. This period is marked by tremendous physical, physiological, psychosocial, and cognitive changes, attainment of developmental milestones, including independent living, employment and financial autonomy, and establishment of self-identity, values, and goals. Transition is not a distinct event, but a process that is often complex and challenging, particularly for those with chronic health conditions or disabilities who are concurrently managing normative developmental tasks and the changing facets of their condition and treatment. In youth with chronic health conditions, transition is a multidimensional construct consisting of developmental preparation for adult life roles and the transfer of care from pediatric to adult health care providers. Factors that impact transition for these youths include characteristic challenges of this age-related stage, general risk factors associated with living with a chronic or physical disability, such as lower self-esteem, as well as disorder-specific issues, such as mobility impairment as found in those with spinal cord injuries (SCI) or osteogenesis imperfecta (OI).

The purpose of this chapter is to provide an overview of the transition process and outcomes in youth with chronic health conditions and physical disabilities. We will describe our experience with pediatric-onset SCI as a model for other chronic health conditions, including OI. We begin with a discussion of transition during adolescence and emerging adulthood. We then identify the main areas of transition and the interplay between transitional issues and the experience of adults with pediatric-onset SCI.

Finally, we conclude with comments generalizing our findings and recommendations for other chronic health conditions, such as OI.

Transitional Care: Shriners Hospitals for Children SCI Program

Shriners Hospitals for Children is a health care system of 22 locations in the U.S., Canada, and Mexico dedicated to improving the lives of children by providing pediatric specialty care, innovative research, and outstanding teaching programs for medical professionals. Children up to age 18 with orthopaedic conditions, burns, spinal cord injuries, and cleft lip and palate are eligible for care and receive all services in a family-centered environment, regardless of the families' ability to pay. Three of the Shriners Hospitals for Children (Chicago, Philadelphia and Northern California) provide rehabilitative care for children with spinal cord injuries up until age 21.

Caring for a child with a spinal cord dysfunction is a dynamic process with developmentally-based goals that change as the child ages and correspond to the youth's uninjured peers (e.g., autonomy).[1] The ultimate goal of our transition program is that young adults with SCI leave our pediatric system with the knowledge and skill set to independently manage their care as well as with the confidence in their ability to participate fully in their community.[2,3] From the onset of injury, rehabilitation goals across the child's lifespan are delineated with the expectation that the child with an SCI will achieve the goals of independence and participation. In addition to the child and his/her parents, these expectations must be embraced by others who are involved in the child's life, including educators, healthcare providers, extended family members, and peers. A successful transition requires an individualized, comprehensive and flexible plan that facilitates the attainment of experiences and skills that are prerequisite to becoming an independent and productive adult.[4] Preparation of the child with an SCI for the transition into adulthood begins during childhood (or at injury onset) and encompasses a variety of areas including, independent living, employment, and psychosocial and sexual function.[2]

Management of pediatric-onset SCI requires an interdisciplinary team who, using a developmental framework, focus on a comprehensive spectrum of issues, including SCI-specific education, skin, bladder and bowel management, mobility, self-care activities, prevention and management of

complications, social services, psychological and vocational counseling, and recreation and leisure time activities. Rehabilitation is individualized, family-centered, and sensitive to the developmental, social, cultural, and spiritual needs of the child and family. The child and parents are encouraged to be an integral part of the health-care team and to actively participate in treatment management and decision-making. Increased participation of the child is particularly critical as the youth progresses towards and through adolescence in preparation for the autonomy of adulthood. Initially, parents are generally responsible for all aspects of the child's care; however, as children progress through childhood and adolescence, they are expected to assume more responsibility in the areas of self-care, self-advocacy, and management of their SCI.

The gradual process of transferring responsibility to the young person is critical as consequences of poor adherence and management may be serious or even life threatening. As an example, pressure ulcers are associated with significant morbidity so that regular pressure reliefs and skin inspections are important in daily care and maintaining skin integrity. Although a school-aged child with an SCI may be able to conduct pressure reliefs and skin inspections, they may forget or dismiss these behaviors due to a lack of developmental readiness in understanding long-term consequences. On the other hand, as parents appreciate the importance of these behaviors and role in long-term health, they may be reluctant to turn the responsibility over to their child. This may result in parent-child conflict as well as in limited opportunities for the child to perform such care independently but while under parental supervision. Due to the challenge of achieving the appropriate balance, which varies for each parent-child dyad, parents need to remain vigilant and provide a safeguard as children gradually assume responsibility for their care. We believe that is the role and responsibility of the interdisciplinary team to provide direction and encouragement for the child and his/her parents throughout this process. Moreover, to help facilitate this transfer of responsibility and management, older children and adolescents spend a portion of their outpatient visit individually with the healthcare provider without their parents.

Areas of Transition

Adolescence and emerging adulthood are developmental periods delineated by the construct of change.[5,6] Adolescence is traditionally viewed as the transitional period occurring between the onset of puberty and the legal age of adulthood, or the ages between 13 and 18 (or 21), while emerging

adulthood is a distinct new period of life occurring between the ages of 18 and 25.[7] Emerging adulthood is a phenomenon found primarily in the United States and other industrialized societies and describes a prolonged journey of independent exploration prior to adulthood, which is historically associated with entering marriage and parenthood. Both adolescence and emerging adulthood are stages of the lifespan characterized by intense change and instability, a search for self-identity and life pathways, development of autonomy and volition, and establishment of meaningful and lasting social relationships. In addition to achieving developmental milestones such as physical and sexual maturity, abstract and future oriented thought, vocational goals, and residential and financial independence, risk behaviors, such as substance use and unprotected sexual activity, peak during these periods as a consequence of decreased parental monitoring and increased independence. Successful navigation of these processes can be exciting as well as arduous. Considerable variability exists among adolescents and emerging adults as a result of the experimental and exploratory quality of these periods. While steering through the already turbulent waters of these developmental stages, youth with chronic health conditions are faced with an additional challenging task of understanding and managing their condition, treatment, and healthcare system, which may also be changing over time.

Education and Employment

Active participation in education and/or employment is a critical component of adolescence and emerging adulthood. Formal vocational training does not typically begin until the high school years or later; however, preparation for employment and career planning usually begins in childhood through activities such as chores and volunteering and during adolescence, through part-time jobs. While the impetus for employment may vary for adolescents and emerging adults (e.g., means to obtain money for social/recreational activities versus opportunity for career exploration), these early experiences promote the procurement of behaviors, skills, and values that assist in the transition to participation in the adult labor force. Moreover, long-term outcome data indicate that achievement of educational and vocational goals are integrally related to residential and financial independence, psychological adjustment, and life satisfaction.[8-10]

According to national data, in 2013, the employment rate for civilian individuals with disabilities was 18% compared with 64% for those without a disability.[11] Within the SCI population, despite educational attainment in

adults with pediatric-onset SCI exceeding that of the general United States population, with over 30% obtaining a bachelor's degree compared to 25% of the general population, individuals with an SCI are significantly less likely to be employed than their able-bodied peers.[12,13] In the pediatric-onset SCI population, factors associated with an increased likelihood of employment include thoracic injury level (versus cervical), white race, higher educational attainment, independent physical mobility, ability to drive independently, fewer medical complications, fewer access-related barriers, greater perceived social support, and lower rates of depressive symptoms.[10,14-16]

Several factors may contribute to these lower rates of employment among individuals with disabilities. First, parental and societal expectations may differ between children with a chronic health condition and able-bodied peers. For example, parents may hold low employment expectations for their child with an SCI and therefore, have minimal or no expectations for their participation in chores or part-time employment. Second, families with children with disabilities may lack the knowledge about the resources and vocational services available to their child.[17] Furthermore, sequelae of a chronic health condition and environmental barriers may make job placement more challenging and thus, discouraging the individual. As a result of their limited experiences and possibly lack of vocationally focused education, adolescents and emerging adults may be less well prepared for their adult roles in the labor force. Therefore, addressing educational goals and job readiness skills is a routine component of clinic visits. We encourage chores and part-time jobs, provide information regarding resources in obtaining such work-related experiences, and address barriers in obtaining these prevocational and early vocational activities.[18]

Independent Living

Living independently is a goal for the vast majority of adults with chronic health conditions, yet emerging adults have a high rate of residential change. During this developmental period, emerging adults live in a variety of housing situations with varying degrees of adult supervision (college dormitories to apartments). Approximately one-third attend college and about 40% live independently and are employed full-time.[19] Although many emerging adults with an SCI are autonomous in activities of daily living, rates of living independently are lower than expected. Only two-thirds of adults 24–37 years of age with pediatric-onset SCI live independently, which is associated with being physically independent, active community participation, employment, and life satisfaction.[9,13]

Transportation

Community access is important at all ages and becomes most important during adolescence. Whether public or private, motorized transportation must be accessible and enhance an adolescent's independence. Driving a motor vehicle is a rite of passage for adolescents symbolizing freedom and independence, but is a major obstacle to those with an SCI. In the general U.S. population, 44% of individuals 19 years of age and younger are licensed drivers. This rate increases to 81% during emerging adulthood and by middle adulthood, over 90% hold a driver's license.[20] Among individuals with SCI ages 16- 21 years, 52% drive independently.[21] In adults aged 24–25 years with a pediatric-onset SCI, 62% drove independently, which is comparable to the 65% national rate of drivers of all ages with a disability.[16,18] In contrast, a long-term outcome study conducted in the United Kingdom found that although 54% of adults with a chronic physical disability had a license, only 19% were actually driving, with medical or financial reasons identified as the main constraints.[22] Because the outlook for independent driving is limited, individuals with SCI rely heavily on others for essential transportation. This is also an area of concern, as 49% of individuals with a disability that impairs ambulation experience difficulty using transportation, such as buses, commuter trains, or paratransit.[23]

Individuals with lesions as high as C5 are capable of driving an appropriately-adapted motor vehicle, so it is imperative that they receive proper driver's evaluations and prescriptions for motor vehicle adaptations. Adolescents with paraplegia should be able to be transfer independently from an ultra-lightweight manual chair to the driver's seat and then transfer the wheelchair into the car. Most adolescents with tetraplegia, especially those who utilize power wheelchairs, will need a modified van with a wheelchair lift and an automatic locking system for their wheelchair. Using an adapted van with a wheelchair lift, adolescents with tetraplegia or paraplegia who use a manual wheelchair can generally transfer themselves into the driver's seat. If the individual transfers onto a motor vehicle seat, a pressure-reducing seating system should be utilized. Individuals of all ages with SCI should be properly restrained in motor vehicles: car seats for infants and toddlers, boosters for older children, specialized restraint systems for children with poor trunk or neck control, three point restraints for appropriated sized older children and adolescents, and approved restraint systems for those who remain in their wheelchairs.

Psychosocial Functioning

In addition to the physical and medical consequences of living with a chronic health condition, there are important psychological and social implications that need to be considered when treating a child and working with his/her family. Youth with chronic health conditions or disabilities are at a greater risk of developing psychological difficulties and social maladjustment compared to youth without these conditions.[24] Moreover, the increased risk persists as these youth transition to adulthood. For example, in a study of adults with pediatric-onset SCI, 27% reported depressive symptoms,[25] while the prevalence rate for U.S. adults is 6.7%.[26] Additionally, rates of suicidal thought are higher in adults with pediatric-onset SCI compared to the general adult U.S. population (7% versus 3.7%).[25,27] Several factors may contribute to this increased risk of psychological maladjustment. For adults with pediatric-onset SCI, depression is associated with incomplete injury, unemployment, and poor perceived mental health, and suicidal ideation is related to male gender, unemployment, dependence in driving and living independently, and decreased life satisfaction.[25]

The development of social relationships is also a critical component of the adolescent and emerging adult years. Establishing and maintaining positive peer relationships is particularly important for youths with chronic health conditions as these relationships may facilitate adjustment to the chronic condition, promote medical adherence, serve as a source of emotional support, and improve life satisfaction.[28] Several facets of a chronic condition or related treatments, such as motor and sensory limitations, altered physical appearance, and frequent absences from school or work, may contribute to feelings of social isolation and possible peer rejection, decreasing opportunities for development of social skills. Environmental barriers (i.e., lack of accessibility) may further limit youths' ability to socialize and participate in recreation and social activities.

The emergence of dating and romantic love provides opportunities for adolescents and emerging adults to explore self-identity (e.g., self-concept, self-esteem), interpersonal skills (e.g., communication, trust), and sexuality (e.g., intimacy, sexual activity). These important developmental experiences have a long-lasting impact on self-esteem and personal values. Similar to social relationships, positive romantic experiences promote sense of identity and development of interpersonal skills and serve as a source of emotional support.[29] Moreover, in a long-term outcomes study of pediatric-onset SCI, relationship status and physical intimacy were positively associated with life

satisfaction, emotional well-being, and adjustment to the SCI.[30,31] While prevalence of sexual intercourse and risky sexual behaviors are similar between youth with chronic conditions and those without, adolescents with physical disabilities, however, are at greater risk of negative romantic experiences, including sexual abuse or exploitation.[32-34]

Risk taking behaviors (e.g., substance use) increase during late adolescence and emerging adulthood. While this is a normative part of adolescence and emerging adulthood, these behaviors may have additional inadvertent consequences for youth with chronic health conditions.[35] For example, use of tobacco and alcohol can impact the effectiveness or adherence to medical treatments and increase the risk of developing complications. Risk taking behaviors may also reflect impairment in adaptive coping strategies. A study of adults with pediatric-onset SCI noted that 15% used substances as a strategy to cope with their SCI.[36]

Although youth with chronic health conditions are susceptible to facing a variety of challenges within the psychosocial domain, as treating health providers, it is imperative to remember that the majority of individuals demonstrate positive psychosocial functioning and outcomes and successfully navigate the challenges of these developmental periods.[28,37] Consequently, transition programs should be aimed at early identification and prevention of psychological and social difficulties as well as promoting resilience. Interventions addressing peer and family relationships may facilitate growth and the development of skills needed for self-management of their chronic health condition (e.g., self-advocacy, confidence, autonomy).

General Health

Throughout the life of individuals with chronic health conditions, we as healthcare providers must address in a developmentally appropriate manner both general health care needs ranging from health care maintenance to prevention as well as disorder-specific heath issues. In addition, many individuals with chronic health conditions are experiencing longer survivals, placing them at risk of developing various complications related to aging both in respect to their general health as well as more disorder-specific complications. As a consequence of the relatively sedentary lives led by many individuals with a chronic health condition, they are at risk of various complications such as obesity and cardiovascular disease. In order to prevent these complications, we encourage age appropriate leisure-time and recreational activities and dietary habits that promote adequate fitness

levels. Dietary interventions and fitness activities are tailored to the age and preferences of the individual and are appropriately modified throughout their lifespan.

Preventing complications must be a major focus of caring for individuals with chronic health conditions in order to maximize function in this patient population. In adults with pediatric-onset SCI, a negative relationship has been found between medical complications and participation, life satisfaction, employment, income, and independent living.[8,38] Due to their relatively long lifespan, individuals with pediatric-onset SCI are at greater risk of complications because of their longer duration of injury compared to those with adult-onset SCI. Therefore, it is important that transition planning incorporate measures to prevent these negative injury-related outcomes. As an example, upper extremity pain is a common problem for adults with pediatric onset SCI (48% shoulder, 15% elbow, and 10% wrist pain).[39] As individuals continue to age, the prevalence of upper extremity pain and its implications will become even more critical; hence, we promote measures during childhood and adolescence that will minimize upper extremity pain and overuse syndromes including proper mechanics of wheelchair propulsion and transfers and judicious use of powered mobility.

Transition to Adult Care

Successful transfer of care to adult providers is an important outcome for youth with chronic health conditions.[4] The transition from interdisciplinary, family-centered pediatric care to more individually focused adult care, however, is often challenging.[40] The loss of the close relationship with their pediatric providers, with whom they have often grown up, may be difficult for these emerging adults, and establishing trust and comfort in new providers takes time. Moreover, whereas pediatric centers often provide opportunities to see multiple medical subspecialists during a single clinic visit, adult health care settings often have less support for coordination of such complex care, placing increased responsibility of managing and coordinating care on the individual. Adult services may often have the expectation that emerging adults should be self-reliant, but this may be an unrealistic assumption for some adults who remain dependent for daily care. Furthermore, adult health providers may have less familiarity or training with the complex nature of the pediatric-onset condition[41] causing increased frustration for the emerging adult. To facilitate successful transition from pediatric to adult-focused care, pediatric providers need to collaborate with adult healthcare providers, including seamless information transfer. There

are various obstacles to successful transition ranging from patient and family factors to provider and infrastructure factors. These include low expectations of the child with a chronic health condition; resistance to transition by patients, parents, and providers; difficulty identifying primary and specialty adult healthcare providers; lack of reimbursement for transition services; variable access to health insurance during emerging adulthood; and lack of institutional support including time for planning, resources, and personnel to provide care.[4,40-42] In order to provide a more sustainable means of promoting these efforts, institutional support and infrastructure are crucial.[4,42,43]

To ensure a successful transition, our SCI program attempts to meet the medical needs of the youth along with addressing cognitive, emotional, and social concerns. As mentioned previously, from an early age, youth are encouraged to actively participate in their health care. Autonomy, self-advocacy, and personal responsibility for decision-making are also encouraged as developmentally appropriate. As part of our treatment goals, team members work together to prepare youth and their families on how to navigate the adult health care system and access information and community resources. Moreover, the transition to adult care seems most successful when there is a period of shared or concurrent care between pediatric and adult providers.

Transition: Relevance to Osteogenesis Imperfecta

Transition into adult healthcare for those with OI needs to take into account their unique orthopaedic and functional impairments. Interventions to prevent long-term complications must occur throughout the individual's life, beginning in childhood. As an example to prevent overuse syndromes such as shoulder pain in individuals with OI, transition from manual wheelchairs to power assist or power wheelchairs as alternative modes of transportation must be considered as they grow older. In addition, the mechanics of wheelchair propulsion should be evaluated as the youth with OI progresses through different developmental stages, which then translates into teaching proper techniques of wheelchair propulsion. Activities to promote fitness and decrease the risk of cardiovascular disease need to be tailored to the individual with OI, both in respect to the age of the individual as well as the specific impairments for the individual. Because of the importance of ready access to one's community, individuals with OI should be evaluated for their ability to drive and accordingly undergo driver's education and adaptation of motor vehicles. Adults with OI should receive care by orthopaedists and

rehabilitation specialists who are experienced in caring for those with OI, as well as general medical care by an internist or family physician who is comfortable caring for individuals with OI and who can tailor the needed care to the individual. Additionally for females with OI, obstetric and gynecologic care should be provided by clinicians with special interest and experience with OI.

Concluding Comments

In this chapter, we have reviewed the process of transition and the major issues related to transition using pediatric-onset SCI as a model for other chronic health conditions. Transition consists of addressing developmental milestones typical of an adolescent and emerging adult as well as the individualized needs of the individual with a chronic health condition. Moreover, transition includes the transfer of care from a pediatric program to an adult service. A critical ingredient for successful transition of individuals with a chronic health conditions is the establishment of expectations that span their lifespan from infancy, through childhood and adolescence, and into adulthood, and are individualized to the youth as well as flexible. The goal of this transition process is they become adults who participate fully in their communities and experience a meaningful and satisfying life. Transition is a continuous process that encompasses several key areas including employment, independent living, transportation, psychosocial functioning, and health. Identifying factors that are predictive of these important developmental and medical outcomes can assist healthcare providers in targeting interventions to individuals at greater risk for maladjustment and impairment. Because survival of individuals with chronic health conditions has improved dramatically in the past few decades, prevention of aging-associated conditions, such as overuse syndromes or cardiovascular disease, is additionally imperative.

ABBREVIATIONS

OI Osteogenesis imperfecta
SCI Spinal cord injury

REFERENCES

1. Betz RR, Mulcahey MJ. Spinal cord injury rehabilitation. In: Weinstein SL, ed. *The Pediatric Spine: Principles and Practice*. New York: Raven Press; 1994: 781-810.

2. Anderson CJ, Johnson KA, Klaas SJ, Vogel LC. Pediatric spinal cord injury: Transition to adulthood. *J Vocat Rehab* 1998;10:103-113.
3. Zebracki K, Anderson CJ, Chlan C, Vogel L. Outcomes of adults with pediatric-onset spinal cord injury: Longitudinal findings and implications on transition to adulthood. *Top Spinal Cord Inj Rehab* 2010;16:17-25.
4. Rosen D, Blum R, Britto M, Sawyer S, Siegal D. Transition to adult health care for adolescents and young adults with chronic conditions: Position paper for the Society of Adolescent Medicine. *J Adolesc Health.* 2003;33:309-311.
5. Rindfuss RR. The young adult years: Diversity, structural change, and fertility. *Demography.* 1991;28:493-512.
6. Williams PG, Holmbeck GN, Greenley RN. Adolescent health psychology. *J Consult Clin Psychol* 2002;70:828-842.
7. Arnett JJ. Emerging adulthood: a theory of development from the late teens through the twenties. *Am Psychol* 2000;55:469-480.
8. Vogel LC, Anderson CJ. Outcomes of adults with pediatric onset spinal cord injury. *Top Spinal Cord Inj Rehab* 2005;10:109-115.
9. Anderson CJ, Vogel LC, Willis KM, Betz RR. Stability of transition to adulthood among individuals with pediatric-onset spinal cord injuries. *J Spinal Cord Med* 2006;29:46-56.
10. Anderson CJ, Vogel LC. Employment outcomes of adults who sustained spinal cord injuries as children or adolescents. *Arch Phys Med Rehabil* 2002;83:791-801.
11. Bureau of Labor Statistics, US Department of Labor. *Persons with a Disability: Labor Force Characteristics: 2013*. Washington, DC: US Department of Labor; 2014. USDL-14-1076.
12. Crissey S. *Current Population Reports: Educational Attainment in the United States, 2007*. Washington, D.C.: U.S. Census Bureau;2009.
13. Anderson CJ, Vogel LC, Betz RR, Willis KM. Overview of adult outcomes in pediatric-onset spinal cord injuries: Implications for transition to adulthood. *J Spinal Cord Med* 2004;27:S98-S106.
14. Vogel LC, Klaas SJ, Lubicky JP, Anderson CJ. Long-term outcomes and life satisfaction of adults who had pediatric spinal cord injuries. *Arch Phys Med Rehabil* 1998;79:1496-1503.
15. Krause JS, Sternberg M, Maides J, Lottes S. Employment after spinal cord injury: Differences related to geographic region, gender, and race. *Arch Phys Med Rehabil* 1998;79:615-624.
16. Burns SM, Boyd BL, Hill J, Hough S. Psychosocial predictors of employment status among men living with spinal cord injury. *Rehabilitation Psychology.* 2010;55:81-90.
17. White PH, Shear ES. Transition/ job readiness for adolescents with juvenile arthritis and other chronic illness. *J Rheumatol* 1992;19:23-27.
18. Anderson CJ, Vogel LC. Preparation for employment in children and adolescents with spinal cord injuries. *Top Spinal Cord Inj Rehab* 2000;6(suppl):170-175.
19. Goldscheider F, Goldscheider C. Leaving and returning home in 20th century America. *Population Bulletin* 1994;48:1-35.

20. Federal Highway Administration. *Distribution of licensed drivers, 2010.* Washington, D.C.: U.S. Department of Transportation September 2011.
21. Anderson CJ, Wright G, Vogel LC. Driving issues for young adults with pediatric spinal cord injuries. *J Spinal Cord Med* 1996;19:115.
22. Oakeshott P, Hunt GM. Long-term outcome in open spina bifida. *Br J Gen Pract* 2003;53:632-636.
23. Bureau of Transportation Statistics. *Freedom to Travel, BTS03-08.* Washington, D.C.: U.S. Department of Transportation;2003.
24. Lavigne J, Faier-Routman J. Psychological adjustment to pediatric physical disorders: A meta-analytic review. *J Pediatr Psychol* 1992;17:133-157.
25. Anderson CJ, Vogel LC, Chlan KM, Betz RR, McDonald CM. Depression in adults who sustained spinal cord injuries as children or adolescents. *J Spinal Cord Med* 2007;30:S76-S82.
26. Kessler RC, Chiu WT, Demier O, E.E. W. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Arch Gen Psychiatry* 2005;62:617-627.
27. Crosby AE, Han B, Ortega LAG, Parks S, Gfroerer J. *Suicidal thoughts and behaviors among adults ≥ 18 years: United States, 2008-2009.* Atlanta, GA: Centers for Disease Control and Prevention;2011.
28. La Greca AM, Bearman KJ, Moore H. Peer relations of youth with pediatric conditions and health risks: Promoting social support and healthy lifestyles. J *Dev Behav Pedia* 2002;23:271-280.
29. Barber B, Eccles J. The joy of romance: Healthy adolescent relationships as an educational agenda. In: Florsheim P, ed. *Adolescent romantic relations and sexual behavior: theory, research, and practical impliations*. Mahwah, NJ: Lawrence Erlbaum; 2003.
30. Zebracki K, Vogel L, Chlan K. Sexuality in adults with pediatric-onset spinal cord injury. *Presentation at: Congress on Spinal Cord Medicine and Rehabilitation*. Dallas, TX2009.
31. Crewe NM, Krause JS. Marital status and adjustment to SCI. *J Am Paraplegia Soc* 1992;15:14-18.
32. Cheng MM, Udry JR. Sexual behaviors of physically disabled adolescents in the United States. *J Adolesc Health* 2002;31:48-58.
33. Suris JC, Parera N. Sex, drugs, and chronic illness: Health behaviors among chronically ill youth. *Eur J Public Health* 2005;15:484-488.
34. Suris JC, Resnick MD, Cassuto N, Blum R. Sexual behavior of adolescents with chronic disease and disability. *J Adolesc Health* 1996;19:124-131.
35. Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: Challenges living, challenges treating. *Lancet* 2007;369:1481–1489.
36. Anderson C, Vogel L, Chlan K, Betz R. Coping with spinal cord injury: Strategies used by adults who sustained their injuries as children or adolescents. *J Spinal Cord Med* 2008;31:290-296.
37. White B, Driver S, Warren AM. Resilience and indicators of adjustment during rehabilitation from a spinal cord injury. *Rehabilitation Psychology.* 2010;55:23-32.

38. Vogel LC, Krajci KA, Anderson CJ. Adults with pediatric-onset spinal cord injuries: Part 3: Impact of medical complications. *J Spinal Cord Med* 2002;25:297-305.
39. Vogel LC, Krajci KA, Anderson CJ. Adults with pediatric-onset spinal cord injury: Part 2: Musculoskeletal and neurological complications. *J Spinal Cord Med* 2002;25:117-123.
40. Kennedy A, Sawyer SM. Transition from pediatric to adult services: Are we getting it right? *Curr Opin Pediatr* 2008;20:403-409.
41. Agrawal R, Shah P, Zebracki K, Sanabria K, Kohrman C, Kohrman A. Barriers to care for children and youth with special health care needs: Perceptions of Illinois Pediatricians. *Clin Pediatr* 2011;51:39-45.
42. Scal P, Ireland M. Addressing transition to adult health care for adolescents with special health care needs. *Pediatrics* 2005;115:1607 -1612.
43. American Academy of Pediatrics, Family Physicians and American College of Physicians, American Society of Internal Medicine. A consensus statement on health care transitions for young adults with special health care needs. *Pediatrics* 2002;110:1304-1306.

2 TRANSITIONAL CARE IN OSTEOGENESIS IMPERFECTA: ESTABLISHMENT OF REGIONAL LINKED CLINICAL RESEARCH CENTERS

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INTRODUCTION

Osteogenesis imperfecta (OI) is not only a rare disorder, but also an extremely complex one. The existence of multiple types, the extreme range of severity, plus the combination of dominant and recessive inheritance mechanisms all contribute to the complexity of the disorder. The underlying causes for OI, mutations in genes associated with type 1 collagen and bone formation lead to an array of symptoms in multiple body systems, particularly those that include collagen rich tissues. Together these issues make understanding and treating OI a significant challenge. Complex clinical care issues, including elucidating how OI affects adults as they age, have brought greater attention on the need for transitional care.

The Need for Post-Pediatric Care

In the past, many conditions, such as OI, were labeled "pediatric." This implied a significantly shortened life span with little hope for living to be an adult. The companion implication for those who lived through their teens was that the condition would become significantly milder or even disappear, possibly by the time the child patient turned age 18 or 21. These pediatric conditions were covered in the training of pediatricians and pediatric specialists in orthopedics, endocrinology, cardiology, pulmonology, etc. There was little incentive to anticipate the needs of adults with these conditions. The result was that OI and other similar conditions were mostly ignored in the training of physicians who expected to work with adult patients. Over time improvements in care led to a phenomenon called "aging-

out" among patients seen in children's hospitals. In other words, they became too old to receive services in a pediatric center. Unfortunately, they soon discovered that almost no one in the adult health care system understood, let alone had any experience, with their disorder. In the case of adults with OI, many tried to continue seeing their pediatric orthopedists especially if they had a serious fracture or a problem with a rod. Pediatric care centers that offered a "transition-to-adult-care" program for their patients tended to cover general topics about understanding insurance and keeping good records, but rarely helped the soon-to-be young adult locate a physician knowledgeable about OI.

In recent years, there has been a growing realization among pediatric specialists that these conditions are really "pediatric-onset conditions." They may begin in infancy, but they are life-long chronic conditions. Improved general health and the hard work of many health care providers, basic and clinical researchers, and family members, brought about this change. Today, adults who have OI recount stories that they "proved" their geneticist or pediatrician wrong by not only living into middle age and beyond but also building productive and interesting lives. These adults explain that integrating the management of their OI into careers, relationships, marriage, and families is important to them. They also explain how difficult it can be to determine when a symptom is normal aging or if it is directly related to OI. They report that their doctors often are uncertain how to treat them for even common illnesses or serious problems such as cancer because of uncertainty about the impact of OI on the conditions or the treatments.

Recognizing that the majority of children who have OI can expect to grow up to be adults and to live at least close to an average life span is a huge change in thinking. It has implications for treatment, social services, education, and health insurance. It illustrates the need for continuity of care across the life span. This change toward recognizing OI as a life-long condition beginning in infancy is more than just words. It means that a full complement of primary care physicians and specialists needs to become knowledgeable about OI. It illustrates the need for changes in the training of physicians, nurses, physical therapists, and other health care providers. However, when one looks for evidence-based recommendations for managing OI during the adult years, the lack of information is shocking. This new focus brings to light the fact that research into the natural history of OI after puberty, as well as research in the specific clinical problems that concern adults more than children, lags far behind research into the basic science of OI and treatments for children.

OI is More Than a Fragile Skeleton

The other change in focus that has important implications for transitional care arose out of the increased awareness that the mutations causing OI affect many more body systems than simply the skeleton. Repairing fractures and bone deformities, responding to muscle atrophy from immobilization, and testing treatments with bone building drugs during childhood had been the focus of treatment for OI for many years. By taking a "big picture" look at the collagen defect, investigators became more aware that the vision, heart, kidney, and respiratory problems seen in adults might not just be "normal aging," but consequences of OI. This new information significantly expands the array of topics that transition to adult care programs need to address.

REASSESSING TRANSITIONAL-CARE

The adult-care system is complex, confusing, and disjointed. This can be a problem for anyone, but for a person with a rare and life-long condition like OI the issues can be overwhelming. To function effectively in the adult-care system, young people need training in becoming self-advocates and they need to become knowledgeable about their disorder and personal health history. They need to know how to locate primary care and medical specialists who also understand OI. As they transition into the adult care system, youth need the skills and information to maintain their health, preserve or improve their level of function to meet the demands of adulthood, maintain continuity of medical/surgical care, and manage their psychosocial health and relationships[1]. The lack of evidence-based care guidelines hampers these efforts. Beyond the personal case records of a few physicians who see adults, there is little or no information about how OI affects adults. There is also little or no information about how OI does or does not affect treatments for other medical issues faced by the adult. In addition, because the adult-care system is much more fractured and disjointed than pediatric care offered through a children's medical center, it is often difficult to locate a primary care physician let alone a specialist with experience treating individuals with OI.

The Linked Clinical Research Center Idea

An increased life span, expanded awareness that OI affects all collagen-rich tissues, a shortage of physicians with experience caring for the adult with OI, and a lack of evidence-based care guidelines are the trends that laid the groundwork for the Linked Clinical Research Center (LCRC) idea. In the

1990s, leaders in the OI Foundation and the Children's Brittle Bone Foundation came to the realization that continuing to separately fund annual grants to basic and clinical researchers was not enough. Something else was required. Both organizations agreed that a need existed for bigger studies, for more clinical care studies and for studies that included adults with OI. In addition, both organizations saw a need for initiatives to improve physician knowledge and awareness about OI. Working together, the two foundations convened a study group composed of leaders from the medical and family communities. The study group evaluated many plans and for a short time considered endowing a medical center to focus on OI research. The group liked the fact that a medical center typically has experience collecting information on a large number of people, keeping detailed records and tightly controlling each research protocol. Nevertheless, the medical center model proved to be impractical when they determined that not one of the OI clinics in existence at the time had a sufficient patient population to represent all types and ages of people with OI. The alternative, building a center from scratch, was cost prohibitive. These issues and others relating to geography and patient access led the group to embrace the idea of a virtual research center and the linked center concept was born. The plan that emerged involved establishing a network of OI Clinics all using the same central database and following identical research protocols. In this manner, the virtues of a large center could be achieved in a manner that was accessible to the far-flung OI community in the United States and Canada.

Even without construction costs, a linked center program was an ambitious project. From the beginning, the goal was to seek partial funding from the National Institutes of Health (NIH). Therefore, the planning group chose to use data processing technology and a management system that was already familiar to the NIH and thoroughly tested. Rather than postpone the program, the OI Foundation decided that the need was too great to wait and make the risky decision to self-fund this very large project. In January 2009, after having raised enough money to fund three years of operation the Linked Clinical Research Center (LCRC) program was officially announced and an initial group of three centers was chosen.

The LCRC Program

The OI Foundation's LCRC program sought to shape the future of OI care by:

- Addressing barriers to research for a rare disorder
- Speeding up the pace of research, especially research focused on clinical care

- Addressing the gap in information and care faced by adults with OI
- Improving guidance for managing OI for youth who are transitioning from pediatric to adult care.

The LCRC program was a multi-year, multi-center program. It aimed to improve care for people with all types of OI and to expand understanding about the health problems and level of daily functioning experienced across the life span. As a group, the linked centers pursued research into OI, referred children and adults who have OI to care providers and provided information to researchers and health care providers. Data collected at each center visit was maintained in a secure de-identified manner. The identity of each person was open only to her/his own doctors but allowed in-depth analysis of the contents. To be considered for a slot as a linked center, each center needed:

- A team of primary care and specialist physicians with expertise treating OI;
- Experience doing quality clinical research;
- The ability to follow a specific data entry protocol; and
- Facilities that could accommodate both children and adults.

The requirement of providing care for adults who have OI led a number of pediatric centers with well-established OI programs to re-examine their procedures. Several centers began to identify and work with the physicians – orthopedists, internists, and endocrinologists – who were already seeing adult patients in their communities. They began to expand their in-house "transition-to-adult-care" programs. When a children's hospital could not accommodate adult patients, new partnerships were formed with nearby medical centers that had appropriate programs such as an orthopedics center, a bone dysplasia clinic, or an endocrine clinic.

An initial group of three centers was selected to test the protocols and operating procedures. Two additional centers were added a year later. The OI Foundation's linked centers included:

- Baylor Medical Center, Houston, TX
- Kennedy Krieger Institute, Baltimore, MD and its partner DuPont Hospital for Children, Wilmington, DE
- Oregon Health & Science University / Portland Shriners Hospital, Portland, OR
- Shriners Hospital for Children, Chicago, IL
- Shriners Hospital for Children, Montreal, Quebec, Canada

First LCRC Study

The first LCRC study was titled "The Longitudinal Study of Osteogenesis Imperfecta." This kind of study is sometimes referred to as a "natural history study." It is designed to collect and analyze information about the health of people who have OI, but it does not offer a specific treatment to the participants. The objective is to conduct a multi-year, multidisciplinary investigation of the natural history, current therapeutic interventions, morbidity, and mortality in people with OI. Children and adults with a diagnosis of OI were eligible to participate. Study participants visited a center once a year for 3-5 years. Each person completed a detailed medical history and received an extensive annual physical exam. Various diagnostic studies such as a DEXA, motor function tests, and lung function tests are part of the exam. The goal of this study was to enroll 500 participants who represented the different OI types from early childhood through old age. In all, 560 people participated.

Analysis of data from the first two years was very encouraging. Evidence-based height and weight charts for children with different types of OI and a chart of developmental milestones were among the first products. Additional data on the overall health of adults who have OI were also obtained and analyzed.

EXPANSION

In 2014, the LCRC program became the Brittle Bone Disorders Consortium as part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network. The Brittle Bone Disorders Consortium is a multi-center program built on the LCRC foundation. It focuses on understanding and providing better treatment options for all types of osteogenesis imperfecta. The change expanded and updated the LCRC idea by:

- Extending the Longitudinal Study of OI.
- Adding more centers to the network.
- Increasing the number and scope of clinical research studies.
- Offering an improved patient registry.

In addition, the Brittle Bone Disorders Consortium includes opportunities for out-reach to physicians and other health care providers. The consortium program makes evidence-based information on diagnosing and treating people with OI more readily available to a wider audience through on-line materials, medical society meetings and continuing medical education.

Research and Rare Disorders: Impact of LCRCs

The success of studies of rare disorders like OI depends on solving two fundamental problems: getting enough people to participate so that the observations are meaningful, and gathering data that can be compared across different medical centers. Approximately 20,000 - 40,000 people of all ages have OI. They live in every region of the United States. Many people living with OI have never met another person with their diagnosis, or only those in their own family. Many are the only OI patient seen by their primary care physician. Historically, this reality of a widely dispersed patient population led to studies for OI and other rare disorders that had very small samples. Consequently, the resulting data could not provide definite answers to the research questions or provide specific guidelines for care/management of the rare condition. This lack of information is particularly problematic in OI because it is an extremely variable condition. One solution to this problem is to gather information from multiple medical centers. An ongoing challenge with multiple center studies is collecting the exact same data in exactly the same manner at each site. The LCRC program, as designed by the OI Foundation, aimed to overcome these problems by making it possible to combine information from hundreds of people with OI from across the United States and Canada. Years were spent planning, writing definitions, and developing systems to ensure that all of the information on each participant is collected in exactly the same way. This infrastructure makes it possible to analyze all of the data from all of the centers together as one study.

Increasing the Pace of OI Research

Besides recruiting a large enough group of study participants, another way to increase the pace of research is to identify topics related to OI that need to be studied. Advancing understanding about OI, improving clinical care, and addressing the social and functional needs of the person with OI require ongoing research in many different areas. Basic genetic and bone biology studies are needed to identify targets for new therapies. Clinical care studies are needed to identify effective management for fractures, scoliosis, and multiple other OI related issues. Function and mobility issues that arise at different stages of life need to be explored. Through its scientific meetings, grant programs, and linked centers, the OI Foundation seeks to encourage advancements in all of these areas.

Addressing the Gaps in OI Knowledge and Improving Transitional-Care

The Longitudinal Study of Osteogenesis Imperfecta is expected to contribute to establishing care guidelines for older teens and adults with OI of all ages. The long-term nature of the study and the participation of a sufficient number of people of different ages and OI types will help draw a picture of OI across the life span. By identifying trends in health status, the LCRC data helps to initiate an answer to the classic question – "Is it OI or aging?" – regarding observed changes in fracture incidence, bleeding, strength, pain, and mobility. Identifying health trends may open the door to creating care guidelines that not only indicate which treatments are successful, but might also anticipate when age-related problems and/or age-plus-OI problems might begin. This information would allow adults who have OI and their doctors to be proactive about promoting life-long health. This information would also help pediatricians and parents as they try to anticipate a child's future needs.

OI FOUNDATION HISTORY

The OI Foundation is the only organization in the United States that is solely dedicated to serving people who live with OI. The mission of the OI Foundation is broad – to improve the quality of life for people affected by OI through information, mutual support, and research. From the beginning in 1970, the leaders and members of the OI Foundation have been eager to increase research into the causes and treatments for OI. Over the years, support for research has been provided through:

- The Geisman Fellowship Program that provides grants for young investigators who are just beginning their careers and who are interested in investigating questions relevant to OI;
- Clinical and Seed Grants for established researchers;
- Scientific Conferences and Think-Tank Meetings to explore single-topics relevant to understanding OI and to foster collaboration between scientists;
- Support for International Scientific Meetings focused on OI;
- Establishing a registry to collect contact information from people in the OI community who are interested in participating in research and basic descriptive data about their experiences with OI; and
- Creating the Adult Health Initiative, and sponsoring a survey of adults who have OI to create a profile of their health status.

To effectively increase knowledge about the causes, consequences and treatments for OI, it is necessary to harness the efforts of many people. The OI Foundation works to encourage collaborative studies that allow the scientist and clinician to look at data from different perspectives, to ask questions, and to share ideas. The OI Foundation is also an advocate for the needs of people living with OI. In this capacity, it brings the questions raised by members of the OI community to the attention of basic scientists and clinical researchers.

Establishing a network of linked centers was a very ambitious project for a small foundation focused on one rare disorder, but that is exactly what the Osteogenesis Imperfecta Foundation has done. The success of the original Linked Clinical Research Center program led directly to including brittle bones in the NIH Rare Diseases Clinical Research Network. The Brittle Bone Disorders Consortium initiatives will benefit the young person making the transition from pediatric to adult care. Research conducted through the LCRC program and its replacement, the Brittle Bone Disorders Consortium, has great potential to expand understanding about OI, and improve care for people with all types of OI across their entire life span.

REFERENCE

Shapiro JR, and Germain-Lee EL. Osteogenesis imperfecta: effecting the transition from adolescent to adult medical care. *Journal of Musculoskeletal Neuronal Interaction*. 2012 March: 12(1:24-7).

3 BIOMECHANICS OF OSTEOGENESIS IMPERFECTA: CURRENT CONCEPTS AND EMERGING HORIZONS

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INTRODUCTION

Osteogenesis imperfecta (OI) is associated with bone fragility. Long bone fractures are a common occurrence in individuals with OI. Although there have been significant advances in understanding the genetic defects associated with OI, the mechanisms behind bone fragility in this patient population are not yet well understood. This fragility is believed to stem in part from characteristic bone mass deficiencies. Research further suggests that the material properties of the bone are also compromised in individuals with this disorder. There is currently no quantitative method available to assess bone fracture risk in individuals with OI. This chapter examines several critical elements needed to assess bone fracture risk through a unified biomechanical modeling approach. Finite element modeling (FEM) lies at the core of this approach with reliance upon material property and load data. The former stems from micro- and macrostructural scale characterization of bone material properties while the latter derives from assessment of mobility and other activities. As improved tools are developed for fracture risk assessment, clinicians will be afforded more effective methods to examine interventional effects and rehabilitative strategies in the short- and long-term with an ultimate goal of fracture reduction.

MECHANICS AND MICROSTRUCTURE OF THE BONE MATERIAL

Bone Mass

Low bone mass is a characteristic of OI, as evidenced by very low areal bone mineral density as well as sparse material distribution in bone biopsies.[1-4] These findings indicate that individuals with OI have less bone material available to support musculoskeletal loading, and that these loads are distributed over a smaller bone cross-sectional area, resulting in increased stresses (local intensity of forces per area) within the bone for a given load.

Bone Composition

Abnormalities related to bone tissue composition and microstructure in OI have been described, which, in addition to bone mass deficiencies, may contribute to bone fragility.

OI is the result of genetic defects related to type I collagen, an important structural component of bone, or to other proteins that interact with type I collagen for *post-translational modification and/or folding*. For example, OI type I, a mild form, is attributed to an insufficient quantity of type I collagen;[5-8] while OI types III and IV, which are more severe, are associated with defects within the collagen.[8-10] Thus, it is perhaps not surprising that irregularities in collagen molecules size have been observed within this population.[11-13]

Abnormalities in the mineral component of bone have also been observed in OI. The size, shape, and composition of the mineral crystals have been shown to be affected,[11,14-17] and mineralization density was found to be higher than normal.[4,17-19]

Bone Properties at the Microstructural Scale

The idea that bone material properties are compromised in OI is supported by findings from studies of mouse and human bone tissues.

Bone is a highly hierarchical material having distinct structural features at different length scales. Therefore, it displays different mechanical behavior depending on the scale at which it is tested. A few studies have used nanoindentation, a mechanical test in which a small diamond-tip is pressed into the polished surface of a specimen, to measure the mechanical

properties of surgical and biopsy bone specimens from children with OI. In this test, the resulting indent is a few microns in width, allowing measurement of mechanical properties on a small area within the bone microstructure (e.g., intra-osteon).

From nanoindentation tests, two material properties can be determined: the elastic modulus, representing the material's stiffness (i.e., resistance to non-permanent deformation); and hardness, representing the resistance to permanent deformation. Surveying the literature on nanoindentation testing of pediatric OI bone, the following observations are made regarding elastic modulus and hardness at the microstructural scale. Overall, these properties tend to be higher in children with mild vs. severe phenotypes;[20] but they do not appear to differ between moderately severe and severe OI phenotypes.[21] Importantly, however, there have been conflicting observations regarding how these properties compare with those of normal bone. In one study, higher elastic modulus and hardness were observed in children with severe and moderately severe OI (types III and IV),[18] while in a more recent study these properties were lower in children with mild to severe OI vs. control specimens.[17] These divergent observations have not been explained. However, these studies may have been focused on different regions within the bone microstructure. Nanoindentation properties have been shown to vary between interstitial versus secondary osteon lamellar regions.[20]

Interestingly, elastic modulus and hardness measured by nanoindentation were not found to be altered by pamidronate treatments,[18] and these properties are not correlated with age in children with OI.[20-22] A positive correlation, however, has been observed between elastic modulus and local tissue mineral density.[17]

Bone Properties at the Macrostructural Scale

Due to limited access to bone tissue specimens from humans with OI, little data is yet available to describe their material strength. Recently, a testing methodology was developed and validated to enable measurement of bone material strength using small bone specimens obtained from osteotomy procedures used to correct long bones deformities.[23,24] These small, irregular-shaped osteotomy specimens can be machined into even smaller rectangular-shaped beams, from which the material strength can be determined. Preliminary results indicate that this bone material property is reduced in children with OI relative to typical children.[23,24] Further research is needed to confirm whether this is consistently true in all forms of OI, and

how this property is affected by factors such as age, gender, anatomic site, and genotype. Nonetheless, the consequence of low bone material strength is that the bone tissue itself is less resistant to internal loading, and will fracture more easily.

Bone Microstructure

In a recent study of three-dimensional bone microstructure, several abnormalities have been noted in cortical bone specimens from children with OI versus control tissues.[25] In particular, abnormally elevated vascular porosity was observed in cortical bone tissue in OI. This observation is consistent with those of a recent two-dimensional scanning electron microscopy study.[26] These findings indicate that, in contrast with normal bone, cortical bone tissue in OI has a highly porous structure, which can affect internal stress distribution within the material.

Future Directions

Further study is warranted toward exploring relationships between bone material properties at the microscale and the local variations in mineral and collagen composition with respect to the various OI genotypes. Future studies should also aim to establish relationships between bone properties at the mesoscale and the three-dimensional microstructure. Finally, future directions in material characterization of bone tissues in OI should explore how the bone material properties and microstructure are affected by factors such as: donor age, genotype, antiresorptive therapies, mobility level, and anatomic site.

STRUCTURAL MECHANICS OF WHOLE LONG BONES

Several studies have characterized the structural and material-level mechanical properties of bones in murine models of OI.

In Mov13 mice, a model for OI type I, cortical bone material is weaker than that of control mice.[27] However, the Mov13 whole femur as a structure exhibits load to failure similar to that of controls, which appears associated with greater cross-sectional area and bending moment of inertia.[28]

In the oim/oim mouse, a model of OI type III, reduced whole bone structural strength is associated with reduced material strength and toughness.[29-31] In that mouse model, the collagen is weaker than normal.[32] However,

demineralized bone properties do not differ from those of controls, indicating that the weakness of bone tissue in the oim/oim mouse is likely attributed to incompetent mineral-matrix interaction rather than to the collagen matrix itself.[30]

The Brtl mouse, a model representative of OI type IV, exhibits reduced whole bone structural strength, which, interestingly, increases as the animal aged.[33,34] This improvement of whole bone strength with age is associated with an increased material strength rather than an improvement in the cross-section geometry.[33,34]

It is not clear whether all the above observations are also true in the human forms of OI, nonetheless, these models offer valuable insight into the mechanisms of the bone fragility in OI. Moreover, the availability of murine models has enabled the evaluation of several therapies for OI and their impact on bone structure and strength. For example, therapies such as alendronate, pamidronate, RANKL inhibition, *in utero* transplantation of adult bone marrow, sclerotin antibody, and whole body vibration have been studied in various murine models of OI.[29,31,34-39]

Finite Element Studies of Human OI Bones

Structurally, OI bone exhibits characteristics that point to decreased strength even in response to everyday loading. Histomorphometric data indicates that OI bone exhibits decreased cortical and trabecular thickness as well as reduced bone volume fraction.[24] Normal human long bone develops with the bulk of its material aligned with the mechanical axis of loading, such as predominantly along the length of the femur. This partially explains why bone is strongest in compression along its longitudinal axis. However, OI long bones often exhibit deformations consisting of bowing in the lateral or anterior directions or a combination of both along with torsional deformations. Such geometric alterations shift the locus (area and mass moment) of the material with respect to the ideal mechanical loading axis. As more bone material is moved away from this axis, this bone undergoes higher stresses and becomes an increased risk for fracture.

Developing a better understanding of OI bone biomechanics as well as when and why fractures may occur in OI bone would be largely beneficial to the population. However, it is often not feasible to study bone biomechanics *in vivo*. Thus, modeling has the potential to play a key role in understanding how OI bones respond to loading experienced during various activities,

especially ambulation. Biomechanical modeling can provide insight into bone fracture risks, such as fracture type and location, from single applied loads or repetitive loading. One method for obtaining this information is via finite element analysis (FEA).

Finite element analysis (FEA) has long been used to assess the response of materials to various loading conditions through computational modeling. Finite element (FE) models can be developed and processed for loading conditions that would be too costly, time consuming, or impractical to perform with traditional mechanical testing. The application of FEA to biomechanics was introduced in 1972 by Brekelmans et al. to investigate the stresses experienced in human bone under physiologic loading conditions.[40] Since that time, FEA has been widely used in orthopaedic biomechanics and bone assessments as it allows estimations of *in vivo* responses of biological tissues to various loading conditions.[41,42] Patient-specific FE models have been an effective tool for both bone strain and fracture strength assessment.[43,44] One important developing application is the use of FEA to predict fractures in OI.[45,46]

The first FE model for OI was published by Fritz et al. in 2009 and examined the fracture risk of the right femur during normal ambulation of a 12-year-old female with OI type I.[45] It is a patient-specific model that incorporated loading from inverse dynamics and muscle activations based on clinical gait analysis. The model was analyzed across all seven phases of gait. Material property assignment in this model was taken from literature on nanoindentation testing of bone specimens from children with mild OI. Model geometry (size and lateral bowing) was matched to the patient based on her femoral x-rays by scaling and manipulating an existing three-dimensional (3D) model for FEA of the standardized femur. Initial analysis showed that the femoral stresses were highest during mid-stance and located at the lateral aspect of the bowing deformity and migrated through the gait cycle.[45] Fritz et al. also examined the sensitivity of the model to changes in applied loading from muscle forces during mid-stance. They concluded that the model was sensitive to force changes from the gluteus maximus and gluteus medius muscles.[46] Since their initial work, Fritz and colleagues have implemented an improved mesh and updated the material property assignments to reflect the most recent OI bone mechanical property data.[24,45,46]

Other FE models for assessing OI bones have recently been developed. Orwoll et al. used FEA to estimate vertebral strength in a study of the effects of teriparatide treatment in adults with OI.[47] Caouette et al. have developed FE models of tibias to biomechanically assess fracture risk in children with OI.[48] These tibia models examined fracture risk via principal strain criteria through the modeling of two-legged hopping loading, lateral loading, and torsional loading. Geometry of the tibia models was created by combining 3D reconstructions from peripheral quantitative computed tomography (pQCT) and bi-planar tibial x-rays matched to a standardized 3D tibial model into a 3D model for FE analysis. Material property (elastic modulus and Poisson's ratio) data was assigned based on nanoindentation data from a group of children with OI type IV (cortical regions),[21,49] or estimated based upon patient-specific bone apparent density measures obtained at three different sites by pQCT (trabecular regions).[48] Although this method did not enable site-specific assignment of material properties throughout the whole tibia, it provided patient-specific estimates of bone properties with limited radiation exposure to the patient compared to a whole bone computed tomography (CT) scan. This approach also provided more specific estimates of effective trabecular properties than would have the use of data obtained from non patient-specific *in vitro* mechanical studies.

Future Directions

Advancing knowledge of bone mechanical properties and musculoskeletal biomechanics associated with OI increases the capabilities of FE modeling for fracture risk assessment of OI bones. Patient-specific parameters for FE models include material properties, geometry, boundary, and loading conditions. Along with the implementation of new mechanical properties of OI bone, researchers are looking to understand how musculoskeletal biomechanics and muscle activation patterns and levels may vary in persons with OI compared to normal data. Muscle activation timing and levels play a key role in the direct loading exerted on long bones at each muscle attachment site. Fritz et al. showed that the stresses within the femur are sensitive to changes in muscle forces from the gluteus maximus and gluteus medius during the mid-stance phase of gait in an FE model of an OI femur.[46] This observation has led to implementation of additional surface electromyography (EMG) data being collected during gait analysis studies of minors with OI and age-matched controls. Future investigations into the exact forces being exerted on OI bones by muscle activation may further benefit from musculoskeletal modeling and simulation. Advanced knowledge of muscle forces along with motion analysis during various

activities will provide patient-specific data for the boundary and loading conditions necessary for FE models of OI bones. A better understanding of the dynamic application of loads during various activities (walking, running, jumping, etc.) will enable estimation of the stresses and strains that these loads induce within bones. Ultimately, these models will help to evaluate the load levels that may induce fracture and locate the site within the bone where a fracture is most likely to occur.

The heterogeneity of the OI population requires that these FE models take into account the patient's clinical severity (phenotype and possibly genotype) and physical activity level, and how these factors affect the bone from a mechanical perspective. A more precise method for applying patient-specific material properties for FE models of bones involves the acquisition of CT scans of the bone to be modeled. Geometric and mechanical property data can both be extracted from CT scans.[50] However, this comes with the caveat of radiation exposure, which is not desirable or feasible in minors with OI who already undergo frequent x-ray scans due to fractures and routine clinical examinations.

Future work should examine the necessity of acquiring 3D images of OI bones for geometric modeling. As discussed earlier, not all current models are created from direct 3D reconstructions of the patient's bone. Fritz et al. use a method that employs planar x-ray data to scale an existing 3D femur model while Caouette et al. use a combination of pQCT and scaling to create their tibia models.[45,48] Magnetic resonance imaging (MRI) data collection may be a safe – though expensive – alternative to acquiring exact 3D geometry of patients without radiation exposure. As discussed earlier, the altered geometry of OI bones often leads to more material being moved away from the mechanical axis and, thus, leaving long bones more susceptible to fracture during routine loading conditions such as ambulation.

Long bone loading during ambulation is generally associated with the lower extremities, specifically the femur and tibia. However, many persons with OI use assistive devices, such as walkers, Lofstrand crutches, or wheelchairs, for ambulation. While the use of these devices offloads the lower extremity bones, higher magnitudes of cyclic loads are imposed on the upper extremity bones when compared to unassisted ambulation. Upper extremity motion analysis models along with instrumented crutches have provided insight into the joint loading and potential overuse injuries.[51] Such upper extremity load data could be incorporated into FE bone models to assess the impact of these

assistive devices on fracture risk. During assistive device ambulation, the humerus becomes analogous to the femur and geometric alterations such as bowing move material away from the mechanical axis. Like the femur, this is likely to cause increased stress levels and concentrations at the apex of bowing.

Technology and knowledge advances continue to assist in the development of patient-specific FE models for fracture risk assessment. This tool may ultimately prove invaluable for quantification of fracture risk. By simulating various activities, these models could help identify those activities that pose greater risk and thus reduce the risk of fractures through activity modification. These models could also enable persons with OI to participate actively and safely in a broader range of activities that are assessed to pose lower risk. Finite element fracture risk models may also provide novel quantitative insight in deciding if and when a patient's bowing deformity should be surgically corrected.

MOBILITY

The need for quantitative mobility and activity assessment is fundamental to the FEM process that lies at the core of fracture risk assessment. Dynamic load application during ambulation, assisted ambulation, and other activities induces stresses and strains within the bones. Analysis of these dynamic loads has become a critical phase of the fracture risk assessment.

Human motion analysis offers a sophisticated laboratory method for characterizing loads during ambulation. This process of analysis is used frequently today for clinical and research applications and has evolved well beyond basic descriptions of ambulatory patterns to include triaxial joint kinematics and kinetics (dynamics) as well as surface and fine-wire EMG. Knowledge about body segment anthropometry and segmental kinematics can be combined with EMG and muscle evaluation data to drive further models of muscle contributions to bone and joint loading. SIMM (Musculographics Inc., Santa Rosa, CA), OpenSim (Simbios,NIH), Biomechanics of Bodies (The MathWorks Inc., Natick, MA), AnyBody (AnyBody Technology Inc., Salem, MA) and MADYMO (Tass International, Livonia, MI) are a few examples of simulation models that offer various options for including muscle contributions to joint dynamics.

Historically, lower extremity motion analysis has played a vital role in the advancement of surgical treatment of children and young adults from the

days of isolated procedures to the current comprehensive, multilevel approaches.[52-55] Lower extremity motion analysis has long proven useful in studies of neuromuscular disorders[56-60], joint replacement[61-71], athletic performance and injury[72-75], prosthetics[76-80], orthotics[81-84], and assistive devices.[85-87] While simple observational analysis of ambulation by a trained observer is clinically useful, current technology supports precise analysis of joint angles, angular velocities and angular accelerations; ground reaction forces; joint reaction moments and forces; joint power generation and absorption; and EMG. This technology also supports analyses of upper extremity contributions to assisted ambulation and other activities with similar precision. In children and young adults with OI, mobility assessment has included analysis of ambulation during use of wheelchairs and assistive devices.

Ambulation

The largest predictor of walking ability in a study of 70 children with OI (types I, III and IV) is reported by Engelbert et al. to be the severity of collagen defect.[88] While all children of the type I group were able to ambulate, 85% were able to ambulate household distances without assistive devices. In an examination of functional limitations, Takken et al. reported that children with OI type I fatigued easily, possibly due to muscle weakness and diminished peak maximal oxygen consumption.[89] Studies have also been performed to improve the process of evaluation of children with OI by assessing gait and selected functional measures. These have extended to a broader investigation of bony fracture through biomechanical modeling and material characterization as described earlier in this chapter. In a study of ten subjects with OI type I and 22 age-matched controls, Graf et al. performed gait analysis, including kinematics and kinetics.[90] Gait data was collected at 120 frames per second using a passive-reflective marker set and a 14 Vicon MX camera motion analysis system (Vicon Motion Systems, Ltd., Oxford, UK). Spherical reflective markers were placed at anatomical landmarks on the pelvis and lower extremities in accordance with the validated Vicon Plug-in-Gait Model (Vicon Workstation v 5.2.4).[91-93] Twin force plates (AMTI, Newton, MA) were used to measure ground reaction forces. System calibration assured an accuracy of less than 1 mm.[94,95] Participants walked at a freely selected pace for 10 to 15 trials with a minimum of three trials selected for analysis. Kinematics and kinetics were computed for all trials.

Temporal analysis showed that the period of double limb support was increased and that foot off occurred later in the gait cycle in the OI group

when compared to controls. Cadence (steps/min), single limb support duration, and walking speed were not significantly different between groups. Kinematic analysis showed a significantly reduced mean peak ankle plantar flexion during third rocker for the OI group (mean: -3.6°) as compared to the controls (mean: -12.1°). There was a significantly reduced ankle range of motion during stance in the OI group (OI: 21.5°; controls: 28.0°). Significant differences were also found at the pelvis, with greater downward obliquity during stance in the OI group (OI: -4.4°; controls: -2.4°). With regard to event timing, peak ankle dorsiflexion during stance phase occurred at 52% gait cycle (GC) for the OI group and 43% GC for controls. Several other events occurred significantly later in the GC for the OI group including: peak hip extension, peak knee extension, and peak external foot progression angle (all during stance) and peak knee flexion during swing. In the kinetic analysis, the OI group peak ankle push off power (generation) was significantly reduced and occurred significantly later during the gait cycle (2.7 W/kg at 58% GC) when compared to the controls (3.7 W/kg at 52% GC).

Peak ankle power generation during push off in the OI group was significantly less than that of the controls. This decrease was thought to be related to the flexibility of the OI foot as well as an avoidance of excess force in the presence of bone fragility. Further developments, findings, and expanded opportunities for contribution to a better understanding of ambulation in children and young adults with OI can be found in the chapter by Adam Graf and colleagues later in this book.

Wheeled Mobility

Slavens et al. have reported on unique quantitative, three-dimensional (3D) evaluations of upper extremity (UE) joint dynamics at the shoulder complex, elbow, and wrist during pediatric wheelchair use.[96] Work on pediatric-wheeled mobility assessment has also been reported by Schnorenberg et al. with an advanced biomechanical model for evaluation of UE joint dynamics.[86] An inverse dynamics model was used to characterize 3D UE joint kinematics and kinetics during pediatric wheelchair mobility using a SmartWheel (Mesa, AZ) instrumented hand rim system. The bilateral model included thorax, clavicle, scapula, upper arm, forearm, and hand segments, as well as the sternoclavicular, acromio-clavicular, glenohumeral, elbow, and wrist joints. Previous, validated UE models for the evaluation of pediatric assisted mobility[51,97-100] provided a foundation for development of this model which incorporated International Society of Biomechanics (ISB) recommendations[101] as well as custom features specific to the pediatric

population. The marker set used to describe the thorax was refined to reduce the influence of shoulder girdle movement on thoracic kinematics. A regression method was applied for determining glenohumeral (GH) joint center that used the positions of five markers on the scapula.[102] A tracking method was described for the scapula markers to reduce the effects of skin motion artifact as well as possible marker-wheelchair interaction.[103] Body segment parameters were calculated with equations specifically developed for pediatric application.[104,105] The model was applied to an adolescent to demonstrate utility in identifying motion and loading patterns. This model may provide valuable new insight and is biomechanically appropriate for application in children and young adults with OI.

Assistive Devices – Crutches and Walkers

Upper extremity dynamics during crutch-assisted gait have been of interest for several decades following an early history of work done to characterize the lower extremities.[106-110] Premature development of degenerative arthritis and disruption of the rotator cuff associated with assistive device usage has been of concern to a number of authors who have initiated UE studies.[111,112] Model limitations, however, have tended to slow progress. An early study by Requejo et al. contributed information on kinematics and kinetics for a single subject with spinal cord injury.[113] Complete UE dynamics were later reported in a study by Slavens et al. in 2007 for five children with myelomeningocele during Lofstrand crutch-assisted gait.[114] This work incorporated standards suggested by the ISB Standardization and Terminology Committee and analyzed two types of gait patterns, reciprocal and swing-through. The study found that walking speed, cadence, and stride length were highest during swing-through gait. For both patterns, the thorax and elbows remained in flexion while the shoulders exhibited both flexion and extension throughout the gait cycles. Larger ranges of motion were seen in swing-through gait for all UE joints. Peak forces were noted in the crutches during swing-through gait. This work supported continued testing and development for pediatric assessment. A follow-up study comparing reciprocal and swing-through gait patterns was reported in 2009 by Slavens et al. for nine children with myelodysplasia. Temporal and distance parameters showed significant differences between the two gait patterns in terms of stride length and stance duration.[99] Joint ranges of motion were all greater during swing-through gait. Kinetics were significantly different between the two gait patterns at all joints for superior/inferior force, range of force, and maximum inferior force. The authors also reported that functional outcomes were correlated with joint dynamics. In 2011, Slavens

et al. presented a UE inverse dynamics model for pediatric Lofstrand crutch-assisted gait.[51] The model described dynamics at the shoulders, elbows, wrists, and crutches and was compliant with the ISB recommended standards. A custom designed Lofstrand crutch system with four, six degree-of-freedom dynamometers was used with the model to assess triaxial UE joint reaction forces and moments. The pediatric system was demonstrated in children with diplegic cerebral palsy, incomplete spinal cord injury, and OI type I. A continuation of this combined modeling and instrumentation approach is described in the chapter by Slavens et al. later in this text with a specific focus on children with OI.

Upper extremity assessment during walker-assisted gait has also been a topic of interest and development for several decades. As with work in crutch-assisted gait, walker assessment largely began with analysis of the lower extremities.[85,115-117] In the case of walkers, however, much attention was and continues to be devoted to a comparison of differences in anterior versus posterior walker use. In 2008, Strifling et al. reported on a comparison of UE kinematics in children with cerebral palsy using anterior and posterior walkers.[118] Ten children were analyzed in the comparative study in which each participant was tested using both types of walker following a period of acclimation. Overall results were similar. Shoulders were extended, elbows flexed and wrists extended with both walkers. Energy expenditure, walking speed, and stride lengths were also similar for both walker types. While not statistically significant in the relatively small population, anterior torso tilt was reduced with the posterior walker and shoulder extension and elbow flexion were increased. A year later in 2009, Strifling et al. presented findings from an UE study of GH joint forces in children using anterior and posterior walkers.[119] Weight bearing on the GH joints was analyzed in five children with cerebral palsy using both anterior and posterior walkers fitted with six-axis handle transducers. In general, posterior walker use created larger GH joint forces. While not statistically significant, the authors noted that, over time and with repetitive loading, the findings could bear clinical significance. In a similar population study, Konop et al. reported on a biomechanical analysis of UE kinetics in children with cerebral palsy using anterior and posterior walkers.[97] Upper extremity joint kinetics were calculated for ten children with cerebral palsy using both anterior and posterior walkers. Triaxial joint reaction forces and moments were fully characterized for the wrist, elbow, and shoulder joints for both walker types. Statistical comparisons showed no significant differences in kinetic joint parameters between walker types. Joint reaction forces at the shoulder ranged from

5.7% body weight (BW) in the superior direction to 4.3% inferiorly, 7.4% posteriorly, and 2.3% medially. Joint reaction moments were similar to values reported by others in previous studies. Posterior joint reaction forces at the GH joints were similar or larger in magnitude compared to superior forces. The greatest joint reaction moments seen at the shoulders were lateral bending and external rotation. In concluding, the authors noted that identification of risk factors could support changes in gait training routines, walker prescription, or walker design. Unique technical and model design details specific to UE joint demands during walker use in a child with OI are provided in the chapter by Konop et al. later in this text.

Future Directions

Quantitative mobility and activity assessment is fundamental to the FEM process that lies at the core of fracture risk assessment. Dynamic loading induces stresses and strains within the bones and must be well described in order to advance the process of fracture risk assessment. Current work in assessing children with OI has shown promise with unique findings, and these research efforts will likely continue to offer new clinical insight with future applications. Anticipated areas for expansion include improved musculoskeletal modeling and simulation approaches, and development of more refined multi-segmental models for kinetic assessment of joint loads.

From a technical perspective, it is encouraging to know that more advanced methods are becoming available for quantitative analysis of joint demands arising from a variety of mobility and daily living activities. Through a better understanding of the underlying biomechanics and associated joint loads, it is anticipated that improved methods will evolve for fracture risk assessment, activity prescription, and clinical approaches to care. Future work will likely address these issues through development of more precise biomechanical models, larger and more focused clinical studies of children with OI, and exploration of new methods to improve mobility while reducing joint demands. Advances in technology and reductions in cost will also drive opportunities to migrate much of this advanced technology to the community and home environments.

REFERENCES

1. Rauch F, Plotkin H, Zeitlin L, Glorieux FH. Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous

pamidronate therapy. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2003;18(4):610-614.
2. Rauch F, Travers R, Parfitt AM, Glorieux FH. Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. *Bone.* 2000;26(6):581-589.
3. Rauch F, Tutlewski B, Schonau E. The bone behind a low areal bone mineral density: peripheral quantitative computed tomographic analysis in a woman with osteogenesis imperfecta. *Journal of musculoskeletal & neuronal interactions.* 2002;2(4):306-308.
4. Roschger P, Fratzl-Zelman N, Misof BM, Glorieux FH, Klaushofer K, Rauch F. Evidence that abnormal high bone mineralization in growing children with osteogenesis imperfecta is not associated with specific collagen mutations. *Calcif Tissue Int.* 2008;82(4):263-270.
5. Barsh GS, David KE, Byers PH. Type I osteogenesis imperfecta: a nonfunctional allele for pro alpha 1 (I) chains of type I procollagen. *Proc Natl Acad Sci U S A.* 1982;79(12):3838-3842.
6. Sykes B, Francis MJ, Smith R. Altered relation of two collagen types in osteogenesis imperfecta. *The New England journal of medicine.* 1977;296(21):1200-1203.
7. Willing MC, Deschenes SP, Scott DA, et al. Osteogenesis imperfecta type I: molecular heterogeneity for COL1A1 null alleles of type I collagen. *American journal of human genetics.* 1994;55(4):638-647.
8. Wenstrup RJ, Willing MC, Starman BJ, Byers PH. Distinct biochemical phenotypes predict clinical severity in nonlethal variants of osteogenesis imperfecta. *American journal of human genetics.* 1990;46(5):975-982.
9. Byers PH, Wallis GA, Willing MC. Osteogenesis imperfecta: translation of mutation to phenotype. *Journal of medical genetics.* 1991;28(7):433-442.
10. Marini JC, Forlino A, Cabral WA, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. *Hum Mutat.* 2007;28(3):209-221.
11. Cassella JP, Ali SY. Abnormal collagen and mineral formation in osteogenesis imperfecta. *Bone Miner.* 1992;17(2):123-128.
12. Cassella JP, Barber P, Catterall AC, Ali SY. A morphometric analysis of osteoid collagen fibril diameter in osteogenesis imperfecta. *Bone.* 1994;15(3):329-334.
13. Stoss H, Freisinger P. Collagen fibrils of osteoid in osteogenesis imperfecta: Morphometrical analysis of the fibril diameter. *American Journal of Medical Genetics.* 1993;45:257.
14. Vetter U, Eanes ED, Kopp JB, Termine JD, Robey PG. Changes in apatite crystal size in bones of patients with osteogenesis imperfecta. *Calcif Tissue Int.* 1991;49(4):248-250.
15. Traub W, Arad T, Vetter U, Weiner S. Ultrastructural studies of bones from patients with osteogenesis imperfecta. *Matrix Biol.* 1994;14(4):337-345.
16. Boskey AL. Bone mineral crystal size. *Osteoporosis International.* 2003;14(Suppl 5):S16-S21.

17. Imbert L, Auregan JC, Pernelle K, Hoc T. Mechanical and mineral properties of osteogenesis imperfecta human bones at the tissue level. *Bone.* 2014.
18. Weber M, Roschger P, Fratzl-Zelman N, et al. Pamidronate does not adversely affect bone intrinsic material properties in children with osteogenesis imperfecta. *Bone.* 2006;39(3):616-622.
19. Boyde A, Travers R, Glorieux FH, Jones SJ. The mineralization density of iliac crest bone from children with osteogenesis imperfecta. *Calcif Tissue Int.* 1999;64(3):185-190.
20. Albert C, Jameson J, Toth JM, Smith P, Harris G. Bone properties by nanoindentation in mild and severe osteogenesis imperfecta. *Clinical biomechanics.* 2013;28(1):110-116.
21. Fan Z, Smith PA, Harris GF, Rauch F, Bajorunaite R. Comparison of nanoindentation measurements between osteogenesis imperfecta Type III and Type IV and between different anatomic locations (femur/tibia versus iliac crest). *Connect Tissue Res.* 2007;48(2):70-75.
22. Fan Z, Smith PA, Eckstein EC, Harris GF. Mechanical properties of OI type III bone tissue measured by nanoindentation. *J Biomed Mater Res A.* 2006;79(1):71-77.
23. Albert C, Jameson J, Harris G. Design and validation of bending test method for characterization of miniature pediatric cortical bone specimens. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine.* 2013;227(2):105-113.
24. Albert C, Jameson J, Smith P, Harris G. Reduced diaphyseal strength associated with high intracortical vascular porosity within long bones of children with Osteogenesis Imperfecta. *Bone.* 2014;66:121-130.
25. Jameson J, Albert C, Busse B, Smith P, Harris G. 3D micron-scale imaging of the cortical bone canal network in human osteogenesis imperfecta (OI). Proceedings of SPIE, Medical Imaging 2013: Biomedical Applications in Molecular, Structural, and Functional Imaging; Feb 9, 2013, 2013; Lake Buena Vista, FL.
26. Pazzaglia UE, Congiu T, Brunelli PC, Magnano L, Benetti A. The Long Bone Deformity of Osteogenesis Imperfecta III: Analysis of Structural Changes Carried Out with Scanning Electron Microscopic Morphometry. *Calcif Tissue Int.* 2013;93(5):453-461.
27. Jepsen KJ, Schaffler MB, Kuhn JL, Goulet RW, Bonadio J, Goldstein SA. Type I collagen mutation alters the strength and fatigue behavior of Mov13 cortical tissue. *J Biomech.* 1997;30(11-12):1141-1147.
28. Bonadio J, Jepsen KJ, Mansoura MK, Jaenisch R, Kuhn JL, Goldstein SA. A murine skeletal adaptation that significantly increases cortical bone mechanical properties. Implications for human skeletal fragility. *J Clin Invest.* 1993;92(4):1697-1705.
29. Misof BM, Roschger P, Baldini T, et al. Differential effects of alendronate treatment on bone from growing osteogenesis imperfecta and wild-type mouse. *Bone.* 2005;36(1):150-158.
30. Miller E, Delos D, Baldini T, Wright TM, Pleshko Camacho N. Abnormal mineral-matrix interactions are a significant contributor to fragility in oim/oim bone. *Calcif Tissue Int.* 2007;81(3):206-214.

31. Rao SH, Evans KD, Oberbauer AM, Martin RB. Bisphosphonate treatment in the oim mouse model alters bone modeling during growth. *J Biomech.* 2008;41(16):3371-3376.
32. Misof K, Landis WJ, Klaushofer K, Fratzl P. Collagen from the osteogenesis imperfecta mouse model (oim) shows reduced resistance against tensile stress. *J Clin Invest.* 1997;100(1):40-45.
33. Kozloff KM, Carden A, Bergwitz C, et al. Brittle IV mouse model for osteogenesis imperfecta IV demonstrates postpubertal adaptations to improve whole bone strength. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2004;19(4):614-622.
34. Uveges TE, Kozloff KM, Ty JM, et al. Alendronate treatment of the Brtl osteogenesis imperfecta mouse improves femoral geometry and load response before fracture but decreases predicted material properties and has detrimental effects on osteoblasts and bone formation. *Journal of Bone and Mineral Research.* 2009;24(5):849-859.
35. Delos D, Yang X, Ricciardi BF, Myers ER, Bostrom MP, Camacho NP. The effects of RANKL inhibition on fracture healing and bone strength in a mouse model of osteogenesis imperfecta. *J Orthop Res.* 2008;26(2):153-164.
36. Camacho NP, Raggio CL, Doty SB, et al. A controlled study of the effects of alendronate in a growing mouse model of osteogenesis imperfecta. *Calcif Tissue Int.* 2001;69(2):94-101.
37. Panaroni C, Gioia R, Lupi A, et al. In utero transplantation of adult bone marrow decreases perinatal lethality and rescues the bone phenotype in the knockin murine model for classical, dominant osteogenesis imperfecta. *Blood.* 2009;114(2):459-468.
38. Sinder BP, White LE, Salemi JD, et al. Adult Brtl/+ mouse model of osteogenesis imperfecta demonstrates anabolic response to sclerostin antibody treatment with increased bone mass and strength. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2014.
39. Vanleene M, Shefelbine SJ. Therapeutic impact of low amplitude high frequency whole body vibrations on the osteogenesis imperfecta mouse bone. *Bone.* 2013;53(2):507-514.
40. Viceconti M, Davinelli M, Taddei F, Cappello A. Automatic generation of accurate subject-specific bone finite element models to be used in clinical studies. *J Biomech.* 2004;37(10):1597-1605.
41. Boyd SK, Muller R. Smooth surface meshing for automated finite element model generation from 3D image data. *J Biomech.* 2006;39(7):1287-1295.
42. Shim VB, Pitto RP, Streicher RM, Hunter PJ, Anderson IA. The use of sparse CT datasets for auto-generating accurate FE models of the femur and pelvis. *J Biomech.* 2007;40(1):26-35.
43. Edwards WB, Troy KL. Simulating distal radius fracture strength using biomechanical tests: a modeling study examining the influence of boundary conditions. *Journal of biomechanical engineering.* 2011;133(11):114501.

44. Edwards WB, Troy KL. Finite element prediction of surface strain and fracture strength at the distal radius. *Medical engineering & physics.* 2012;34(3):290-298.
45. Fritz JM, Guan Y, Wang M, Smith PA, Harris GF. A fracture risk assessment model of the femur in children with osteogenesis imperfecta (OI) during gait. *Medical engineering & physics.* 2009;31(9):1043-1048.
46. Fritz JM, Guan Y, Wang M, Smith PA, Harris GF. Muscle force sensitivity of a finite element fracture risk assessment model in osteogenesis imperfecta - Biomed 2009. *Biomed Sci Instrum.* 2009;45:316-321.
47. Orwoll ES, Shapiro J, Veith S, et al. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. *J Clin Invest.* 2014;124(2):491-498.
48. Caouette C, Rauch F, Villemure I, et al. Biomechanical analysis of fracture risk associated with tibia deformity in children with osteogenesis imperfecta: a finite element analysis. *Journal of musculoskeletal & neuronal interactions.* 2014;14(2):205-212.
49. Fan Z, Smith PA, Rauch F, Harris GF. Nanoindentation as a means for distinguishing clinical type of osteogenesis imperfecta. *Composites Part B: Engineering.* 2007;38(3):411-415.
50. Helgason B, Taddei F, Palsson H, et al. A modified method for assigning material properties to FE models of bones. *Medical engineering & physics.* 2008;30(4):444-453.
51. Slavens BA, Bhagchandani N, Wang M, Smith PA, Harris GF. An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait. *J Biomech.* 2011;44(11):2162-2167.
52. DeLuca PA. Gait analysis in the treatment of the ambulatory child with cerebral palsy. *Clinical orthopaedics and related research.* 1991(264):65-75.
53. Gage J, Schwartz M, Koop S, Novacheck T. *The identification and treatment of gait problems in cerebral palsy.* Cambridge2009.
54. Miller F. *Cerebral Palsy.* Singapore: Springer; 2005.
55. Perry J, Burnfield J. *Gait Analysis: Normal and pathological function. .* 2nd ed. Thorofare, NJ: Slack, Inc.; 2010.
56. Olney SJ, Griffin MP, Monga TN, McBride ID. Work and power in gait of stroke patients. *Archives of physical medicine and rehabilitation.* 1991;72(5):309-314.
57. Sutherland DH. Gait analysis in neuromuscular disease. Paper presented at: San Diego Children's Hospital instructional course1990.
58. Wagenaar RC, Beek WJ. Hemiplegic gait: a kinematic analysis using walking speed as a basis. *J Biomech.* 1992;25(9):1007-1015.
59. Wren TA, Otsuka NY, Bowen RE, et al. Outcomes of lower extremity orthopedic surgery in ambulatory children with cerebral palsy with and without gait analysis: results of a randomized controlled trial. *Gait Posture.* 2013;38(2):236-241.
60. Chang FM, Rhodes JT, Flynn KM, Carollo JJ. The role of gait analysis in treating gait abnormalities in cerebral palsy. *Orthop Clin North Am.* 2010;41(4):489-506.
61. Berman AT, Quinn RH, Zarro VJ. Quantitative gait analysis in unilateral and bilateral total hip replacements. *Archives of physical medicine and rehabilitation.* 1991;72(3):190-194.

62. Berman AT, Zarro VJ, Bosacco SJ, Israelite C. Quantitative gait analysis after unilateral or bilateral total knee replacement. *The Journal of bone and joint surgery. American volume.* 1987;69(9):1340-1345.
63. Collopy MC, Murray MP, Gardner GM, DiUlio RA, Gore DR. Kinesiologic measurements of functional performance before and after geometric total knee replacemtn: one-year follow-up of twenty cases. *Clinical orthopaedics and related research.* 1977(126):196-202.
64. Murray MP, Gore DR, Laney WH, Gardner GM, Mollinger LA. Kinesiologic measurements of functional performance before and after double compartment Marmor knee arthroplasty. *Clinical orthopaedics and related research.* 1983(173):191-199.
65. Olsson E. Gait analysis in hip and knee surgery. *Scandinavian journal of rehabilitation medicine. Supplement.* 1986;15:1-55.
66. Rittman N, Kettelkamp DB, Pryor P, Schwartzkopf GL, Hillberry B. Analysis of patterns of knee motion walking for four types of total knee implants. *Clinical orthopaedics and related research.* 1981(155):111-117.
67. Wykman A, Olsson E. Walking ability after total hip replacement. A comparison of gait analysis in unilateral and bilateral cases. *The Journal of bone and joint surgery. British volume.* 1992;74(1):53-56.
68. Casartelli NC, Item-Glatthorn JF, Bizzini M, Leunig M, Maffiuletti NA. Differences in gait characteristics between total hip, knee, and ankle arthroplasty patients: a six-month postoperative comparison. *BMC Musculoskelet Disord.* 2013;14:176.
69. Astephen Wilson JL, Wilson DA, Dunbar MJ, Deluzio KJ. Preoperative gait patterns and BMI are associated with tibial component migration. *Acta Orthop.* 2010;81(4):478-486.
70. McGinnis K, Snyder-Mackler L, Flowers P, Zeni J. Dynamic joint stiffness and co-contraction in subjects after total knee arthroplasty. *Clinical biomechanics.* 2013;28(2):205-210.
71. Leardini A, O'Connor JJ, Giannini S. Biomechanics of the natural, arthritic, and replaced human ankle joint. *J Foot Ankle Res.* 2014;7(1):8.
72. Andriacchi TP, Mikosz RP. Musculoskeletal dynamics, locomotion and clinical applications. In: Mow VC, Hawes WC, eds. *Basic orthopaedic biomechanics*. New York, NY: Raven Press; 1991:51-92.
73. Jacobs R, van Ingen Schenau GJ. Intermuscular coordination in a sprint push-off. *J Biomech.* 1992;25(9):953-965.
74. Di Stasi SL, Snyder-Mackler L. The effects of neuromuscular training on the gait patterns of ACL-deficient men and women. *Clinical biomechanics.* 2012;27(4):360-365.
75. Cobb SC, Tis LL, Johnson JT, Wang YT, Geil MD. Custom-molded foot-orthosis intervention and multisegment medial foot kinematics during walking. *J Athl Train.* 2011;46(4):358-365.
76. Colborne GR, Naumann S, Longmuir PE, Berbrayer D. Analysis of mechanical and metabolic factors in the gait of congenital below knee amputees. A comparison of the SACH and Seattle feet. *Am J Phys Med Rehabil.* 1992;71(5):272-278.

77. Gitter A, Czerniecki JM, DeGroot DM. Biomechanical analysis of the influence of prosthetic feet on below-knee amputee walking. *Am J Phys Med Rehabil.* 1991;70(3):142-148.
78. Skinner HB, Effeney DJ. Gait analysis in amputees. *Am J Phys Med.* 1985;64(2):82-89.
79. Waters RL, Perry J, Antonelli D, Hislop H. Energy cost of walking of amputees: the influence of level of amputation. *The Journal of bone and joint surgery. American volume.* 1976;58(1):42-46.
80. Su PF, Gard SA, Lipschutz RD, Kuiken TA. The effects of increased prosthetic ankle motions on the gait of persons with bilateral transtibial amputations. *Am J Phys Med Rehabil.* 2010;89(1):34-47.
81. Brodke DS, Skinner SR, Lamoreux LW, et al. Effects of ankle-foot orthoses on the gait of children. *J Pediatr Orthop.* 1989;9(6):702-708.
82. Lehmann JF, Condon SM, de Lateur BJ, Price R. Gait abnormalities in peroneal nerve paralysis and their corrections by orthoses: a biomechanical study. *Archives of physical medicine and rehabilitation.* 1986;67(6):380-386.
83. Lehmann JF, Condon SM, Price R, deLateur BJ. Gait abnormalities in hemiplegia: their correction by ankle-foot orthoses. *Archives of physical medicine and rehabilitation.* 1987;68(11):763-771.
84. Smith PA, Hassani S, Graf A, et al. Brace evaluation in children with diplegic cerebral palsy with a jump gait pattern. *The Journal of bone and joint surgery. American volume.* 2009;91(2):356-365.
85. Logan L, Byers-Hinkley K, Ciccone CD. Anterior versus posterior walkers: a gait analysis study. *Dev Med Child Neurol.* 1990;32(12):1044-1048.
86. Schnorenberg AJ, Slavens BA, Wang M, Vogel LC, Smith PA, Harris GF. Biomechanical model for evaluation of pediatric upper extremity joint dynamics during wheelchair mobility. *J Biomech.* 2014;47(1):269-276.
87. Slavens BA, Bhagchandani N, Wang M, Smith PA, Harris GF. Motion Analysis of the Upper Extremities During Lofstrand Crutch-Assisted Gait in Children with Orthopaedic Disabilities. *Journal of Experimental & Clinical Medicine.* 2011;3(5):218-227.
88. Engelbert RH, Uiterwaal CS, Gulmans VA, Pruijs H, Helders PJ. Osteogenesis imperfecta in childhood: prognosis for walking. *J Pediatr.* 2000;137(3):397-402.
89. Takken T, Terlingen HC, Helders PJM, Pruijs H, van Der Ent CK, Engelbert RHH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. *The Journal of Pediatrics.* 2004;145(6):813-818.
90. Graf A, Hassani S, Krzak J, et al. Gait characteristics and functional assessment of children with type I osteogenesis imperfecta. *J Orthop Res.* 2009;27(9):1182-1190.
91. Davis Iii RB, Õunpuu S, Tyburski D, Gage JR. A gait analysis data collection and reduction technique. *Human Movement Science.* 1991;10(5):575-587.
92. Gutierrez EM, Saraste H. Measuring center of mass displacement during gait: whole-body kinematic model vs. ground reaction force calculation. 4th World Congress of Biomechanics 2002; Calgary, AB.

93. Kadaba MP, Ramakrishnan HK, Wootten ME. Measurement of lower extremity kinematics during level walking. *J Orthop Res.* 1990;8(3):383-392.
94. Kidder SM, Abuzzahab FS, Jr., Harris GF, Johnson JE. A system for the analysis of foot and ankle kinematics during gait. *IEEE Trans Rehabil Eng.* 1996;4(1):25-32.
95. Myers KA, Wang M, Marks RM, Harris GF. Validation of a multisegment foot and ankle kinematic model for pediatric gait. *IEEE Trans Neural Syst Rehabil Eng.* 2004;12(1):122-130.
96. Slavens BA, Schnorenberg AJ, Aurit CM, et al. Evaluation of pediatric manual wheelchair mobility using advanced biomechanical methods. *Biomed Res Int.* 2015;2015:634768.
97. Konop KA, Strifling KM, Wang M, et al. A biomechanical analysis of upper extremity kinetics in children with cerebral palsy using anterior and posterior walkers. *Gait Posture.* 2009;30(3):364-369.
98. Slavens BA, Graf A, Krzak J, Vogel L, Harris GF. Upper extremity wheelchair kinematics in children with spinal cord injury. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:8158-8161.
99. Slavens BA, Sturm PF, Bajournaite R, Harris GF. Upper extremity dynamics during Lofstrand crutch-assisted gait in children with myelomeningocele. *Gait Posture.* 2009;30(4):511-517.
100. Slavens BA, Sturm PF, Harris GF. Upper extremity inverse dynamics model for crutch-assisted gait assessment. *J Biomech.* 2010;43(10):2026-2031.
101. Wu G, van der Helm FC, Veeger HE, et al. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion--Part II: shoulder, elbow, wrist and hand. *J Biomech.* 2005;38(5):981-992.
102. Meskers CG, van der Helm FC, Rozendaal LA, Rozing PM. In vivo estimation of the glenohumeral joint rotation center from scapular bony landmarks by linear regression. *J Biomech.* 1998;31(1):93-96.
103. Senk M, Cheze L. A new method for motion capture of the scapula using an optoelectronic tracking device: a feasibility study. *Comput Methods Biomech Biomed Engin.* 2010;13(3):397-401.
104. Jensen RK. Changes in segment inertia proportions between 4 and 20 years. *J Biomech.* 1989;22(6-7):529-536.
105. Yeadon MR, Morlock M. The appropriate use of regression equations for the estimation of segmental inertia parameters. *J Biomech.* 1989;22(6-7):683-689.
106. Bartonek A, Gutierrez EM, Haglund-Akerlind Y, Saraste H. The influence of spasticity in the lower limb muscles on gait pattern in children with sacral to mid-lumbar myelomeningocele: a gait analysis study. *Gait Posture.* 2005;22(1):10-25.
107. Gabrieli AP, Vankoski SJ, Dias LS, et al. Gait analysis in low lumbar myelomeningocele patients with unilateral hip dislocation or subluxation. *J Pediatr Orthop.* 2003;23(3):330-334.
108. Gutierrez EM, Bartonek A, Haglund-Akerlind Y, Saraste H. Characteristic gait kinematics in persons with lumbosacral myelomeningocele. *Gait Posture.* 2003;18(3):170-177.

109. Gutierrez EM, Bartonek A, Haglund-Akerlind Y, Saraste H. Kinetics of compensatory gait in persons with myelomeningocele. *Gait Posture.* 2005;21(1):12-23.
110. Vankoski S, Moore C, Statler KD, Sarwark JF, Dias L. The influence of forearm crutches on pelvic and hip kinematics in children with myelomeningocele: don't throw away the crutches. *Dev Med Child Neurol.* 1997;39(9):614-619.
111. Klimaitis A, Carroll G, Owen E. Rapidly progressive destructive arthropathy of the shoulder--a viewpoint on pathogenesis. *J Rheumatol.* 1988;15(12):1859-1862.
112. Lal S. Premature degenerative shoulder changes in spinal cord injury patients. *Spinal Cord.* 1998;36(3):186-189.
113. Requejo PS, Wahl DP, Bontrager EL, et al. Upper extremity kinetics during Lofstrand crutch-assisted gait. *Medical engineering & physics.* 2005;27(1):19-29.
114. Slavens BA, Frantz J, Sturm PF, Harris GF. Upper extremity dynamics during Lofstrand crutch-assisted gait in children with myelomeningocele. *J Spinal Cord Med.* 2007;30 Suppl 1:S165-171.
115. Greiner BM, Czerniecki JM, Deitz JC. Gait parameters of children with spastic diplegia: a comparison of effects of posterior and anterior walkers. *Archives of physical medicine and rehabilitation.* 1993;74(4):381-385.
116. Levangie PK, Guihan MF, Meyer P, Stuhr K. Effect of altering handle position of a rolling walker on gait in children with cerebral palsy. *Phys Ther.* 1989;69(2):130-134.
117. Park ES, Park CI, Kim JY. Comparison of anterior and posterior walkers with respect to gait parameters and energy expenditure of children with spastic diplegic cerebral palsy. *Yonsei Med J.* 2001;42(2):180-184.
118. Strifling KM, Lu N, Wang M, et al. Comparison of upper extremity kinematics in children with spastic diplegic cerebral palsy using anterior and posterior walkers. *Gait Posture.* 2008;28(3):412-419.
119. Strifling KM, Konop KA, Wang M, Harris GF. Comparison of upper extremity glenohumeral joint forces in children with cerebral palsy using anterior and posterior walkers - biomed 2009. *Biomed Sci Instrum.* 2009;45:304-309.

SECTION 2

Biology

4 GENOTYPE-PHENOTYPE CORRELATIONS IN AUTOSOMAL DOMINANT OSTEOGENESIS IMPERFECTA

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ABSTRACT

Osteogenesis imperfecta is a bone fragility disorder, secondary in most cases to mutations in *COL1A1* or *COL1A2* genes that encode the two collagen type I α chains, α1(I) and α2(I). The latter mutations usually follow an autosomal dominant pattern of inheritance with a wide clinical spectrum of severity. In this chapter, we aimed at providing an overview of genotype–phenotype correlations in OI patients who have mutations affecting collagen type I, based on retrospective studies in our OI patient's population and review of the literature.

INTRODUCTION

Osteogenesis imperfecta is a bone fragility disorder with a wide clinical spectrum of severity in association with some extra-skeletal features, including blue sclera, dentinogenesis imperfecta, and a variable degree of postpubertal hearing deficit. The skeletal phenotype can range from nearly asymptomatic individuals with normal stature and mild predisposition to fracture, to significant mobility impairment with severe bone deformities and very short stature, and to perinatal lethality at the very end of spectrum severity.[1]

Based on pure clinical presentation Sillence had classified OI in four main types.[2] The mildest form is OI type I, with normal or near to normal stature, blue sclerae, and infrequently, dentinogenesis imperfecta. However, OI type

I patients can present with vertebral compression fractures and develop a mild scoliosis. OI type II is classically perinatally lethal, with in-utero onset of severe long bone deformities, rib fractures, and respiratory compromise that leads to death. OI type III is the most severe viable form of OI. Patients have severe long bone deformities with recurrent multiple fractures and mobility impairment, very short stature, and severe scoliosis with a high risk of respiratory compromise. They typically present with DI and blue sclerae. OI type IV varies in severity between types I and III, and patients classically present with grey or normal sclerae and inconstant DI.

This classification, although clinically useful, might be subject to variation, depending on personal clinical interpretation and on the available data at the time of evaluation. It can also vary with therapeutic intervention (physiotherapy, ergotherapy, medical and or surgical treatment), as successful management can convert an OI type III to type IV, versus an unsuccessful surgical intervention that can convert an OI type I to an OI type IV with bone deformities and impaired mobility. On the other hand, due to currently limited techniques, there is often a discrepancy between the prenatal diagnosis based on ultrasound findings and the postnatal diagnosis. For instance, a diagnosis of OI type II prenatally turns out to be compatible with life, and is reclassified postnatally as OI type III or even type IV as a result of an adequate multidisciplinary approach. Therefore, the Sillence classification can be a dynamic classification and is subject to variation depending on several factors.

Most of autosomal dominant OI patients have an identifiable mutation in *COL1A1* or *COL1A2*, the genes that encode respectively for pro-alpha-1 and pro-alpha-2 chains of collagen type I. Each pro-alpha chain is boarded by two propeptides at each end (N-propeptide and C-propeptide) that are essential for the pro-alpha chain association and triple helix formation. The latter starts at the carboxy-terminal propeptide and extends in a zipper like manner to the amino-terminal end, resulting in the heterotrimer collagen type I molecule consisting of one alpha-2 chain and two alpha-1 chains. The triple helical domains consist of uninterrupted repeats of the Gly-X-Y tripeptide. The glycine residue in every third position is crucial for triple helix formation, as it is the only small enough amino acid able to fit into the restricted space at the inside of the helix.

Two main classes of mutations in collagen I can result in OI, namely, the haploinsufficiency mutations, and the helical glycine mutations.

Haploinsufficiency mutations classically result in a mild phenotype (OI type I),[3] and are usually the consequence of a nonsense or a frameshift mutation, and less frequently can be the consequence of some splice-site mutations and C-propeptide mutations in the *COL1A1* gene. These mutations introduce a stop codon in the reading frame of the *COL1A1* allele and trigger a nonsense mediated m RNA decay.[4] Consequently, the structure of the *COL1A1* protein is not affected. However, the protein amount is reduced by half.

The second class of mutations includes the helical glycine mutations, affecting either the *COL1A1* gene or the *COL1A2* gene, and typically resulting in structural defects in the collagen type I protein. In fact, glycine substitutions disrupt the Gly-X-Y sequence, therefore disrupting the triple helix formation, and impairing the function of collagen I by affecting its stability and its interactions with the extracellular matrix. Glycine mutations exert a dominant negative effect since the mutated chain also disrupts the formation and function of the normal alpha-1 or alpha-2 chain produced by the non-mutated *COLlA1* or *COL1A2* gene.

The cellular and molecular consequences of collagen type I mutations have been examined in several small patients' groups or individual OI patients, essentially in skin fibroblasts; however, few data are available on osteoblasts. We currently have limited knowledge on how a specific collagen type I mutation results in a particular phenotype. As a broad and a general rule, the severity of the phenotype will depend mainly on the affected alpha chain, the position of the mutation, the substituting amino acid, or a combination of these three variables

As of December 2011, there are around 2000 different collagen type I mutations identified in OI patients and listed in the Dalgleish database (http://www.le.ac.uk/ge/collagen/).[5,6] With the continuous increase in the number of identified mutations in *COL1A1* and *COL1A2* genes, genotype to phenotype correlation in OI patients becomes more and more pertinent.

In this chapter, we aim at providing an overview of genotype–phenotype correlations in autosomal dominant OI patients with mutations in collagen type I.

OVERVIEW

Lethality

Marini et al had published in 2007 in a consortium for OI, an analysis of 832 mutations in the triple helical domain of type I collagen that had been identified until then.[5-7] The majority of mutations result in OI types II, III or IV, with 2 main groups of mutations: the helical glycine mutations (point mutations, n=682), and the splice site mutations (n=150).

Lethality was the only phenotypic characteristic analyzed in this study, in other words, if an affected baby had survived the immediate postnatal period or not.

The alpha-1 chain of collagen type I was the site of more frequent glycine substitutions compared to glycine substitutions in the alpha-2 chain (57% vs. 43%), and were more likely to be lethal (36% of alpha-1 vs.19% of alpha-2 mutations were lethal).

If a glycine substitutions occurred in the first 200 residues of the alpha-1 chain, they were usually non-lethal, and had a variable outcome thereafter. In addition, there were two reported exclusively lethal regions in *COL1A1* gene (helix positions 691–823 and 910–964), plus eight other clusters of lethality in *COL1A2* gene, all of which seemed to align with major ligand binding regions for extracellular matrix proteins. This observation might shed light on the lethal outcome following glycine substitutions in such specific areas of *COL1A1* and *COL1A2* genes.

The identification of such 'lethal clusters' can be useful for genetic counseling. However, there are exceptions to the rule that are important to be aware of, especially in the context of prenatal diagnosis. In fact, a recent study identified seven patients with mutations in these presumably lethal areas who had a non lethal outcome[8] (one patient with a glycine substitution in a lethal alpha-1 region and six patients with mutations in the lethal alpha-2 regions).

Marini at al had also reported in the same study[7] that glycine substitutions by a charged (like aspartate or glutamate acid or arginine) or a branched (valine) amino acid C-terminal of position 200 in the alpha-1 chain is more likely to have a lethal outcome. Such a relationship has not been observed in the alpha-2 chain. However glycine substitutions in the alpha-2 chain are

more likely to be concordant for the lethal outcome than glycine substitutions in the alpha-1 chain.

Deformities and Fractures at Birth

In a study of 117 OI patients, the type of affected collagen type I alpha chain or the position of the glycine mutation within the alpha chain did not show a significant relationship with the presence of limb deformities and fractures at birth.[8] A bigger percentage of patients with serine substitutions in alpha-1 had fractures or deformities at birth than patients with arginine substitutions (83% vs. 44%, $p<0.05$). In the alpha-2 chain, there was no identifiable relationship between the substituting amino acid and the prevalence of fractures or deformities at birth.

Anthropometry in OI Patients

Lund had found in a study of 86 OI patients that mean standing height, truncal height, and arm span z-score were reduced in all OI types, but were significantly more marked in patients with qualitative collagen defects compared to those with quantitative defects.[9] The arm span to height ratio was increased in patients with qualitative collagen defects ($p<0.05$), but not in those with a quantitative collagen defect. Head circumference was increased in all OI types, and more significantly in patients with qualitative collagen defects. Moreover, head circumference was disproportionate to height, and this finding was more pronounced in the group of patients with qualitative collagen defects.

A study of 161 OI patients[8] (median age: 13 years) with glycine mutations in the triple helical domain of collagen type I revealed similar average height z-scores for mutations in either *COL1A1* or *COL1A2* genes. However, there was an inverse relationship between the location of the mutation in the triple helical domain of the alpha-2 chain and the height (Figure1). Thus, the closer the mutation to the carboxy-terminal end of the triple helical domain of alpha-2, the more detrimental effect it would have on height. There was no such correlation in the alpha-1 chain (Figure1). The observed pattern in the alpha-2 chain was consistent with the gradient model of disease severity, where the closer the mutation to the carboxy-terminal end of the alpha-2 chain, the more disruptive was the triple helix formation, resulting in a more severe phenotype.

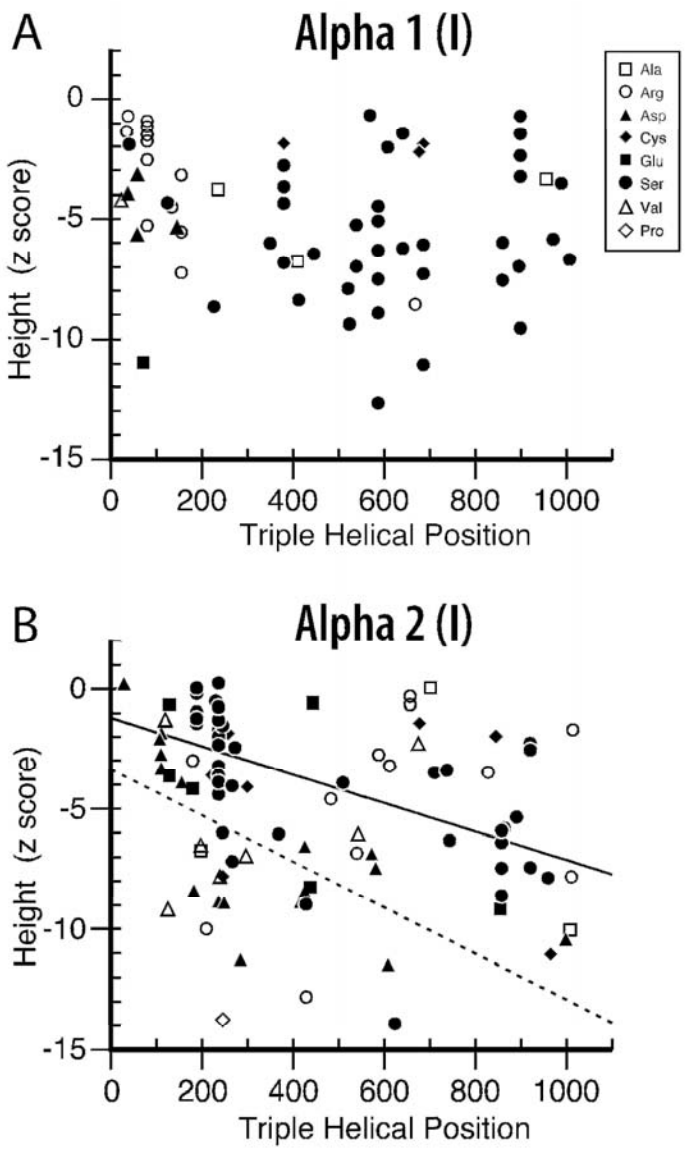

Figure 1. Relationship between the positions of glycine substitutions in the triple helical domain of type I collagen and height z-scores in a1 chain of collagen I (A) and a2 chain of collagen I (B). The oblique solid line in B represents the regression line between the position of serine substitutions in a2 chain of collagen I and height (r=-0.73, P<0.001; Spearman's rank correlation). The oblique dashed line in (B) represents the regression line between the position of aspartate substitutions in a2 chain of collagen I and height (r=-0.75, P<0.001). A mutation closer to the carboxy-terminal end of the triple helical domain of alpha 2 chain had a more detrimental effect on height (B). No such correlation was observed in the alpha 1 chain (A). Adapted with some modification from.[10]

Not only did the location of the glycine mutation affect the height, but so did the nature of the substituting amino acid.[8] The most frequent substituting amino acid in either alpha-1 or alpha-2 chain was serine. However, the average stature was shorter with serine substitutions in the alpha-1 chain.[8] The second most frequent mutations in the alpha-1 chain were arginine substitutions, which lead to a less severe short stature than the serine substitutions. The second most frequent mutations in the alpha-2 chain were aspartate substitutions, which on average lead to severe short stature.[8] There were few more substituting amino acids, but evidence was not sufficient to draw any statistical conclusion.

A study of 192 OI patients (age range 3 weeks to 16.9 years) exploring the relationship between the skeletal phenotype and the genotype revealed that patients carrying a haploinsufficiency mutation were, on average, taller (height z-score -1.3 [SD: 1.1] compared to patients with helical mutation in alpha-2 chain (mean height z-score -5.3 [SD: 3.3]) or the alpha-1 chain (mean height z-score -5.5 [SD: 3.1]).[10]

Dental Phenotype

Histologically, dentinogenesis imperfecta (DI) is defined as an abnormal dentine structure, and is clinically characterized by discoloration of the teeth, ranging from grey brown to opalescent blue. One study had shown that there was no correlation between teeth discolorations, yellow/ brown or opalescent grey, and a particular type of OI.[11]

DI was present in 28% of a population study involving 88 OI patients,[12] with the majority (96%) having a qualitative collagen defect and the remaining 4% having a quantitative collagen defect. Both collagen and molecular studies failed to show any association between DI and either any specific structural abnormality or any particular position of the abnormality along the collagen I alpha chains.[12]

Rauch et al.[8] found that the prevalence of DI did not vary significantly according to the affected alpha chain (71% in the alpha-1 chain vs. 66% in the alpha-2 chain, p=0.53). The majority of OI patients with a glycine mutation had clinically recognizable DI, which is in accordance with previous studies. However, DI prevalence varied with the type of substituting aminoacid (89% with serine vs. 25% with arginine substitutions in the alpha-1 chain).[8] Moreover, it seems that DI presence or absence depends on the

position of the substituting amino acid in the alpha chain, since patients with glycine substitutions affecting the first 120 amino acids of the collagen type I triple helical domain were DI free (Figure 2). So far, we have no mechanistic link between DI and the collagen type I mutations. However, there seems to be a high degree of concordance for the dental phenotype in patients with the same glycine substitutions. Thus, DI is more likely to be directly linked to the collagen abnormality rather than modifier genes or environmental factors.

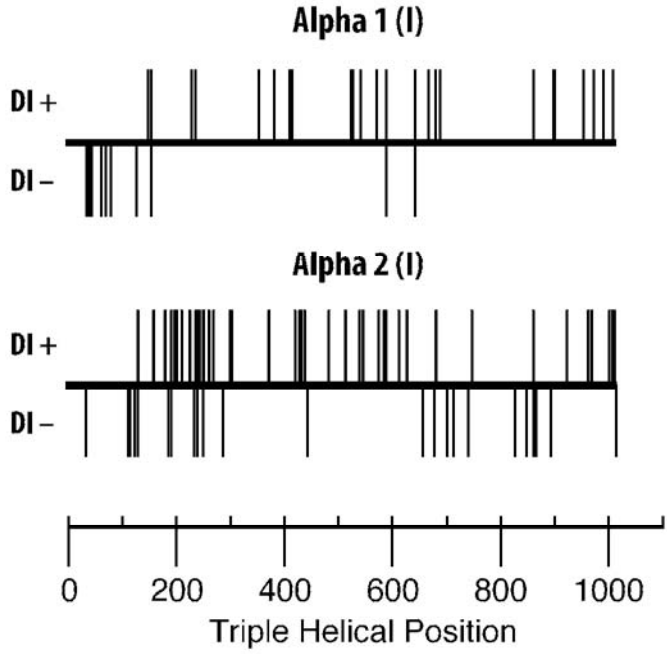

Figure 2. Relationship between the triple helical position of glycine mutations in collagen type I a chains and the presence (+) or absence (-) of dentinogenesis imperfecta (DI). Adapted from Rauch et al.[8]

Blue Sclera

According to Rauch at al.[8] patients with mutations in the alpha-2 chain tended to have blue sclerae (57%) less frequently than those with mutations in the alpha-1 chain (75%). Moreover, if a mutation occurs in the first 120 amino acids of the triple helical domain, the phenotype consistently included blue sclerae (Figure 3). Overall, there was lesser concordance for the scleral phenotype than the dental phenotype, for patients who shared the same collagen type I mutation. This could be explained by the variable character of

blue sclera as a feature, compared to DI, and the fact that blue sclerae tend to become less obvious with age.

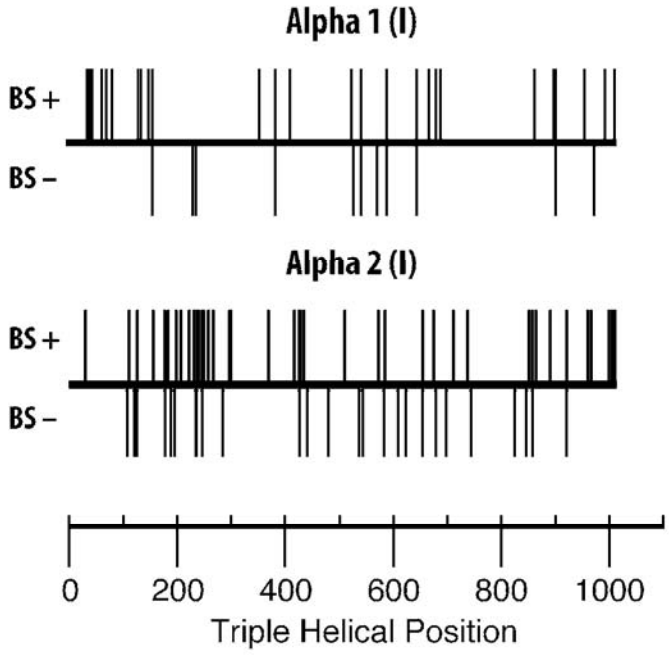

Figure 3. Relationship between the triple helical position of glycine mutations in collagen type I a chains and the presence (+) or absence (-) of blue sclera. Adapted from Rauch et al.[8]

Skeletal Phenotype

Bone Mineral Density

A retrospective study on 192 OI patients showed that patients with haploinsufficiency mutations had a higher mean lumbar spine areal bone mineral density (aBMD) Z-score (- 3.4 [SD: 1.0]) compared to patients with helical mutations in the alpha-1 chain (-4.9 [SD: 1.5]) or the alpha-2 chain (-5.0 [SD: 1.3]).[10] The mean lumbar spine aBMD Z-scores remained higher by 0.7 in the haploinsufficiency group than the two helical mutation groups, after adjustment for height Z-scores, sex, and age. Despite the marked difference in clinical phenotype between these two groups of OI the difference in aBMD was not as marked. Thus, probably factors other than aBMD can influence the severity of the bone disease. On the other hand, there were no significant associations between the lumbar spine aBMD Z-scores

and the position of the mutation in the triple helical mutations, or with the substituting amino acid or the affected alpha chain.[10]

Iliac Bone Histomorphometry

In a study of 96 OI patients, histomorphometry analysis revealed that the cortical width and the amount of trabecular bone were all significantly lower in OI patients compared to healthy controls. The bone size and the amount of trabecular bone were not significantly different between the helical glycine mutations and the haploinsufficiency mutation groups[10] (Figure 4). However, the cortical width was higher in the latter group. This can be related mainly to differences in bone modeling on the endocortical and the periosteal bone surfaces (Figures 4, 5).

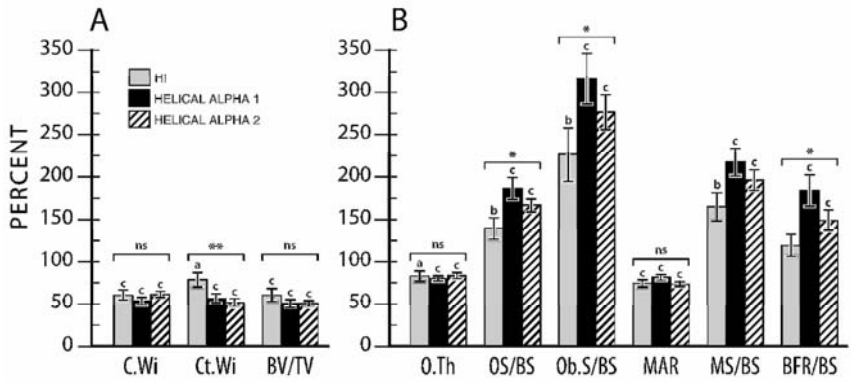

Figure 4. Iliac bone histomorphometric results in patients with COL1A1 haploinsufficiency mutations (HI), as well as with COL1A1 and COL1A2 mutations leading to glycine substitutions in the helical domain of collagen type I. Results are expressed as a percentage of the average result in the age-specific reference range.[13] The letters above the bars indicate the significance of the difference from 100% (ie, the average result in healthy controls): a: $p<0.05$; b: $p<0.01$; c: $p<0.001$. The significance of the variation between genotype groups is indicated by the symbols above the bar groups: ns=not significant; *$p<0.05$; **$p<0.01$; (A) C.Wi=core width; Ct.Wi=cortical width; BV/TV=bone volume per tissue volume; (B) O.Th=osteoid thickness; OS/BS=osteoid surface per bone surface, Ob.S/BS=osteoblast surface per bone surface; MAR=mineral apposition rate; MS/BS=mineralizing surface per bone surface; BFR/BS=bone-formation rate per bone surface. Adapted with modification from Rauch et al.[10]

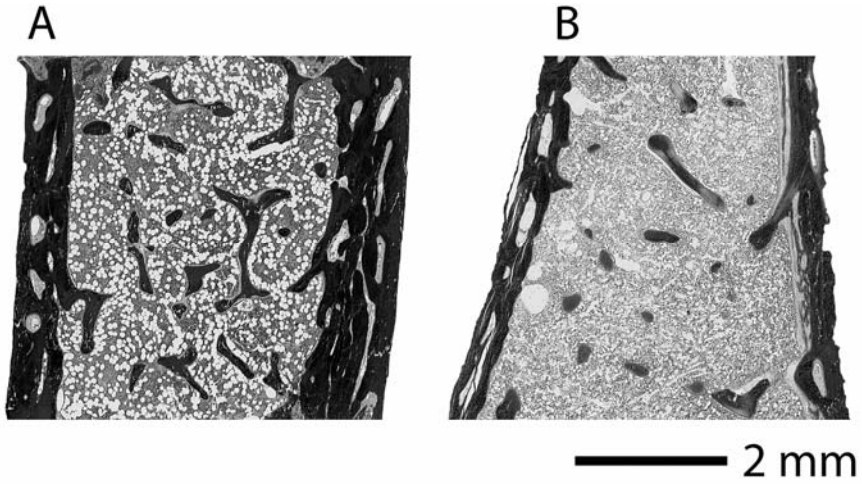

Figure 5. Representative examples of iliac bone samples. (A) Haploinsufficiency mutation, in a 4-year-old boy with a c.1981C>T nucleotide change in COL1A1 that creates a stop codon (p.Gln661X). Core width 4.8 mm, cortical width 765mm, bone volume per tissue volume 12.9%. (B) Helical glycine mutation, 9-year-old boy with a c.1090G>A nucleotide change in COL1A2 that creates an amino acid change (p.Gly364Ser). Core width 4.2 mm, cortical width 449mm, bone volume per tissue volume 8.9%. Adapted from Rauch et al.[10]

In terms of trabecular bone metabolism, there was a little difference between the genotypic groups. Bone turnover, although generally elevated in OI patients, was more markedly elevated in patients with helical glycine mutations. There was no obvious association between the histomorphometric parameters and the affected alpha chain, the position of the mutation, or the substituting amino acid in the helical mutation group (Figure 4).

In summary, the skeletal phenotype was milder in patients with haploinsufficiency mutations, and there was no obvious association between the skeletal phenotype and the genotype in the helical glycine mutation group.

Wormian Bones

Wormian bones are accessory skull bones surrounding suture lines. They can be a useful diagnostic feature in OI patients, and can be helpful in cases of child abuse. However, Wormian bones are not always present, and are not pathognomonic of OI.

Semler et al found in a study of 195 OI patients with a median age of 11.8 years that 59% of cases had a significant number of Wormian bones.[14] A similar prevalence of Wormian bones was found in a smaller study population.[15] Semler found a strong correlation between the genotype and the prevalence of Wormian bones, as they were present in 96% of patients with helical glycine mutation in the alpha-1 chain, 72% of patients with helical glycine mutation in the alpha-2 chain, 48% of patients with splice site mutations, 33% of patients with C–propeptide mutations, and 29% of patients with haploinsufficiency mutations.[14]

In the same study, the height z-score and glycine substitutions were the main patient characteristics found to be associated with the presence of Wormian bones. The finding of Wormian bones on a skull x-ray of a two week old boy with OI suggests that these are likely to develop in-utero, and that they tend to persist with time, as Wormian bones do not 'disappear' on serial skull x-rays evaluations.

Cranial Base Abnormalities

OI patients are prone to several cranial base abnormalities. The upward migration of the odontoid process (the top of C2) into the foramen magnum is the radiological definition for the basilar invagination (Figure 6). The flattening of the cranial base or the flattening of the anterior cranial base angle (the nasion-sella-basion angle) is defined as platybasia (Figure 7). Basilar impression is the consequence of an upward displacement of basilar and condylar regions of the occipital bone, leading to an unfolding of the foramen magnum and a translocation of the upper cervical spine into the brainstem, which shows translation on x-ray, by the positioning of the odontoid process far above the caudal borders of the skull.[16]

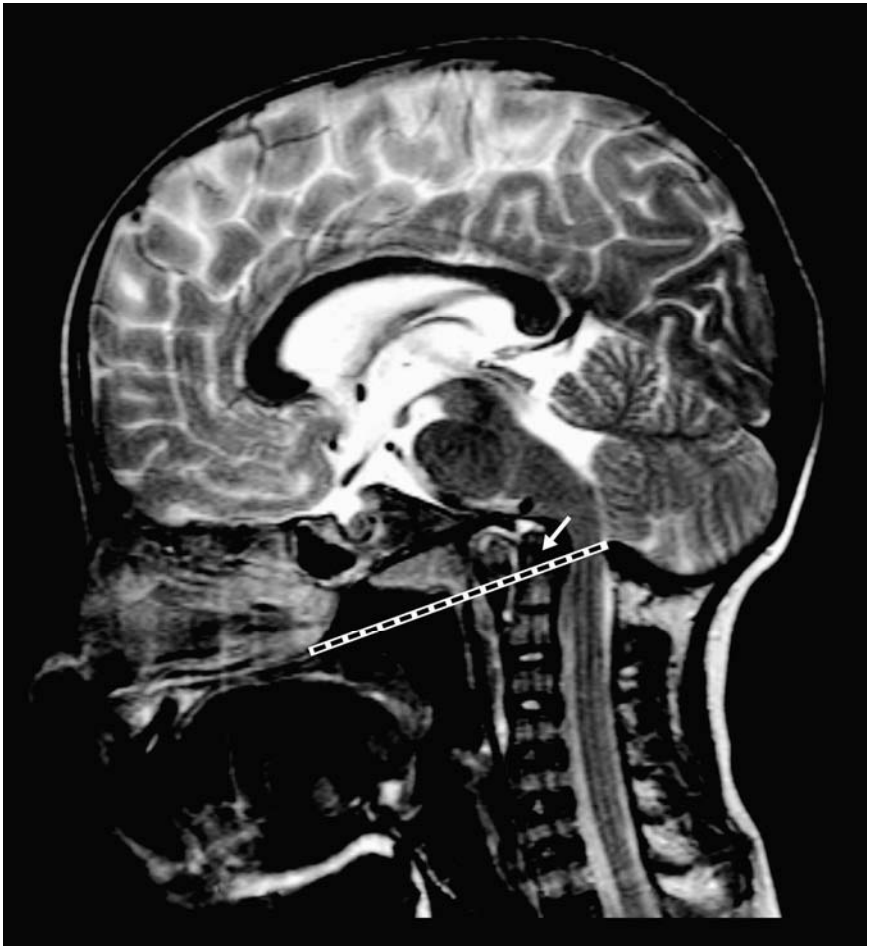

Figure 6. Basilar impression on brain MRI. The tip of the odontoid process (arrow) projects> 5 mm above Chamberlain (line between the hard palate and the opisthion which is the mid-point on the posterior margin of the foramen magnum). Adapted from Eaqeib et al.[17]

Cranial base abnormalities (comprising at least one of the above mentioned entities) were present in 22% of OI patients, based on the results of a cephalometric analysis of 187 OI patients (mostly pediatric cases).[18] Basilar invagination was the least common finding (4%), preceded by basilar impression (6%), and platybasia was the most frequent cranial base anomaly in OI patients (16%). A smaller study of adult OI patients showed similar prevalence of cranial base abnormalities.[15]

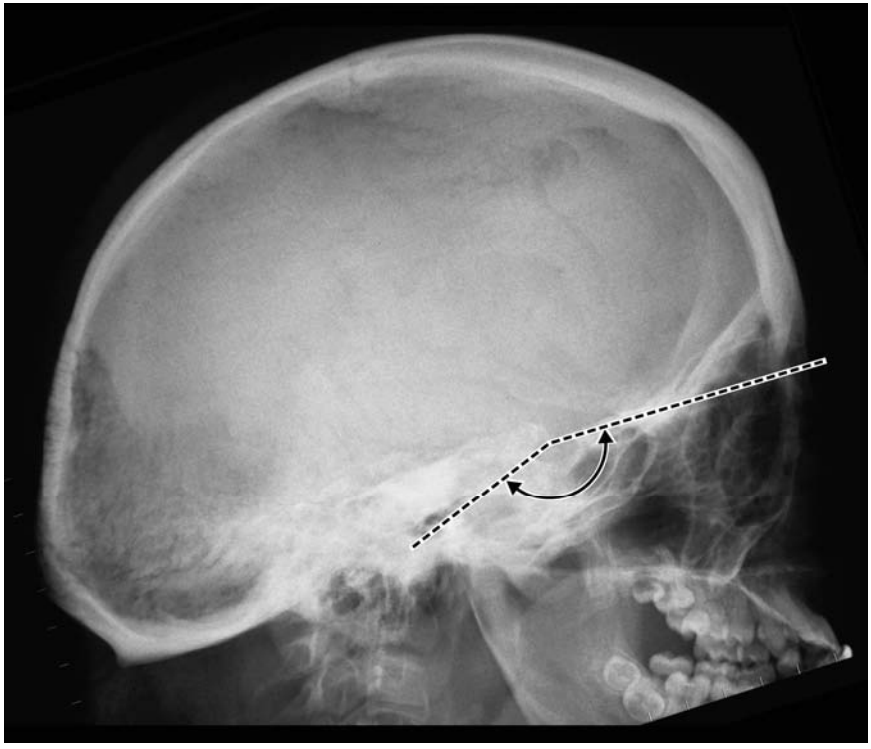

Figure 7. Platybasia: A flat cranial base as a consequence of a flat nasion-sella-basion angle (Welcher basal angle or sphenoid angle> 140°). Adapted from Eaqeib et al.[17]

Cheung et al showed some correlation between the genotype and the prevalence of cranial base abnormalities, since 6% of patients with haploinsufficiency mutations were identified with such anomalies, versus 17% of patients with splice-site mutations in either *COL1A1* or *COL1A2*, 32% of patients with helical glycine substitutions in alpha-2, and 43% of patients with helical glycine substitutions in alpha-1.[18] However, in OI patients, only the height z-score but not the genotype was found to be a significant independent predictive factor of cranial base abnormalities on a regression analysis. Thus, cranial base abnormalities seem to be associated more with the severity of the skeletal phenotype, rather than being a direct result from collagen type I mutations.

Other Genotype-Phenotype Correlations

Intracranial Hemorrhage and Limb Anomalies

A report on three unrelated patients with OI type III and a particular clinical phenotype were carrier of mutations located in exon 49 of the *COL1A2* gene

that encodes for the carboxy-terminal end of the alpha-2 triple helical domain[19] (Figure 8). The two girls and the boy in that report had small feet and hands, brachydactyly with marked shortening of the distal phalanges, associated with loose skin around fingers and hypoplastic nails (Figure 9). The other particular feature observed in these three patients was the development of intracranial hemorrhage at different ages (between 4 months and 15 years of age). So far, there is no mechanistic explanation for this phenotypic association.

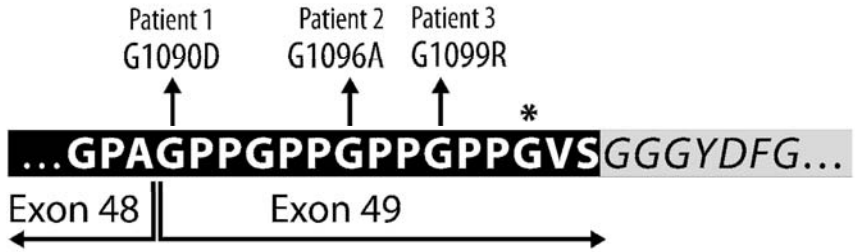

Figure 8. Amino acid sequence of collagen a2 (I) between residues 1087 and 1111. Residues that are part of the triple-helical domain are shown on black background. The first residues of the C-telopeptide are shown in italics and on gray background. The asterisk indicates the glycine residue that is affected in a boy with OI type IV who has normal height and a normal appearance of hands and feet. Adapted from Kovero et al.[19]

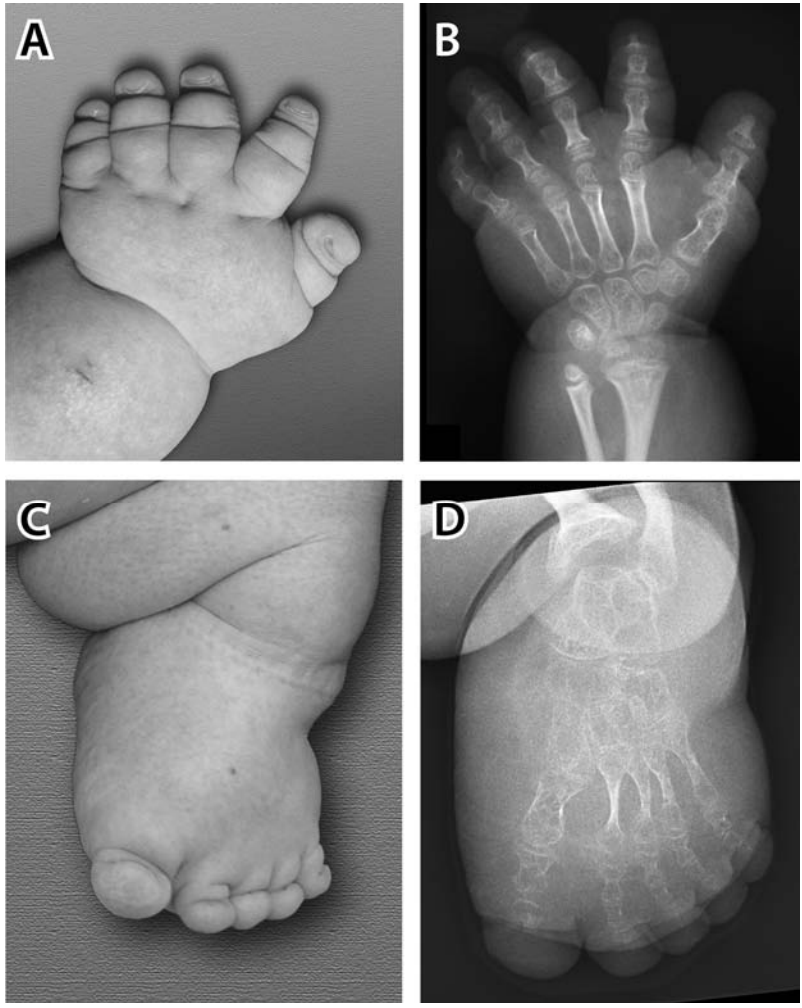

Figure 9. Radiographs of hands and feet in a 15 years old female. Small stubby hands and feet with hypoplastic nails (A,C) Severe shortening and thinning of all tubular bones including metacarpal and metatarsal bones, especially marked at the distal phalanges (B,D). Adapted with modification from Kovero et al.[19]

Russell–Silver Phenotype Like Presentation

Praker et al, described two patients with a phenotypic overlap between OI and RSS at early presentation, both of whom were found to be carriers of a COL1A1 mutation.[20] The authors suggested that a type 1 collagenopathy should be considered in the differential diagnosis of syndromic short stature.

Ehlers-Danlos Syndrome (EDS) Association

The non-glycine substitutions in the triple helical domain of collagen type I are rarely disease causing. A particular arginine to cysteine substitution in the alpha-1 triple helical domain at position 888 leads to a specific phenotype that combines features of both OI and EDS.[21] Several other reports on non-glycine substitutions in alpha-1 and alpha-2 chains have been associated with different phenotypes, including Caffey disease with joint laxity,[22] Marfan variant,[23] osteopenia, and vascular rupture.[24]

Hearing

In a recent study of 180 patients with OI (aged 3 to 89 years), approximately 52.2% demonstrated some degree of hearing loss unilaterally (7.7%) or bilaterally (44.5%). Different patterns were observed: pure conductive, mixed, and pure sensorineural hearing loss in 8.5%, 37.8%, and 11.6% of OI ears, respectively.[25] So far, not much data are available on the relationship between genotype and hearing loss in OI. H owever, a recent study[26] in 114 OI subjects did not reveal any association between the nature of the mutation in *COL1A1* or *COL1A2* genes and the occurrence, type or severity of hearing loss. There was a strong intrafamilial variability of audiological features, which could be explained partly by the variation in age, but the likely explanation for the basis of hearing loss in OI is that it is a complex and multifactorial trait. These findings are in accordance with previous report by Hartikka et al.[27]

Mosaic Carrier of Type I Collagen Mutations

In a mosaic carrier, both normal and mutant collagen type I cell populations are present in both somatic and germline tissues. Classically, the mosaic carrier is unaffected, while his offspring can randomly inherit a germline mutation and present with OI, in addition to a high risk of recurrence at each pregnancy compared to the general population. One study had shown, based on the result of cell culture of both fibroblasts and osteoblasts on two mosaic carriers, that a 40%–75% burden of osteoblasts heterozygous for a *COL1A1* mutation was substantially compatible with normal skeletal growth, density, and histology.[28]

SUMMARY OF MAIN POINTS

- The most frequent type of mutation in the triple helix domains of the collagen type I alpha-1 and alpha-2 chains are glycine-to-serine substitutions.
- Serine substitutions in the alpha-1 chain tend to lead to a more severe phenotype than serine substitutions in the alpha-2 chain.
- The phenotypic severity of serine substitutions correlates with the position of the mutation in the alpha-2 chain, but not in the alpha-1 chain.
- Glycine substitutions in the alpha-1 chain by arginine, aspartate, glutamate or valine beyond the first 200 amino acid residues are generally lethal, but tend to have a variable outcome in the alpha-2 chain.
- Mutations located in the first 120 amino acids of the collagen type I triple helix seem to be associated with blue sclera, but not with dentinogenesis imperfecta
- Three quarters of patients with glycine substitutions in the alpha-2 chain and one quarter of patients with haploinsufficiency mutations have Wormian bones, whereas glycine substitutions in the alpha-1 chain are almost always associated with the presence of Wormian bones.
- Only 1 in 20 patients with haploinsufficiency mutations have cranial base abnormalities, but more than a third of patients with glycine substitutions in the alpha-1 or alpha-2 chains develop such anomalies.
- Specific mutations localized at the C-terminal end of the alpha-2 chain are associated with a particular phenotype involving limb anomalies and intracranial hemorrhage.
- So far, no correlation has been found between the hearing pattern in OI and the mutated gene or the mutation type.

These are general rules for genotype-phenotype correlation in autosomal dominant OI patients. Exceptions are possible, and it is particularly important to be aware of this in the context of genetic counseling, especially in prenatal cases.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

aBMD	Areal bone mineral density
COL1A1	Collagen 1 A1
COL1A2	Collagen 1 A2
DI	Dentinigenesis imperfecta
EDS	Ehlers Danlos syndrome
OI	Osteogenesis imperfecta
RSS	Russell Silver syndrome

REFERENCES

1. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet.* Apr 24 2004;363(9418):1377-1385.
2. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet.* Apr 1979;16(2):101-116.
3. Byers PH. Collagens: building blocks at the end of the development line. *Clin Genet.* Oct 2000;58(4):270-279.
4. Byers PH. Killing the messenger: new insights into nonsense-mediated mRNA decay. *J Clin Invest.* Jan 2002;109(1):3-6.
5. Dalgleish R. The human type I collagen mutation database. *Nucleic Acids Res.* Jan 1 1997;25(1):181-187.
6. Dalgleish R. The Human Collagen Mutation Database 1998. *Nucleic Acids Res.* Jan 1 1998;26(1):253-255.
7. Marini JC, Forlino A, Cabral WA, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. *Hum Mutat.* Mar 2007;28(3):209-221.
8. Rauch F, Lalic L, Roughley P, Glorieux FH. Genotype-phenotype correlations in nonlethal osteogenesis imperfecta caused by mutations in the helical domain of collagen type I. *Eur J Hum Genet.* Jun 2010;18(6):642-647.
9. Lund AM, Muller J, Skovby F. Anthropometry of patients with osteogenesis imperfecta. *Arch Dis Child.* 1999;80(6):524-528.
10. Rauch F, Lalic L, Roughley P, Glorieux FH. Relationship between genotype and skeletal phenotype in children and adolescents with osteogenesis imperfecta. *J Bone Miner Res.* Jun 2010;25(6):1367-1374.
11. Majorana A, Bardellini E, Brunelli PC, Lacaita M, Cazzolla AP, Favia G. Dentinogenesis imperfecta in children with osteogenesis imperfecta: a clinical and ultrastructural study. *Int J Paediatr Dent.* Mar 2010;20(2):112-118.
12. Lund AM, Jensen BL, Nielsen LA, Skovby F. Dental manifestations of osteogenesis imperfecta and abnormalities of collagen I metabolism. *J Craniofac Genet Dev Biol.* Jan-Mar 1998;18(1):30-37.
13. Glorieux FH, Travers R, Taylor A, et al. Normative data for iliac bone histomorphometry in growing children. *Bone.* Feb 2000;26(2):103-109.
14. Semler O, Cheung MS, Glorieux FH, Rauch F. Wormian bones in osteogenesis imperfecta: Correlation to clinical findings and genotype. *Am J Med Genet A.* Jun 25 2010;152A(7):1681-1687.

15. Kovero O, Pynnonen S, Kuurila-Svahn K, Kaitila I, Waltimo-Siren J. Skull base abnormalities in osteogenesis imperfecta: a cephalometric evaluation of 54 patients and 108 control volunteers. *J Neurosurg.* Sep 2006;105(3):361-370.
16. Hayes M, Parker G, Ell J, Sillence D. Basilar impression complicating osteogenesis imperfecta type IV: the clinical and neuroradiological findings in four cases. *J Neurol Neurosurg Psychiatry.* Mar 1999;66(3):357-364.
17. Ben Amor IM, Glorieux FH, Rauch F. Genotype-phenotype correlations in autosomal dominant osteogenesis imperfecta. *J Osteoporos.* 2011;2011:540178.
18. Cheung MS, Arponen H, Roughley P, et al. Cranial base abnormalities in osteogenesis imperfecta: Phenotypic and genotypic determinants. *J Bone Miner Res.* Aug 18 2010.
19. Faqeih E, Roughley P, Glorieux FH, Rauch F. Osteogenesis imperfecta type III with intracranial hemorrhage and brachydactyly associated with mutations in exon 49 of COL1A2. *Am J Med Genet A.* Mar 2009;149A(3):461-465.
20. Parker MJ, Deshpande C, Rankin J, et al. Type 1 collagenopathy presenting with a Russell-Silver phenotype. *Am J Med Genet A.* Jun 2011;155A(6):1414-1418.
21. Cabral WA, Makareeva E, Letocha AD, et al. Y-position cysteine substitution in type I collagen (alpha1(I) R888C/p.R1066C) is associated with osteogenesis imperfecta/Ehlers-Danlos syndrome phenotype. *Hum Mutat.* Apr 2007;28(4):396-405.
22. Gensure RC, Makitie O, Barclay C, et al. A novel COL1A1 mutation in infantile cortical hyperostosis (Caffey disease) expands the spectrum of collagen-related disorders. *J Clin Invest.* May 2005;115(5):1250-1257.
23. Phillips CL, Shrago-Howe AW, Pinnell SR, Wenstrup RJ. A substitution at a non-glycine position in the triple-helical domain of pro alpha 2(I) collagen chains present in an individual with a variant of the Marfan syndrome. *J Clin Invest.* Nov 1990;86(5):1723-1728.
24. Malfait F, Symoens S, De Backer J, et al. Three arginine to cysteine substitutions in the pro-alpha (I)-collagen chain cause Ehlers-Danlos syndrome with a propensity to arterial rupture in early adulthood. *Hum Mutat.* Apr 2007;28(4):387-395.
25. Swinnen FK, Dhooge IJ, Coucke PJ, et al. Audiologic Phenotype of Osteogenesis Imperfecta: Use in Clinical Differentiation. *Otol Neurotol.* Dec 2 2011.
26. Swinnen FK, Coucke PJ, De Paepe AM, et al. Osteogenesis imperfecta: the audiological phenotype lacks correlation with the genotype. *Orphanet J Rare Dis.* Dec 29 2011;6(1):88.
27. Hartikka H, Kuurila K, Korkko J, et al. Lack of correlation between the type of COL1A1 or COL1A2 mutation and hearing loss in osteogenesis imperfecta patients. *Hum Mutat.* Aug 2004;24(2):147-154.
28. Cabral WA, Marini JC. High proportion of mutant osteoblasts is compatible with normal skeletal function in mosaic carriers of osteogenesis imperfecta. *Am J Hum Genet.* Apr 2004;74(4):752-760.

5 CHALLENGES OF STEM CELL THERAPIES FOR OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Osteogenesis imperfecta (OI) is a heterogeneous disorder that affects skeletal tissues in which type I collagen is the major protein component. The disease results from mutations that affect the genes which encode the polypeptide chains of type I collagen.[1] Some recessive forms of the disease are now attributed to mutations in the genes that encode noncollagenous proteins; some of these proteins play a role in post-translational modification of the type I collagen polypeptide chains.[2-4] Owing to its clinical heterogeneity, Sillence classified the disease into four types; I, II, III and IV, based on clinical and radiographic findings.[5] These OI types result from mutations in the genes that encode polypeptide chains of type I collagen, thus leading to structural defects in type I collagen molecules.

Newly identified recessive forms of OI, types V, VI, VII, VIII, IX, X and XI[2] have been added to the list; these phenotypes do not fall into the classical OI phenotypes originally described by Sillence.[5] They are not caused by structural mutations in type I collagen chains, but result from noncollagenous protein defects.[2] Defects in any component of the collagen 3-hydroxylation complex is one of the examples in which noncollagenous proteins have been shown to lead to OI phenotypes VII, VIII and IX.[2] The complex is comprised of prolyl 3-hydroxylase 1 (P3H), cartilage associated protein (CRTAP), and peptidyl-prolyl cis-trans isomerase B or cylophilin B.[2] This complex is responsible for the hydroxylation of a single proline residue at position 986 in each of the α1 chains of type I and II collagens[2,6,7] and several proline residues in types IV and V collagen chains. Other examples include mutations in the gene that encodes pigment epithelium derived factor (PEDF) which has recently been associated with defects in OI type VI; patients with OI type VI have defects in mineralization.[8-10] The role of PEDF

in bone mineralization is not known, but recent findings indicate that PEDF enhances human MSCs differentiation and increases matrix mineralization.[11-13] These recessive OI forms may be amenable to cell therapy approaches.

Presently, controversies exist regarding application of stem cells to treat OI. Original reports in mice and clinical trials in humans suggested that mesenchymal stem cells or multipotent mesenchymal stromal cells (MSCs) harvested from bone marrow have potential to treat OI.[14] Results from human clinical trials showed that patients who received cell transplant exhibited reduction in fracture rate as well as increase in growth.[15,16] The level of donor cell engraftment was, however, extremely low; how such low engraftment led to the improvement observed in patients' bones was not explained. Subsequent studies have generated conflicting reports regarding application of stem cells to treat OI. Most of the controversies result from studies in which stem cells are intravenously delivered into animal models of the disease. Several investigators including us have shown that MSCs are transplantable and the cells will home and engraft in the bones of the recipients specifically in developing animals or in utero.[17-22] It has not been clearly established, however, whether the cells that migrate to the bones contribute to the cell phenotype and to the regenerative process of the recipient bones. We used two approaches to examine contribution of MSCs to brittle bone regeneration using osteogenesis imperfecta mouse (oim) model. In one approach, MSCs were transplanted in newborn OI mice and in a second approach, cells were directly infused into the femurs of the mice. Contribution of the cells to the regenerative process was assessed.

MATERIALS AND METHODS

Cell Isolation

Bone marrow stromal cells (BMSC) were isolated by flushing marrow from the femurs and tibia of normal mice syngeneic to oim mice; after marrow flush, the bones were split open and the cells associated with bone were scrapped and combined with the marrow harvested cells.[17,19] The BMSCs were cultured in T25 flasks in DMEM supplemented with 10% FBS, 1% penicillin/streptomycin (P/S, v/v). After 4 days of culture, the medium was replaced and the cells were maintained in culture for expansion. At passage 3, cells were transduced with a retrovirus carrying the enhanced green fluorescent protein (GFP) and Zeocin resistant genes to facilitate selection of GFP+ cells.

Cell Transduction

To aid in donor cell tracking in vivo, cells were transduced with a retrovirus carrying GFP and Zeocin resistant genes following methods we described previously.[19] To select a population of cells expressing eGFP, the transduced cells were maintained in DMEM supplemented with 10% FBS and 25 μg/ml of Zeocin. The eGFP-Zeor+ BMSCs were maintained in culture in presence of Zeocin until use.

Assessment of BMSCs Differentiation

Cells for transplantation were first assessed for osteogenic and adipogenic differentiation in vitro prior to use. Methods established previously were used.[18, 19]

Transplantation of MSCs into Neonatal Oim Mice

Because of poor engraftment of MSCs in adult mice bones following systemic transplantation, we tested whether transplantation of the cells into neonatal mice would lead to better engraftment. Clinical trials of MSCs were done in infants with OI; we therefore wanted to recapitulate this process in baby mice. Detailed methods for transplanting MSCs in neonatal mice were reported previously by us and will be briefly described here.[17-19] We generated single cell expanded MSCs by serial dilution of MSCs prepared from bone marrow. This was done in order to determine if there were subpopulations of MSCs in bone marrow that exhibited a higher propensity for migration and engraftment in skeletal tissues following systemic transplantation. Recipient neonatal mice were sublethally irradiated prior to cell injection; 4 hrs after radiation, $5x10^5$ GFP+ cells suspended in PBS were injected into neonatal mice via the superficial temporal vein (Figure 1).[23] Recipient mice were assessed at 2, 4 or 6 weeks following cell infusion by histological analysis and recovery of the cells from the recipient tissues.

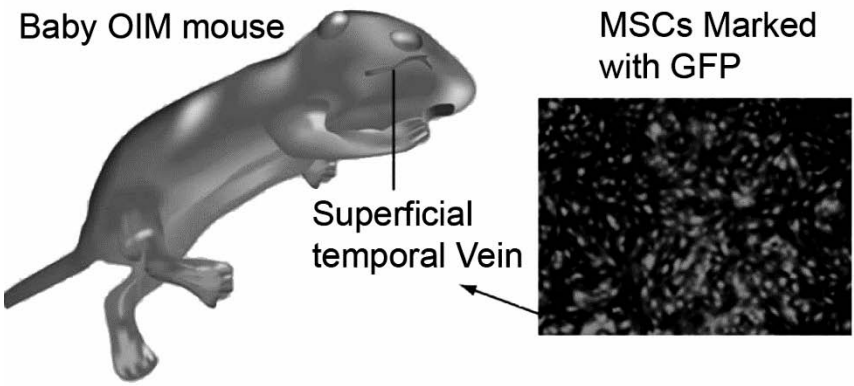

Figure 1. A technique for injecting cells into newborn mice. GFP+ MSCs are injected via the superficial temporal vein into newborn mice. Donor cells are tracked in various tissues based on GFP expression. Figure modified from Niyibizi C and Li F.[20]

Infusion of GFP Marked Cells into Mice Femurs

Because of low engraftment when cells are systemically transplanted into adult mice, we infused the cells directly into brittle femurs. By this approach, the number of cells for injection can be controlled. For femoral injections, 1×10^6 MSCs suspended in 20 µl of PBS containing pepsin solubilized bovine type I collagen (0.1 mg/ml) or collagen alone or PBS were injected through the femoral condyles into the femoral cavities. Each group of mice was sublethally irradiated prior to treatment as described previously.[21] Four hours after irradiation, the mice were anesthetized by subcutaneous injection of 1 ml of Ketamine and Xylazine (100 mg/ml, 2:1)/kg body weight. To distribute donor cells within the entire bone cavity, a tunnel was created within the femur cavity using a 26 gauge needle. This was followed by insertion of a smaller gauge needle (30 gauge) attached to a syringe containing cells for injection. The cells were introduced within the bone cavity by slowly retracting the needle while depositing BMSCs.[21] Femurs (contralateral) that did not receive cells were treated similarly but no cells were injected. Recipient mice were sacrificed at 2 and 6 weeks following experimental procedures, femurs were harvested and processed for histology and biomechanical testing.

Histological Analysis

For histological analysis of the donor GFP+ cells in vivo, a method described previously was used.[18,19] Briefly, bones harvested from the recipient mice were immediately fixed in freshly prepared 4% paraformaldehyde in PBS,

containing 10% sucrose and kept at 4 °C for 24 h in the dark. After 24 h, the bones were rinsed in PBS and then demineralized in 0.5 M EDTA in PBS containing 10% sucrose at 4 °C h in the dark for 48h. Following demineralization, bones were slowly frozen in cold isopentane cooled on a dry ice bath. Frozen bones were embedded in Tissue-Tek optimal cutting temperature Compound (OCT), and 10-µm sections were cut and mounted on glass slides. The slides were directly observed under a fluorescent microscope without the cover slips, but the sections were kept hydrated in PBS to reduce autofluorescence. Images were acquired using the Spot RT SE digital camera (Diagnostics Instruments Inc., Sterling Heights, MI). Serial tissue sections were stained with hematoxylin and eosin.

Histological Analysis, Paraffin Embedded Tissue Sections

Femurs harvested from recipient mice at 6 weeks post MSCs or PBS infusion were paraffin embedded using methods described previously. Ten micron longitudinal tissue sections were cut, deparaffinized, and stained in hematoxylin and eosin (H and E). Some of the tissue sections were used for immunofluorescence and immunohistochemistry staining for GFP and osteoclacin.[21]

Biomechanical Testing

Six weeks following cell infusion, femurs were harvested and subjected to biomechanical testing. The femurs were loaded to failure in three-point bending using a small animal biomechanical testing instrument (ElectroForce 3100, Bose Corporation, Prairie, MN). Results from each group were collected and analyzed by assessing differences in load to failure of the right and left femurs of the same mouse. The stiffness for each bone was also assessed. In all cases the right femur was set as experimental and the left femur served as a control. Data were expressed as percent of control; left femur served as a control regardless of treatment in all cases. The results were compared within groups but not across groups.

RESULTS

Since most of the work described here has been reported by us in various publications, we will only highlight significant findings of the studies with relevant references. We will first discuss transplantation experiments in neonatal mice.

Transplantation of the Selected Progenitors into Oim Neonatal Mice and Histological Analysis

From single cell cloning, one clone showed higher potential to engraft in most of the mouse skeletal tissues following transplantation.[19] Cells expanded from this clone were used for transplantation into neonatal oim mice. Distribution of the cells in various tissues of recipient mice was assessed by histology and recovery of donor cells from various tissues. Donor cells had extravasated into several skeletal tissues, mostly all the bones of the recipient mice.[18,19] Donor cells were present in all the femurs, tibias, fore limbs, scapulas, and ribs of the recipient mice at 4 weeks following cell transplantation. All the recipient mice showed the presence of donor cells in the lungs. In bone, the level of cell engraftment was variable in different mice; the engraftment ranged from 0.3% to 28% of total cells as assessed by quantitative PCR for the GFP at 4 weeks (Table 1). Tissue sections made from the tibia of the recipient mouse at 4 weeks showed that the GFP cells were distributed in the entire tibia, the ends of the bones toward the knee joint, and toward the foot demonstrating higher concentration (Figure 2). Donor GFP+ cells were confirmed by immunofluorescence staining for GFP.[18,19]

Table 1. Tissue distribution of donor MSCs in different mice at 2 and 4 weeks following transplantation in newborn mice. Donor cells were mostly present in skeletal tissues. Single cells were MSCs expanded from a single cell clone of marrow-derived cells. From Li F et al.[16]

Mouse	2 weeks					4 weeks				
No.	1	2	3	4	5	1	2	3	4	5
Bone	+	+	+	+	+	+	+	+	+	-
Lung	+	+	+	+	+	+	+	+	+	+
Heart	-	+	+	-	+	-	-	+	+	-
Rib	-	-	+	-	+	+	-	+	-	-
Liver	-	+	-	-	-	-	-	-	-	-
Spleen	-	-	-	-	-	-	-	-	-	-
Kidney	-	-	-	-	-	-	-	-	-	-
Brain	-	-	-	-	-	-	-	-	-	-
GFP+ *	n/a	n/a	n/a	n/a	n/a	2.9 ±0.7%	1.2 ±0.4%	28 ±3.0%	9.1 ±2.8%	0.3 ±0.2%

* Percentage of GFP+ cells in the tibia of recipient mice.

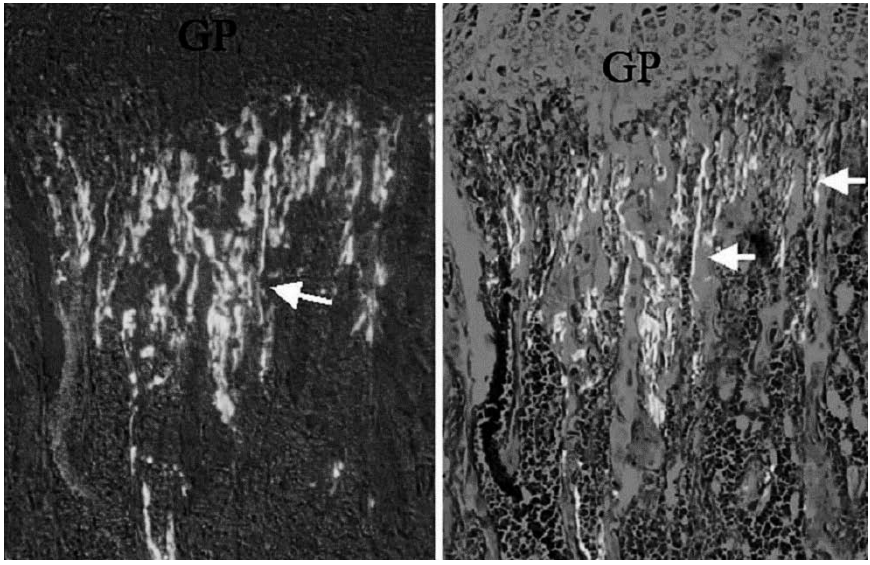

Figure 2. Histological sections from a tibia of a recipient mouse showing location of donor cells at 4 weeks. Left) Donor cells (green) are located at the end of bone in the spongiosa just below the growth plate (GP). Right) An overlay image of the GFP fluorescence for donor cells with a serial tissue section stained with H and E. New bone formation in the areas of GFP+ donor cells is evident (arrows). Figure modified from Wang et al.[15]

The donor cells were retrieved from various tissues of the recipient mouse at 2 and 4 weeks following cell transplantation and were used for genotyping and gene expression analysis.

The cells associated with the bones were retrieved by placing bone chips from the bones of the recipient mice in culture and allowing donor cells to crawl out. The cells retrieved from various tissues were expanded in culture in the presence of Zeocin to obtain a sufficient number of cells for analysis. FACS analysis for GFP indicated that the cells were more than 99% GFP+.

The cells retrieved from various tissues were assessed for possible fusion with the endogenous cells in vivo as described.[19] The cells were also assessed for expression of selected specific genes of the tissues from which donor cells were retrieved. Donor cells retrieved from bone at 4 weeks following transplantation expressed osteoblast-specific genes; osterix and osteocalcin (Figure 3). The cells retrieved from the lungs expressed lung surfactants A and B genes, and the cells retrieved from the heart expressed *NKx2.5*, a gene that has been shown to play a crucial role in myocardial development (Figure 3). These data suggested that MSCs will differentiate into cells of the tissues

in which they engraft perhaps as a result of the cues from the host tissues. The extent of the donor cells contribution to the host tissue, however, has not been established.

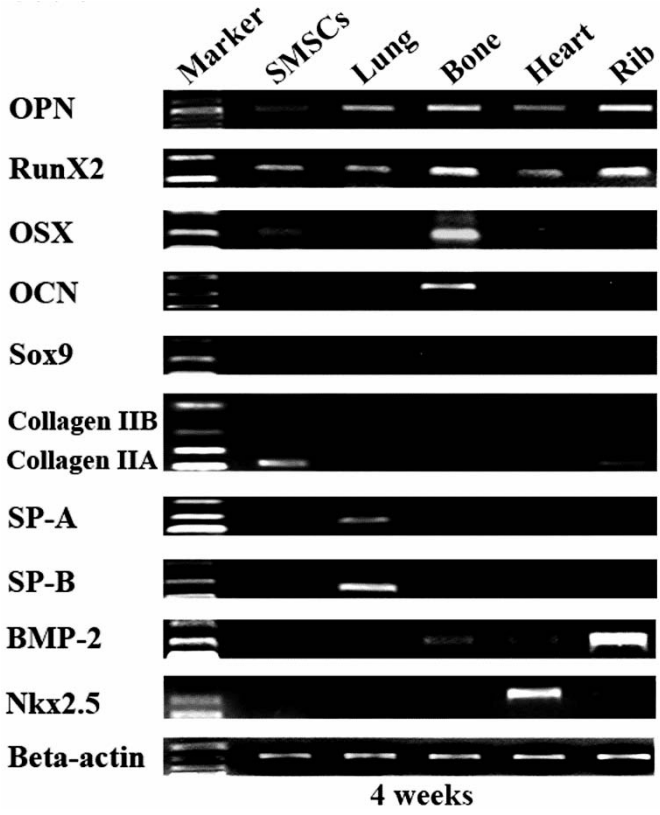

Figure 3. Expression of selected genes by donor cells retrieved from various tissues. Donor cells transplanted in newborn mice were retrieved from respective tissues at 4 weeks. Donor cells retrieved from bone show expression of osteoblast related genes suggesting differentiation of MSCs in vivo. SMSCs denote single cell expanded MSCs used for transplantation. OSX=Osterix, OCN=Osteocalcin, SP-A and SP-B denote lung surfactant A and B respectively. Figure adapted from Li et al.[16]

Infusion of MSCs into Femurs of Oim Mice

Because of variability of cell engraftment in baby mice, to assess contribution of MSCs to brittle bone regeneration, cells were infused directly into femurs. Owing to the fact that a large number of cells can be concentrated into one bone, this approach offers an opportunity for determining contribution of donor MSCs cells to the structural integrity of the recipient bones. Oim mice femurs that were infused with MSCs were assessed at 2 and 6 weeks

following infusion. Histological analysis of the recipient femurs at 2 weeks demonstrated new bone formation in metaphyseal regions of the recipient femurs.[21] Examination of the serial tissue sections for the donor cells by fluorescence microscopy, revealed that a high number of GFP+ donor cells were concentrated at the injected sites with few donor cells within the newly made bone.[21] These data suggested that the newly deposited bone may have resulted from a combination of donor and host cells. Tissue sections of oim femurs injected with PBS showed minimal or absence of trabecular bone. The results clearly established that the donor cells contribute to bone formation in vivo either by depositing new bone or by inducing endogenous cell differentiation.

Six weeks following donor MSCs infusion into femurs, recipient bones demonstrated presence of newly made trabecular bone (Figure 4). In addition, there was an increase in cortical thickness of the femurs.[21] At this time point, recipient bones were subjected to biomechanical testing to assess contribution of donor cells to structural integrity. Biomechanical testing results indicated that femurs which were infused with MSCs which were suspended in collagen were stronger than those infused with PBS, collagen matrix in PBS only or MSCs in PBS alone (Figure 5). Femurs infused with MSCs suspended in PBS, however, were stronger than femurs injected with PBS or collagen matrix.[21] These data indicated that increase in bone strength was the result of donor MSCs not collagen matrix. These data clearly demonstrated that MSCs transplantation into OI bones will contribute to the structural integrity of the bones but a high level of donor engraftment is required.

In summary, data from the two approaches showed that MSCs transplanted into brittle bones will contribute to the regenerative process of the bones but a high level of engraftment is required. The benefits, however, appeared to be short lived at least in these animal models of the disease because the number of donor cells diminished with time.

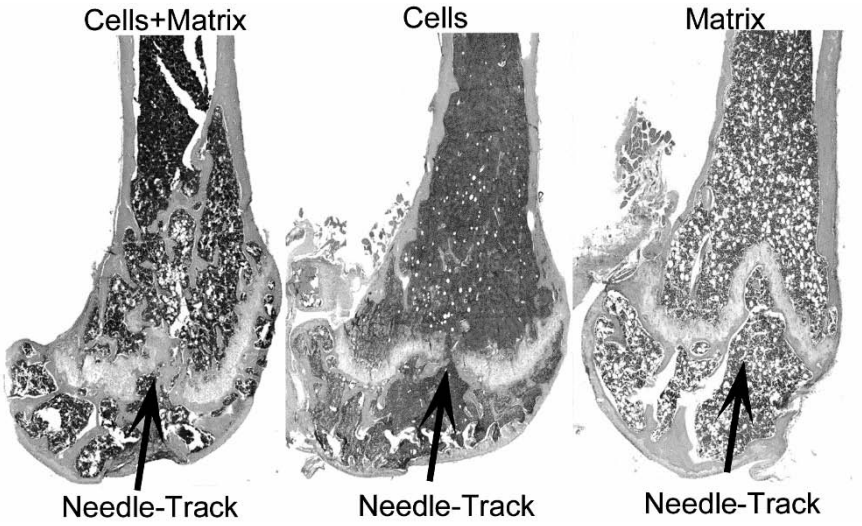

Figure 4. Femurs from oim mouse infused with MSCs and assessed at 6 weeks. Femurs infused with MSCs demonstrate new bone formation (Cells+Matrix). Femurs injected with cells show less bone formation (Cells). Femurs that were not injected with cells do not show any bone formation (Matrix). Donor infusion sites are indicated by arrow. Figure adapted from Li et al.[18]

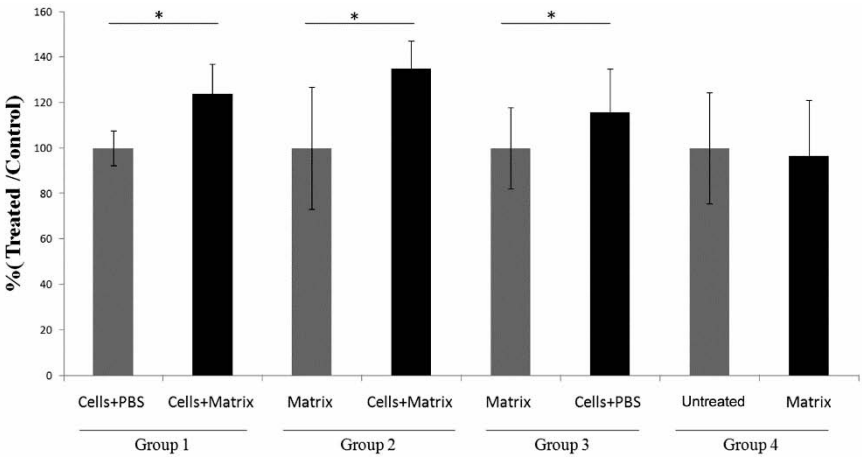

Figure 5. Biomechanical testing results showing femurs infused with cells in matrix or cells alone are stronger. Matrix alone did not have an effect on mechanical properties of the femurs. From Li et al.[18] *$p<0.05$.

DISCUSSION

Stem cell therapies for treating OI raised high expectations when bone marrow cells were originally transplanted in mice. Subsequent clinical trials using marrow-derived cells in babies with OI, also raised hope that MSCs possessed potential for reversing defects in OI patients. Following clinical trials, however, controversies rose over the effectiveness of MSCs to treat OI. Transplantation of whole marrow or BMSCs in babies with OI was shown to lead to reduction in frequency of fracturing and increase in growth velocity of the patients.[15,16] The number of donor cells present in the bones of the recipient patients was extremely low. It was not clear how such small number of cells could have contributed to the improvements in the structural properties of the patients' bones. Subsequent studies in mice generated conflicting results regarding application of MSCs to treat OI.[24,25] Some studies showed that MSCs transplanted in animal models will migrate to bone but the level of engraftment to be low. The level of engraftment could be improved by selecting populations of MSCs with propensity to migrate to bone or by enhancing their migration by surface or gene modifications.[26,27] These approaches are experimentally possible but present a challenge for clinical application.

The data from transplantation of MSCs in baby mice showed that the cells will migrate into most of the bones of recipient mice and contribute to new bone and reparative process. The cells that had engrafted were shown to differentiate into osteoblasts in vivo but the extent of contribution to the new bone formation by differentiation was not demonstrated. The results showed that MSCs will migrate and engraft in the bones of young mice better than in adult mice. These findings are supported by in utero transplantation experiments in animal models of the disease.[20,22] In one report, human fetal blood MSCs were transplanted in utero into fetuses of oim mice. Twelve weeks postnatal, bone analysis demonstrated new bone formation in recipient animals. The new bone contributed to improvement in bone mechanical properties[20] and reduction in fracture rate. In related studies, but using a different mouse model of OI, transplantation of MSCs in utero led to improved mechanical properties as well as reduction in the rate of fracturing.[22] Taken together, the results from these transplantation studies demonstrate that MSCs transplanted into developing animals will lead to improvements in the bones of the recipients. There is one report in literature in which MSCs were transplanted in utero into a fetus shown to have OI.[28] The level of donor cell engraftment in the bones was extremely low and only

one patient was involved in this clinical trial, thus making data interpretation difficult.

The mechanisms by which donor cells contributed to the improved mechanical properties or reduction in fracture rates are not clearly understood. Recent paradigm for the therapeutic nature of MSCs is that the cells generate trophic factors that modulate microenvironment of the host tissues, thus enhancing the host cells to carry out the reparative process. Direct infusion of MSCs into oim mice femurs appears to support this suggestion. Two weeks following infusion of BMSCs into the femurs of oim mice, extensive new bone deposition was present as revealed by histological analysis; the new bone, however, appeared to contain fewer donor cells based on GFP positive cells within the recipient femurs. These data suggested that not only did the donor cells contribute to bone formation in vivo, but that the endogenous cells participated in this process as well. It is likely that the presence of donor cells led to the recruitment of endogenous cells, which initiated the reparative process. The femurs injected with PBS or collagen alone showed absence or minimal bone deposition. These observations suggest that as the donor cells differentiate, they induce or recruit endogenous cells to initiate a reparative process. These conclusions are consistent with current concepts that indicate that stromal cells secrete factors that modulate microenvironments for tissue repair.[29,30] Strong evidence in support of these concepts has come from studies on transplantation of MSCs into infracted hearts.[31] Results from these studies indicated that therapeutic effects of MSCs were due to the production of trophic factors by donor cells. This was clearly demonstrated when medium conditioned by MSCs was able to produce similar effects as the cells that were injected in an animal model of infracted heart.[31] Whether similar mechanisms occur when MSC are transplanted into bone has not been established.

Dominant negative mutations in OI pose significant problems to treat by cell therapy. Cell therapies for dominant negative forms of OI present a challenge because in these OI forms, defective collagen molecules are synthesized, secreted, and deposited in bone matrix. Approaches to prevent their production would have to be developed in order to apply cell therapy approaches. To accomplish this, a combination of stem and gene therapies will have to be applied. The best approach would be to manipulate the patient's own cells, for example, by eliminating the mutant allele or replacing the mutant genes in cases of recessive forms and then returning the cells to

the patient. Gene therapy approaches are complicated by the genetic heterogeneity present in dominant negative mutations. Gene targeting proposed by Chamberlain *et al.* targets mutant alleles in stem cells and the corrected stem cells can then be returned to the patients from whom the cells were harvested.[32] This attractive approach would entail harvesting stem cells from a patient, correcting the defect, and then returning the cells to the same patient. Since the cells would be harvested from the patient, potential for cell rejection would be avoided. If this approach is possible, returning the corrected cells to the patients' still poses a major challenge.

Stem-cell therapy for OI remains a distant future. Results from animal models indicate that early treatment preferably in utero may be the best approach; because MSCs once transplanted are short lived, the type of cells to transplant will have to be sought. In addition, methods to target cells to skeletal tissues and to increase the level of engraftment would have to be developed. The extent of donor cell contribution to host bone matrix needs to be established. If the main function of the donor cells is to enhance host cell function, this would not be appropriate for OI treatment. Investigation into the potential use of induced pluripotent stem cells (iPSC) for transplantation in OI is attractive because of the potential to generate patient-specific ESC for transplantation. This technology, however, is still further away for clinical application.

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ABBREVIATIONS

BMSCs	Bone marrow mesenchymal stem ells
DMEM	Dulbecco's modified eagle's medium
ESC	Embryonic stem cells
FACS	Flow activated cell sorting
FBS	Fetal bovine serum
GFP, eGFP	Green fluorescent; enhanced green fluoresce protein
iPSC	Induced pluripotent stem cells
v/v	Volume/volume

REFERENCES

1. Prockop, D.J., 1992, "Seminars in medicine of the Beth Israel Hospital, Boston. Mutations in collagen genes as a cause of connective-tissue diseases". N Engl J Med. 326(8): pp. 540-6.
2. Forlino, A., W.A. Cabral, A.M. Barnes, and J.C. Marini, 2011, "New perspectives on osteogenesis imperfecta". Nat Rev Endocrinol. 7(9): pp. 540-57.
3. Morello, R., T.K. Bertin, Y. Chen, J. Hicks, L. Tonachini, M. Monticone, P. Castagnola, F. Rauch, F.H. Glorieux, J. Vranka, H.P. Bachinger, J.M. Pace, U. Schwarze, P.H. Byers, M. Weis, R.J. Fernandes, D.R. Eyre, Z. Yao, B.F. Boyce, and B. Lee, 2006, "CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta". Cell. 127(2): pp. 291-304.
4. Cabral, W.A., W. Chang, A.M. Barnes, M. Weis, M.A. Scott, S. Leikin, E. Makareeva, N.V. Kuznetsova, K.N. Rosenbaum, C.J. Tifft, D.I. Bulas, C. Kozma, P.A. Smith, D.R. Eyre, and J.C. Marini, 2007, "Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta". Nat Genet. 39(3): pp. 359-65.
5. Sillence, D.O., A. Senn, and D.M. Danks, 1979, "Genetic heterogeneity in osteogenesis imperfecta". J Med Genet. 16(2): pp. 101-16.
6. Marini, J.C., W.A. Cabral, A.M. Barnes, and W. Chang, 2007, "Components of the collagen prolyl 3-hydroxylation complex are crucial for normal bone development". Cell Cycle. 6(14): pp. 1675-81.
7. Glorieux, F.H., L.M. Ward, F. Rauch, L. Lalic, P.J. Roughley, and R. Travers, 2002, "Osteogenesis imperfecta type VI: a form of brittle bone disease with a mineralization defect". J Bone Miner Res. 17(1): pp. 30-8.
8. Becker, J., O. Semler, C. Gilissen, Y. Li, H.J. Bolz, C. Giunta, C. Bergmann, M. Rohrbach, F. Koerber, K. Zimmermann, P. de Vries, B. Wirth, E. Schoenau, B. Wollnik, J.A. Veltman, A. Hoischen, and C. Netzer, 2011, "Exome sequencing identifies truncating mutations in human SERPINF1 in autosomal-recessive osteogenesis imperfecta". Am J Hum Genet. 88(3): pp. 362-71.
9. Homan, E.P., F. Rauch, I. Grafe, C. Lietman, J.A. Doll, B. Dawson, T. Bertin, D. Napierala, R. Morello, R. Gibbs, L. White, R. Miki, D.H. Cohn, S. Crawford, R. Travers, F.H. Glorieux, and B. Lee, 2011, "Mutations in SERPINF1 cause osteogenesis imperfecta type VI". J Bone Miner Res. 26(12): pp. 2798-803.
10. Venturi, G., A. Gandini, E. Monti, L. Dalle Carbonare, M. Corradi, M. Vincenzi, M.T. Valenti, M. Valli, E. Pelilli, A. Boner, M. Mottes, and F. Antoniazzi, 2011, "Lack of expression of SERPINF1, the gene coding for pigment epithelium-derived factor causes progressively deforming osteogenesis imperfecta with normal type I collagen". J Bone Miner Res.
11. Li, F., N. Song, J. Tombran-Tink, and C. Niyibizi, 2014, "Pigment epithelium derived factor suppresses expression of Sost/sclerostin by osteocytes: Implication for its role in bone matrix mineralization". Journal of cellular physiology.
12. Gattu, A.K., E.S. Swenson, Y. Iwakiri, V.T. Samuel, N. Troiano, R. Berry, C.D. Church, M.S. Rodeheffer, T.O. Carpenter, and C. Chung, 2013, "Determination of mesenchymal stem cell fate by pigment epithelium-derived factor (PEDF) results in increased adiposity and reduced bone mineral content". The FASEB Journal. 27(11): pp. 4384-4394.

13. Li, F., N. Song, J. Tombran-Tink, and C. Niyibizi, 2013, "Pigment Epithelium-Derived Factor Enhances Differentiation and Mineral Deposition of Human Mesenchymal Stem Cells". Stem Cells. 31(12): pp. 2714-2723.
14. Pereira, R.F., M.D. O'Hara, A.V. Laptev, K.W. Halford, M.D. Pollard, R. Class, D. Simon, K. Livezey, and D.J. Prockop, 1998, "Marrow stromal cells as a source of progenitor cells for nonhematopoietic tissues in transgenic mice with a phenotype of osteogenesis imperfecta". Proc Natl Acad Sci U S A. 95(3): pp. 1142-7.
15. Horwitz, E.M., D.J. Prockop, L.A. Fitzpatrick, W.W. Koo, P.L. Gordon, M. Neel, M. Sussman, P. Orchard, J.C. Marx, R.E. Pyeritz, and M.K. Brenner, 1999, "Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta". Nat Med. 5(3): pp. 309-13.
16. Horwitz, E.M., P.L. Gordon, W.K. Koo, J.C. Marx, M.D. Neel, R.Y. McNall, L. Muul, and T. Hofmann, 2002, "Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone". Proc Natl Acad Sci U S A. 99(13): pp. 8932-7.
17. Niyibizi, C., S. Wang, Z. Mi, and P.D. Robbins, 2004, "The fate of mesenchymal stem cells transplanted into immunocompetent neonatal mice: implications for skeletal gene therapy via stem cells". Mol Ther. 9(6): pp. 955-63.
18. Wang, X., F. Li, and C. Niyibizi, 2006, "Progenitors systemically transplanted into neonatal mice localize to areas of active bone formation in vivo: implications of cell therapy for skeletal diseases". Stem Cells. 24(8): pp. 1869-78.
19. Li, F., X. Wang, and C. Niyibizi, 2007, "Distribution of single-cell expanded marrow derived progenitors in a developing mouse model of osteogenesis imperfecta following systemic transplantation". Stem Cells. 25(12): pp. 3183-93.
20. Guillot, P.V., O. Abass, J.H. Bassett, S.J. Shefelbine, G. Bou-Gharios, J. Chan, H. Kurata, G.R. Williams, J. Polak, and N.M. Fisk, 2008, "Intrauterine transplantation of human fetal mesenchymal stem cells from first-trimester blood repairs bone and reduces fractures in osteogenesis imperfecta mice". Blood. 111(3): pp. 1717-25.
21. Li, F., X. Wang, and C. Niyibizi, 2010, "Bone marrow stromal cells contribute to bone formation following infusion into femoral cavities of a mouse model of osteogenesis imperfecta". Bone. 47(3): pp. 546-55.
22. Panaroni, C., R. Gioia, A. Lupi, R. Besio, S.A. Goldstein, J. Kreider, S. Leikin, J.C. Vera, E.L. Mertz, E. Perilli, F. Baruffaldi, I. Villa, A. Farina, M. Casasco, G. Cetta, A. Rossi, A. Frattini, J.C. Marini, P. Vezzoni, and A. Forlino, 2009, "In utero transplantation of adult bone marrow decreases perinatal lethality and rescues the bone phenotype in the knockin murine model for classical, dominant osteogenesis imperfecta". Blood. 114(2): pp. 459-68.
23. Niyibizi, C. and F. Li, 2009, "Potential implications of cell therapy for osteogenesis imperfecta". International Journal of Clinical Rheumatology. 4(1): pp. 57-66.
24. Anjos-Afonso, F., E.K. Siapati, and D. Bonnet, 2004, "In vivo contribution of murine mesenchymal stem cells into multiple cell-types under minimal damage conditions". J Cell Sci. 117(Pt 23): pp. 5655-64.
25. Wang, L., Y. Liu, Z. Kalajzic, X. Jiang, and D.W. Rowe, 2005, "Heterogeneity of engrafted bone-lining cells after systemic and local transplantation". Blood. 106(10): pp. 3650-7.

26. Lien, C.Y., K. Chih-Yuan Ho, O.K. Lee, G.W. Blunn, and Y. Su, 2009, "Restoration of bone mass and strength in glucocorticoid-treated mice by systemic transplantation of CXCR4 and cbfa-1 co-expressing mesenchymal stem cells". J Bone Miner Res. 24(5): pp. 837-48.
27. Karp, J.M. and G.S. Leng Teo, 2009, "Mesenchymal stem cell homing: the devil is in the details". Cell Stem Cell. 4(3): pp. 206-16.
28. Le Blanc, K., C. Gotherstrom, O. Ringden, M. Hassan, R. McMahon, E. Horwitz, G. Anneren, O. Axelsson, J. Nunn, U. Ewald, S. Norden-Lindeberg, M. Jansson, A. Dalton, E. Astrom, and M. Westgren, 2005, "Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta". Transplantation. 79(11): pp. 1607-14.
29. Caplan, A.I., 2007, "Adult mesenchymal stem cells for tissue engineering versus regenerative medicine". J Cell Physiol. 213(2): pp. 341-7.
30. Gnecchi, M., Z. Zhang, A. Ni, and V.J. Dzau, 2008, "Paracrine mechanisms in adult stem cell signaling and therapy". Circ Res. 103(11): pp. 1204-19.
31. Gnecchi, M., H. He, O.D. Liang, L.G. Melo, F. Morello, H. Mu, N. Noiseux, L. Zhang, R.E. Pratt, J.S. Ingwall, and V.J. Dzau, 2005, "Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells". Nat Med. 11(4): pp. 367-8.
32. Chamberlain, J.R., U. Schwarze, P.R. Wang, R.K. Hirata, K.D. Hankenson, J.M. Pace, R.A. Underwood, K.M. Song, M. Sussman, P.H. Byers, and D.W. Russell, 2004, "Gene targeting in stem cells from individuals with osteogenesis imperfecta". Science. 303(5661): pp. 1198-201.

6 MOUSE MODELS OF OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Osteogenesis Imperfecta (OI) has a broad clinical spectrum that has been subdivided into distinct classifications (Figure 1) based originally upon the severity of the bone phenotype, from mild Type I to lethal Type II OI with moderate to severe Types III and IV in between.[1] In most cases, OI is caused by a deficiency of and/or a defect in the major matrix protein of bone, type 1 collagen. About 90% of human cases are caused by a dominant mutation in one of two genes, *COL1A1* and *COL1A2*, encoding for the proα1(I) and proα2(I) chains that comprise type I collagen;[2] in most of the remaining cases, the disease is linked to recessively inherited mutations in genes encoding proteins involved in the post-translational modification of type I collagen.[3-7] The identification of the genetic cause for recessively inherited OI has generated additional OI classifications.[1,8-10] Since type I collagen is also expressed in other connective tissues, e.g., tendon, skin, cornea, and blood vessel walls,[11,12] it is not surprising that additional symptoms often accompany the bone disease, including skin fragility and bruising, dentinogenesis imperfecta, hearing loss, cardiopulmonary problems (chest wall defect and vertebral compression leading to restricted lung disease), and blue sclera.[13]

Our understanding of the pathogenesis of OI has been greatly enhanced by the development of several mouse models of the disease. Indeed mouse bone, in general, has been used extensively to elucidate bone biology[14,15] since it shares similar developmental processes, cellular makeup and matrix composition with human bone. Among many advantages of using mouse models in the study of human genetic disease are the relative ease of making genetic modifications in mice and the relatively short lifespan of this species, which allows for longitudinal studies within a reasonable time frame.

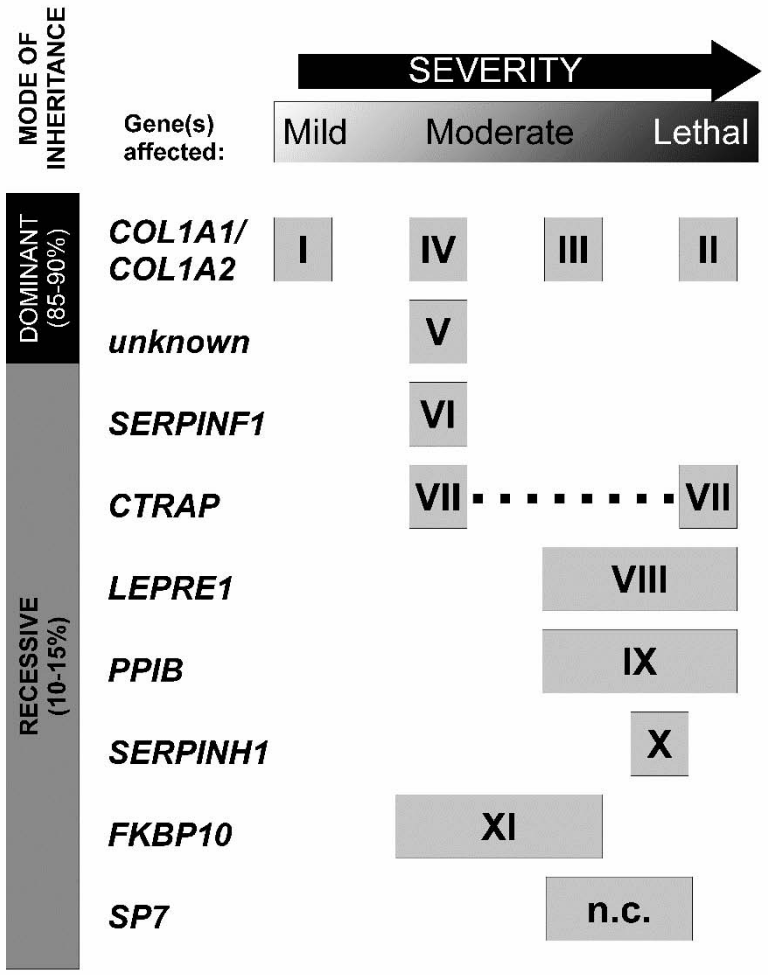

Figure 1. Clinical classifications of OI. Human OI is clinically categorized based on severity of the disease and mode of inheritance (dominant or recessive). At the time of writing, there are eleven recognized classifications of OI.[137] A mutation in *SP7* causes an OI-like phenotype[79] which is not yet classified "n.c.". Since this chapter was completed, Type V OI has been attributed to the IFITM5 gene and Type XII OI has been attributed to SP7. See, Valadares, E.R. et al., What is new in genetics and osteogenesis imperfecta classification. J Pediatria. 90(6): p. 536-541.

Furthermore in mice, genetic background and other factors such as diet and lifestyle that confound human studies can be controlled. Isolation of cells or serum for detailed molecular or biochemical assays can be done under reproducible conditions and with sufficient sample size for robust statistical

analysis. More invasive assessments of the disease, such as studying the effects the disease has on other organs, are difficult to justify in human subjects but are easily done in mice. Finally, the mouse is already a well-established preclinical model for testing potential therapeutics.

Notwithstanding these compelling arguments for working with mouse models, there are limitations. In spite of many similarities, there are multiple noteworthy skeletal differences between mice and men. From a biomechanical standpoint, mice are quadrupedal and therefore have different skeletal stress and strain patterns than bipedal humans. Developmentally, the growth plate fuses in adult human long bone whereas in mice it never entirely disappears. Cellularly, *ex vivo* stromal cell populations from mice contain a higher percentage of hematopoietic cells than do human stromal populations[16,17] and have different growth requirements in culture.[18] Physiologically, mice, unlike humans, can synthesize ascorbic acid, an important cofactor in collagen synthesis. Biochemically, the cysteine-rich repeat region of the N-propeptide of type I collagen in mouse (and other rodents) has less sequence similarity to human than to some non-mammals, opening up the possibility that it may have species-specific functions.[19] Practically, since mouse bones are small, multiple histological sections from the same sample are often required to provide enough data for analysis. Finally, measures for improvement in the quality of life and reduced pain levels, outcomes that are important to people with OI, are harder to assess in mice.

In this chapter, we summarize currently published mouse models of OI, beginning with those with dominant mutations in the *Col1a1* or *Col1a2* genes. These models have taught us a great deal about collagen biochemistry-biosynthesis, the physical, cellular and molecular effects these mutations have on bone, and, to a lesser extent, on other tissues and organs. Although several reviews of mouse models of OI are already available,[20-22] this update also describes many newer models and findings, such as models of recessively inherited OI, and includes a brief section on therapeutic approaches being tested in mouse.

MOUSE MODELS OF OI

Dominant Negative Models with Mutations in the Genes for Type I Collagen

Mouse models of dominant negative OI, like their human counterparts, have spontaneous or engineered mutations in one of the two genes encoding for type I collagen. The collagen mutations associated with them are summarized in Table 1 and the consequences of these mutations on the primary sequence for the corresponding proα1(I) or proα2(I) peptides are illustrated in Figure 2.

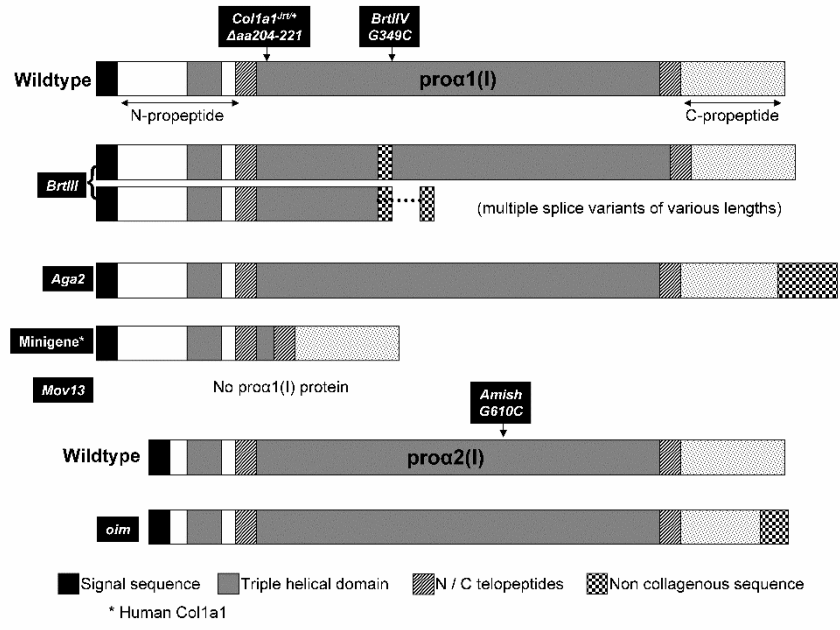

Figure 2. Schematic diagram of mutant α1(I) and α2(I) chains from mouse models OI with type I collagen mutations. The wildtype proα1(I) chain is depicted at the top with the relative positions of the Col1a1$^{Jrt/+}$ and BrlIV mutations as indicated. BrtlII generates several alternatively spliced transcripts — one creating a peptide product with a small non-collagenous insertion in the middle of the helical domain and three with stop codons producing products of various lengths of non-collagenous sequences. In *Aga2*, the last 48 amino acids of *cola1a* are replaced with a 138 amino acid non-collagenous sequence derived from the inclusion of a few intronic sequences and the resulting frameshift. Wildtype proα2(I) chain, depicted in the lower half of the diagram, has a shorter N-propeptide. The approximate position of the *Amish G610C* mutation is indicated on the wildtype diagram. The *oim* mutation is a deletion that causes a frame shift changing the last 49 amino acids of the C-terminal propeptide to a 50 amino acid non-collagenous sequence.

Table 1. Mouse models of osteogenesis imperfecta.

Model Name	Gene Affected	Brief Description of Mutation and Effect	Similar to Human OI Type
Mov13 *Mov13*/+[23, 26]	*Col1a1*	integration of a murine retrovirus within the first intron of the α 1(I) collagen gene results in a null allele blocked at the level of transcription	II and I respectively
Brittle II[27]	*Col1a1*	non-collagenous sequences, derived from the floxed stop cassette with an intronic placement, were inserted into collagen helical sequence by alternative splicing.	II
Brittle IV (BrtlIV or Brtl)[27]	*Col1a1*	G349C mutation that replicates a human OI case	IV
minigene[30]	COL1A1	minigene introduction of human COL1A1 gene with in-frame deletion (loss of 41 exons in triple helical domain)	II
Aga2[28]	*Col1a1*	C-terminal frameshift mutation predicted aa replaces last 48 aa and adds additional 90 aa, ER stress mediated apoptosis	II
Col1a1$^{Jrt/+}$[29]	*Col1a1*	T to C mutation in splice donor leading to skipping of exon 9 and deletion of 18 aa	IV/ED**
oim/oim and *oim*/+[24, 26]	*Col1a2*	proα2(I) not secreted.G deletion at pro α 2(I) nucleotide 3983; this results in an alteration of the sequence of the last 48 amino acids	III and I respectively
G610C OI (*Amish*)[31]	*Col1a2*	glycine in the middle of the helical domain is replaced with a disulfide bonding cysteine residue	IV

P3H1 null[65]	Leprecan 1 (P3H1)*	post-translational modification of type I collagen (prolyl3 hydroxylase 1)	VIII
Crtap-/-[3]	*Crtap**	loss or decrease of type I collagen prolyl 3-hydroxylation	VII
Ppib-/-[66]	Peptidyl prolyl isomerase B *(Ppib)* or cyclophilin B*	loss or decrease of type I collagen prolyl 3-hydroxylation	IX
Opt-/-[72]	Osteopotentia *(Opt)**	rER membrane protein post-translational modification or trafficking	n.c.
Zmpste24-/-[71]	*Zmpste24**	rER Zinc metalloproteinase may affect removal of misfolded protein	n.c.
Hsp47-/-[69]	Heat shock protein 47 *(Hsp47)**	collagen chaperone protein	n.c.
fro/fro[82]	*Smpd3**	mutation in the sphingomyelin phosphodiesterase3 is thought to affect mineralization	n.c.
OASIS[77]	Old astrocyte specifically induced substance *(OASIS)**	null mutation of the ER stress transducer and transcription factor that activates the *Col1a1* gene	n.c.

*Recessively inherited
**Ehlers-Danlos syndrome
"n.c." Not classified

The two earliest described OI mouse models, *Mov13*[23] and *oim,*[24] have a complete loss of one of the two polypeptide chains comprising the type I collagen molecule. In *Mov13*, insertion of a murine retrovirus into the first intron of the *Col1a1* gene effectively abrogates its transcription. Mice homozygous for the *Mov13* insertion die at embryonic day 11 since cells are unable to produce the proα1(I) chain without which type I collagen is not secreted.[25] *Oim* mice, on the other hand, do not express the proα2(I) chain due to a spontaneously occurring frameshift mutation near the 3' end of the

Col1a2 gene, resulting in a portion of the C-terminal propeptide being replaced by a non-collagenous sequence. Mice homozygous for the *oim* mutation survive past birth and exhibit an OI type III phenotype. The heterozygote littermates of both *oim* and *Mov13* mice, each with one intact wildtype allele, have a milder phenotype and display traits consistent with OI type I.[26]

Since then, the collection of mouse models with dominant mutations in the *Col1a1* gene has grown to include the BrtlII, BrtlIV,[27] *Aga*2(Abnormal Gait 2)[28] and Col1a1$^{Jrt/+}$[29] mice. Whereas mutations in the BrtlII and *Aga2* mice affect the C-terminal propeptide of α1(I) and cause embryonic lethality (Type II OI), mutations in the BrtlIV and Col1a1$^{Jrt/+}$ affect residues within the helical domain and produce a moderate phenotype similar to human OI type IV. A line of transgenic mice carrying a minigene expressing a human COL1A1 gene with a large in-frame deletion in the helical domain has also been generated.[30] Depending on the expression level of the minigene, the phenotype varies from moderate to neonatal lethal.

In addition to the *oim* mouse, a second mouse model to have a mutation in the *Col1a2* gene is the recently-described *G610C Amish* mouse.[31] Like the *Col1a1* mutant BrtlIV mouse,[27] the *Amish* mouse was engineered to mimic a human mutation. Both of these mice have a point mutation in the helical domain of their respective proα(I) chains and both mice are models of OI type IV.

Insights into Collagen Biochemistry-Biosynthesis

The proα1(I) chain is required for type I collagen folding and secretion

Cells from *oim* homozygous mice, which cannot make the proα2(I) chain, secrete matrix containing homotrimers of proα1(I) chains. Although the matrix properties may be altered, this result nonetheless shows that the α2(I) chains are dispensible. In contrast, cells from the *Mov13* mice which lack the α1(I) chain produce no type I collagen, with the exception of the rare cases where the viral insertion is spliced out.[32] Consistent with this finding, the *Mov13* mutation is homozygous lethal whereas *oim* is not.

Association of the collagen trimer proceeds from the C-terminal end

It has been reported that the C-terminal propeptide sequences are important for the association of the collagen trimer and that the winding of the helical domain proceeds in a C- to N-terminal direction.[33-35] In keeping with this

finding, the *Aga2* mouse, in which C-propeptide residues are replaced by a non-collagenous sequence, has the most severe phenotype of the dominant mouse OI models. Conversely, BrtlIV, *G610C* and Col1a1$^{Jrt/+}$ mice, whose mutations occur within the helical domain of type I collagen, have less severe phenotypes suggesting a higher degree of tolerance in the folding and secretory pathways of type I collagen for structural abnormalities in this domain. The BrtlIV proα1(I) peptide, for example, is secreted into the matrix despite a disrupted Gly-X-Y motif in the triple helical domain and the added potential for aberrant disulfide bonding through the substituting cysteine residue.[36] Further support is found in the minigene model. Even a human proα1(I) with a large deletion in the helical domain is both incorporated into a human/mouse chimeric collagen molecule and successfully secreted in the minigene model.[30] Processing of mutant chains, however, is not as efficient as that of normal chains. In BrtlIV mice, pulse chase analysis of steady state levels of the three possible species (2 mutant α1(I) chains, 1 mutant:1 wildtype chain, and 2 wildtype chains) has shown that collagen molecules containing mutant chains, particularly those with a single mutant chain, are preferentially retained intracellularly.[37]

Glycosylation is not needed for collagen secretion

Cells from *Mov13* homozygotes, which normally do not express *Col1a1* mRNA, have proven useful in studying the role of the carbohydrate moiety.[38] By transfecting these cells with a functional mouse *Col1a1* gene, they can be induced to secrete type I collagen. Since a mutant *Col1a1* gene encoding for an α1(I) chain missing the oligosaccharide attachment point could also reconstitute matrix secretion, it was concluded that the highly conserved C-propeptide high-mannose, N-linked carbohydrate moiety of the α1(I) chain is not required for collagen type I assembly, secretion and efficient incorporation into the matrix.

Physical and Mechanical Properties of OI Bone

Mouse models have been particularly helpful in providing insights into the physical and mechanical properties of OI bone. Though new technologies are being developed to study the material properties of human OI bone such as nanoindentation,[39] parameters such as yield and post-yield properties have only been published for mouse models. One consistent feature of the *Mov13*, *oim* and BrtlIV mice is the decrease in the ultimate stress value, reflecting the brittleness of the diseased bone.[40-43] Other parameters such as Young's Modulus have not been found or reported to be affected as consistently.

To determine what causes bone brittleness in OI, researchers looked for clues in bone composition and found that in *oim* bone, hydroxyapatite crystals are smaller and less organized[44] and the mineral to matrix ratio is higher.[45] Surprisingly, the material properties of the matrix itself in *oim*/*oim* mice was not found to differ from that of wildtype matrix in a study of demineralized bone.[43] This suggests that the defect in bone property is due to the mineral phase although a previous study of *oim* mice suggested the opposite to be true.[46] In the latter study, tendon collagen, not bone collagen, was tested for strength. Since the *oim* matrix contains unusually high levels of α1(I) homotrimers, it is doubtful whether the results from *oim* bone can be extrapolated to bone from other models.

Cellular Changes in OI Bone

The fact that bone turnover is altered in humans and in mouse models of OI,[28, 47-50] has led to the conclusion that there is a cellular component to OI pathophysiology. Osteoblasts are obvious candidates, as they are known to markedly upregulate the expression of the genes for type I collagen during differentiation[51, 52] and numerous studies indicate that a normal collagenous matrix is required for osteoblast differentiation-maturation.[53] Changes in the osteoclast populations have also been found, although these are more likely to be secondary consequences of changes in the osteoblast population. Studies in several mouse models of OI support a role for both osteoblasts and osteoclasts in the OI phenotype, but they differ in their conclusions about exactly how these populations are affected.

Osteoblast anomalies

Assessment of osteogenic differentiation in stromal cell cultures from *oim*/*oim* mice has suggested that *oim*/*oim* osteoblastic cells are less mature than their wildtype counterparts, as judged by their lower alkaline phosphatase activity.[54] A more recent analysis, using the differentiation stage-specific promoters Col3.6 and Col2.3 to drive respectively the preosteoblast- or the mature osteoblast-to-osteocyte-specific expression of GFP reporter genes, confirmed that the population of mature osteoblasts was decreased in *oim* bone although the preosteoblast population was unaffected.[55] Other models have shown similar results suggesting that there is a problem with osteoblast differentiation, maturation and/or activity in OI. Col1a1$^{Jrt/+}$ stromal cells formed similar numbers of colony forming units (CFU-F) as did wildtype mice, but fewer of these colonies were able to

mineralize.[29] Differentiation of MC3T3-E1 cells transfected with the truncated human proα1(I) plasmid used in the minigene model[56] was also affected, but whereas the expression of alkaline phosphatase was decreased as in *oim* cells, an increase in osteocalcin protein was also found.

When osteoblast activity of *oim*/*oim* and *oim*/+ mice was assessed using a 3.6kb *Col1a1* promoter-driven reporter transgene (chloramphenicol acetyltransferase reporter or CAT), it was not found to be affected in young *oim*/*oim* and *oim*/+ mice but was increased in adult mice.[49] In agreement with these higher levels of *oim* osteoblast marker expression, the osteoblast surface to bone surface ratio (Ob.S/BS) in both *oim*/*oim* and *oim*/+ mice bone was increased. Since the mineral apposition rate (MAR) was not affected, it is likely that the increase in osteoblast marker expression is due to increased osteoblast number and not activity. In homozygous *oim* mice, both bone formation rate (BFR) and percentage of double-labeled surfaces was increased. This result indicates that the formation period is disproportionately high compared to the combined erosion and quiescent periods and may be a sign of increased initiation of and/or sustained remodeling.

Work on the BrtlIV and Col1a1$^{Jrt/+}$ mouse models show, however, differing age-related effects on osteoblast activity than in *oim* mice. In Col1a1$^{Jrt/+}$, *Col1a1* levels are elevated in young, but not in mature mice.[29] In the BrtlIV mouse, osteoblast activity appeared unaffected in younger mice as in the *oim* mice, but by 6 months of age, the MAR and BFR/BS indices were reduced in comparison to wildtype controls.

While collagen mutations clearly affect the osteoblast population, there are no consistent results with respect to how — through changes in osteoblast number, activity or matrix protein expression — and when — during early or late osteoblast differentiation — these effects occur. In fact there is evidence to suggest that the same mutation can even affect the osteoblast population differently depending on the age of the animal in question. These disparate data not only emphasize the complexity of the disease phenotype but underscore how more work needs to be done to characterize these different mutants.

Osteoclast anomalies

The osteoclast has also been reported to be affected in some models of OI. Elevated levels of urinary deoxypyridinoline (DPD) crosslinks suggested that

there is increased bone resorption in *oim*/*oim* mice.[49] In these same mice, osteoclast number expressed per bone area (OcN/B.Ar) was also increased. In BrtlIV mice, an increased number of osteoclasts, and higher Oc.S/BS and activity were found, as evidenced by larger and more intensely stained tartrate-resistant acid phosphatase-positive (TRACP+) cells.[57] In the case of *oim/oim*, bone marrow-derived osteoclast cultures showed that the increased resorption was associated with increased osteoclast activity.[58] Since the reported increase in TRACP+ cell numbers in mutant cultures compared to controls exceeded the corresponding increase in resorption area, an alternative interpretation would be that the increased resorption is due to an increase in osteoclast number.

Given that osteoclasts do not themselves express type I collagen, how do mutations in the *Col1a1* or *Col1a2* genes bring about increases in their number and/or activity? An *in vitro* study showed that *oim* osteoblasts induced more osteoclastogenesis from bone marrow mononuclear cells, a source of osteoclast progenitors with which they were co-cultured, than did wildtype osteoblasts.[55] Expression levels of TNF-α, an inflammatory cytokine which works synergistically with RANKL to promote osteoclastogenesis in inflammatory osteolytic disease,[59,60] were elevated in *oim* osteoblast. Furthermore anti- TNF-α antibody blocked osteoclastogenesis in the co-cultures suggesting that the *oim* mutation operates through this pathway.

Misfolded proteins, enlarged endoplasmic reticulum (ER) and a stress response

Williams and Prockop coined the term 'protein suicide' to describe how the presence of mutant proα1(I) chains impedes correct procollagen trimer folding leading to rapid degradation of the trimer.[61] As a result, only a quarter of the translated collagen in heterozygous mutants is expected to be secreted, leaving the cell to dispose of the remainder, something that must have consequences for the osteoblast. In several mouse models, this has been shown to lead engorgement of the ER as in, for example, BrtlIV[37] and Col1a1$^{Jrt/+}$[29] mice, and/or an induction of the ER-stress response, as in BrtlIV[62] and *Aga2*[28] mice. In *Aga2*, the ER-stress response leads to increased apoptosis and expression of the chaperone protein, Hsp47, in the osteoblast.[28] In studies of the BrtlIV mouse proteome, a correlation was found between the expression profile of ER stress related proteins and phenotype severity; increased expression of the apoptosis-inducing Gadd153/CHOP was associated with the lethal phenotype whereas increased chaperone α crystalline B chain levels was associated with the non-lethal phenotype.[62] The introduction of ER-resident protein genes to the growing

group of genes mutated in recessively inherited OI (discussed in the next section) provides further support for the role of the ER responses in OI cellular pathology.

Recessive Mouse Models of OI

Proteins Involved in Collagen Biosynthesis

Relatively new classes of human OI have been assigned based on the identification of mutations in proteins necessary for the post-translational modification and folding of type I collagen.[3-6] These proteins are described briefly here and the OI disease classifications corresponding to their loss is given in Table 1. In particular, a heterotrimeric complex found in the rough ER (rER) and consisting of the cartilage-associated protein (CRTAP), prolyl 3-hydroxylase 1 (P3H1, also known as leucine proline-enriched proteoglycan or LEPRE1) and cyclophilin B (CYPB, also known as peptidyl prolyl isomerase B, PPIB) proteins, is responsible for the 3-hydroxylation of specific prolyl residues in procollagen I (one site per α1 chain).[63] This modification stabilizes the triple helical domain, increases the melting temperature of collagen and is necessary for fibril self-assembly in ionic buffers.[64] Together these observations have led to suggestions that the function of hydroxylation is to adapt the molecule to physiological temperatures and ionic strengths. Mouse knockouts of *Crtap* and P3H1 and *Ppib* (encoding CYPB) have been generated that confirm the role these genes play in autosomal recessive types of OI.[3,65,66] Studies on these models further underline the importance of post-translational modifications, in particular the hydroxylation of a single proline residue, and procollagen trafficking in the formation of morphologically normal fibrils.

A protein complex with a chaperone function consisting of Hsp47 (heat shock protein 47 also known as SERPINH1) and FKBP65 (65-kDa FK506-binding protein) has also been implicated in human OI.[67,68] Though Hsp47 is not specific for type I collagen but affects other matrix proteins as well, *Hsp47-/-* mice nevertheless offer useful insight into the matrix formation process.[69,70] Loss of *Hsp47* results in lethality at about embryonic day 11.5 (as in the case of the *Mov13*, a type I collagen null), and fibroblasts isolated from *Hsp47-/-* embryos have a reduction in the propeptide-processed form of α1(I) collagen; secreted type I collagen from *Hsp-/-* fibroblasts is sensitive to proteases, which suggests that the triple helical domain is not properly folded and that Hsp47 is required in the process.[69] By extension, any mutant

procollagen that is unable to bind to Hsp47 might be reasonably expected to suffer a similar fate.

The potential roles of two additional ER proteins, Zmpste24 and the more recently discovered osteopotentia (Opt), have also been described.[71,72] Both *Zmpste24* and *Opt* null mice have features of brittle bone disease with high rates of bone fractures as well as defects in osteoblast differentiation. Zmpste24 is a metalloproteinase that has been shown to cleave prelamin A to form lamin A. More recently, the increased unprocessed prelamin A in *Zmpste24-/-* mice was found to increase basal autophagy levels which may have an indirect effect on procollagen processing.[73] Stromal cells from *Zmpste24-/-* mice cultured in osteogenic medium exhibited reduced levels of RUNX2 protein expression, an osteoblastic fate-determining transcription factor, and bone from these mice had noticeably fewer osteoblasts suggesting that the bone defect is due to an impaired ability of osteoprogenitors to form mature matrix-secreting osteoblasts.[74] Osteopotentia is a ubiquitous rER protein that contains a SUN (Sad/unc84 homology) domain (SUN1 and SUN2 are involved in nuclear positioning and tethering centromeres). In *Opt* null osteoblasts, the ER is small and fragmented. It is therefore hypothesized that Opt is needed for ER expansion to accommodate the large amount of collagen being produced by the osteoblasts and that defects in this process cause the poor production as well as over-modification of collagen that leads to the OI phenotype.[72]

SERPINF1, which encodes for pigment epithelium-derived factor (PEDF), has very recently been identified in humans as the gene mutated in OI type VI.[6] Unlike the other proteins involved in recessive OI, PEDF is an extracellular protein and is hypothesized to bring about the OI phenotype by interfering with collagen function as it has been shown to bind to collagen near its α1β1 integrin binding site.[75] Interestingly, an OI phenotype has not been reported for the *Serpinf1*$^{-/-}$ mouse.[76]

OI-like Models

The rather broad spectrum of OI phenotypes, built upon the distinguishing features of fragile and easily fractured bone, has resulted in the inclusion of mutations in genes affecting the transcription of type I collagen, and even a mutation that results in an osteomalacic phenotype but has no obvious link to collagen, as OI-causing mutations. The latter emphasizes the need for clarity on the phenotype-genotype OI continuum, but we include the new models here based on their OI-like phenotype.

In the *OASIS* (old astrocyte specifically induced substance) knockout mouse, loss of this basic leucine zipper transcription factor causes loss of collagen on two levels and leads to osteopenia resembling type I OI.[77,78] Bones from *OASIS* null mice have decreased *Col1a1* and *Col1a2* mRNA expression and some matrix proteins including procollagen1a1 accumulate in the ER of mutant osteoblasts, an observation attributed to a reduction in transcription levels of genes encoding for proteins involved in the secretory pathway. A human with a mutation in another transcription factor required for osteogenesis, Osterix (SP7), has been reported to exhibit clinical features of OI.[79] Osterix has been shown to bind sequences in the *Col1a1* promoter[80] and in the mutant protein the third zinc finger DNA-binding motif is predicted to be absent. Incidently, Osterix null mice have greatly reduced levels of *Col1a1* mRNA and fail to make membranous bone.[80]

Originally classified as a form of congenital hypophosphatasia,[81] the *fro/fro* mouse was later proposed to be a model of recessive OI.[82] Mice homozygous for this mutation are osteopenic and phenocopy Type II OI. The mutation was later mapped to the Sphingomyelin phosphodiesterase 3 gene.[83] The mechanism by which this mutated gene brings about defective mineralized tissue has not been established, but some possibilities have been put forth. In one, the sphingomyelinase is thought to be involved in the mineralization initiated by matrix vesicles since the loss of sphingomyelin, purportedly via the conversion of sphingomyelin to ceramide by the sphingomyelinase,[84] has been associated with this process.[85] Alternatively, ceramide is an inhibitor of osteoclast activity,[86] which suggests a role for resorption in the osteopenic phenotype exhibited by *fro/fro* mice.

FACTORS AFFECTING THE SEVERITY OF OI

There have been clinical reports of some OI patients having a marked decrease in fracture rate around puberty followed by a resumption of fracturing upon menopause.[87] This has lead some to postulate the existence of a "postpubertal adaptative mechanism".[88] Although a reduction in high intensity physical activity and greater musculoskeletal control plays a part in this phenomenon, sex steroids may play an additional role since an improvement in fracture rate disappears in postmenopausal OI females.[9]

Studies on the *Mov13* mice provided the first demonstration of age-related skeletal adaptation in a mouse OI model.[89] Mice heterozygous for the *Mov13* mutation exhibit a milder phenotype reminiscent of type I OI. When the

mechanical properties of *Mov13*/+ mice were tested at 8 and 15 weeks of age, an improvement in the failure load of *Mov13*/+ mice was noted at the post-pubertal age (15 wks); indeed, the values obtained surpassed those of age-matched controls, which was attributed to an improved cross-sectional geometry of the bones coinciding with an increase in the density of osteocyte lacunae in the cortical bone.

A thickening of the periosteum associated with increased collagen was taken as evidence of postpubertal adaptation in *oim* mice.[90] This thickening disappeared at 24 months, paralleling the age-related decline in bone quality observed in human OI.[90] The cross-sectional geometry of the *oim* bone was also found to improve, in terms of promoting mechanical strength, upon aging.[91] Evidence of changes in the cortical bone that improved its mechanical properties was also found in BrtlIV mice.[88] At young ages, BrtlIV mice had thinner cortices however at 6 months of age, this difference had disappeared. Other cortical parameters such as cross-sectional area and bending moment eventually attained wildtype levels at 12 months.

In addition to age-related changes, it is likely that genetic modifiers exist since unrelated patients with identical mutations have been reported as having differing disease severities.[92,93] Background mouse strain has been shown to affect the severity of the OI phenotype resulting from the *oim* mutation. For example, bone from mice with the *oim* mutation in the C57BL/6J (B6) background was generally of equal or poorer mechanical quality when compared with bone from *oim* mutants in an outbred background.[94] Though bones from B6 are smaller, normalized material properties and not just structural properties were inferior at several ages. Strain-related differences were also noted when Col1a1$^{Jrt/+}$ mice were backcrossed onto the FVB background, where the mutation had a stronger effect than seen on the mixed C3H/HeJ/B6 background of the founder.[29]

MOUSE AS A PRECLINICAL MODEL FOR OI THERAPIES

Drug Therapies

Bisphosphonates such as aledronate, pamidronate and risedronate, widely used in the treatment of osteoporosis, are the only available drugs for treating OI at present. It is commonly believed that these antiresorptives work by promoting osteoclast apoptosis although some data suggest this is not the only mode of action nor are these cells their only target.[95] In spite of positive outcomes in bisphosphonate-treated OI children,[96-99] concerns remain that in growing children, the use of bisphosphonates can lead to undesirable long-term side effects such as accumulation of microfractures and defective fracture healing. Of particular concern is the long half-life of the bone-bound drug.[100] Several of these drugs have now been associated with an increased risk for osteonecrosis of the jaw.[101,102] Concerns over potential acute cardiac effects related to temporary hypocalcemia caused by pamidronate treatment have also been raised.[103] The use of mouse models have been useful in providing a preview of how these drugs affect OI bone properties and in particular bone architecture.

The effects of alendronate treatment have been studied extensively in the *oim*/*oim* mouse.[41,42,104,105] It was repeatedly found that *oim* mice treated with alendronate had a reduced incidence of fracture, which has been attributed to the observed increase in metaphyseal bone volume. Intrinsic or material properties of the *oim* bone such as ultimate stress, Young's Modulus, toughness and brittleness, remained unchanged by treatment.[41,42] Structural properties of the *oim* mice, including ultimate load and work to failure, were also unaffected by alendronate treatment, although stiffness was increased in one report. An undesirable side effect was found in these mice, however, as administration of alendronate was found to decrease bone length. Further analysis showed the growth plate in treated *oim* mice was thicker than those in untreated mice, particularly in the hypertrophic zone, and there was an observed persistence of mineralized cartilage.

Alendronate did not produce the same negative effects on growth and bone length in BrtlIV mice, but the material properties of the treated bone were poorer than those of non-treated bones with decreased material strength and modulus of elasticity.[106] Whether these differences are mutant-specific or merely reflect differences in drug regime and dosing is currently unclear.

The authors did, however, find an increase in femoral BMD and also noted the presence of mineralized cartilage in treated BrtlIV bone as was found in the *oim* mouse. They also reported a reduction in the bone formation rate (BFR/BS) in treated versus untreated mutant bone suggesting that osteoblasts in treated BrtlIV bone are negatively impacted by the drug.

Pamidronate has also been tested in *oim* mice and it was found to reduce fractures in homozygotes,[107] though no benefit was found in the more mildly affected heterozygotes. In female mice, pamidronate treatment caused a decrease in ulna and humerus length in either genotype, but the same was not true for male mice. The growth plate was thickened in treated mice, even in the males where the bone length was unaffected, and in addition to the enlarged hypertrophic zone found in alendronate-treated *oim* mice, the proliferative zone was also increased. Pamidronate treatment of both homozygotes and heterozygotes resulted in a reduction in the number of osteoclasts when normalized to bone surface area.[107] In another study, the same group found that pamidronate treatment of *oim* bone improved its mechanical properites.[108] The cross-sectional moment of inertia was higher and, in three-point mechanical tests, the treated *oim* bone was stiffer than vehicle-treated bone, however treatment did not change other material and structural properties such as ultimate load, energy to failure or Young's Modulus.

Considering the difference in pathophysiology of recessive models of this disease, it is useful to know whether bisphosphonate treatment is effective for these classes of OI. Administration of risedronate has been tested and shown to increase trabecular bone volume in *OASIS* mice by inhibiting resorption.[78] A qualitative improvement in the knockout-associated abnormal rER expansion was also observed.

From these mouse studies, much has been learned about the positive and negative effects of these drugs on bone, some of which are even gender-specific. A major benefit to treatment is a reduction in fractures, though work on the *oim* mouse suggests that this is not true for the milder heterozygous phenotype. No improvement in material properties have been shown and a serious drawback is the reported reduction in long bone growth. Based on these findings, one might hesitate to treat young children with mild type I OI, particularly young females, with bisphosphonates.

Antibody Therapies

A more recent development is the use of antibodies to target proteins involved in cellular processes. One strategy is to block the interaction between soluble RANKL and its receptor RANK on osteoclast progenitors, which blocks osteoclastogenesis, in a sense mimicking the action of the naturally occurring soluble decoy receptor, osteoprotegrin. Denosumab, a human antibody against RANKL, has been tested in mice expressing humanized RANKL and demonstrated to inhibit bone resorption and increase bone mineral density.[109] Since Denosumab does not bind murine RANKL, RANK-Fc, an inhibitor of murine RANKL, was similarly tested on *oim*/*oim* mouse to investigate the effects of this treatment on bone quality.[110] Although parameters such as stiffness, cortical thickness and metaphyseal density were improved in six week-old *oim*/*oim* mice treated with RANK-Fc for a period of eight weeks, this did not translate into a reduction in fracture frequency. Retention of mineralized cartilage was the only reported side effect of this therapy and the authors reported that treated mice did not show any decrease in bone length. However, since "adolescent" animal subjects were used, the mouse skeleton was nearly mature and marked effects of RANK-Fc on longitudinal bone growth would not have been expected.

Hormone Therapies

Whereas most therapies aim to improve the strength of bone in OI patients, another important clinical feature that also needs to be addressed is increasing patient size and height. Moderate to severe cases of OI are always associated with short stature[111] as in the case of their mouse counterparts. Studies done in humans to determine whether growth hormone levels are affected in OI and whether treatment with growth hormone can improve growth rates has met with varying results.[111-114] When human growth hormone was administered to heterozygous *oim* mice during the growth phase, treated mice had a significant increase in vertebral and femoral longitudinal growth compared with untreated mutant mice.[115] This treatment also resulted in some structural improvements in the mechanical properties of the bone. Since *oim*/+ mice do not differ appreciably in size from their control littermates, it would be more useful to see what effect growth hormone has on a model in which the mutants do differ. Such studies would further our understanding of the factors required for growth hormone treatment to be effective.

Gene Therapies

Gene therapy is a field of intense interest and its use in the treatment of OI has been reviewed elsewhere.[116] As noted above, it has been found that null mutations, those that result in the reduction of wildtype type I collagen secretion, cause a milder form of OI than those in which the mutant protein is expressed and secreted.[117,118] One approach to treating clinically severe OI is to selectively destroy the mutant transcript thereby converting the severe phenotype to the milder type I phenotype. Antisense gene therapy targeting the mutant sequence in the severe minigene model of OI has been used successfully to reduce the rate of neonatal death.[119] While exciting, this strategy has limited applications. Single point mutations commonly found in the human OI population cannot be treated this way since the high degree of sequence similarity between the mutant and normal gene would lead to destruction of both mutant and normal transcript.

To address this challenge, hammerhead ribozymes have been developed as an alternate gene therapy strategy. Hammerhead ribozymes are specially engineered to bind the mutant transcript through a unique complementary sequence and cleave it leading to its rapid degradation. What makes this suitable for treatment of OI caused by point mutations is that these ribozymes are capable of distringuishing between two transcripts that differ by as little as one single nucleotide.[120] Their disadvantage is that not all mutant transcripts have conveniently located ribozyme cleavage sites.[22] Results from studies using either dermal fibroblasts cultured from patients or a murine calvarial osteoblast cell line (MC3T3-E1) stably expressing the minigene construct are promising,[121-123] but to date no study has been published in which the approach has been performed directly on mice.

A third approach is to remove all — both mutant and normal — transcripts using either hammerhead ribozymes, asRNA, RNAi, or dsRNA, by targeting a common sequence in them while simultaneously adding a collagen promoter-driven normal collagen gene whose transcripts are capable of escaping recognition by the removal system chosen because of alternately selected coding sequences.[97]

Stem Cell Transplantation

Systemically infused bone marrow stromal cells (BMSCs) have been shown to travel via the circulatory system and to home to various tissues, such as bone and lung, where they take up residence and contribute to tissue

formation.[124,125] Transplantation of normal BMSCs into the minigene and *oim* mouse models shows promise as a therapeutic source of normal osteoprogenitors.[125-128] However, although engraftment clearly occurs, the number of donor cells that successfully engraft is relatively small. Currently, attempts are being made to use a more direct approach by infusing BMSCs from wildtype mice into the femoral marrow cavity of *oim* mice. Cells introduced this way have been found to both contribute to new bone formation and bring about a significant improvement in bone mechanical properties.[129] In related work, intrauterine transplant of BMSCs has provided some hope for treating severe OI early in development.[130]

FUTURE DIRECTIONS

In addition to being useful preclinical models for testing therapeutics, there is still much about bone biology to be learned from mouse OI models. In particular, protein biochemistry will help us better understand the role of the C- and N-propeptides and how they may affect fibrillogenesis and the interaction of bone matrix with other proteins and mineral. The roles of type I collagen in kidney,[131] ear,[132] teeth,[133] the cardiovascular system,[134] and even secondary roles of collagen via bone quality on articular cartilage and the development of osteoarthritis[135,136] deserve additional study in relation to the co-morbities of OI. Finally, the lack of consistent cellular and molecular changes in the multiple models currently being studied points to the complexity of the disease and to our lack of understanding of how changes in the collagenous and non-collagenous matrix alter differentiation, osteoblast activity, mineralization, cell signaling and gene expression at different bone sites. Perhaps no single treatment will cure all OI types, but rather several options will be found whose implementation will depend on our understanding of the full etiology of the disease. If so, the more OI mouse models we have at our disposal, the better.

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ABBREVIATIONS

BFR	Bone formation rate
BFR/BS	Bone formation rate/Bone surface
BMD	Bone mineral density
BMSCs	Bone marrow stromal cells
COL1A1, Col1a1	Collagen, type I, alpha 1
COL1A2, Col1a2	Collagen, type I, alpha 2
DPD	Deoxypyridinoline
ER, rER	Endoplasmic reticulum, rough endoplasmic reticulum
MAR	Mineral apposition rate
Ob.S./BS	Osteoblast surface to bone surface ratio
Oc.S/BS	Osteoclast surface to bone surface ratio
OcN/B.Ar	Osteoclast number expressed per bone area
OI	Osteogenesis imperfecta
proα1(I)	Pro alpha 1(I) collagen
proα2(I)	Pro alpha 2(I) collagen
RANK/RANKL	Receptor activator of nuclear factor kappa-B/Receptor activator of nuclear factor kappa-B ligand
RNA, asRNA, RNAi, or dsRNA	Ribonucleic acid, antisense, interference, double stranded
TNF-α	Tumor necrosis factor-alpha
TRACP+	Tartrate-resistant acid phosphatase-positive

REFERENCES

1. Sillence, D.O., A. Senn, and D.M. Danks, Genetic heterogeneity in osteogenesis imperfecta*. J. Med. Genet.*, 1979. 16(2): p. 101-16.
2. Kuivaniemi, H., G. Tromp, and D.J. Prockop, Mutations in fibrillar collagens (types I, II, III, and XI), fibril-associated collagen (type IX), and network-forming collagen (type X) cause a spectrum of diseases of bone, cartilage, and blood vessels*. Human Mutation*, 1997. 9(4): p. 300-15.

3. Morello, R., et al., CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta. *Cell*, 2006. 127(2): p. 291-304.
4. Cabral, W.A., et al., Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. *Nat. Genet.*, 2007. 39(3): p. 359-65.
5. Barnes, A.M., et al., Lack of Cyclophilin B in osteogenesis imperfecta with normal collagen folding. *N. Engl. J. Med.*, 2010. 362(6): p. 521-8.
6. Homan, E.P., et al., Mutations in SERPINF1 cause osteogenesis imperfecta type VI. *J. Bone Miner. Res.*, 2011. 26(12): p. 2798-803.
7. Becker, J., et al., Exome sequencing identifies truncating mutations in human SERPINF1 in autosomal-recessive osteogenesis imperfecta. *Am. J. Human Genet.*, 2011. 88(3): p. 362-71.
8. Rauch, F. and F.H. Glorieux, Osteogenesis imperfecta. *Lancet*, 2004. 363(9418): p. 1377-85.
9. Marini, J.C., *www.ENDOTEXT.org*, in *Osteogenesis Imperfecta*. 2010, MDTEXT.COM, INC.: S. Dartmouth, MA. p. 1-28.
10. Bishop, N., Characterising and treating osteogenesis imperfecta. *Early Hum. Dev.*, 2010. 86(11): p. 743-6.
11. Chu, M.L., et al., Cloning and characterization of five overlapping cDNAs specific for the human pro alpha 1(I) collagen chain. *Nucleic Acids Res.*, 1982. 10(19): p. 5925-34.
12. Myers, J.C., et al., Cloning a cDNA for the pro-alpha 2 chain of human type I collagen. *Proc. Natl. Acad. Sci. U. S. A.*, 1981. 78(6): p. 3516-20.
13. Vetter, U., et al., Osteogenesis imperfecta: a clinical study of the first ten years of life. *Calcif. Tissue Int.*, 1992. 50(1): p. 36-41.
14. Wagner, E.F. and G. Karsenty, Genetic control of skeletal development. *Current Opinion Genetics Develop.*, 2001. 11(5): p. 527-32.
15. Günther, T. and T. Schinke, Mouse genetics have uncovered new paradigms in bone biology. *Trends in Endocrinol. Metab.*, 2000. 11(5): p. 189-93.
16. Keating, A., et al., Effect of different promoters on expression of genes introduced into hematopoietic and marrow stromal cells by electroporation. *Experiment. Hematol.*, 1990. 18(2): p. 99-102.
17. Owen, M. and A.J. Friedenstein, Stromal stem-cells - Marrow-derived osteogenic precursors. *Ciba Foundation Symposia*, 1988. 136: p. 42-60.
18. Kuznetsov, S. and P. Gehron Robey, Species differences in growth requirements for bone marrow stromal fibroblast colony formation In vitro. *Calcif. Tissue Int.*, 1996. 59(4): p. 265-70.
19. Bornstein, P., The NH2-terminal propeptides of fibrillar collagens: highly conserved domains with poorly understood functions. *Matrix Biology*, 2002. 21(3): p. 217-26.
20. Shapiro, J.R., D.J. McBride, Jr., and N.S. Fedarko, OIM and related animal models of osteogenesis imperfecta. *Connect. Tiss. Res.*, 1995. 31(4): p. 265-8.
21. Kamoun-Goldrat, A.S. and M.F. Le Merrer, Animal models of osteogenesis imperfecta and related syndromes. *J. Bone Miner. Metab.*, 2007. 25(4): p. 211-8.
22. Forlino, A. and J.C. Marini, Osteogenesis imperfecta: Prospects for molecular therapeutics. *Mol. Genet. Metab.*, 2000. 71(1-2): p. 225-32.
23. Schnieke, A., K. Harbers, and R. Jaenisch, Embryonic lethal mutation in mice induced by retrovirus insertion into the alpha 1(I) collagen gene. *Nature*, 1983. 304(5924): p. 315-20.
24. Chipman, S.D., et al., Defective pro alpha 2(I) collagen synthesis in a recessive mutation in mice: a model of human osteogenesis imperfecta. *Proc. Natl. Acad. Sci. U. S. A.*, 1993. 90(5): p. 1701-5.

25. Harbers, K., et al., Insertion of retrovirus into the first intron of alpha 1(I) collagen gene to embryonic lethal mutation in mice. *Proc. Natl. Acad. Sci. U. S. A.*, 1984. 81(5): p. 1504-8.
26. Saban, J., et al., Heterozygous oim mice exhibit a mild form of osteogenesis imperfecta. *Bone*, 1996. 19(6): p. 575-9.
27. Forlino, A., et al., Use of the Cre/lox recombination system to develop a non-lethal knock-in murine model for osteogenesis imperfecta with an alpha1(I) G349C substitution. Variability in phenotype in BrtlIV mice. *J. Biol. Chem.*, 1999. 274(53): p. 37923-31.
28. Lisse, T.S., et al., ER Stress-mediated apoptosis in a new mouse model of osteogenesis imperfecta. *PLoS Genetics*, 2008. 4(2): p. e7.
29. Chen, F., et al., First mouse model for combined Osteogenesis Imperfecta and Ehlers-Danlos syndrome. *J. Bone Miner. Res.* 2014. 29(6): p1412-23.
30. Khillan, J.S., et al., Transgenic mice that express a mini-gene version of the human gene for type I procollagen (COL1A1) develop a phenotype resembling a lethal form of osteogenesis imperfecta. *J. Biol. Chem.*, 1991. 266(34): p. 23373-79.
31. Daley, E., et al., Variable bone fragility associated with an Amish *COL1A2* variant and a knock-in mouse model. *J. Bone Miner. Res.*, 2010. 25(2): p. 247-261.
32. Kratochwil, K., et al., Retrovirus-induced insertional mutation in Mov13 mice affects collagen I expression in a tissue-specific manner. *Cell*, 1989. 57(5): p. 807-16.
33. Fessler, L.I. and J.H. Fessler, Protein assembly of procollagen and effects of hydroxylation. *J. Biol. Chem.*, 1974. 249(23): p. 7637-46.
34. Doege, K.J. and J.H. Fessler, Folding of carboxyl domain and assembly of procollagen I. *J. Biol. Chem.*, 1986. 261(19): p. 8924-35.
35. Dion, A.S. and J.C. Myers, COOH-terminal propeptides of the major human procollagens - Structural, functional and genetic comparisons. *J. Molec. Biol.*, 1987. 193(1): p. 127-43.
36. Kuznetsova, N.V., et al., Structure, stability and interactions of type I collagen with GLY349-CYS substitution in alpha 1(I) chain in a murine Osteogenesis Imperfecta model. *Matrix Biology*, 2004. 23(2): p. 101-12.
37. Forlino, A., et al., Selective retention and degradation of molecules with a single mutant alpha1(I) chain in the Brtl IV mouse model of OI. *Matrix Biology*, 2007. 26(8): p. 604-14.
38. Lamande, S.R. and J.F. Bateman, The type-I collagen pro-alpha-1(I) COOH-terminal propeptide N-linked oligosaccharide - Functional-analysis by site-directed mutagenesis. *J. Biol. Chem.*, 1995. 270(30): p. 17858-65.
39. Weber, M., et al., Pamidronate does not adversely affect bone intrinsic material properties in children with osteogenesis imperfecta. *Bone*, 2006. 39(3): p. 616-22.
40. Jepsen, K.J., et al., Type I collagen mutation alters the strength and fatigue behavior of Mov13 cortical tissue. *J. Biomech.*, 1997. 30(11-12): p. 1141-47.
41. McCarthy, E.A., et al., Alendronate treatment for infants with osteogenesis imperfecta: demonstration of efficacy in a mouse model. *Pediatr. Res.*, 2002. 52(5): p. 660-70.
42. Misof, B.M., et al., Differential effects of alendronate treatment on bone from growing osteogenesis imperfecta and wild-type mouse. *Bone*, 2005. 36(1): p. 150-8.
43. Miller, E., et al., Abnormal mineral-matrix interactions are a significant contributor to fragility in oim/oim bone. *Calcif. Tissue Int.*, 2007. 81(3): p. 206-14.

44. Fratzl, P., S. Schreiber, and K. Klaushofer, Bone mineralization as studied by small-angle x-ray scattering. *Connect. Tiss. Res.,* 1996. 34(4): p. 247-54.
45. Camacho, N.P., W.J. Landis, and A.L. Boskey, Mineral changes in a mouse model of osteogenesis imperfecta detected by Fourier transform infrared microscopy. *Connect. Tiss. Res., 1996. 35(1-4): p. 259-65.*
46. Misof, K., et al., Collagen from the osteogenesis imperfecta mouse model (oim) shows reduced resistance against tensile stress. *J. Clin. Invest.*, 1997. 100(1): p. 40-5.
47. Braga, V., et al., Bone turnover markers in patients with osteogenesis imperfecta. *Bone*, 2004. 34(6): p. 1013-6.
48. Rauch, F., et al., Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. *Bone*, 2000. 26(6): p. 581-9.
49. Kalajzic, I., et al., Osteoblastic response to the defective matrix in the osteogenesis imperfecta murine (oim) mouse. *Endocrinol.,* 2002. 143(5): p. 1594-601.
50. Cepollaro, C., et al., Osteogenesis imperfecta: Bone turnover, bone density, and ultrasound parameters. *Calcif. Tissue Int.*, 1999. 65(2): p. 129-32.
51. Rowe, D.W. and B.E. Kream, Regulation of collagen synthesis in fetal rat calvaria by 1,25-dihydroxyvitamin D3. *J. Biol. Chem.*, 1982. 257(14): p. 8009-15.
52. Liu, F., L. Malaval, and J.E. Aubin, Global amplification polymerase chain reaction reveals novel transitional stages during osteoprogenitor differentiation. *J. Cell Sci., 2003. 116(9): p. 1787-96.*
53. Franceschi, R.T., B.S. Iyer, and Y. Cui, Effects of ascorbic acid on collagen matrix formation and osteoblast differentiation in murine MC3T3-E1 cells. *J. Bone Miner. Res.*, 1994. 9(6): p. 843-54.
54. Balk, M.L., et al., Effect of rhBMP-2 on the osteogenic potential of bone marrow stromal cells from an osteogenesis imperfecta mouse (oim). *Bone*, 1997. 21(1): p. 7-15.
55. Li, H.T., et al., Immature osteoblast lineage cells increase osteoclastogenesis in osteogenesis imperfecta murine. *Am. J. Pathol.*, 2010. 176(5): p. 2405-13.
56. Wenstrup, R.J., D.P. Witte, and J.B. Florer, Abnormal differentiation in MC3T3-E1 preosteoblasts expressing a dominant-negative type I collagen mutation. *Connect. Tiss. Res.,* 1996. 35(1-4): p. 249-57.
57. Uveges, T.E., et al., Cellular mechanism of decreased bone in Brtl mouse model of OI: Imbalance of decreased osteoblast function and increased osteoclasts and their precursors. *J. Bone Miner. Res.*, 2008. 23(12):1983-94.
58. Zhang, H., et al., Increased resorptive activity and accompanying morphological alterations in osteoclasts derived from the Oim/Oim mouse model of osteogenesis imperfecta. *J. Cell. Biochem.*, 2007. 102(4): p. 1011-20.
59. Lam, J., et al., TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J. Clin. Invest.*, 2000. 106(12): p. 1481-8.
60. Kitaura, H., et al., Marrow stromal cells and osteoclast precursors differentially contribute to TNF-alpha-induced osteoclastogenesis in vivo. *J. Immunol.*, 2004. 173(8): p. 4838-46.
61. Williams, C.J. and D.J. Prockop, Synthesis and Processing of a Type-I Procollagen Containing Shortened Pro-Alpha1(I) Chains by Fibroblasts from a Patient with Osteogenesis Imperfecta. *J. Biol. Chem.*, 1983. 258(9): p. 5915-21.
62. Forlino, A., et al., Differential expression of both extracellular and intracellular proteins is involved in the lethal or nonlethal phenotypic variation of BrtlIV, a murine model for osteogenesis imperfecta. *Proteomics*, 2007. 7(11): p. 1877-91.

63. Kefalides, N.A., Structure and biosynthesis of basement membranes. *Int. Rev. Connect. Tissue Res.*, 1973. Vol. 6: p. 63-104.
64. Perret, S., et al., Unhydroxylated triple helical collagen I produced in transgenic plants provides new clues on the role of hydroxyproline in collagen folding and fibril formation. *J. Biol. Chem.*, 2001. 276(47): p. 43693-8.
65. Vranka, J.A., et al., Prolyl 3-Hydroxylase 1 Null mice display abnormalities in fibrillar collagen-rich tissues such as tendons, skin, and bones. *J. Biol. Chem.*, 2010. 285(22): p. 17253-62.
66. Choi, J.W., et al., Severe osteogenesis imperfecta in cyclophilin B-deficient mice. *PLoS Genet*, 2009. 5(12): p. e1000750.
67. Christiansen, H.E., et al., Homozygosity for a missense mutation in SERPINH1, which encodes the collagen chaperone protein HSP47, results in severe recessive osteogenesis imperfecta. *Am. J. Hum. Genet.*, 2010. 86(3): p. 389-98.
68. Alanay, Y., et al., Mutations in the gene encoding the RER protein FKBP65 cause autosomal-recessive osteogenesis imperfecta. *Am. J. Hum. Genet.*, 2010. 86(4): p. 551-9.
69. Ishida, Y., et al., Type I Collagen in Hsp47-null cells is aggregated in endoplasmic reticulum and deficient in N-propeptide processing and fibrillogenesis. *Mol. Biol. Cell*, 2006. 17(5): p. 2346-55.
70. Marutani, T., et al., Accumulation of type IV collagen in dilated ER leads to apoptosis in Hsp47-knockout mouse embryos via induction of CHOP. *J Cell Sci*, 2004. 117(24): p. 5913-22.
71. Bergo, M.O., et al., Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. *Proc. Natl. Acad. Sci. U. S. A.*, 2002. 99(20): p. 13049-54.
72. Sohaskey, M.L., et al., Osteopotentia regulates osteoblast maturation, bone formation, and skeletal integrity in mice. *J. Cell. Biol.*, 2010. 189(3): p. 511-25.
73. Mariño, G., et al., Premature aging in mice activates a systemic metabolic response involving autophagy induction. *Hum. Mol. Genet.*, 2008. 17(14): p. 2196-211.
74. Rivas, D., et al., Accelerated features of age-related bone loss in Zmpste24 metalloproteinase-deficient mice. *J. Gerontol. Series A: Biol. Sciences Med. Sciences*, 2009. 64A(10): p. 1015-24.
75. Meyer, C., L. Notari, and S.P. Becerra, Mapping the type I collagen-binding site on pigment epithelium-derived factor. *J. Biol. Chem.*, 2002. 277(47): p. 45400-07.
76. Doll, J.A., et al., Pigment epithelium-derived factor regulates the vasculature and mass of the prostate and pancreas. *Nat. Med.*, 2003. 9(6): p. 774-80.
77. Murakami, T., et al., Signalling mediated by the endoplasmic reticulum stress transducer OASIS is involved in bone formation. *Nat Cell Biol*, 2009. 11(10): p. 1205-11.
78. Sekiya, H., et al., Effects of the bisphosphonate risedronate on osteopenia in *OASIS*-deficient mice. *J. Bone Miner. Metab.*, 2010. 28(4): p. 384-94.
79. Lapunzina, P., et al., Identification of a frameshift mutation in Osterix in a patient with recessive osteogenesis imperfecta. *Am. J. Hum. Genet.*, 2010. 87(1): p. 110-14.
80. Nakashima, K., et al., The novel zinc finger-containing transcription factor Osterix is required for osteoblast differentiation and bone formation. *Cell*, 2002. 108(1): p. 17-29.
81. Eteson, D.J., et al., The mouse skeletal mutants: models for the human skeletal dysplasias. *Prog. Clin. Biol. Res.*, 1985. 187: p. 141-51.

82. Sillence, D.O., et al., Fragilitas ossium (fro/fro) in the mouse: a model for a recessively inherited type of osteogenesis imperfecta. *Am. J. Med. Genet.*, 1993. 45(2): p. 276-83.
83. Aubin, I., et al., A deletion in the gene encoding sphingomyelin phosphodiesterase 3 (Smpd3) results in osteogenesis and dentinogenesis imperfecta in the mouse. *Nat. Genet.*, 2005. 37(8): p. 803-5.
84. Hannun, Y.A., The sphingomyelin cycle and the second messenger function of ceramide. *J. Biol. Chem.*, 1994. 269(5): p. 3125-28.
85. Wu, L.N.Y., et al., Changes in phospholipid extractability and composition accompany mineralization of chicken growth plate cartilage matrix vesicles. *J. Biol. Chem.*, 2002. 277(7): p. 5126-33.
86. Takeda, H., et al., Sphingomyelinase and ceramide inhibit formation of F-actin ring in and bone resorption by rabbit mature osteoclasts. *FEBS Lett.*, 1998. 422(2): p. 255-8.
87. Paterson, C.R., S. McAllion, and J.L. Stellman, Osteogenesis Imperfecta after the Menopause. *N. Engl. J. Med.*, 1984. 310(26): p. 1694-6.
88. Kozloff, K.M., et al., Brittle IV mouse model for osteogenesis imperfecta IV demonstrates postpubertal adaptations to improve whole bone strength. *J. Bone Miner. Res.*, 2004. 19(4): p. 614-22.
89. Bonadio, J., et al., A murine skeletal adaptation that significantly increases cortical bone mechanical-properties - Implications for human skeletal fragility. *J. Clin. Invest.*, 1993. 92(4): p. 1697-705.
90. Pereira, R.F., et al., Bone fragility in transgenic mice expressing a mutated gene for type I procollagen (COL1A1) parallels the age-dependent phenotype of human osteogenesis imperfecta. *J. Bone Miner. Res.*, 1995. 10(12): p. 1837-43.
91. McBride, D.J., Jr., J.R. Shapiro, and M.G. Dunn, Bone geometry and strength measurements in aging mice with the oim mutation. *Calcif. Tissue Int.*, 1998. 62(2): p. 172-6.
92. Zhuang, J., et al., Substitution of arginine for glycine at position 154 of the alpha 1 chain of type I collagen in a variant of osteogenesis imperfecta: comparison to previous cases with the same mutation. *Am. J. Med. Genet.*, 1996. 61(2): p. 111-16.
93. Trummer, T., et al., Recurrent mutations in the COL1A2 gene in patients with osteogenesis imperfecta. *Clin. Genet.*, 2001. 59(5): p. 338-43.
94. Carleton, S.M., et al., Role of genetic background in determining phenotypic severity throughout postnatal development and at peak bone mass in Col1a2 deficient mice (oim). *Bone*, 2008. 42(4): p. 681-94.
95. Russell, R., et al., Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos. Int.*, 2008. 19(6): p. 733-59.
96. Land, C., et al., Osteogenesis imperfecta type VI in childhood and adolescence: effects of cyclical intravenous pamidronate treatment. *Bone*, 2007. 40(3): p. 638-44.
97. Millington-Ward, S., et al., Strategems in vitro for gene therapies directed to dominant mutations. *Hum. Mol. Genet.*, 1997. 6(9): p. 1415-26.
98. Plotkin, H., et al., Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J. Clin. Endocrinol. Metab.*, 2000. 85(5): p. 1846-50.
99. Rauch, F., et al., The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta.[see comment]. *J. Clin. Invest.*, 2002. 110(9): p. 1293-9.

100. Rauch, F., et al., Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J. Clin. Endocrinol. Metab.*, 2006. 91(4): p. 1268-74.
101. Marx, R.E., Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J. Oral Maxillofac. Surg.*, 2003. 61(9): p. 1115-17.
102. Ruggiero, S.L., et al., Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J. Oral Maxillofac. Surg.*, 2004. 62(5): p. 527-34.
103. Rothenbuhler, A., et al., Risk of corrected QT interval prolongation after pamidronate infusion in children. *J. Clin. Endocrinol. Metab.* 95(8): p. 3768-70.
104. Camacho, N.P., et al., A controlled study of the effects of alendronate in a growing mouse model of osteogenesis imperfecta. *Calcif. Tissue Int.*, 2001. 69(2): p. 94-101.
105. Evans, K.D., et al., Alendronate affects long bone length and growth plate morphology in the oim mouse model for Osteogenesis Imperfecta. *Bone*, 2003. 32(3): p. 268-74.
106. Uveges, T.E., et al., Alendronate treatment of the brtl osteogenesis imperfecta mouse improves femoral geometry and load response before fracture but decreases predicted material properties and has detrimental effects on osteoblasts and bone formation. *J. Bone Miner. Res.*, 2009. 24(5): p. 849-59.
107. Evans, K.D., et al., Pamidronate alters the growth plate in the oim mouse model for osteogenesis imperfecta. *Internat. J. Biomed. Science*, 2009. 5(4): p. 345-51.
108. Rao, S.H., et al., Bisphosphonate treatment in the oim mouse model alters bone modeling during growth. *J. Biomech.*, 2008. 41(16): p. 3371-76.
109. Kostenuik, P.J., et al., Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J. Bone Miner. Res.*, 2009. 24(2): p. 182-95.
110. Bargman, R., et al., RANKL inhibition improves bone properties in a mouse model of osteogenesis imperfecta. *Connective Tissue Research*, 2010. 51(2): p. 123-31.
111. Marini, J.C., et al., Positive linear growth and bone responses to growth hormone treatment in children with types III and IV osteogenesis imperfecta: high predictive value of the carboxyterminal propeptide of type I procollagen. *J. Bone Miner. Res.*, 2003. 18(2): p. 237-43.
112. Marini, J.C., et al., Evaluation of growth hormone axis and responsiveness to growth stimulation of short children with osteogenesis imperfecta. *Am. J. Med. Genet.*, 1993. 45(2): p. 261-4.
113. Vieira, N.E., et al., Effect of growth hormone treatment on calcium kinetics in patients with osteogenesis imperfecta type III and IV. *Bone*, 1999. 25(4): p. 501-5.
114. Vieira, N.E., et al., Calcium kinetics in children with osteogenesis imperfecta type III and IV: pre- and post-growth hormone therapy. *Calcif. Tissue Int.*, 2000. 67(2): p. 97-100.
115. King, D., et al., Growth hormone injections improve bone quality in a mouse model of osteogenesis imperfecta. *J. Bone Miner. Res.*, 2005. 20(6): p. 987-993.
116. Niyibizi, C., et al., Gene therapy approaches for osteogenesis imperfecta. *Gene Ther.*, 2004. 11(4): p. 408-16.
117. Barsh, G.S., K.E. David, and P.H. Byers, Type-I osteogenesis imperfecta - a non-functional allele for pro-alpha-1(I) chains of type-I procollagen. *Proc. Natl. Acad. Sci. U. S. A.*, 1982. 79(12): p. 3838-42.

118. Willing, M.C., et al., Osteogenesis imperfecta type-I is commonly due to a Col1a1 null allele of type-I collagen. *Am. J. Hum. Genet.*, 1992. 51(3): p. 508-15.
119. Khillan, J.S., S.W. Li, and D.J. Prockop, Partial rescue of a lethal phenotype of fragile bones in transgenic mice with a chimeric antisense gene directed against a mutated collagen gene. *Proc. Natl. Acad. Sci. U. S. A.*, 1994. 91(14): p. 6298-302.
120. Phylactou, L.A., P. Tsipouras, and M.W. Kilpatrick, Hammerhead ribozymes targeted to the FBN1 mRNA can discriminate a single base mismatch between ribozyme and target. *Biochem. Biophys. Res. Commun.*, 1998. 249(3): p. 804-10.
121. Dawson, P.A. and J.C. Marini, Hammerhead ribozymes selectively suppress mutant type I collagen mRNA in osteogenesis imperfecta fibroblasts. *Nucleic Acids Res.*, 2000. 28(20): p. 4013-20.
122. Smicun, Y., et al., Enhanced intracellular availability and survival of hammerhead ribozymes increases target ablation in a cellular model of osteogenesis imperfecta. *Gene Ther.*, 2003. 10(24): p. 2005-12.
123. Toudjarska, I., et al., Delivery of a hammerhead ribozyme specifically downregulates mutant type I collagen mRNA in a murine model of osteogenesis imperfecta. *Antisense Nucleic Acid Drug Dev.*, 2001. 11(5): p. 341-6.
124. Niyibizi, C., et al., The fate of mesenchymal stem cells transplanted into immunocompetent. neonatal mice: Implications for skeletal gene therapy via stem cells. *Molecular Therapy*, 2004. 9(6): p. 955-63.
125. Pereira, R.F., et al., Marrow stromal cells as a source of progenitor cells for nonhematopoietic tissues in transgenic mice with a phenotype of osteogenesis imperfecta. *Proc. Natl. Acad. Sci. U. S. A.*, 1998. 95(3): p. 1142-47.
126. Wang, X., F. Li, and C. Niyibizi, Progenitors systemically transplanted into neonatal mice localize to areas of active bone formation in vivo: Implications of cell therapy for skeletal diseases. *Stem Cells*, 2006. 24(8): p. 1869-78.
127. Li, F., X. Wang, and C. Niyibizi, Distribution of single-cell expanded marrow derived progenitors in a developing mouse model of osteogenesis imperfecta following systemic transplantation. *Stem Cells*, 2007. 25(12): p. 3183-93.
128. Pereira, R.F., et al., Cultured adherent cells from marrow can serve as long-lasting precursor cells for bone, cartilage, and lung in irradiated mice. *Proc. Natl. Acad. Sci. U. S. A.*, 1995. 92(11): p. 4857-61.
129. Li, F., X. Wang, and C. Niyibizi, Bone marrow stromal cells contribute to bone formation following infusion into femoral cavities of a mouse model of osteogenesis imperfecta. *Bone*, 2010. 47(3): p. 546-55.
130. Guillot, P.V., et al., Intrauterine transplantation of human fetal mesenchymal stem cells from first-trimester blood repairs bone and reduces fractures in osteogenesis imperfecta mice. *Blood*, 2008. 111(3): p. 1717-25.
131. Brodeur, A.C., et al., Type I collagen glomerulopathy: postnatal collagen deposition follows glomerular maturation. *Kidney Int.*, 2007. 71(10): p. 985-93.
132. Chen, W., et al., Single-nucleotide polymorphisms in the COL1A1 regulatory regions are associated with otosclerosis. *Clin. Genet.*, 2007. 71(5): p. 406-14.
133. Franco, G.E.L., et al., Increased Young's modulus and hardness of Col1a2(oim) dentin. *J. Dent. Res.*, 2006. 85(11): p. 1032-6.
134. Pfeiffer, B.J., et al., Alpha 2(I) collagen deficient oim mice have altered biomechanical integrity, collagen content, and collagen crosslinking of their thoracic aorta. *Matrix Biology*, 2005. 24(7): p. 451-8.
135. Helminen, H.J., et al., An inbred line of transgenic mice expressing an internally deleted gene for type II procollagen (COL2A1). Young mice have a variable phenotype of a chondrodysplasia and older mice have osteoarthritic changes in joints. *J. Clin. Invest.*, 1993. 92(2): p. 582-95.

136. Blair-Levy, J.M., et al., A type I collagen defect leads to rapidly progressive osteoarthritis in a mouse model. *Arthritis Rheum.*, 2008. 58(4): p. 1096-106.
137. Forlino, A., et al., New perspectives on osteogenesis imperfecta. *Nat Rev Endocrinol*, 2011. 7(9): p. 540-57.

7 RECESSIVE OSTEOGENESIS IMPERFECTA:
rER GENES TAKE THE STAGE

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INTRODUCTION

Osteogenesis imperfecta (OI) was associated with mutations in type I collagen genes, *COL1A1* and *COL1A2*, in the early 1980's.[1] Although this systemic connective tissue disorder is most commonly an autosomal dominant disease, alternative mechanisms of inheritance were suspected due to the recurrence of OI in children of healthy parents. These instances, representing about 10-15% of all reported OI cases, are not caused by type I collagen mutations and were tentatively diagnosed as recessive OI or OI-like syndromes. Some of these cases were classified outside of the classical OI types (I-IV) based on bone histology, certain clinical aspects of the disease or having a genetic linkage to a region that doesn't contain type I collagen genes.[2-4] The identification of the first gene responsible for specific cases of recessive OI was made over 25 years following the emergence of the recessive OI hypothesis. The initial gene discovered, *CRTAP* (encoding Cartilage-associated protein),[5] paved the way for the identification of several novel genes that, when mutated, cause recessive forms of OI. Unlike dominant OI caused by mutations in type I collagen genes, novel genes associated with recessive OI encode for proteins that mainly reside in the rough endoplasmic reticulum (rER) and are involved in type I collagen post-synthetic modifications or trafficking. Such genes include *LEPRE1* (encoding prolyl 3-hydroxylase 1 or *P3H1*), *PPIB* (encoding Cyclophilin B or *CYPB*), *SERPINH1* (encoding *HSP47*) and *FKBP10* (encoding FKBP65). However, more recently, mutations in a gene encoding a secreted protein, such as SERPINF1 (encoding pigmented epithelium derived factor or PEDF), have also been identified as the cause of some cases of recessive OI. This chapter will offer readers an overview on the molecular and clinical aspects that

characterize each of the recessive forms of OI and discuss potential mechanisms of the disease.

Classification of Recessive forms of OI and Clinical Features

Osteogenesis imperfecta was classified over 3 decades ago into four basic types, I-IV, based on genetic, clinical, and radiographic features,[6,7] with type I being the mildest followed by type IV, III and II in increasing order of severity.

With the discoveries of genes involved in recessive forms of OI, new types of OI (VI-XI) have been proposed following a strictly genetic classification. The 2010 Revision of the Nosology and Classification of Genetic Skeletal Disorders[8] has agreed to implement the Sillence classification as the conventional process to classify OI severity, yet to also have it independent from direct molecular reference. Since the Sillence Classification has been used over the past three decades, and because it offers instant feedback on the clinical severity of the disease, it is unlikely that physicians will cease to employ it as a way to establish diagnosis, and hence administer therapy, at least until the underlying genetic mutation is clearly stated. On the other hand, an entirely genetic classification of recessive OI may prove advantageous, as each genetic etiology may underlie a different mechanism of disease and hence require a dedicated therapeutic approach. Table 1 provides a genetic classification of recessive OI, describes each of the recessive OI types identified to date, and the clinical severity that each defect ultimately leads to.

Molecular Pathophysiology of Recessive OI

Type I collagen comprises 85-90% of total bone protein content. It is a trimeric molecule formed by two α1(I) and one α2(I) chains that contains a long triple helical domain composed of a series of Gly-X-Y repeats where "Y" is often a 4-hydroxyproline. Mutations in the two genes encoding type I collagen, *COL1A1* and *COL1A2*, cause dominant OI. However, mutations in collagen modifier genes cause recessive forms of OI. These include genes encoding CRTAP, P3H1, and Cyclophilin B (CYPB) which associate to form the so-called prolyl 3-hydroxylation complex.[5] This complex has prolyl 3-hyroxylase, prolyl cis-trans isomerase and collagen chaperone activity (discussed in the next section). A loss of any of the three components disrupts

the function of the complex and leads to early post-translational defects in procollagen synthesis. The ensuing over-modification of additional prolyl and lysyl residues in the collagen triple helical domain is the result of a delay in the winding of the triple helix. Collagen over-modification, in the absence of 3-Hyp at Pro986, was shown in mouse models with loss of function mutations of *Crtap*, *Lepre1* and *Ppib.*[5,9,10] An increase in the diameter of the collagen fibrils and decreased irregular deposition of extracellular matrix (ECM) were also shown. Moreover, fibroblasts from a patient carrying a homozygous null *CRTAP* mutation were recently reported to deposit less collagen in the matrix.[11] Loss of function of the prolyl 3-hydroxylation complex leads most of the time to a lethal to severe OI phenotype comparable to that of type II/ III dominant OI. Moreover, quantitative backscattered electron imaging studies identified higher calcium content in the bone matrix of *Crtap*-null mice and OI-VII patient iliac biopsies.[12] This as well as other data suggested that a defect in collagen structure due to improper post-translational modification, may lead to abnormal mineral stoichiometry and mineralization kinetics.

In recessive OI caused by mutations in either *FKBP10* or *SERPINH1* there is normal prolyl 3-hydroxylation and procollagen chain modification but altered collagen transport between the rER and Golgi apparatus. While the role of FKBP65 or SERPINH1 in procollagen synthesis is downstream to that of the prolyl 3-hydroxylation complex, the resulting OI phenotype with mutations of these genes is still quite severe and comparable to that seen in type III/IV OI. Type VI OI caused by *SERPINF1* mutations is characterized by a mineralization defect with non-mineralized osteoid persistence on cancellous bone; this indicates a different pathogenetic mechanism compared to all other types of OI.[13] Mutations in both *PLOD2* (Bruck syndrome type II) and *FKBP10* genes cause joint contractures besides the usual OI clinical features; therefore a careful physical examination may help to narrow down the genetic screening to identify mutations in these patients. The underlying pathogenetic mechanism of *SP7/OSX* mutations in recessive OI remains unclear. Type I collagen is a target of *OSX* and hence its expression may be down-regulated in response to *OSX* mutations.

Biochemical, Molecular, and Clinical Aspects of Recessive OI

Crtap and the Formation of the Prolyl 3-hydroxylation Complex

Two members of the Leprecan family of proteins have been associated with recessive OI, Cartilage-associated protein (CRTAP) and Prolyl 3-hydroxylase 1 (P3H1 or Leprecan, encoded by the *LEPRE1* gene). As mentioned, *CRTAP* was the first identified gene whose mutations cause recessive OI.[5] The loss of function of this gene in mice causes an osteochondrodysplasia with kyphosis, rhizomelia (i.e., the shortening of the first segment of the limb), and severe osteopenia.[5] *Crtap*-/- mice have normal osteoclast counts and function but histomorphometric analysis of their bones showed normal counts of dysfunctional osteoblasts; a decreased mineral apposition rate (MAR) led to a decreased bone formation rate (BFR). In addition, osteoid surfaces and volumes were reduced and the mineralization lag time was shorter in the mutant mice. A survey of extra-skeletal tissues in the *Crtap*-/- mice identified primary lung and kidney defects associated with increased cell proliferation. The skin of the mutant mice showed laxity with decreased thickness, stiffness, and overall strength.[14] Type I collagen fibrils were shown to form in the extracellular matrix of *Crtap-/-* skin fibroblasts by transmission electron microscopy, although they had a significantly increased diameter.

While Crtap has no enzymatic activity, the binding to P3h1 in the rER stabilizes the two proteins and is believed to somehow allow prolyl 3-hydroxylase activity. Indeed, at the biochemical level, *Crtap* deficiency causes lack of conversion of Pro^{986} into the 3-hydroxyproline normally found toward the C-terminal end of the collagen triple helical domain of α1(I), α1(II) and α2(V).[5,14]

Ward et al. characterized a moderately severe, "rhizomelic", recessive form of OI in a large consanguineous family from Northern Quebec and classified it as OI type VII.[15] It was shown to be caused by a single base-pair change in intron 1 of *CRTAP,* which triggers an abnormal splicing in about 90% of the transcripts and acts as a hypomorphic mutation with residual little expression of normal protein.[5] Complete loss of function mutations of *CRTAP* however, cause total absence of the protein and result in a very severe to lethal recessive OI in humans.[5,16] Recessive OI due to *CRTAP* mutations has been tentatively classified as OI type VII and includes clinically severe OI cases originally classified as Sillence type IIB-III.

Crtap forms a trimeric complex with prolyl 3-hydroxylase 1 and cyclophilin B (CypB, encoded by *PPIB*) in the rER.[5] The other components of the complex were subsequently considered new candidate genes for causing recessive OI. Mutations in *LEPRE1* were identified in patients diagnosed with a recessive form of OI (tentatively classified as OI type VIII) that lacked *COL1A1*, *COL1A2* or *CRTAP* mutations.[17] Newborns having either *CRTAP* or *LEPRE1* mutations have somewhat indistinguishable phenotypes characterized by extremely low bone mineralization, multiple healing fractures**,** and short tubular femurs with lack of modeling.[18-20] They usually have white sclerae. P3h1 is the enzyme responsible for converting a proline into 3-hydroxyproline (3Hyp).[21] *LEPRE1* loss of function mutations cause a severe decrease or absence of 3-Hyp at Pro986 of type I collagen.[17] Interestingly, *CRTAP* loss of function mutations cause lack of CRTAP protein but also loss of P3H1 protein in tissues and in fibroblast cultures; likewise, loss of P3H1 due to *LEPRE1* mutations is associated with loss of CRTAP protein.[14,22,23] These results suggested that CRTAP and P3H1 are essential for each other's stability and the function of the prolyl 3-hydroxylation complex; thus loss of function mutations in either *CRTAP* or *LEPRE1* likely cause a common pathogenic mechanism and similar clinical features. While the identification of subtle defects in lungs, kidneys, and skin in *Crtap-/-* mice confirms a systemic connective tissue disease, these tissues have not been yet analyzed in the recently generated *Lepre1* null mice which have an otherwise similar skeletal phenotype to that of *Crtap-/-* mice.[10] These subtle defects may also be indicative of a primary defect in the OI lung, as respiratory distress and failure have been previously reported in types VII and VIII patients.[18]

The third member of the prolyl 3-hydroxylation complex, Cyclophilin B (CypB, encoded by the *PPIB* gene), may localize in the rER along with P3H1 and Crtap[24] or be secreted extracellularly,[25] unlike most Cyclophilins that are either present in the nucleus or in the cytosol. Being a component of the prolyl 3-hydroxylation complex, CypB became the subsequent logical candidate for causing recessive forms of OI. Cyclophilins, together with FKBPs (FK506-binding proteins) and Parvulins, share peptidyl-prolyl cis-trans isomerase (PPIase) activity.[26] This is a conformational change that catalyzes the peptide bond preceding a proline residue between its *cis* and *trans* form and is thought to be the rate-limiting step for the folding of type I collagen which contains about 20% proline residues.[26] Recently, mutations in *PPIB* were identified in three distinct families affected with recessive OI.[22,27] Loss of *PPIB* does not cause rhizomelia but results in shorter, under-tubulated, bowed and fractured long bones. A varying degree of severity was

described: Van Dijk et al. showed four probands with severe type IIB/III OI and frameshift mutations in either exon 4 or 5;[22] another report showed moderately severe OI in two siblings who reached independent ambulation and were homozygous for a missense mutation changing the initial methionine into arginine with loss of the protein.[27] Recessive OI due to *PPIB* mutations has tentatively been classified as type IX OI. Interestingly, Van Dijk et al. also reported that fibroblasts from patients with *PPIB* mutations and severe OI exhibited over-modification of type I collagen chains, and a severe reduction in Pro986 3-hydroxylation, although levels of hydroxylation remained higher than those observed with either *CRTAP* or *LEPRE1* mutations. Conversely, Barnes et al. reported that patients having moderate OI showed normal levels of collagen modification and prolyl 3-hydroxylation.

Cyclophilin B appears to be the most independent member of the prolyl 3-hydroxylation complex. Loss of Cyclophilin B clearly had a moderate effect on CRTAP or P3H1 protein stability.[22] Loss of function mutations in the genes encoding members of the trimeric prolyl 3-hydroxylation complex (*Crtap*, *Lepre1* and/or *Ppib*), have been generated in the mouse.[5,9,10] The phenotype of these mice presents common features including severe osteopenia, skin laxity, kyphosis, lack of collagen prolyl 3-hydroxylation, and collagen fibrils abnormality detected at the ultra-structural level. These animal models have been useful for the biochemical and molecular characterization of recessive OI and will further help in the understanding of its pathophysiology and testing of potential therapeutic approaches.

The FK506 Binding Proteins (FKBPs)

Another protein with PPIase activity and residing in the rER is FKBP65/FKBP10 (encoded by the *FKBP10* gene). In the rER FKBP65 functions as a chaperone for both tropoelastin as well as type I collagen.[28,29] Although FKBP65 is not a component of the prolyl 3-hydroxylation complex, mutations in the gene encoding this immunophilin were reported in an American family of Mexican origin as well as in few Turkish families that were diagnosed with a progressive, severe type of recessive OI.[30] These probands had a history of long bone fractures leading to progressive deformities of the limbs but they were born with normal height and weight. They lacked manifestation of dentinogenesis imperfecta or hearing loss but suffered progressive kyphoscoliosis with flattened and wedged vertebral bodies and were diagnosed with a recessive form of OI.[30] Primary fibroblasts from these patients synthesized procollagen chains that were not over-modified and had normal level of Pro986 3-hydroxylation. This suggested a

molecular defect downstream of the prolyl 3-hydroxylation complex. Further analyses showed a delay in the secretion of type I collagen chains with dilation of the rER cisternae and evidence of abnormal intracellular collagen trafficking.[30] A second report described additional patients with mutations in the *FKBP10* gene; these were also diagnosed with a recessive form of OI but also exhibited large joint contractures similar to those described in Bruck syndrome.[31]

The most recent report describes a child born to healthy consanguineous Italian parents with a progressive form of recessive OI.[32] This patient was initially diagnosed with mild OI, which then progressed into a severe form of the disease. Born with normal height and weight, the patient exhibited the first fractures at 8 months consisting of a right tibia greenstick fracture and pathological rib fractures.[32] At age 4, a physical examination showed features of an OI phenotype: the boy was short and thin, with white sclerae, long fingers and toes, moderate small joint laxity but no arthrogryposis, dentinogenesis imperfecta or other phenotypic anomalies. Radiographic findings included wormian bones, thin cortices of the long bones and a flattening of a vertebral body with progressive scoliosis. A novel homozygous splicing mutation in *FKBP10* was identified which resulted in defective mRNA processing and ultimately lack of FKBP65. Gel electrophoresis of the proband's type I collagen showed normal amounts of α1(I) and α2(I) in the medium although qPCR indicated an up-regulation in COL1A1 transcript levels. Biochemically, C-terminal cross-linked telopeptide of type I collagen (CTX) levels were extremely high. There were no alterations in the levels of alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxy vitamin D (25OHD) or calcium, as CTX remained above normal levels.[32] Patients with *FKBP10* mutations can be genetically classified as having OI type XI.

The SERPINS

The SERPINS, serine protease inhibitors, constitute a protein superfamily that includes important regulators of various pathway enzymes. SERPINS have been classified in two distinct groups: the first constituting protease inhibitors responsible for the regulation of extracellular matrix remodeling, inflammation, and blood clotting;[33] and the second including a number of proteins that lack protease inhibitor activity, yet present a large array of functions, including molecular chaperone activities. Two members of the latter group have been associated with recessive OI: heat-shock protein 47 (HSP47, encoded by the *SERPINH1* gene), a collagen chaperone and pigment

epithelium derived factor (PEDF, encoded by the *SERPINF1* gene). A *SERPINH1* homozygous missense mutation was reported in a single proband with a severe form of recessive OI.[34] *Serpinh1* gene defects had been previously described in a dog breed affected with OI.[35] On the other hand, *Serpinh1*-null mice had been created a few years ago and suffered *in utero* lethality likely due to collagen defects in multiple tissues.[36] The patient with the *SERPINH1* mutation displayed typical OI clinical features including: generalized osteopenia, dentinogenesis imperfecta, blue sclerae, thin ribs with healing fractures, joint laxity, platyspondyly, short limbs with bowed femora, and relative macrocephaly. In addition, respiratory distress, renal stones, hypotonia, and pyloric stenosis were also reported.[34] Biochemically, the *SERPINH1* mutation had similar consequences to those observed with mutations in *FKBP10* with lack of over-modification of type I procollagen chains and normal Pro986 3-hydroxylation. Interestingly, the procollagen chains were shown to accumulate in the Golgi apparatus and to also become more susceptible to protease digestion suggesting a compromised helical structure. Thus HSP47 may have a role in monitoring proper triple helical structure assembly and, similarly to FKBP65, it functions downstream of the prolyl 3-hydroxylation complex.[34] Recessive OI caused by mutations in *SERPINH1* has been classified as type X OI.

Mutations in the *SERPINF1* gene encoding pigment epithelium derived factor (PEDF) were recently identified as the cause for a rare form of OI, previously classified as OI type VI.[3,13,37] Patients were homozygous for either frameshift or nonsense mutations, resulting in a premature termination codon and nonsense-mediated RNA decay, and ultimately null alleles. Biochemically, these patients lacked any serum circulating PEDF and had a slight elevation in serum alkaline phosphatase levels as well as in bone turn-over. They were born with normal weight and height, gray-white sclerae and normal facial features; they had no fractures, limb deformities, nor joint laxity. However, these patients suffered early fractures, usually before the first year of life, and experienced progressive clinical manifestation of the disease, acquiring several other fractures during early childhood which would ultimately lead to bone deformities and loss of independent ambulation. The progressive nature of the disease suggests an early post-natal onset of the skeletal phenotype. Histologically, a large amount of un-mineralized osteoid on the surface of cancellous bone was shown in iliac bone biopsies.[3,13] This indicated a mineralization defect characterized at the microscopic level with a 'fish-scale' appearance replacing the normal bone lamellar pattern.[3,13] The mechanisms leading to the recessive form of OI caused by mutations in

SERPINF1 remain unclear. Interestingly, PEDF-deficient mice were generated earlier and exhibited increased stromal vessels and epithelial cell hyperplasia in the prostate and pancreas.[38] Their skeleton however, had not been analyzed carefully. PEDF was described as a multi-functional protein playing significant roles as a potent inhibitor of angiogenesis, a neurotrophic factor and a collagen-interacting molecule, among others.[39-41]

Other Genes

Lysyl-hydroxylase 2 encoded by the *PLOD2* gene is an enzyme that functions as a collagen telopeptide lysyl hydroxylase. Mutations in *PLOD2* were first identified in 2003[42] and associated with a recessive form of OI characterized with joint contractures (Bruck syndrome type II). A locus thought to cause recessive OI with joint contractures had been previously identified on the long arm of chromosome 3 (3q23-q24) which is where *PLOD2* is located. *PLOD2* mutations were conclusively associated with clinical features of OI and arthrogryposis, such as long bone deformities, osteoporosis, scoliosis and congenital joint contractures.[43,44]

The recessive ocular form of OI was characterized with extremely low bone mass, fractures, and severe eye defects that could result in early blindness. These included secondary glaucoma, hyperplasia of the vitreous, corneal opacity, and the formation of retrolental masses resembling a retinoblastoma.[45,46] It was later identified as the osteoporosis pseudoglioma syndrome (OPPG).[47-50] Gong et al. demonstrated that the OPPG locus was linked to the long arm of chromosome 11.[51] Mutations in the gene encoding the LDL-receptor related protein 5 (LRP5) were identified as the underlying cause of the disease.[52] LRP5 functions as a bone mass accrual regulator during growth and as a co-receptor for Wnt molecules in the canonical Wnt pathway.[52] Null mutations in the *LRP5* gene lead to OPPG, while heterozygous carriers also exhibit low bone mass.[52] Several missense mutations in the *LRP5* gene were previously shown to be associated with other conditions such as high bone mass phenotypes,[53-55] and recessive and dominant familial exudative vitreoretinopathy 4.[56,57]

Recently, a Spanish group reported two severe cases of autosomal recessive OI in siblings who were born into a consanguineous Egyptian family.[58] No linkage to any known genes associated with forms of recessive OI was identified, however, homozygosity mapping showed a conserved region on the short arm of chromosome 8 in both affected patients.[58] This region comprised the procollagen I C-terminal propeptide (PICP) endopeptidase

gene, *BMP1*. A homozygous missense mutation within the BMP1 protease domain and involving an amino acid residue that is conserved among all members of the astacin group of metalloproteases was identified. Parents of the probands were both carriers of this mutation.[58] This caused a decreased BMP1 function that led to abnormal type I procollagen processing and was confirmed by the over-expression of wild type and mutant *BMP1* longer isoform (mammalian Tolloid protein (mTLD)) in human primary fibroblasts and in NIH3T3 fibroblasts. There was no increase in proα1(I) cleavage due to the increase in the level of the mutant protein. An overproduction of normal mTLD, however, resulted in a large proportion of proα1(I) being C-terminally processed. Hence, the missense mutation leads to a dysfunctional BMP1/mTLD protein.[58] Both sibs exhibited severe bone deformities, kyphoscoliosis and a relatively large thorax. They also showed small abdomen and large umbilical hernia, scoliosis of thoracic and lumbar spine, platyspondyly, and osteoporosis.[58]

Finally, a homozygous single base pair deletion causing a frameshift and a premature termination codon in the transcription factor Osterix (encoded by the *SP7/OSX* gene) was identified in a unique patient diagnosed with OI.[59] The mutation removes the last of three zinc-finger DNA binding domains at the C-terminus of Osterix and it is probably decreasing its transactivation function. In mice, Osterix is an essential transcription factor for murine skeletal development and homeostasis[60,61] and controls osteoblast lineage differentiation by activating several osteoblast target genes including type I collagen. Although it is likely that type I collagen expression is downregulated with *SP7/OSX* mutations, the mechanism causing the OI phenotype has not yet been characterized.

CONCLUSION

In this chapter an overview of the newly identified forms of recessive OI is provided, with a reference to the underlying genetic defects, the pathophysiology, and the associated clinical features. While dominant OI is caused by mutations in either *COL1A1* or *COL1A2* genes, recessive OI usually results from mutations of genes encoding proteins with a function in type I collagen post-translational modification, transport, folding and proteolytic cleavage. The clinical features of recessive OI can be equally or even more severe than those of dominant OI types. This usually correlates to the impact that each of the synthesis steps being affected has on numerous collagen chains; for instance, loss of function of the prolyl 3-hydroxylation complex leads to altered hydroxylation patterns in alpha-chains of type I, II and V

collagens and thus causes a more generalized defect with clinical features of both OI and Ehlers Danlos. The identification of several new genes whose mutations are associated with recessive OI has significantly improved the genetic testing of rare forms of OI. Once an OI diagnosis is confirmed and the underlying genetic defect is ascertained, a purely genetic classification of recessive OI, as represented in Table 1, may be helpful to the clinician to further evaluate and assess potential differentially associated complications (such as joint contractures) and also recommend a proper therapeutic approach. While young patients affected with recessive OI have been treated similarly to those affected with dominant OI, i.e. with the use of intravenous bisphosphonates, treatment of recessive forms may be different in the future. For instance, initial though limited evidence from treating patients carrying *SERPINF1* mutations has shown no apparent benefit from the use of bisphosphonates.[13]

Mutations in new genes causing rare forms of OI are waiting to be discovered and Table 2 contains a list of some candidate genes that may play a role in connective tissue disease. The recent progress in our understanding of recessive OI has led to improved genetic testing and genetic counseling for families with healthy parents and multiple siblings with OI. Hopefully the increased knowledge of the pathogenetic mechanisms leading to OI will help in the generation and/or improvement of therapeutic protocols for young OI patients.

Table 1. A genetic classification of recessive OI.

OI Type	Gene Defect	Protein	Clinical Features
VI	*SERPINF1*	PEDF	Severe
VII	*CRTAP*	CRTAP	Severe to lethal, rhyzomelia
VIII	*LEPRE1*	P3H1	Severe to lethal, rhyzomelia
IX	*PPIB*	CYPB	Moderate to severe
X	*SERPINH1*	HSP47	Severe
XI	*FKBP10*	FKBP65	Moderate to severe with joint contractures (maybe Bruck syndrome 1)
NC	*PLOD2*	LH2	Moderate to severe with joint contractures and pterygia (Bruck syndrome 2)
NC	*LRP5 (null alleles)*	LRP5	Ocular form of OI, osteoporosis pseudoglioma syndrome
NC	*SP7*	OSX (Osterix)	Moderate to severe
NC	*BMP1*	BMP1	Severe bone deformities, kyphoscoliosis and large thorax

NC = Not classified

Table 2. Partial list of rER resident proteins involved in the modification or folding of collagens.

ER PROTEIN FAMILIES	PROTEINS	GENE SYMBOL	APPROVED NAME	HUMAN DISEASE	CHROMOS.	MOUSE MUTATION
Prolyl 4-hydroxylases*	$\alpha(1)_2\beta_2$	*P4HA1*	prolyl 4-hydroxylase, alpha polypeptide I	Not identified	10q21.3-q23.1	Yes/ Embryonic lethal
	$\alpha(2)_2\beta_2$	*P4HA2*	prolyl 4-hydroxylase, alpha polypeptide II	Not identified	5q31	Yes-viable
	$\alpha(3)_2\beta_2$	*P4HA3*	prolyl 4-hydroxylase, alpha polypeptide III	Not identified	11q13	n/a
Leprecans (Prolyl 3-hydroxylases and adapter proteins)	P3H1	*LEPRE1*	leucine proline-enriched proteoglycan (leprecan) 1	Recessive OI	1p34.1	Yes-viable
	P3H2	*LEPREL1*	leprecan-like 1	Axial myopia	3q29	n/a
	P3H3	*LEPREL2*	leprecan-like 2	Not identified	12q13	n/a
	CRTAP	*CRTAP(LEPREL3)*	cartilage associated protein	Recessive OI	3p22	Yes-viable
	SC65	*LEPREL4(SC65)*	leprecan-like 4	Not identified	17q21	n/a
Lysyl hydroxylases	LH1	*PLOD1*	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1	Ehlers Danlos type VI-A	1p36.3-p36.2	Yes-viable
	LH2	*PLOD2*	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	Recessive OI with joint contractures	3q24	n/a
	LH3	*PLOD3*	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3	Generalized connective tissue defects	7q36	Yes/ Embryonic lethal

Peptidyl-prolyl cis-trans isomerases	Cyclophilin B	*PPIB*	peptidylprolyl isomerase B	Recessive OI	15q21-q22	Yes-viable
	FKBP11(FKBP19)	*FKBP11*	FK506 binding protein 11	Not identified	12q13.12	n/a
	FKBP14(FKBP22)	*FKBP14*	FK506 binding protein 14	Ehlers Danlos with myopathy and hearing loss	7p15	n/a
	FKBP7(FKBP23)	*FKBP7*	FK506 binding protein 7	Not identified	2q31.2	n/a
	FKBP9(FKBP60,63)	*FKBP9*	FK506 binding protein 9	Not identified	7p11.1	n/a
	FKBP10(FKBP65)	*FKBP10*	FK506 binding protein 10	Recessive OI with joint contractures	17q21.2	n/a
Collagen chaperone	HSP47	*SERPINH1*	serpin peptidase inhibitor 1	Recessive OI	11q13.5	Yes/ Embryonic lethal
Zinc transporter	SLC39A13(ZIP13)	*SLC39A13*	solute carrier family 39 (zinc transporter), member 13	Ehlers Danlos spondylocheiro dysplastic form	11p11.12	Yes-viable

* The b sub-unit of prolyl 4-hydroxylases is protein disulfide isomerase (PDI or prolyl 4-hydroxylase, beta polypeptide) encoded by the *P4HB* gene. While genes encoding some of these proteins are still candidates for human disease, mutations in many of the listed genes have already been associated with connective tissue disorders.

ABBREVIATIONS

BFR	Bone formation rate
BMP1	Bone morphogenetic protein 1
Crtap	Cartilage-associated protein
CTX	C-terminal cross-linked telopeptide of type I collagen
CypB	Cyclophylin B
ECM	Extracellular matrix
FKBP10	FK506 binding protein 10
Gly	Glycine
MAR	Mineral apposition rate
LRP5	LDL-receptor related protein 5
OI	Osteogenesis imperfecta
OPPG	Osteoporosis pseudoglioma syndrome
OSX	Osterix
P3h1	Prolyl 3-hydroxylase 1
PEDF	Pigment epithelium derived factor
rER	Rough endoplasmic reticulum
3Hyp	3-hydroxyproline

REFERENCES

1. Chu ML, Williams CJ, Pepe G, Hirsch JL, Prockop DJ, Ramirez F. Internal deletion in a collagen gene in a perinatal lethal form of osteogenesis imperfecta. *Nature.* 1983; 304(5921): 78-80.
2. Glorieux FH, Rauch F, Plotkin H, et al. Type V osteogenesis imperfecta: a new form of brittle bone disease. *J Bone Miner Res.* 2000; 15(9): 1650-1658.
3. Glorieux FH, Ward LM, Rauch F, Lalic L, Roughley PJ, Travers R. Osteogenesis imperfecta type VI: a form of brittle bone disease with a mineralization defect. *J Bone Miner Res.* 2002; 17(1): 30-38.
4. Labuda M, Morissette J, Ward LM, et al. Osteogenesis imperfecta type VII maps to the short arm of chromosome 3. *Bone.* 2002; 31(1): 19-25.
5. Morello R, Bertin TK, Chen Y, et al. CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta. *Cell.* 2006; 127(2): 291-304.
6. Sillence DO, Rimoin DL. Classification of osteogenesis imperfect. *Lancet.* 1978; 1(8072): 1041-1042.
7. Sillence DO. Osteogenesis imperfecta nosology and genetics. *Ann N Y Acad Sci.* 1988; 543: 1-15.
8. Warman ML, Cormier-Daire V, Hall C, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. *Am J Med Genet A.* 2011;155A(5):943-968.
9. Choi JW, Sutor SL, Lindquist L, et al. Severe osteogenesis imperfecta in cyclophilin B-deficient mice. *PLoS genetics.* 2009; 5(12): e1000750.
10. Vranka JA, Pokidysheva E, Hayashi L, et al. Prolyl 3-hydroxylase 1 null mice display abnormalities in fibrillar collagen-rich tissues such as tendons, skin and bones. *J Biol Chem.* 2010; 285(22): 17253-17262.

11. Valli M, Barnes AM, Gallanti A, et al. Deficiency of CRTAP in Non-lethal Recessive Osteogenesis Imperfecta Reduces Collagen Deposition into Matrix. *Clin Genet.* 2011; doi: 10.1111/j.1399-0004.2011.01794.
12. Fratzl-Zelman N, Morello R, Lee B, et al. CRTAP deficiency leads to abnormally high bone matrix mineralization in a murine model and in children with osteogenesis imperfecta type VII. *Bone.* 2010; 46(3): 820-826.
13. Homan EP, Rauch F, Grafe I, et al. Mutations in SERPINF1 cause Osteogenesis imperfecta Type VI. *J Bone MinerRes* 2011; 26(12): 2798-2803.
14. Baldridge D, Lennington J, Weis M, et al. Generalized connective tissue disease in Crtap-/- mouse. *PloS one.* 2010; 5(5): e10560.
15. Ward LM, Rauch F, Travers R, et al. Osteogenesis imperfecta type VII: an autosomal recessive form of brittle bone disease. *Bone.* 2002; 31(1): 12-18.
16. Barnes AM, Chang W, Morello R, et al. Deficiency of cartilage-associated protein in recessive lethal osteogenesis imperfecta. *New Engl J Med.* 2006; 355(26): 2757-2764.
17. Cabral WA, Chang W, Barnes AM, et al. Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. *Nat Genet.* 2007; 39(3): 359-365.
18. Baldridge D, Schwarze U, Morello R, et al. CRTAP and LEPRE1 mutations in recessive osteogenesis imperfecta. *Hum Mutat.* 2008; 29(12): 1435-1442.
19. Willaert A, Malfait F, Symoens S, et al. Recessive osteogenesis imperfecta caused by LEPRE1 mutations: clinical documentation and identification of the splice form responsible for prolyl 3-hydroxylation. *J Med Genet.* 2009; 46(4): 233-241.
20. Marini JC, Cabral WA, Barnes AM. Null mutations in LEPRE1 and CRTAP cause severe recessive osteogenesis imperfecta. *Cell Tissue Res.* 2010; 339(1): 59-70.
21. Vranka JA, Sakai LY, Bachinger HP. Prolyl 3-hydroxylase 1: Enzyme characterization and identification of a novel family of enzymes. *J Biol Chem.* 2004; 279(22): 23612-23621.
22. van Dijk FS, Nesbitt IM, Zwikstra EH, et al. PPIB mutations cause severe osteogenesis imperfecta. *Am J Hum Genet.* 2009; 85(4): 521-527.
23. Chang W, Barnes AM, Cabral WA, Bodurtha JN, Marini JC. Prolyl 3-hydroxylase 1 and CRTAP are mutually stabilizing in the endoplasmic reticulum collagen prolyl 3-hydroxylation complex. *Hum Mol Genet.* 2010; 19(2): 223-234 .
24. Pemberton TJ, Kay JE. Identification and comparative analysis of the peptidyl-prolyl cis/trans isomerase repertoires of H. sapiens, D. melanogaster, C. elegans, S. cerevisiae and Sz. pombe. *Comp Funct Genomics.* 2005; 6(5-6): 277-300.
25. Yao Q, Li M, Yang H, Chai H, Fisher W, Chen C. Roles of cyclophilins in cancers and other organ systems. *World J Surg* 2005; 29(3): 276-280.
26. Gothel SF, Marahiel MA. Peptidyl-prolyl cis-trans isomerases, a superfamily of ubiquitous folding catalysts. *Cell Mol Life Sci.* 1999; 55(3): 423-436.
27. Barnes AM, Carter EM, Cabral WA, et al. Lack of cyclophilin B in osteogenesis imperfecta with normal collagen folding. *New Eng J Med* 2010; 362(6): 521-528.
28. Patterson CE, Abrams WR, Wolter NE, Rosenbloom J, Davis EC. Developmental regulation and coordinate reexpression of FKBP65 with extracellular matrix proteins after lung injury suggest a specialized function for this endoplasmic reticulum immunophilin. *Cell Stress Chaperones.* 2005; 10(4): 285-295.
29. Ishikawa Y, Vranka J, Wirz J, Nagata K, Bachinger HP. The rough endoplasmic reticulum-resident FK506-binding protein FKBP65 is a molecular chaperone that interacts with collagens. *J Biol Chem.* 2008; 283(46): 31584-31590.
30. Alanay Y, Avaygan H, Camacho N, et al. Mutations in the gene encoding the RER protein FKBP65 cause autosomal-recessive osteogenesis imperfecta. *Am J Hum Genet.* 2010; 86(4): 551-559.

31. Kelley BP, Malfait F, Bonafe L, et al. Mutations in FKBP10 cause recessive osteogenesis imperfecta and Bruck syndrome. *J Bone Miner Res* 2011; 26(3): 666-672.
32. Venturi G, Gandini A, Monti E, et al. Lack of expression of SERPINF1, the gene coding for pigment epithelium-derived factor causes progressively deforming osteogenesis imperfecta with normal type I collagen. *J Bone Miner Res* 2011; doi: 10.1002/jbmr.1480.
33. van Gent D, Sharp P, Morgan K, Kalsheker N. Serpins: structure, function and molecular evolution. *Int J Biochem Cell Biol.* 2003; 35(11): 1536-1547.
34. Christiansen HE, Schwarze U, Pyott SM, et al. Homozygosity for a missense mutation in SERPINH1, which encodes the collagen chaperone protein HSP47, results in severe recessive osteogenesis imperfecta. *Am J Hum Genet.* 2010; 86(3): 389-398.
35. Drogemuller C, Becker D, Brunner A, et al. A missense mutation in the SERPINH1 gene in Dachshunds with osteogenesis imperfecta. *PLoS genetics.* 2009; 5(7): e1000579.
36. Nagai N, Hosokawa M, Itohara S, et al. Embryonic lethality of molecular chaperone hsp47 knockout mice is associated with defects in collagen biosynthesis. *J Cell Biol.* 2000; 150(6): 1499-1506.
37. Becker J, Semler O, Gilissen C, et al. Exome sequencing identifies truncating mutations in human SERPINF1 in autosomal-recessive osteogenesis imperfecta. *Am J Hum Genet.* 2011; 88(3): 362-371.
38. Doll JA, Stellmach VM, Bouck NP, et al. Pigment epithelium-derived factor regulates the vasculature and mass of the prostate and pancreas. *Nat Med.* 2003; 9(6): 774-780.
39. Dawson DW, Volpert OV, Gillis P, et al. Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. *Science.* 1999; 285(5425): 245-248.
40. Meyer C, Notari L, Becerra SP. Mapping the type I collagen-binding site on pigment epithelium-derived factor. Implications for its antiangiogenic activity. *J Biol Chem.* 2002; 277(47): 45400-45407.
41. Filleur S, Nelius T, de Riese W, Kennedy RC. Characterization of PEDF: a multi-functional serpin family protein. *J Cell Biochem* 2009; 106(5): 769-775.
42. van der Slot AJ, Zuurmond AM, Bardoel AF, et al. Identification of PLOD2 as telopeptide lysyl hydroxylase, an important enzyme in fibrosis. *J Biol Chem.* 2003; 278(42): 40967-40972.
43. Breslau-Siderius EJ, Engelbert RH, Pals G, van der Sluijs JA. Bruck syndrome: a rare combination of bone fragility and multiple congenital joint contractures. *J Ped Orthop B.* 1998; 7(1): 35-38.
44. Ha-Vinh R, Alanay Y, Bank RA, et al. Phenotypic and molecular characterization of Bruck syndrome (osteogenesis imperfecta with contractures of the large joints) caused by a recessive mutation in PLOD2. *Am J Med Genet.* 2004; 131(2): 115-120.
45. Beighton P, Winship I, Behari D. The ocular form of osteogenesis imperfecta: a new autosomal recessive syndrome. *Clin Genet.* 1985; 28(1): 69-75.
46. De Paepe A, Leroy JG, Nuytinck L, Meire F, Capoen J. Osteoporosis-pseudoglioma syndrome. *Am J Med Genet.* 1993; 45(1): 30-37.
47. Beighton P. Osteoporosis-pseudoglioma syndrome. *Clin Genet.* 1986; 29(3): 263.
48. Brude E. Ocular osteogenesis imperfecta. *Clin Genet.* 1986; 29(2): 187.
49. Frontali M, Dallapiccola B. Osteoporosis-pseudoglioma syndrome and the ocular form of osteogenesis imperfecta. *Clin Genet.* 1986; 29(3): 262.
50. Superti-Furga A, Steinmann B, Perfumo F. Osteoporosis-pseudoglioma or osteogenesis imperfecta? *Clin Genet.* 1986; 29(2): 184-185.

51. Gong Y, Vikkula M, Boon L, et al. Osteoporosis-pseudoglioma syndrome, a disorder affecting skeletal strength and vision, is assigned to chromosome region 11q12-13. *Am J Hum Genet.* 1996; 59(1): 146-151.
52. Gong Y, Slee RB, Fukai N, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell.* 2001; 107(4): 513-523.
53. Boyden LM, Mao J, Belsky J, et al. High bone density due to a mutation in LDL-receptor-related protein 5. *New Engl J Med* 2002; 346(20): 1513-1521.
54. Little RD, Carulli JP, Del Mastro RG, et al. A mutation in the LDL receptor-related protein 5 gene results in the autosomal dominant high-bone-mass trait. *Am J Hum Genet.* 2002; 70(1): 11-19.
55. Van Wesenbeeck L, Cleiren E, Gram J, et al. Six novel missense mutations in the LDL receptor-related protein 5 (LRP5) gene in different conditions with an increased bone density. *Am J Hum Genet.* 2003; 72(3): 763-771.
56. Jiao X, Ventruto V, Trese MT, Shastry BS, Hejtmancik JF. Autosomal recessive familial exudative vitreoretinopathy is associated with mutations in LRP5. *Am J Hum Genet.* 2004; 75(5): 878-884.
57. Toomes C, Bottomley HM, Jackson RM, et al. Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. *Am J Hum Genet.* 2004; 74(4): 721-730.
58. Martinez-Glez V, Valencia M, Caparros-Martin JA, et al. Identification of a mutation causing deficient BMP1/mTLD proteolytic activity in autosomal recessive osteogenesis imperfecta. *Hum Mutat* 2012; 33(2): 343-350.
59. Lapunzina P, Aglan M, Temtamy S, et al. Identification of a frameshift mutation in Osterix in a patient with recessive osteogenesis imperfecta. *Am J Hum Genet.* 2010; 87(1): 110-114.
60. Nakashima K, Zhou X, Kunkel G, et al. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. *Cell.* 2002; 108(1): 17-29.
61. Zhou X, Zhang Z, Feng JQ, et al. Multiple functions of Osterix are required for bone growth and homeostasis in postnatal mice. *Proc Natl Acad Sci USA.* 2010; 107(29): 12919-12924.

8 OSTEOGENESIS IMPERFECTA BONE ON THE TISSUE LEVEL

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INTRODUCTION

OI is the most common primary bone disorder. Many different mutations in a variety of genes can give rise to the disease, but the common denominator of all types of OI is osteoblast dysfunction. As osteoblasts are the cells that form extracellular bone matrix, their functional deficit leads to the production of abnormal bone tissue. To elucidate the pathogenesis of OI, it is therefore essential to evaluate the tissue-level features of OI bone.

The best tool to study bone on the tissue level is bone histomorphometry. This technique represents the quantitative evaluation of bone tissue, which in clinical studies is usually obtained from the ilium (transiliac bone biopsy specimen). Both the activity of bone cells and the amount and distribution of bone tissue can be analyzed. When tetracycline labeling is performed prior to biopsy, bone histomorphometry offers the unique possibility to study bone cell function in vivo. Importantly for pediatric use, the growth process does not directly interfere with the measurements. The osteoblast dysfunction in OI affects two basic aspects of tissue-level mechanisms of bone development, bone remodeling and bone modeling. These two processes therefore must be briefly introduced here.

Bone is continuously renewed by remodeling.[1] Remodeling consists of successive cycles of bone resorption and formation on the same bone surface, either trabecular or cortical. The basic features of this process are identical for trabecular and cortical bone.[1] A group of osteoclasts removes a small quantity ('packet') of bone tissue, which after a reversal phase is replaced by a team of osteoblasts. The entire group of cells involved in this process is named remodeling unit or basic multicellular unit. The fact that osteoblast activity is linked to previous osteoclast action has been named 'coupling'.[1] The difference in the amounts of bone which are removed and added in one remodeling cycle is called 'remodeling balance'. The remodeling balance is

typically close to zero so that there is no or little net effect on the amount of bone. However, the remodeling process renews the bone tissue and thereby prevents tissue damage from accumulating.[2]

Bone growth in width occurs through a different mechanism, called modeling.[1] Bone modeling involves the same set of effector cells as bone remodeling: osteoclasts and osteoblasts. However, while in remodeling both cells types are sequentially active on the same bone surface, osteoclasts and osteoblasts act on different surfaces during modeling. During bone growth in width, osteoblasts are typically located on the outer (periosteal) surface of a bone cortex, where they deposit bone matrix and later mineralize it. Thereby, the outer circumference of a long bone or a vertebral body is increased. At the same time, osteoclasts located on the inner (endocortical) surface of the cortex resorb bone, thus increasing the size of the marrow cavity. Since osteoblasts are active without interruption in bone modeling, much more rapid increases in the amount of bone tissue can occur in modeling than in bone remodeling. Osteoclasts usually remove less bone tissue than is deposited by osteoblasts during modeling.[1] Therefore, modeling leads to a net increase in the amount of bone tissue. For example, the difference between osteoblastic matrix deposition and osteoclastic bone resorption leads to cortical thickening.

THE BONE TISSUE LEVEL IN CLASSICAL OI

Modeling and Remodeling Defects in OI Types I, III and IV

In a study on 70 children with OI types I, III, and IV between 1.5 and 13.5 years of age, it was observed that the external size of the biopsy core did not increase with age, and cortical width was generally markedly below normal.[3] Because external bone size and cortical width during growth are determined by modeling processes,[4] these observations suggested a modeling defect in OI. This is an important aspect of the disease because deficient bone modeling will result in smaller cross section and thinner cortices of long bones and thus reduced bone strength.

In addition to diminished external size and cortical width, OI is also characterized by a low amount of cancellous bone, which is largely due to decreased trabecular number (Figure 1). Low trabecular number can result from either increased loss or decreased production of trabeculae. There was

no evidence that children with OI lose secondary trabeculae because trabecular number remained constant with age. By exclusion, this suggested that fewer secondary trabeculae are produced. Trabeculae consist of lamellar bone, but lamellae tend to be thinner than those in healthy children.

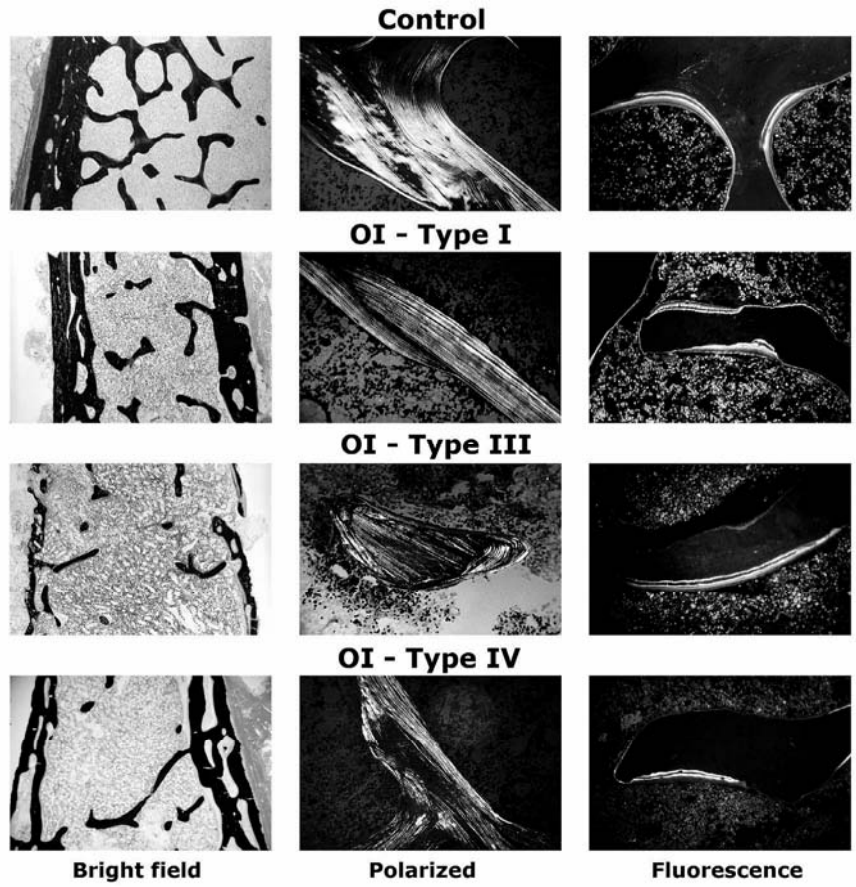

Figure 1. Typical sections of biopsies from a control subject (boy, 9 years) and OI patients (type I: girl, 5 years; type III: boy, 9 years; type IV: boy, 13 years). Original magnifications: left column, 32x, middle column, 200x; right column, 200x. (From: Rauch F, Travers R, Parfitt AM, Glorieux FH. 2000. Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. Bone 26:581-589).

Inadequate trabecular thickening in OI is caused by a defect in bone remodeling. In the control group, each remodeling cycle added 2.8 μm more bone than it resorbed. In OI type I, the positive balance was only 1.1 μm and it was approximately 0 in types III and IV. The insufficient performance of the osteoblast team in all OI types was the consequence of the fact that the amount of work achieved by an individual cell was decreased by

approximately 50%.[3] This was only partly compensated by an increased number of osteoblasts per remodeling unit. Although the amount of bone turned over in individual remodeling cycles is decreased in OI, the number of remodeling cycles that occur on a given bone surface per unit time is increased. The cause of increased recruitment of remodeling teams is not clear, but increased microdamage in the bone matrix due to impaired mechanical resistance is the likely cause.

This study showed that in OI a single genetic defect in the osteoblast interferes with multiple mechanisms that normally ensure adaptation of the skeleton to the increasing mechanical needs during growth.

The Influence of Vitamin D Status on OI Bone Tissue

Vitamin D plays an essential role in calcium homeostasis and in the development and maintenance of the skeleton.[5] One could hypothesize that children with underlying bone fragility such as OI should be especially vulnerable to the additional challenge of a low vitamin D status. A study on 71 patients with a diagnosis of OI type I, III, or IV from age 1.4 to 18 years of age therefore investigated the relationship between serum 25-hydroxyvitamin D (25OHD) levels and histomorphometric parameters.[6] None of these patients had received bisphosphonate treatment before iliac bone biopsy. Serum 25OHD levels ranged from 13 to 103 nmol/L and were in the deficient or inadequate range (<50 nmol/L) in 37 patients (52%). None of the OI patients had radiological signs of rickets or fulfilled the histomorphometric criteria for the diagnosis of osteomalacia (i.e., elevated results for both osteoid thickness and mineralization lag time). Serum 25OHD levels were not correlated with any parameter of bone mineralization or bone mass. Thus, no evidence was found that serum 25OHD levels in the range from 13 to 103 nmol/L were associated with measures of bone mineralization, metabolism or mass in children with OI.

Genotype-Phenotype Correlations in Patients with Collagen Type I Mutations

There are two general classes of mutations in type I collagen that result in OI.[7] The first are mutations that cause a failure to synthesize the products of one COL1A1 allele and thus lead to haploinsufficiency.[8] The second class of mutations results in the synthesis of collagen molecules with structural

abnormalities. This is most frequently caused by the substitution of glycine by another amino acid in the triple helical domain of either the alpha 1 or the alpha 2 chain.[7] The relationship between genotype and histomorphometric phenotype in OI types I, III and IV was examined in a study on 96 patients.[9]

Core width (outer bone size) and trabecular bone volume were similar between patients with haploinsufficiency mutations and those with helical glycine mutations, but cortical width was about 50% higher in the haploinsufficiency group. Parameters reflecting the activity of bone turnover varied significantly with genotype and were lowest in the haploinsufficiency group. This suggests that bone mass differences between these genotypic groups are mainly caused by differences of bone modeling on periosteal and endocortical bone surfaces and less by differences in trabecular bone metabolism.

For helical mutations, there was no obvious relationship between the type of substituting amino acid or the position of the mutation and histomorphometric parameters. The data also suggest that the classification of OI according to phenotypic types provides a better reflection of histological disease severity than the grouping of patients according to mutation type.

THE BONE TISSUE LEVEL IN NEWER OI TYPES

OI Type V

Many OI patients present unusual clinical features. One of these is hyperplastic callus formation, which can appear spontaneously, following fracture, or with intramedullary rodding. While studying bone sections from OI patients, it was realized that those with a history of hyperplastic callus formation also showed an abnormal pattern of lamellation under polarized light.[10] Lamellae were arranged in an irregular fashion and had a coarsened or even mesh-like appearance under polarized light. It was then noted that patients with this particular histological pattern also had distinctive features, including calcifications of the interosseous membrane at the forearm, hyperdense metaphyseal bands, and a lack of mutations in collagen type I. These observations led to the classification of this disease entity as OI type V.[10]

Comparison of quantitative histomorphometric results in OI type V and controls revealed no difference in bone formation and resorption rates.

However, those parameters that reflect bone formation activity in individual remodeling sites were clearly decreased. The rate of bone matrix deposition was less than half of the control value, and correspondingly osteoid seams were very thin. Thus, bone remodeling in OI type V is characterized by a normal rate of activation of remodeling units but an impaired bone formation within individual remodeling units.

OI Type VI

Bone histology and bone histomorphometry also led to the initial identification of another subgroup of OI patients.[11] These individuals initially had been diagnosed with OI type IV on clinical grounds. However, evaluation of iliac crest biopsy samples yielded surprising results. There was loss of the normal orientation of the lamellae and a "fish-scale" pattern under polarized light. A large amount of osteoid was present, and inspection under fluorescent light revealed poor or diffuse uptake of the tetracycline labels. These findings suggested that there was a defect in matrix mineralization in these patients.

Quantitative histomorphometry revealed that cortical width and trabecular thickness were diminished in OI type VI.[11] However, the amount of unmineralized osteoid was significantly increased in OI type VI patients and mineralization lag time was increased, showing a delay of mineralization. Thus, OI type VI is characterized by a mineralization defect on the tissue level. Recent studies have shown that this phenotype is caused by mutations in a gene called *SERPINF1*.[12, 13] However, it is unclear at present how this genetic defect leads to the mineralization defect of OI type VI.

OI Type VII

OI type VII is an autosomal recessive form of OI that is caused by mutations in the *CRTAP* gene.[14] This group is a moderate to severe OI phenotype that is characterized by fractures at birth, bluish sclerae, early deformity of the lower extremities, coxa vara, osteopenia, and rhizomelia.[15] Similar to OI type I, bone size is small, cortical width is reduced, and cancellous bone volume is low in this form of OI. Histomorphometric analyses show that bone turnover is increased but that the activity of osteoblast in individual remodeling sites is low.[15] Thus, the bone tissue level findings in OI type VII are very similar to those of OI types caused by mutations in collagen type I.

EFFECTS OF BISPHOSPHONATE TREATMENT IN OI

In children with OI, the effect of bisphosphonates on bone tissue has been studied in some detail. In a study on 45 children and adolescents with OI type I, III and IV (age 1.4 years to 17.5 years), iliac bone biopsies were obtained at the start of intravenous pamidronate treatment as well as after 2 to 4 years (mean 2.4 years) of therapy (Figure 2).[16] The main bone mass relevant change during the treatment period was an increase in cortical thickness of 88%. The amount of trabecular bone increased by an average of 46% because trabeculae were more numerous. Indicators of cancellous bone remodeling decreased by 26-75%. There was no evidence for a mineralization defect in any of the patients. These results suggested that, in growing children with OI, pamidronate had a twofold effect. With regard to remodeling, bone resorption and formation are coupled and consequently both processes were inhibited. However, during modeling of cortical bone, osteoclasts and osteoblasts are active on different surfaces and are thus uncoupled. Therefore resorption was selectively targeted by pamidronate, and continuing bone formation could increase cortical width.

Similar results were found in a study on 24 young children with OI who had all received pamidronate treatment since the first or second year of life.[17] Their histomorphometric results after three years of pamidronate treatment were compared to those of a historical control group of untreated children with severe OI who were matched for OI type and age. Iliac bone histomorphometry showed 61% higher cortical width and 89% higher cancellous bone volume in pamidronate-treated patients. Bone formation rate per bone surface in the pamidronate group was only 17% that of untreated patients. Thus, pamidronate treatment started in infancy leads to a marked increase in the amounts of both cortical and trabecular bone, but also suppressed bone turnover markedly.

The bone-tissue effects of pamidronate in the newer types of OI were largely similar to those found in 'classical' OI types. In 7 children with OI type V, two years of pamidronate treatment were associated with an average increase of 86% in cortical thickness.[18] Cortical thickness also increased (+53%) after three years of intravenous pamidronate in children and adolescents with OI type VI.[19] However, the mineralization defect that is the characteristic feature of OI type VI, did not change during pamidronate treatment. In OI type VII, cortical width increased with pamidronate treatment, but trabecular bone volume did not change significantly.[20]

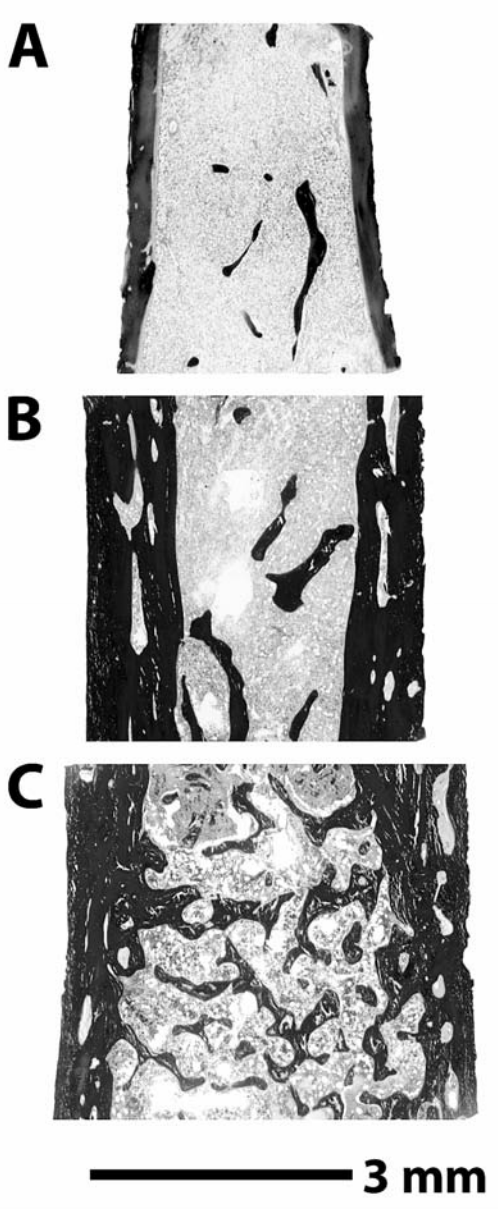

Figure 2. Series of iliac bone samples in a boy with OI type I. A. Sample obtained at the age of 2.2 years, before pamidronate treatment was started. B. After 2.8 years of pamidronate treatment. C. After 5.8 years of pamidronate treatment (From: Rauch F, Travers R, Glorieux FH. Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. J Clin Endocrinol Metab. 2006;91:511-516).

The longer-term effects of pamidronate treatment on the bone tissue were evaluated in a longitudinal study of 25 children and adolescents with OI who had received intravenous pamidronate for >4 years.[21] Iliac bone biopsies were performed at treatment start, after 2.7±0.5 years (mean±SD), and after 5.5±0.7 years of therapy. Mean cortical width and cancellous bone volume increased by 87% and 38%, respectively, between baseline and the first time point during treatment. Thereafter, cortical width did not change significantly, but there was a trend towards higher cancellous bone volume. Average bone formation rate on trabecular surfaces decreased by 70% after pamidronate treatment was initiated, and showed a trend towards a further decline in the second part of the study interval. These results indicate that the gains that can be achieved with pamidronate treatment appear to be largely realized in the first two to four years.

Little is known about the bone tissue-level effects of bisphosphonate compounds other than pamidronate. One study examined the efficacy and safety of oral risedronate in the treatment of pediatric patients with mild OI.[22] Iliac bone biopsies were performed at the end of the two-year study period. Histomorphometric analysis of these transiliac bone biopsies did not show a significant treatment difference in cortical width, trabecular bone volume, or parameters of bone turnover. These results suggest that the skeletal effects of oral risedronate are weaker than those that are commonly observed with intravenous pamidronate treatment.

Adverse Effects of Bisphosphonate Treatment on the Tissue Level

One of the radiological features of intravenous bisphosphonate treatment in growing children is the appearance of transverse lines in the metaphyses of long bones. These lines were examined in the case of a child with OI type VII, where the iliac bone biopsy had inadvertently included part of the iliac growth plate and the adjacent metaphysis.[23] It was seen that these metaphyseal lines corresponded to horizontal trabeculae that were undergoing active remodeling, rather than “frozen growth plate cartilage” as had been hypothesized before.

Changes in the appearance of osteoclasts have previously been noted in children receiving pamidronate and have been interpreted as signs of toxicity.[16,24] A study analyzed osteoclast parameters in paired iliac bone specimens before and after two to four years of cyclical intravenous

pamidronate therapy in 44 pediatric OI patients and found that intravenous pamidronate of young OI patients leads to an increase in osteoclast size[25] (Figure 3). However, the presence of large osteoclasts was not associated with detectable untoward clinical effects.

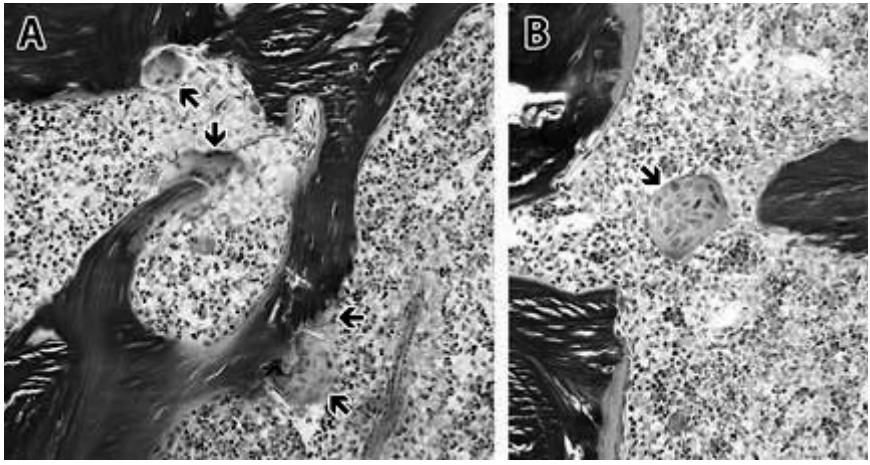

Figure 3. Iliac bone specimen from a 17-year-old adolescent with OI type IV after 2.9 years of pamidronate treatment. Osteoclasts are marked by arrows. The magnification bar corresponds to 100 µm. A. Both osteoclasts with bloated appearance and osteoclasts with normal size are visible. B. Large osteoclast, which appears to be detached from the bone surface.

ABBREVIATIONS

CRTAP	Cartilage-associated protein
OI	Osteogenesis imperfecta
SD	Standard deviation
SERPINF1	Serpin peptidase inhibitor, clade f, member 1

REFERENCES

1. Rauch F. Watching bone cells at work: what we can see from bone biopsies. *Pediatr Nephrol.* Apr 2006;21(4):457-462.
2. Allen MR, Burr DB. Bisphosphonate effects on bone turnover, microdamage, and mechanical properties: What we think we know and what we know that we don't know. *Bone.* Oct 15 2010.
3. Rauch F, Travers R, Parfitt AM, Glorieux FH. Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. *Bone.* 2000;26(6):581-589.
4. Parfitt AM, Travers R, Rauch F, Glorieux FH. Structural and cellular changes during bone growth in healthy children. *Bone.* 2000;27(4):487-494.

5. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics.* Aug 2008;122(2):398-417.
6. Edouard T, Glorieux FH, Rauch F. Relationship between vitamin D status and bone mineralization, mass, and metabolism in children with osteogenesis imperfecta: Histomorphometric study. *J Bone Miner Res.* Sep 2011;26(9):2245-2251.
7. Marini JC, Forlino A, Cabral WA, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. *Hum Mutat.* Mar 2007;28(3):209-221.
8. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. *Nature reviews. Endocrinology.* Sep 2011;7(9):540-557.
9. Rauch F, Lalic L, Roughley P, Glorieux FH. Relationship between genotype and skeletal phenotype in children and adolescents with osteogenesis imperfecta. *J Bone Miner Res.* Jun 2010;25(6):1367-1374.
10. Glorieux FH, Rauch F, Plotkin H, et al. Type V osteogenesis imperfecta: a new form of brittle bone disease. *J Bone Miner Res.* 2000;15(9):1650-1658.
11. Glorieux FH, Ward LM, Rauch F, Lalic L, Roughley PJ, Travers R. Osteogenesis imperfecta type VI: a form of brittle bone disease with a mineralization defect. *J Bone Miner Res.* Jan 2002;17(1):30-38.
12. Homan EP, Rauch F, Grafe I, et al. Mutations in SERPINF1 cause osteogenesis imperfecta type VI. *J Bone Miner Res.* Dec 2011;26(12):2798-2803.
13. Venturi G, Gandini A, Monti E, et al. Lack of expression of SERPINF1, the gene coding for pigment epithelium-derived factor causes progressively deforming osteogenesis imperfecta with normal type I collagen. *J Bone Miner Res.* Nov 23 2011;in press.
14. Morello R, Bertin TK, Chen Y, et al. CRTAP is required for prolyl 3- hydroxylation and mutations cause recessive osteogenesis imperfecta. *Cell.* Oct 20 2006;127(2):291-304.
15. Ward LM, Rauch F, Travers R, et al. Osteogenesis imperfecta type VII: an autosomal recessive form of brittle bone disease. *Bone.* Jul 2002;31(1):12-18.
16. Rauch F, Travers R, Plotkin H, Glorieux FH. The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. *J Clin Invest.* Nov 2002;110(9):1293-1299.
17. Munns CF, Rauch F, Travers R, Glorieux FH. Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: clinical and histomorphometric outcome. *J Bone Miner Res.* 2005;20(7):1235-1243.
18. Zeitlin L, Rauch F, Travers R, Munns C, Glorieux FH. The effect of cyclical intravenous pamidronate in children and adolescents with osteogenesis imperfecta Type V. *Bone.* Jan 2006;38(1):13-20.
19. Land C, Rauch F, Travers R, Glorieux FH. Osteogenesis imperfecta type VI in childhood and adolescence: Effects of cyclical intravenous pamidronate treatment. *Bone.* Mar 2007;40(3):638-644.
20. Cheung MS, Glorieux FH, Rauch F. Intravenous pamidronate in osteogenesis imperfecta type VII. *Calcif Tissue Int.* Mar 2009;84(3):203-209.
21. Rauch F, Travers R, Glorieux FH. Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. *J Clin Endocrinol Metab.* Feb 2006;91(2):511-516.
22. Rauch F, Munns CF, Land C, Cheung M, Glorieux FH. Risedronate in the treatment of mild pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Bone Miner Res.* Jul 2009;24(7):1282-1289.

23. Rauch F, Travers R, Munns C, Glorieux FH. Sclerotic metaphyseal lines in a child treated with pamidronate: histomorphometric analysis. *J Bone Miner Res.* Jul 2004;19(7):1191-1193.
24. Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S. Bisphosphonate-induced osteopetrosis. *N Engl J Med.* Jul 31 2003;349(5):457-463.
25. Cheung MS, Glorieux FH, Rauch F. Large osteoclasts in pediatric osteogenesis imperfecta patients receiving intravenous pamidronate. *J Bone Miner Res.* Apr 2009;24(4):669-674.

SECTION 3

Technology

9 FINITE ELEMENT MODELING AND ANALYSIS APPLICATIONS IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Understanding the biomechanics of bones in persons with osteogenesis imperfecta (OI) is a key component to further understanding the disease, optimizing treatment and quality of life, as well as injury prevention. However, it is not feasible to study bone biomechanics in vivo. Thus, modeling may play a key role in understanding how OI bones respond to the loading experienced during various activities, especially ambulation. Biomechanical modeling can provide insight into bone fracture risks, such as type and location, from single applied loads or repetitive loading. One method for obtaining this information is via a finite element analysis (FEA). FEA is a general technique for mathematically approximating solutions to boundary-value problems.[1] It is a powerful computational tool with numerous applications. These numerical methods are used to obtain an output from a system of differential equations in response to boundary condition inputs in many scenarios. FEA allows for the discretization of a structure into numerous subparts (elements) for analysis. Elements represent regular straight-side geometric 2-D or 3-D shapes that enclose a finite area or volume.[2] Field output variables (stress, strain, etc.) are explicitly calculated at each vertex (node) of every element.[3] These outputs provide information that corresponds to bone strength and, therefore, location and risk for potential fractures.

General FEA Applications

Overall, FEA can also be used to model thermal and dynamic fatigue responses. Several software packages exist to perform FEA. These allow the user to either create or import a model, choose the shape and size of the elements that make up the structure, designate material properties and apply boundary and initial conditions. FEA is becoming a reliable method for mechanical analysis of materials, especially in fatigue testing, as it reduces the testing time. Benefits of FEA include: increased accuracy, enhanced design and better insight into critical design parameters, virtual prototyping, fewer hardware prototypes, a faster and less expensive design cycle and increased productivity.[4] It is also useful in flow dynamics analysis, thermal effects, molecular level analysis and crack propagation.[5, 6] A valid model can considerably shorten the development of a new product or process and allow for testing that could not otherwise be completed.

FEA Applications in Biomechanics

Since its introduction into biomechanics in 1972, FEA has been widely used in orthopaedic biomechanics and the assessment of bone mechanical properties.[7,8] A major benefit of FEA is the ability to perform non-invasive evaluations of biological structures. Finite element (FE) models also demonstrated beneficial clinical applications. Mechanical stresses in bones cannot be measured in living subjects without the use of an invasive surgical procedure.[9] Patient-specific FE models allow estimations of in vivo response of bone to various loading conditions. FE models have been developed for long bones as well as the skull, vertebrae, pelvis, metacarpals and scapula.[10,11] FEA was used as early as 1972 by Brekelmans and colleagues to investigate the stresses acting in human bone under physiologic loading conditions.[10] Gupta and colleagues developed and validated a 3-D FE model of the human scapula.[11] The model was based on geometry and material properties, such as density, which were taken from computed tomography (CT) data. Unlike previous solid models, the model created by Gupta et al used a combination of shell (2-D) and solid (3-D) elements. The researchers used fresh cadaver bones with mounted strain gages as a reference to assess the accuracy of the model's stress and strain analysis of the scapular surface.[11]

While several studies have been completed using FEA, there is no standard analysis criterion for fracture prediction in long bones. Bosisio et al looked

at combining inverse FEA with quantitative ultrasound and peripheral quantitative CT to assess the mechanical properties of the distal radius and fracture risk in osteoporosis patients.[16] Taddei and colleagues used FEA to study the mechanical strength of a femoral reconstruction in pediatric oncology.[17] Their study examined the proximal femur reconstruction of a child afflicted with Ewing sarcoma in an effort to evaluate the risk of fracture. The loading conditions in the FE model were comprised of the hip joint reaction force and abductor muscle force. Taddei et al based risk of fracture upon the ratio between the bone tissue strength and the predicted von Mises equivalent stress.[17] Other criteria for fracture that have been used by various research groups include: distortion energy, Hoffman and a strain-based Hoffman analogue (used for anisotropy), maximum normal stress, maximum normal strain, maximum shear strain, maximum shear stress, Coulomb-Mohr, and modified Mohr failure theories (used for anisotropic, elastoplastic materials). Gómez-Benito, García-Aznar and Doblaré argue that these criteria are not sufficient for the anisotropic behavior of bone. Therefore, they implemented the Cowin fracture criterion based on the Tsai-Wu model which takes into account the anisotropy and porosity of bone.[18] Both of these studies, and others, focused on the proximal femur rather than the entire femur and neither accounted for the full muscle contributions to the intrinsic forces of the bone.

The proximal femur is most commonly studied as most fractures occur at this site and are frequently seen in elderly and obese patients as well as those with osteoarthritis and hip implants. Trauma research has recently led to the development and validation of a lower-limb, non-linear, 3-D FEA model to study the effects of car-pedestrian impact on the thigh.[19,20] More sophisticated models account for the individual muscle forces. These forces can significantly alter the loading distribution on the femur.[19,21-25] This knowledge led to the development of a muscle standardized femur (MSF) model.[24,25] Most proximal femur fracture prediction studies model a static quasi-axial loading scenario, which closely replicates single limb stance during the gait cycle. However, these studies do not take loading from other directions into account. Grassi et al recently completed a study validating a model to replicate forces on the adult human proximal femur during a fall scenario.[26]

FEA Applications in OI

Patient-specific FE models have been an effective tool for both bone strain and fracture strength assessment.[12,13] They are used alongside motion

analysis for gait pathologies, rehabilitation, and sports training. One important developing application is the use of FEA to predict fractures in OI.[14,15] Fracture prediction in OI patients may lead to altered prescription of activities and improved physical therapy.

While several groups are examining adult femoral fracture risk and bone strength using FE models, studies on pediatric bone are scarce. Even rarer is the availability of information on fracture risk and strength of pediatric bones in OI. Across all types of OI, poor bone quality poses major orthopaedic and rehabilitation challenges. All treatments are performed with the goal of maximizing function, minimizing deformity, maintaining patient comfort and allowing for independent living. Treatment strategies are generally personalized based on motor function, functional needs and fracture risk. However, fracture risk is difficult to evaluate and is not quantitatively assessed in the clinical environment. Numerous factors contribute to fractures in OI patients including, but not limited to: altered bone material properties, geometry and loading. Therefore, these are three key components for a predictive model of OI long bone fracture. Models are currently being developed to examine the fracture risk assessment and validity of FEA applied to the whole OI femur.[14, 15] Ideally, these analyses will allow the implementation of better patient-specific models for persons with OI which will provide quantitative guidelines for activity limitations to increase function and reduce fracture risk.[27]

METHODS

FE Parameters for Patient-Specific Models

Key contributions to any FE model, including that of a long bone, include: the geometry of model, boundary and loading conditions and material properties. Changes in any of these parameters can affect the output of the model. All of these factors can be dependent on the patient whose bone is being modeled.

Long Bone Geometry

Current methods employ a digital image to determine the size and amount of femoral bowing by matching the size (length and width) and level of bowing from planar x-rays. Ideally, model geometry would be directly obtained from individual CT scans. Several groups have worked on creating automated FE models from 3-D images. Most of the methods use reconstruction of CT

images to obtain patient-specific geometry and material properties. Converting a CT scan into a 3-D image file for modeling is more computationally intensive than using a "standard" geometry, but it provides a better option for a patient-specific match of geometry.[7] However, this is not feasible for children, especially those with OI, due to the high levels of radiation involved in CT scans and the high number of x-rays already acquired clinically. As CT radiation is reduced through technical advances, individual scans may become feasible. Reduced radiation exposure to obtain more accurate geometry increases the validity of the resulting models. Appropriate model geometry is essential in determining the locations of the femur that are at risk for fracture as well as the level of the risk across the entire femur (stress, strain, etc.). The effects of altering the geometry were examined to emphasize the importance of patient-specific geometry.

Boundary and Loading Conditions

Boundary and loading conditions are fundamental to an accurate FE model. They describe the allowed motion of the structure being modeled as well as the external loads. For the current patient-specific model of the femur, the modeled load scenario replicates normal ambulation. Thus, the boundary and loading conditions are obtained from gait kinematics and kinetics as well as internal muscle loading. Accurate boundary and loading conditions help replicate physiologic mechanical conditions of the femur during walking. The forces from muscle contractions during gait are estimated based on EMG activation patterns and literature.[28] The muscles are modeled as a force equal to a prescribed percentage of body weight during the various gait cycle phases. The lines of action are determined from gait kinematics and muscle origin and insertion locations on the femur. The effects of altering the loads from muscle forces were assessed to determine contributions to fracture risk in the OI femur.[14]

Material Properties

Material properties are a major determinant as to how a structure responds to loading. Structures can be defined as having the same response to mechanical loading regardless of loading direction (isotropic). Alternatively, their mechanical response may be dependent on loading direction (anisotropic). Another possibility is that the response of the material is the same in the transverse directions, but varies between the transverse and longitudinal directions (transverse isotropy). These distinctions are important when assigning material properties to an FE model. The OI femur

is currently modeled by our group as a linear elastic material, thus, Young's modulus (E) and Poisson's ratio (ν) are required inputs. We have modeled this femur as both isotropic and transversely isotropic based on literature and recent studies of OI bone specimens.[29] The isotropic model required E and ν, whereas the transversely isotropic model also required shear modulus (G) values.

Model Development

Our FE model of the OI femur was originally developed and analyzed in Abaqus CAE (Dassault Systèmes Simulia Corp.; Providence, RI) with geometry and gait dynamics derived from studies of a 12-year-old female with OI type I. This model was then used to examine parameter alteration effects on the fracture risk in the femur. Over the past few years, our FE models for fracture risk assessment of the OI femur have evolved to include isotropic tetrahedral elements as well as transversely isotropic hexahedral elements.[15, 29] The various versions follow developments to enhance model parameter with improved meshing techniques. The current model was meshed in IA-FEMesh to allow for hexahedral elements.[30] The model was altered and analyzed with Abaqus CAE. Figure 1 illustrates the improved mesh quality of the complex femoral geometry with the implementation of hexahedral meshes. Comparative analysis of the FE OI femur has been used to illustrate the importance of patient-specific parameters.[29]

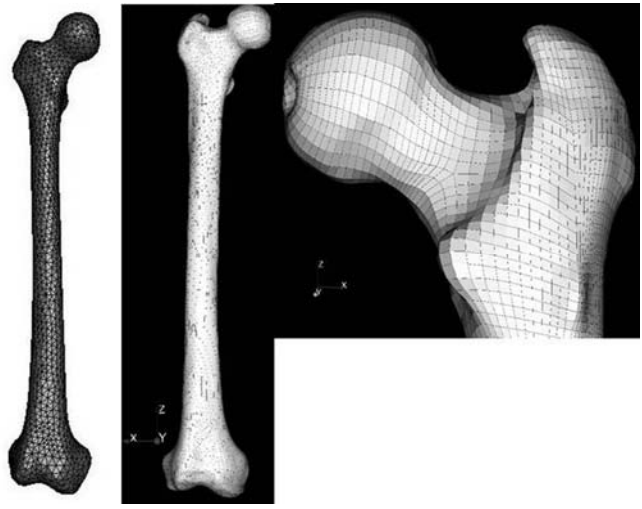

Figure 1. OI femur model with tetrahedral mesh (left) and improved hexahedral mesh (middle). A zoomed image shows the ability of the hexahedral mesh to follow the complex, curved geometry of the femoral head (right).

RESULTS

Each of the patient-specific parameters impacts the FEA results in the femoral OI model. Altering the force contributions from the femoral muscle attachments showed that stress sensitivity was greatest for loads from the gluteus medius and maximus muscles.[14] These stresses are direct contributing factors to femoral fracture risk. As stress increases, fracture risk also increases. Geometric alterations also affect the stress levels and fracture risk. A parametric study examining the effects of lateral bowing showed a positive linear increase in fracture risk with increased lateral bowing (Figure 2).[27] Other model alterations examine OI bone mechanical properties. Modeling the OI femur as a transversely isotropic material rather than an isotropic material not only affects the levels of stress, but also the stress distribution (Figure 3). The percent difference in maximum and minimum principal stresses along the longitudinal direction of a 15 mm laterally bowed OI femur showed a 5% and 7% increase, respectively, between the isotropic and transversely isotropic models.[29] The process of examining model parameter effects has continued with development of the FEA approach.

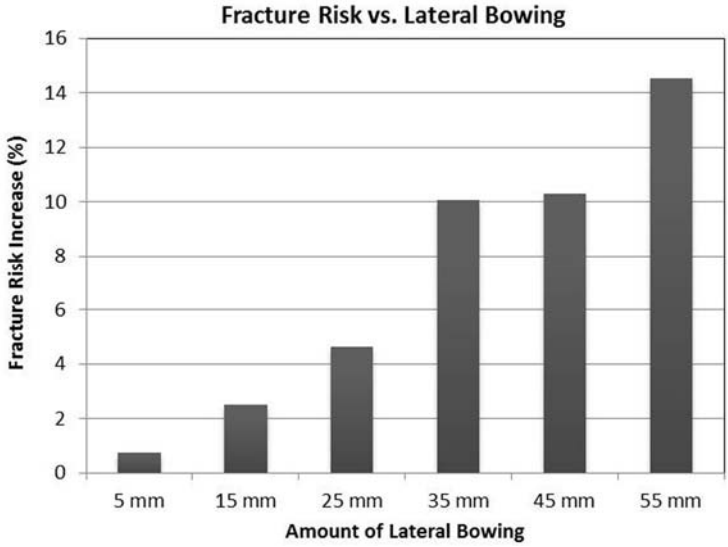

Figure 2. Fracture risk with increased lateral bowing of the OI femur.

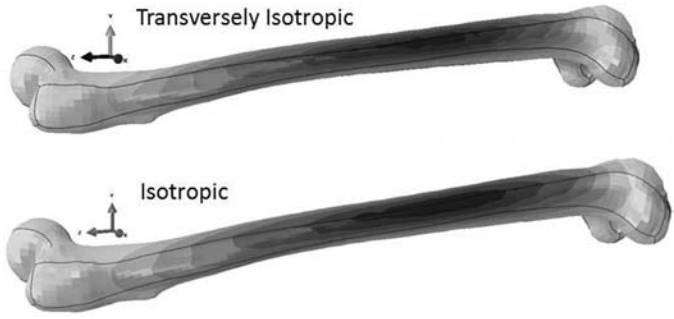

Figure 3. Contour plots of maximum principal stress on a 15 mm bowed femur for previous (top) and current (bottom) FE models. In the femoral diaphysis, stress levels increase from light to dark shading.

DISCUSSION AND CONCLUSIONS

Patient-specific parameters are essential to accurately employ FEA as a means to assess fracture risk in long bones of persons with OI. These include bone geometry, loading, and mechanical properties of OI bones. Ideally, bone geometry would be obtained from CT scans to reproduce exact 3-D geometries. However, this is often not feasible in OI patients due to high

levels of radiation exposure. In lieu of CT reconstruction, a 3-D model of long bone can be altered to match geometries measured through standard planar x-rays obtained clinically. This allows a 3-D model to be created without additional radiation exposure. A MATLAB (MathWorks; Natick, MA) program can be used to obtain various measurements from digital images of these x-rays. Our 3-D model can be modified in Abaqus CAE by altering the positions of the nodes (element vertices) of the appropriate area of the femoral diaphysis. Model loading includes both internal and external forces. Internal forces derive from contraction of muscles with origins/insertions on the modeled bone. External forces result from activities, such as gait. The parameter of greatest current interest is the mechanical properties of OI bone.

Our FE model for fracture risk assessment of the OI femur has been presented here with techniques suitable for application to any long bone. Orwoll et al. recently employed FE models to estimate vertebral bone strength in adults with OI.[31] Caouette et al. also recently published work on FE models for fracture risk assessment of the tibia in children with OI.[32] These are both discussed in more detail earlier in this text. Work has also been completed towards development of an FE model of the OI humerus.[33,34] In OI patients who use assistive devices for ambulation, humeral injuries become a greater concern than in those without assistive devices. Current study indicates that crutch walking results in high humeral loading.[35]

Accurate patient-specific FE models to assess fracture risk in long bones can help direct treatment and activity prescriptions in children with OI. Knowledge about the likelihood and location of bone fracture may also allow advances that improve the safety of various recreational and rehabilitative activities. Improved bone geometry, loading and material characterization parameters will allow continued advancement of FE models applied to quantitatively assess fracture risk in children with OI.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

OI	Osteogenesis imperfecta
FEA	Finite element analysis
FE	Finite element
CT	Computed tomography
MSF	Muscle standardized femur
E	Young's modulus
ν	Poisson's ratio
G	Shear modulus

REFERENCES

1. Becker, E.B., G.F. Carey, and J.T. Oden, *Finite Elements: An Introduction*. Vol. 1. 1981, Englewood Cliffs, NJ: Prentice-Hall, Inc.
2. Slavens, B. and G.F. Harris, Biomechanics, in *Biomedical Engineering Education and Advanced Bioengineering Learning: Interdisciplinary Concepts*, Z.O. Abu-Faraj, Editor 2012, Medical Information Science Reference (an imprint of IGI Global): Hershey, PA. 284-337.
3. Hutton, D.V., Fundamentals of finite element analysis. *International ed. McGraw-Hill series in mechanical engineering* 2004, Boston: McGraw-Hill. Xiv, 494 p.
4. Hasting, J.K., M.A. Juds, and J.R. Brauer. Accuracy and economy of finite element magnetic analysis. In *33rd Annual National Relay Conference*. 1985.
5. Zavattieri, P.D., Modeling of crack propagation in thin-walled structures using a cohesive model for shell elements. *Journal of Applied Mechanics: Transaction of the ASME* 2006;73:948-958.
6. Guo, X., et al., Critical strain of carbon nanotubes: An atomic-scale finite element study. *Journal of Applied Mechanics* 2007;74:347-351.
7. Shim, V.B., et al., The use of sparse CT datasets for auto-generating accurate FE models of the femur and pelvis. *Journal of Biomechanics* 2007;40:26-35.
8. Boyd, S.K. and R. Müller, Smooth surface meshing for automated finite element model generation from 3D image data. *Journal of Biomechanics* 2006;39:1287-1295.
9. Aamodt, A., et al., In vivo measurements show tensile axial strain in the proximal lateral aspect of the human femur. *Journal of Orthopaedic Research* 1997;15(6):927-931.
10. Viceconti, M., et al., Automatic generation of accurate subject-specific bone finite element models to be used in clinical studies. *Journal of Biomechanics* 2004;37:1597-1605.
11. Gupta, S., et al., Development and experimental validation of a three-dimensional finite element model of the human scapula. *Proceedings of the Institution of Mechanical Engineers Part H, Journal of Engineering in Medicine* 2004;218:127-142.
12. Edwards, W.B. and K.L. Troy, Finite element prediction of surface strain and fracture strength at the distal radius. *Medical Engineering & Physic*s 2012;34(3):290-298.
13. Edwards, W.B. and K.L. Troy, Simulating distal radius fracture strength using biomechanical tests: a modeling study examining the influence of boundary conditions. *Journal of Biomechanical Engineering* 2011;133(11):114301.

14. Fritz, J.M., P.A. Smith, and G.F. Harris, Muscle force sensitivity of a finite element fracture risk assessment model in osteogenesis imperfecta. *Biomedical Sciences Instrumentation* 2009;45:316-321.
15. Fritz, J.M., et al., A fracture risk assessment model of the femur in children with osteogenesis imperfecta (OI) during gait. *Medical Engineering & Physics* 2009;31:1043-1048.
16. Bosisio, M.R., et al., Apparent Young's modulus of human radius using inverse finite-element method. *Journal of Biomechanics* 2007;40: 2022-2028.
17. Taddei, F., et al., Mechanical strength of a femoral reconstruction in paediatric oncology: A finite element study. *Proceedings of the Institution of Mechanical Engineers Part H, Journal of Engineering in Medicine* 2003;217:111-119.
18. Gómez-Benito, M.J., J.M. García-Aznar, and M. Doblaré, Finite element prediction of proximal femoral fracture patterns under different loads. *Journal of Biomechanical Engineering* 2005;127:9-14.
19. Schuster, P.J., et al. Development and validation of a pedestrian lower limb non-linear 3-D finite element model. In *445h Stapp Car Crash Conferences*. 2000.
20. Matsui, Y., G. Schroeder, and U. Bosch. Injury pattern and response of human thigh under lateral loading simulating car-pedestrian impact. In *2004 SAE World Congress*. 2004. Detroit, MI.
21. Duda, G.N., et al., Influence of muscle forces on femoral strain distribution. *Journal of Biomechanics* 1998;31:841-846.
22. Duda, G.N., E. Schneider, and E.Y.S. Chao, Internal forces and moments in the femur during walking. *Journal of Biomechanics* 1997;30(9):933-941.
23. Lu, T.-W., et al., Influence of muscle activity on the forces in the femur: an in vivo study. *Journal of Biomechanics* 1997;30(11/12):1101-1106.
24. Polgár, K., et al., Strain distribution within the human femur due to physiological and simplified loading: Finite element analysis using the muscle standardized femur model. *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine* 2003;217:173-189.
25. Viceconti, M., et al., The muscle standardized femur: A step forward in the replication of numerical studies in biomechanics. *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine* 2003;217:105-110.
26. Grassi, L., et al., Accuracy of finite element predictions in sideways load configuragiont for the proximal human femur. *Journal of Biomechanics* 2012;451(2):349-399.
27. Fritz, J., Grosland, N., Smith, P., Harris, G.: Improved mesh for a finite element model of fracture risk assessment in osteogenesis imperfecta. *Proceedings of the American Society of Biomechanics* 2011. August 10-14, Long Beach, CA.
28. Fritz, J., M.S. Thesis: A patient-specific finite element model for femur fracture risk assessment in osteogenesis imperfecta type I, Marquette University, Department of Biomedical Engineering, 10/07, 80 p.
29. Fritz, J., Grosland, N., Smith, P., Harris, G.: Brittle bone fracture risk with transverse isotropy. *Proceedings of the American Society of Biomechanics* 2013. September 4-7, Omaha, NE.
30. Grosland, N.M., Shivanna, K.H., Magnotta, V.A., Kallemeyn, N.A., DeVries, N.A., Tadepalli, S.C., and Lisle, C., IA-FEMesh: An open-source, interactive, multiblock approach to musculoskeletal finite element model development, *Computer Methods and Programs in Biomedicine* 2009 Apr;94(1):96-107.
31. Orwoll ES, Shapiro J, Veith S, et al. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. J Clin Invest. Feb 3 2014;124(2):491-498.

32. Caouette C, Rauch F, Villemure I, et al. Biomechanical analysis of fracture risk associated with tibia deformity in children with osteogenesis imperfecta: a finite element analysis. Journal of musculoskeletal & neuronal interactions. Jun 2014;14(2):205-212.
33. Grover, P., Albert, C., Wang, M., Harris, G.F., Mechanical characterization of fourth generation composite humerus. Journal of Engineering in Medicine, Part H, Journal of Engineering in Medicine, 2011, 225 (12): 1169-1176.
34. Grover, P., Grindel, S. and Harris, G., Osteoanatomy of the adult humerus for rehabilitative assessment: referenced to the NIH Visible Human Project (NIH-VHP), Journal of Critical Reviews in Physical Medicine and Rehabilitation, 2011, 23(1-4): 79-93.
35. Slavens, B., Bhagchandani, N., Wang, M., Smith, P., Harris, G., An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait, Journal of Biomechanics, 2011, 44 (11) : 2162-2167.

10 NIH VISIBLE HUMAN PROJECT HUMERUS NUMERICAL AND PHYSICAL MODELS: CHARACTERIZATION FOR OSTEOGENESIS IMPERFECTA FRACTURE STUDY

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INTRODUCTION

Long bone fractures in the osteogenesis imperfecta (OI) population present with a bimodal age distribution, in the pre-adolescent and post–middle age groups.[1] The humerus is the most common upper extremity bone to fracture.[1] The fractures are most commonly transverse, subperiosteal, minimally displaced,[1] not prone to nonunion,[1] and often located at the convexity of the curved diaphysis.[2] The increased fracture risk has been attributed to multiple genetic mutations that result in quantitative (OI type I) and/or qualitative (OI types II-IV) changes in type I collagen.[3] Consequent alterations in bone material-properties and structure have been documented. The major cortical and cancellous bone material-properties affected include bone mineral density,[4,5] longitudinal modulus and hardness.[6,7] Alterations in structure at the microscopic level include thinning of trabeculae,[8] loss of cancellous and cortical bone volume,[9] loss of Haversian lamellar bone structure and resemblance to fetal woven bone[1] Structural alterations at the macroscopic level include a reduction in cross-sectional area as well as cortical width.[10,11]

Refracture at or close to the site of previous fracture is also well documented.[1] Proposed contributory factors for refracture include joint contractures and deformity of the upper extremities.[12] Humeral deformities are most common in the postero-medial (35.6%) and medial (32.2%) planes,

followed by the antero-medial plane (27.1%). Pure posterior (3.4%) and anterior (1.7%) deformities are much less common.[13] The greatest incidence of deformity has been attributed variably to both OI type I[1] and type III.[13] Amako further quantified the incidence of severity of humeral deformity in OI type III. Overall, the "no deformity" group was larger than any of the deformity groups. Among the "deformity" groups, the "30-59 degrees" was the largest group, followed by the "greater than 60 degrees" and "0-29 degree" groups.

In addition to humeral deformity, additional loads imposed on the humerus in the OI subpopulation ambulating with assistive devices such as Lofstrand crutches could further increase fracture risk.[14] This predisposition of the humerus to fracture and refracture in OI, as a consequence of altered material properties and geometry, as well as increased functional requirements (ambulatory aids) is presented in Figure 1, and can be studied at the macroscopic structural level using anatomic humerus models and corresponding 3D computational geometry.

The only known anatomic models of the human humerus are the Composite humerus models (3rd and 4th generation, Sawbones Worldwide, Pacific Research Labs, Vashon, WA). The 4th generation cortical and cancellous simulation materials in these models have been designed to closely simulate human bone material properties, including fracture toughness, fatigue life, strength, modulus and thermal stability.[15] Consistent geometry and small-range variability in material properties have allowed researchers to use similar femur and tibial models for clinical applications,[16,17] as an alternative to cadaveric bones, which require strict preservation and handling precautions.[18] However, increased fracture risk in the humerus in OI has not been studied using these models.

In addition, the 3D-computational geometry of these models lacks the potential for source-derived addition of muscle attachments, as would be possible for an anatomic model derived from a complete body visceral and musculoskeletal image dataset, such as the NIH Visible Human Project.[19] This presently non-extant muscle attachment-mapped geometry of the humerus, analogous to the existing "Standardized 3D computational geometry" of the composite femur,[20] has benchmark value.

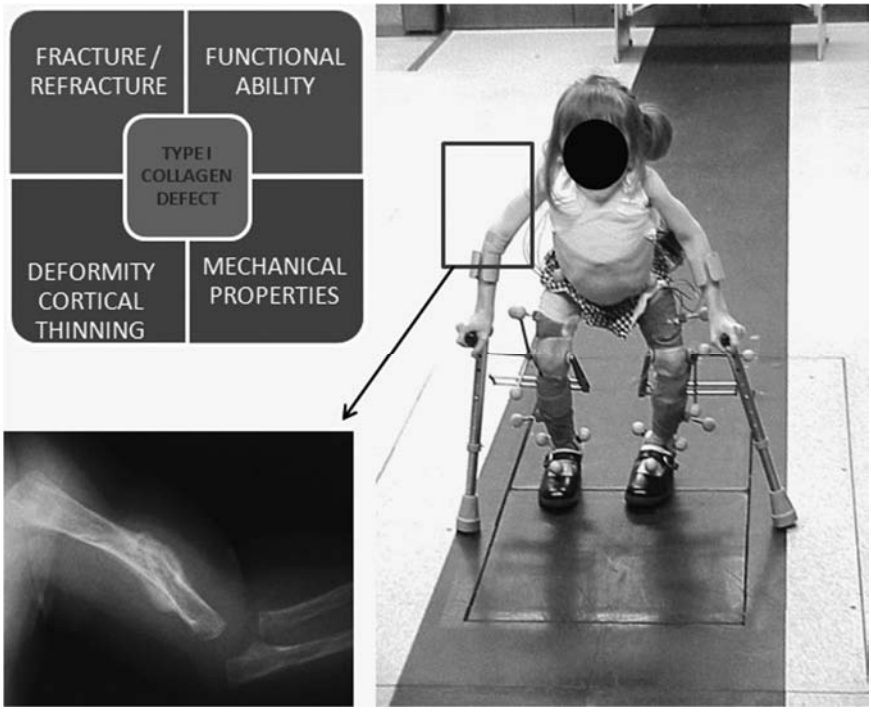

Figure 1. Factors predisposing the humerus to fracture and refracture in osteogenesis imperfecta.

Finally, the NIH Visible Human Project (NIH VHP) image-dataset based anatomic humerus physical model and its corresponding 3D-computational geometry can be used together as a "Reference Humerus" model to create a finite element (FE) humerus model. This FE model can be modified to simulate OI, and study both pathology-specific and patient-specific fracture risk. No standardized physical model and corresponding computational geometry for developing FE models of the humerus has been reported in the literature.

The goal of the overall project is to study humeral fracture risk in OI, especially in the subpopulation ambulating with Lofstrand crutches, using a mechanically and anatomically characterized "Reference Humerus" tool. The project is divided into three phases. The present study focuses on the first phase of this project, namely, the design and development of the a "Reference Humerus" model, comprising both a physical model and computational geometry, from the NIH Visible Human Project, based upon identified "definition-of-reference" criteria. Anatomic and mechanical

characterizations of this model, followed by the model's application to OI for studying fracture risk, comprise the second and third phases, respectively.

METHODS

"Definition-of-reference" criteria were identified and incorporated in the development process of the "Reference Humerus" model. The development process was comprised of three sequential phases, namely, (a) development of 3D-humerus geometry from the NIH Visible Human Project image dataset, (b) development of a physical model, the Humerus-Visible Human Project (H-VHP) from the 3D-humerus geometry, and (c) development of 3D-computational geometry of the H-VHP. The physical model, H-VHP, and its 3D-computational geometry together comprise the "Reference Humerus" model.

"Definition-of-Reference" Criteria

Five criteria were defined for the development of the "Reference Humerus" model. The first four criteria were used to accomplish the first phase of the project, which is the focus of this publication. The fifth criterion is pertinent to the second phase.

Physical Model, H-VHO: Standard Source of Geometry

The NIH Visible Human Project, comprised of MRI, CT, and new and old anatomical image subsets, has been used for a multitude of technical (image processing, virtual reality) and clinical (diagnosis, presurgical planning) research and teaching projects, as well as for commercial applications extending from art to industry, by approximately 2,000 licensees in over 48 countries.[19] As a source of geometry for an FE model of the humerus, the NIH VHP offers significant advantage over both composite humerus models [15] and cadaveric humeri. This is because this standard source of accurate, accessible, and complete musculoskeletal and visceral high-resolution anatomic data of one specific human enables potential addition of soft tissues such as muscles and ligaments, as well as joints to the osteoanatomy of the humerus. Among the data subsets, the new anatomic image subset is preferred to the CT scan subset, since the latter is lower in resolution and lacks complete definition of the distal humerus. A sample image slice from the NIH VHP newer anatomic image dataset demonstrating complete visceral and musculoskeletal image data is presented in Figure 2.

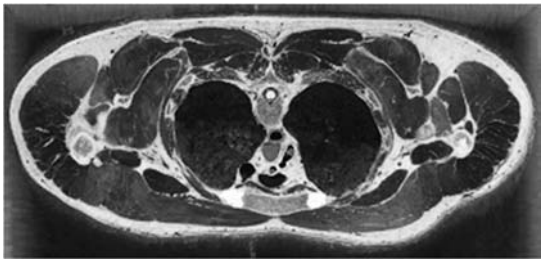

Figure 2. Sample image slice from the NIH VHP newer anatomic image dataset demonstrating complete visceral and musculoskeletal image data (distributed by National Technical Information Service, Springfield, VA 22161).

Standard Physical Model, H-VHP: Standard Development Protocol

Standard image segmentation techniques and software (Image J[21] and Mimics, M**aterialise US,** 44650 Helm Court, Plymouth, MI 48170, USA) were first identified from literature as part of the design process to create a 3D-humerus geometry from the Visible Human Project image dataset. The development criteria required identification of a standard manufacturer of long bone models, modification of the 3D-humerus geometry as per the physical model (H-VHP) manufacture requirements, and consensus on the minimum acceptable standards for the rapid prototyping manufacturing process.

Physical Model, H-VHP: Standard Materials of Manufacture

State-of-the-art cortex-simulation and cancellous-simulation materials were chosen to manufacture the physical (H-VHP) model. The cortex-simulation material is comprised of short-fiber reinforced epoxy, and the cancellous-simulation material is made of rigid polyurethane foam. Manufacturer documented properties for the 4th generation cortex-simulation material include longitudinal and transverse tensile moduli of 16.0 and 10.0 GPa, respectively, a compressive longitudinal modulus of 16.7 GPa, and material density of 1.64 gm/cc. Cancellous- simulation material properties include a modulus of 0.155 GPa, and density of 0.27 gm/cc.[15]

Standard 3D-Computational Geometry of H-VHP: Development Criteria

A standardized protocol involving sequential image processing (Mimics, Materialise US, Plymouth, MI 48170, USA), computer aided design (Solidworks, Dassault Systèmes SolidWorks Corporation, Waltham, MA 02451), and finite element techniques (Abaqus, Simulia, Rising Sun Mills,

Providence, RI, USA) was developed to derive the 3D-computational geometry from the physical model, H-VHP.

Reference Humerus: Clinical and Research Applicability Criteria

Protocols for the second phase of the project, namely, mechanical characterization of the physical model, H-VHP, and anatomic characterization of the corresponding 3D-computational geometry, were defined in accordance with this criterion. The protocol for mechanical characterization was guided by studies on experimental evaluation of mechanical properties of other composite and cadaveric humeri.[22] The anatomic characterization protocol was defined with reference to literature on surgical procedures and shoulder and elbow arthroplasty implant design.[23,24] Figure 3 presents some of the surgical anatomic parameters of the humerus that were identified.

"Reference Humerus" Model Development

Development of 3D-Humerus Geometry from the Visible Human Project Image Dataset

Cross-sectional anatomic image slices from the Visible Human Project Male Thorax image dataset were imported into Image J for preliminary evaluation. For the purpose of further importing these slices into Mimics, the image slices were converted into a stack of .bmp format images using the Batch Converter tool in Image J. However, preliminary examination of the dataset revealed three misaligned slices. To accurately realign these image slices using the StackReg tool in Image J, the .bmp data stack was converted into three .tiff data stacks, with an overlap of one image for each consecutive set. The three .tiff stacks were then realigned using the StackReg tool, and were converted back into one accurately aligned .bmp format stack. However, owing to the large image data size (9.7 MB/ image) as well as limitations on the size of imported stacks in Mimics, the data had to be imported from Image J into Mimics as three contiguous .bmp subset image stacks.

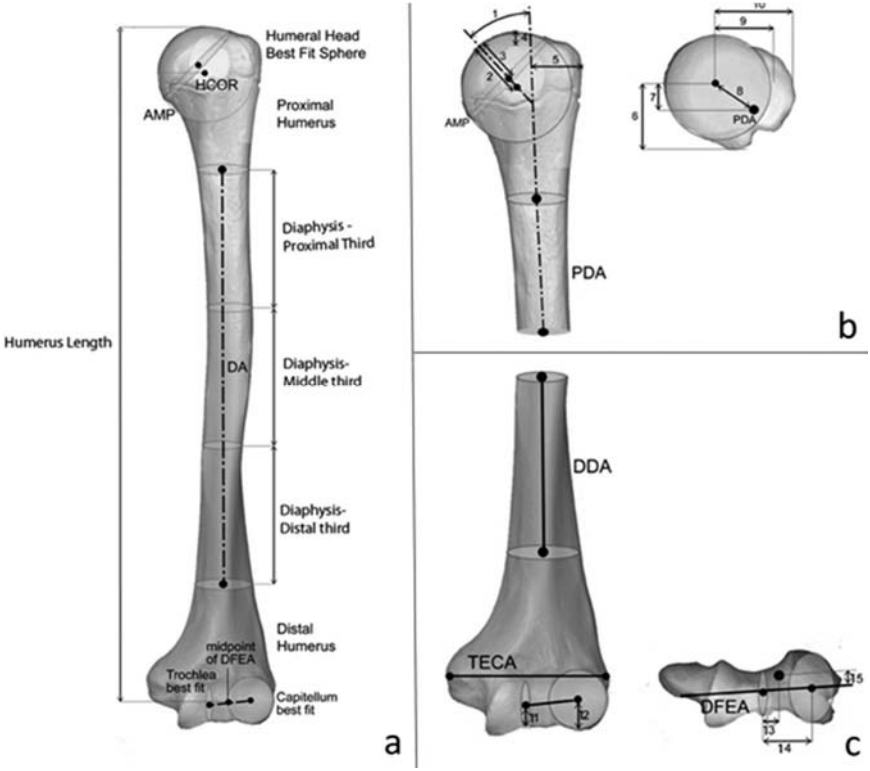

Figure 3. Surgical anatomic parameters of the humerus identified from the literature on shoulder and elbow arthroplasty for future anatomic characterization of the "Reference-Humerus" model. A. Humerus anatomic best-fits; b. Proximal humerus parameters; c. Distal humerus parameters. Parameters Illustrated: 1. Inclination; 2. Proximal Articular Surface radius; 3. Humeral Head height; 4.Humeral Head to Greater Tuberosity height; 5.Greater Tuberosity width; 6. Lesser Tuberosity — Anterior Offset; 7.Humeral Head — Posterior Offset; 8.Humeral Head — Total Offset; 9.Humeral Head — Medial Offset; 10.Greater tuberosity — Lateral Offset; 11.Trochlear Sulcus — Radius of Curvature; 12. Capitellum — Radius of Curvature; 13.Distal Flexion Extension Axis — Medial Offset; 14. Distal Flexion Extension Axis length; 15. Distal Flexion Extension Axis —Anterior Offset.

Mimics 9.0 was then used to window, threshold and segment the cross-sectional image slices within the stacks to include a smaller image area surrounding the humerus, and thus reduce the overall data size of each stack. The resulting three smaller sized stacks were combined into one, and reprocessed with windowing and thresholding to segment out the *outer cortex*, *inner cortex/outer cancellous* and *inner cancellous surfaces*. The three fine triangular geometric mesh surfaces were refined further and exported in .stl format.

Development of Physical Model, H-VHP from 3D-Humerus Geometry

The *outer cortex* and *inner cortex/outer cancellous surface* geometries (.stl format) were sent to a standard manufacturer of composite bones, Sawbones Worldwide (Pacific Research Labs, Vashon, WA, USA). Based upon these two .stl files, stereolithography files were generated, which were used to create individual molds for the cortex and the core, respectively, using the rapid prototyping technique. Additional manufacturing requirements necessitated the use of two transverse cross-pins, one each in the proximal and distal segments of the humerus, and a mandrel that spanned approximately the proximal three-fourths of the length of the model and exited at the proximal end.

The initial step in the model manufacturing process from the molds required the placement of the mandrel and crosspins into the core mold. The cavity of the core mold was filled with solid polyurethane foam cancellous-simulation material to encapsulate the mandrel and cross-pins. The core was then transferred to the cortex mold, where it was suspended in place by the mandrel and the cross-pins. Short-glass fiber reinforced epoxy cortex-simulation material was then injected around the core. Following heat-curing, the mandrel and cross-pins were removed, the model was cooled down, and the parting line of the model was trimmed. The model was then heat post-cured and modified to regain the original anatomic configuration.

Development of 3D-Computational Geometry of the H-VHP

The physical model was scanned into 320 transverse sections using a CT scanner, at a resolution of 512 x 512 x 320 pixels, with a voxel size of 0.3mm x 0.3mm x 1.25mm at 8 bits. The transverse images were imported into Mimics, and mutually exclusive 3D *cortical, cancellous and medullary surfaces* of the H-VHP physical model were developed and exported as .stl files. To convert the .stl files into a usable format for ABAQUS, the .stl geometric mesh surface files (comprised of triangles) were imported into Solidworks.

Using the Scan-to-3D tool in Solidworks, the triangle mesh surfaces were then converted into polygon geometric mesh surfaces, since the polygons better approximated the curved osteoanatomy of the humerus, compared with triangles. The polygon geometry mesh surfaces were then imported into ABAQUS as three volumes. These three volumes, namely, the *cortical volume,* the *cancellous volume,* and the *medullary canal volume* were merged, while

retaining intersecting surfaces to ensure that consecutive volumes shared adjacent surfaces but did not overlap (Figure 4).

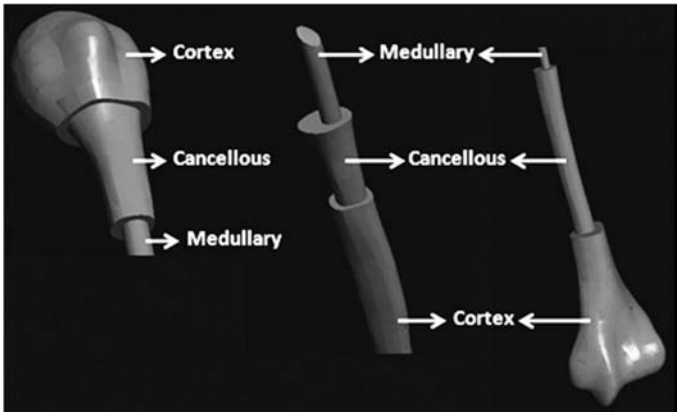

Figure 4. 3D-computational geometry of H-VHP: Cortical, cancellous and medullary canal volumes, with retained intersecting surfaces.

RESULTS

3D Humerus Geometry Developed from the NIH Visible Human Project Image Dataset

The 3D-humerus geometry developed from the NIH Visible Human Project image dataset included three non-intersecting geometric mesh surfaces, namely, the *outer cortex, inner cortex/outer cancellous and inner cancellous surfaces*. Each mesh surface was composed of thousands of very small triangles that helped to closely approximate the curved surfaces in the humerus osteoanatomy. Anterior, posterior, lateral oblique and medial oblique views of the 3D-humerus geometry are presented in Figure 5.

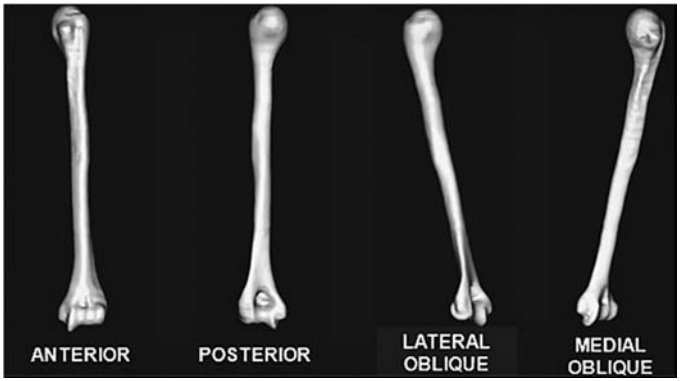

Figure 5. 3D-humerus geometry developed from the Visible Human Project image dataset.

Reference Humerus Model

Physical Model, H-VHP

The layers of the physical model were identical to the source 3D-computational geometry, and were comprised of the *cortex and cancellous layers* and a *medullary canal*. The *cortex layer* was the outer volume between the cortex mold and the core mold. The *cancellous layer* was the inner volume between the core mold and the mandrel. The *medullary canal* was the inner hollow cavity in the model that was open proximally and blind-ended distally, and was based upon the circular-cross-sectional tapered cylinder mandrel geometry. Anterior, posterior, lateral and medial views of the physical model, H-VHP, are presented in Figure 6.

3D-Computational Geometry of the H-VHP

The 3D-computational geometry of the H-VHP was comprised of three surfaces, and three derivative non-overlapping, contiguous volumes. The three surfaces were the outer cortical surface, the inner cortical/outer cancellous surface, and the inner cancellous surface. The three volumes were the outer cortical volume, between the outer and inner cortical surfaces, the inner cancellous volume, between inner cortical and inner cancellous surface, and the medullary canal volume, based upon the mandrel geometry. Anterior, posterior, lateral oblique and medial oblique views of the 3D-computational geometry of the H-VHP are presented in Figure 7.

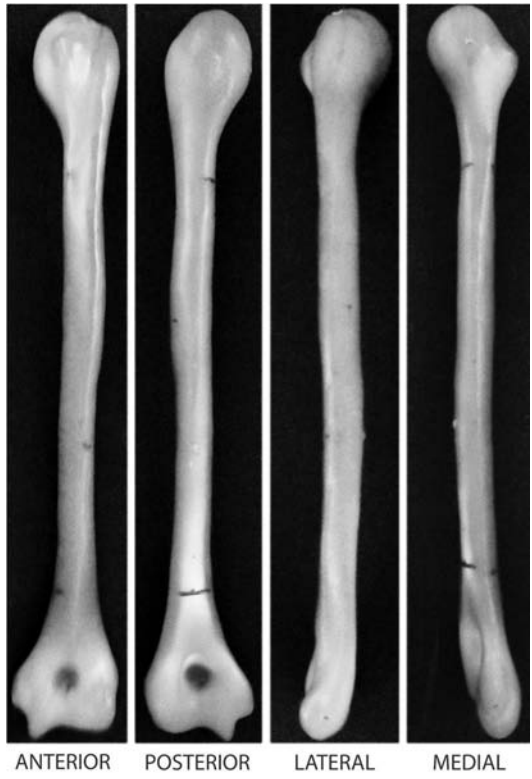

Figure 6. Physical model, H-VHP.

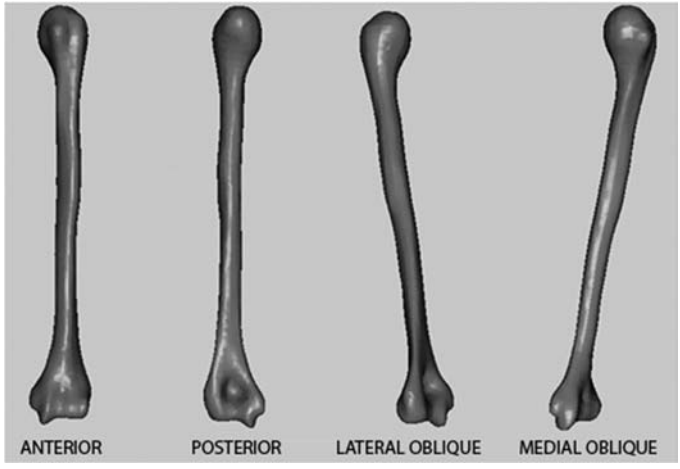

Figure 7. 3D-Computational geometry of the H-VHP.

DISCUSSION

The "Reference Humerus" model, developed based upon "definition-of-reference" criteria, from the NIH Visible Human Project, is a biomechanical tool with many applications. The model is comprised of comprising a structurally characterized physical model, H-VHP, and anatomically characterized corresponding 3D-computational geometry. Some possible clinical applications include surgical technique practice on the physical model, H-VHP, and presurgical planning with the 3D-computational geometry. Potential research applications include evaluation of trauma-fixation and arthroplasty implants using both the physical model and the geometry. The 3D-computational geometry can also be used for the development of finite element (FE) models of the humerus, which can then be used to study various musculoskeletal pathologies, including osteoporosis, bone metastasis, and OI.

Many characteristic features of OI make the evaluation of fracture risk in this pathology amenable to study by the FE method (Pathology-specific FE modeling). First, the skeletal system is the major system affected by the underlying qualitative/quantitative alteration in Type I collagen.[3] Since the FE method is already a well documented tool for studying other musculoskeletal pathologies,[25] and bones and muscles can be modeled with anatomic accuracy in FE simulations, this method is suitable for studying the skeletal manifestations in OI. Second, the clinical predisposition to fracture can be correlated with the magnitude and distribution of predefined fracture criteria parameters such as Von Mises stress and principal strain[26] that are provided by the FE solver. Third, the alteration in material properties of bone in OI, especially the longitudinal modulus, can be easily incorporated into the FE model.

Combined with bone material property and cross-sectional geometry information specific to OI, the "Reference Humerus" model, with its undeformed 3D-computational geometry, is sufficient to study the quantitative effect of altered material properties and cross-sectional geometry on fracture risk in OI. Preliminary sensitivity studies conducted by the authors indicate maximum sensitivity of fracture-risk strain criteria to the longitudinal modulus of the cortex (among material property parameters), followed by the cortical thickness and the cortical cross-sectional area (among cross-sectional geometry parameters).

Additional OI population patient-specific inputs to the pathology-specific FE model developed from the "Reference Humerus" model (Patient-specific FE modeling) can guide management of individual OI patients. The two main inputs include deformity and (kinetic and kinematic) motion analysis data. Patient-specific humeral geometry of the deformity can be obtained non-invasively using radiographic methods. These methods could involve low-radiation single-plane (plane-of-maximum-deformity) or two-plane (orthogonal) digital X-rays or, less likely, given the radiation concerns in weakened bone, higher-radiation CT scans. The 2D-geometric information can then be used to alter the "Reference Humerus" model 3D-computational geometry[27] to closely simulate patient-specific humerus geometry (OI patient-specific "Reference Humerus" FE model).

Patient-specific motion analysis data can be obtained from task-specific clinical trials, such as for Loftstrand crutch-aided ambulation. This data can then be incorporated into the OI patient-specific "Reference Humerus" FE model as loads and boundary conditions to develop an OI patient-specific task-specific "Reference Humerus" FE model. These models can provide quantitative output on the magnitude and distribution of strains in the humerus model specific to the task, which could then be used to guide individualized rehabilitation of patients.

An additional input that can increase the sophistication of the FE model for Loftstrand crutch-aided ambulation is the electromyography (EMG) data of shoulder and elbow muscles that attach on the humerus and are involved in this task. The important muscles are the Biceps for flexion, Triceps for extension, Deltoid for abduction, and Pectoralis major and Latissmus dorsi for adduction.[28] The EMG data can be used to derive muscle force magnitude[29] using muscle-modeling software.[30] This information on magnitude can be combined with task-specific line(s) of muscle action data in extant literature[31] to model EMG-based muscle action as force vectors. Individual muscle force vectors can then be applied as distributed vector loads at the respective muscle attachments on the "Reference Humerus" model 3D-computational geometry to include the effect of the major muscles in determining humerus fracture risk in OI.

While accurate mapping of the muscle attachments on to the "Reference Humerus" model 3D-computational geometry is a work in progress, the available image data from the same-source complete musculoskeletal NIH Visible Human Project image dataset will ensure accuracy. Future design

work on the "Reference Humerus" model includes development of shoulder and elbow FE models. While the utility of this tool by our research group is focused on OI, the availability of this tool to the research community for studying humerus involvement in trauma/musculoskeletal pathology is also planned. Ultimately, it is hoped that this tool will contribute to the current initiative towards standardization and establishment of worldwide data repositories.

ABBREVIATIONS AND SPECIFIC TERMINOLOGY

FE	Finite element
H-VHP	Physical model of the humerus derived from the 3D humerus geometry of the Visible Human Project
NIH VHP	National Institutes of Health Visible Human Project
OI	Osteogenesis imperfecta
Reference-Humerus	H-VHP and its 3D-Computational Geometry
3D-Humerus Geometry	Humerus geometry derived from the NIH VHP
3D-Computational Geometry	Computational geometry derived from the physical model, H-VHP

REFERENCES

1. King JD, Bobechko WP. Osteogenesis Imperfecta: an orthopaedic description and surgical review. *J Bone Joint Surg Br.* 1971;53-B(1):72-89.
2. Falvo KA, Root L, Bullough PG. Osteogenesis Imperfecta: clinical evaluation and management. *J Bone Joint Surg Am.* 1974; 56(4):783-793.
3. Sillence DO, Senn A, Danks DM. *Genetic heterogeneity in Osteogenesis Imperfecta. J Med Genet.* 1979;16:101-116.
4. Wekre LL, Eriksen EF, Falch JA. Bone mass, bone markers, and prevalence of fractures in adults with Osteogenesis Imperfecta. *Arch Osteoporos.* 2011;6(1-2):31-38.
5. Zionts LE, Nash JP, Rude R, Ross T, Stott NS. Bone mineral density in children with mild Osteogenesis Imperfecta. *J Bone Joint Surg Br.* 1995;77(1):143-147.
6. Fan Z, Smith PA, Harris GF, Rauch F, Bajorunaite R. Comparison of nanoindentation measurements between Osteogenesis Imperfecta Type III and Type IV and between different anatomic locations (femur/tibia versus iliac crest). *Connect Tissue Res.* 2007;48(2):70-75.
7. Fan Z, Smith PA, Eckstein EC, Harris GF. Mechanical properties of OI type III bone tissue measured by nanoindentation. *J Biomed Mater Res A.* 2006;79(1):71-77.
8. Jones SJ, Glorieux FH, Travers R, Boyde A. The microscopic structure of bone in normal children and patients with Osteogenesis Imperfecta: a survey using backscattered electron imaging. *Calcif Tissue Int.* 1999;64(1):8-17.
9. Rauch F, Travers R, Parfitt AM, Glorieux FH. Static and dynamic bone histomorphometry in children with Osteogenesis Imperfecta. *Bone.* 2000;26(6):581-589.

10. Gatti D, Colapietro F, Fracassi E, Sartori E, Antoniazzi F, Braga V, Rossini M, Adami S. The volumetric bone density and cortical thickness in adult patients affected by Osteogenesis Imperfecta. *J Clin Densitom.* 2003;6(2):173-177.
11. Hanscom DA, Winter RB, Lutter L, Lonstein JE, Bloom BA, Bradford DS. Osteogenesis Imperfecta. Radiographic classification, natural history, and treatment of spinal deformities. *J Bone Joint Surg Am.*1992;74(4):598-616.
12. Primorac D, Rowe DW, Mottes M, Barisić I, Anticević D, Mirandola S, Gomez Lira M, Kalajzić I, Kusec V, Glorieux FH. Osteogenesis Imperfecta at the beginning of bone and joint decade. *Croat Med J.* 2001;42(4):393-415.
13. Amako M, Fassier F, Hamdy RC, Aarabi M, Montpetit K, Glorieux FH. Functional analysis of upper limb deformities in Osteogenesis Imperfecta. *J Pediatr Orthop.* 2004;24(6):689-694.
14. Slavens BA, Bhagchandani N, Wang M, Smith PA, Harris GF. An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait. *J Biomech.* 2011;44(11):2162-2167.
15. Sawbones Worldwide website. http://www.sawbones.com. Accessed February 19, 2012.
16. Sangiorgio SN, Ebramzadeh E, Longjohn DB, Dorr LD. Effects of dorsal flanges on fixation of a cemented total hip replacement femoral stem. *J Bone Joint Surg Am*. 2004;86-A(4):813-820.
17. Peindl RD, Zura RD, Vincent A, Coley ER, Bosse MJ, Sims SH. Unstable proximal extraarticular tibia fractures: a biomechanical evaluation of four methods of fixation. *J Orthop Trauma.* 2004;18(8):540-545.
18. Taddei F, Martelli S, Reggiani B, Cristofolini L, Viceconti M. Finite-element modeling of bones from CT data: sensitivity to geometry and material uncertainties. *IEEE Trans Biomed Eng.* 2006;53(11):2194-2200.
19. National Institutes of Health Visible Human Project website. http://www.nlm.nih.gov/research/visible/visible_human.html. Updated Feb 19 2012. Accessed Feb 19, 2012.
20. Viceconti M, Casali M, Massari B, Cristofolini L, Bassini S, Toni A. The 'standardized femur program' proposal for a reference geometry to be used for the creation of finite element models of the femur. *J Biomech.* 1996; 29(9):1241.
21. Abramoff MD., Magelhaes PJ, Ram SJ. Image Processing with ImageJ. *Biophotonics International*. 2004; 11(7):36-42.
22. Grover P, Albert C, Wang M, Harris GF. Mechanical characterization of fourth generation composite humerus *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine.* 2011; 225(12):1169-1176.
23. Pearl ML. Proximal humeral anatomy in shoulder arthroplasty: Implications for prosthetic design and surgical technique. *J Shoulder Elbow Surg.* 2005;14(1 Suppl S):99S-104S.
24. Brownhill JR, King GJ, Johnson JA. Morphologic analysis of the distal humerus with special interest in elbow implant sizing and alignment. *J Shoulder Elbow Surg.* 2007;16(3 Suppl):S126-132.
25. Büchler P, Ramaniraka NA, Rakotomanana LR, Iannotti JP, Farron A. A finite element model of the shoulder: application to the comparison of normal and osteoarthritic joints. *Clin Biomech (Bristol, Avon).* 2002;17(9-10):630-639.
26. Nalla RK, Kinney JH,Ritchie RO. Mechanistic fracture criteria for the failure of human cortical bone *Nature Materials* 2003; 2:164–168.
27. Zheng G, Gollmer S, Schumann S, Dong X, Feilkas T, González Ballester MA. A 2D/3D correspondence building method for reconstruction of a patient-specific 3D bone surface model using point distribution models and calibrated X-ray images. *Med Image Anal.* 2009;13(6):883-899.

28. Standring S. 40th ed. *Gray's Anatomy*. Churchill-Livingstone; 2009.
29. Lawrence JH, De Luca CJ. Myoelectric signal versus force relationship in different human muscles. *J Appl Physiol.*1983; 54(6):1653-1659.
30. Delp SL, Anderson FC, Arnold AS, Loan P, Habib A, John CT, Guendelman E, Thelen DG. OpenSim: open-source software to create and analyze dynamic simulations of movement. *IEEE Trans Biomed Eng.* 2007;54(11):1940-1950.
31. Ackland DC, Pandy MG. Lines of action and stabilizing potential of the shoulder musculature. *J.Anat.*2009:215:184-197.

11 MATERIAL AND STRUCTURAL ASPECTS OF BONE IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Bone fragility is a fundamental problem in individuals with osteogenesis imperfecta (OI). The mechanisms behind this fragility, however, are not yet well understood. Multiple factors appear to contribute to the increased fracture risk in OI. At the structural level, bone mass deficiency can result in increased stress levels within bones. The underlying mineral and collagen abnormalities that define OI are also believed to result in compromised material-level properties. The variability of collagen biochemical irregularities causing OI and the corresponding heterogeneity of disease severity result in abnormalities that are not easily generalized within the OI population.

The aims of this chapter are to introduce basic mechanical notions pertaining to the strength of structures and materials, and to present a synthesis of existing literature regarding the mechanical properties of bones in OI.

STRUCTURAL MECHANICS

The maximum load that a structure such as a bone can withstand without fracturing is referred to in engineering terms as structural strength. The structural strength of a bone is dependent on its size and shape, how the

material is distributed within the bone, the intrinsic (material-level) properties of the bone, and the type of loading.

Physiological loads generally include a combination of four types of loading: tension, compression, torsion and bending (Figure 1). When subjected to these loads, bones will deform by elongating, compressing, twisting, and bending, respectively.

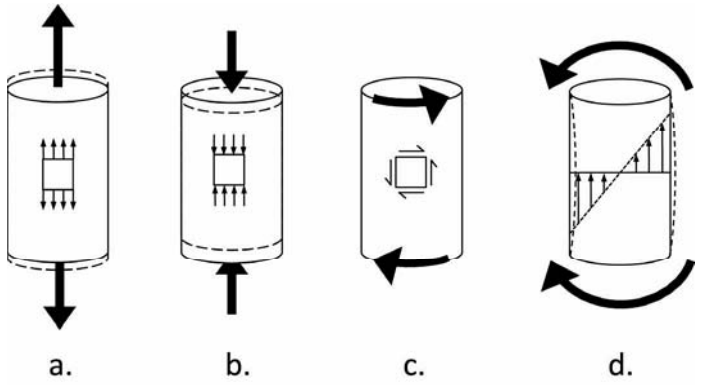

Figure 1. Four major types of loading: tension, generating tensile stresses (a); compression, generating compressive stresses (b); torsion, generating shear stresses (c); and bending, generating a combination of tensile and compressive stresses (d).

When an applied load remains sufficiently low, the structure behaves elastically and the deformation will reverse once the load is removed. The ratio between the load applied and the resulting deformation is called stiffness. For example, under pure tensile loading the ratio between the tensile load and the resulting elongation is the tensile stiffness of the structure. Similarly, under a bending load, the ratio between the applied load and the deformation, i.e., deflection, is bending stiffness.

The load threshold above which a structure will sustain permanent damage is called structural strength. Loosely speaking, stiffness and structural strength are sometimes referred to as "structural properties", although these quantities are not true properties because they are not constant. Instead, they vary greatly as a function of the size and geometry of the structure and the loading configuration. For example, for a structure such as a cylinder or a bone under tension or compression loading, structural strength is equal to the strength of the material itself (this property will be discussed in the Mechanics of Materials section of this chapter) multiplied by the cross sectional area perpendicular to the load. Thus, for a given material, a

structure (e.g., bone shaft) with a greater cross-sectional area will be able to withstand greater tensile and compressive loads (Figure 2, left).

In bending and torsion, structural strength is affected not only by the cross-sectional area of material carrying the load, but also by how far away the material is located from a central axis. For example, with a given cross sectional area, stiffness and structural strength in bending and torsion will be higher in for wider bone shaft than for a narrower one, the latter having more bone material situated further from the central axis (Figure 2, right).

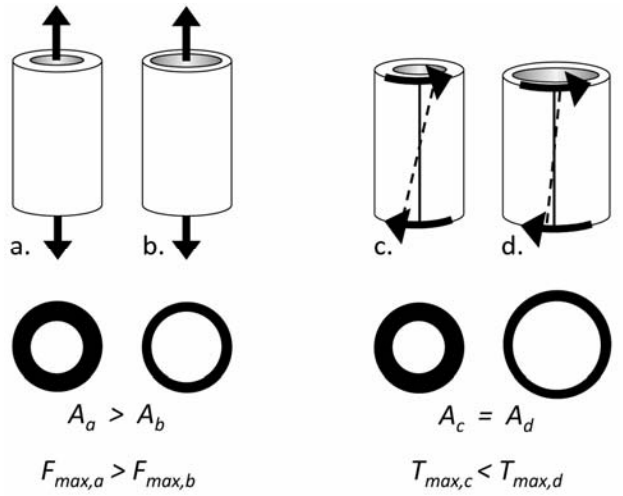

Figure 2. Cylinders in tension (left) and torsion (right). In tension, structural strength, i.e., the maximum force that can be carried without fracture (F_{max}), is proportional to the cross-sectional area (A). If cylinders a and b are made of the same material, cylinder a, having a greater cross-sectional area, will have greater structural tensile strength. Torsional strength, i.e., the maximum torque that can be applied without fracture (T_{max}), is also proportional to how far away the material is located from a central axis. Thus, although cylinders c and d have the same cross-sectional area, cylinder d can resist a higher torque because of its wider diameter.

BONE STRUCTURE IN OI

From a structural perspective, individuals with OI tend to have low bone mass. There is diminished bone density, cortical thickness, and bone shaft diameter. In histomorphometric studies of iliac crest biopsies, reduced amounts of cortical (compact) bone and trabecular (spongy) bone were observed in children with OI when compared with controls.[1,2] Biopsy core width, cortical width, and trabecular bone volume were significantly decreased, and the decreased trabecular bone volume was attributed to a reduction in trabecular number and trabecular thickness. Cortical width and

trabecular bone volume was, on average, lower in OI types III and IV than in OI type I.[1]

In the diaphysis (shaft portion) of long bones, where many fractures tend to occur, variable cortical diameters and thicknesses are observed within the OI population. However, individuals with the more severe OI types tend to have narrower diaphyses and thinner cortical shells than do typical individuals. A significant amount of bowing can also develop in children with moderate and severe OI. Having smaller bones and lower bone mass means that there is less bone material to carry applied loads. Individuals with OI can therefore be at a "structural" disadvantage in resisting all types of loads. This disadvantage is most pronounced in individuals with moderate and severe forms of the disorder, for whom the bone volume can be especially low and the presence of bowing can generate additional bending loads.

MECHANICS OF MATERIALS

As discussed earlier, structural strength is a variable measure. Therefore, how can we determine if a level of force is sufficiently low to avoid damage or fracture? To address this question, the engineering concepts of stress and strain are introduced. Let's first consider a simple type of loading: pure tension. Under a tensile load, a structure such as a rod or a bone will deform by elongating. To predict how much elongation will occur and how much load (force, F) a structure can carry without fracturing, the load and the resulting deformation must be normalized to account for the size of the structure (Figure 3). The normalized load is called stress (σ) and is equal to force F divided by cross-sectional area A. The normalized deformation is called strain (ε) and it is equal to the change in length divided by initial length, For example, if a rod is stretched to 101% of its initial length, it will have a strain of 1%.

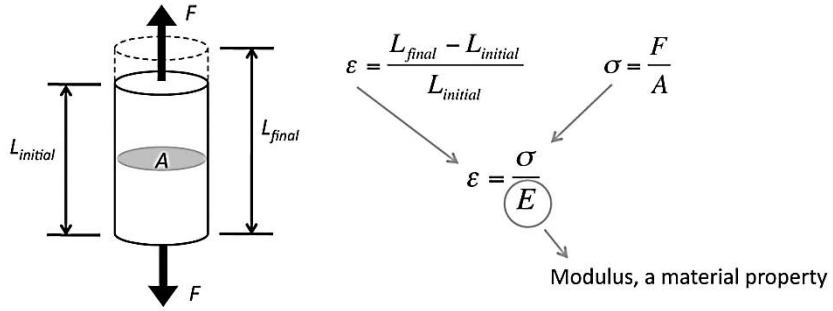

Figure 3. Rod in tension. The relationship between elongation ($L_{final} - L_{initial}$) and applied load (F), is related to the geometry of the rod, i.e., its initial length ($L_{initial}$) and cross sectional area (A), and a material property called elastic modulus (E).

There are three types of stresses: tensile, compressive and shear (Figure 4). Each type of loading results in a different configuration of stresses within a structure (Figure 1). Tensile loading results in tensile stresses, compression loading in compressive stresses, and torsion in shear stresses. Bending results in a combination of stresses. For example, when a straight rod is subjected to bending loads deflection occurs, causing tensile stresses on the convex side and compressive stresses on the concave side (Figure 1d).

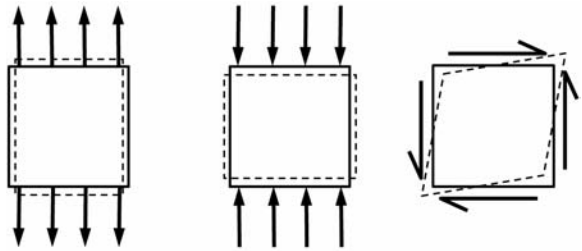

Figure 4. Types of stresses: tensile (left), compressive (center) and shear (right). Each type of stress induces deformation within the material (dashed lines).

In reality, most structures, including bones, are subjected to multiple (combined) loads simultaneously and the resulting stresses within the material are compounded among these loads. For example, when a bone is subjected to bending and compressive loads simultaneously, the compressive stress within the bone will be equal to the sum of the compressive stresses caused by the compressive load and those resulting from the bending load.

For many materials, a linear relationship exists between stress and strain up to a certain stress level (Figure 5). These materials, which include most metals and ceramics, exhibit mechanical behavior that is 'linear elastic', and

the ratio between stress and strain in this linear region, i.e., the slope of the stress-strain curve, is a constant. In tension and compression, this constant is a material property called the elastic modulus (E). Elastic modulus is a constant that describes a material's stiffness, i.e., its ability to resist elastic (recoverable) deformation under load. Materials with a high elastic modulus such as steels deform little, whereas materials with a low modulus such as cork or wood deform much more under a given load.

Strictly speaking, bone is not a linear elastic material because its elastic modulus is affected by temperature and strain rate, i.e., how fast it is deformed. Nonetheless, it is often appropriate to assume that the material behavior of bone is linear elastic at a specific strain rate and temperature, such as physiological body temperature.

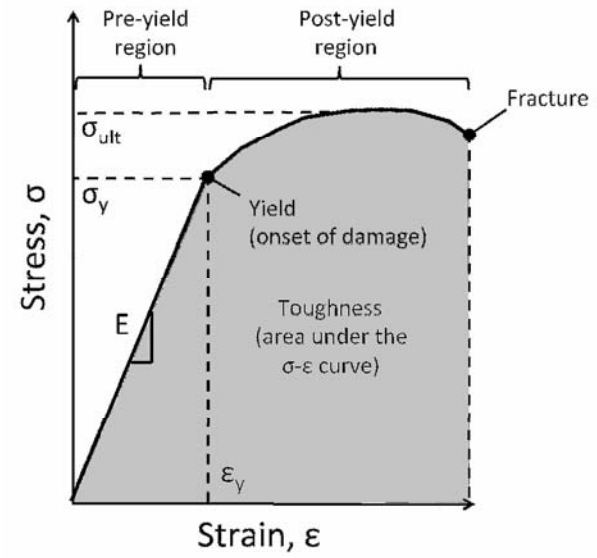

Figure 5. Tensile properties for a material exhibiting linear elastic behavior: Elastic modulus (E), yield strength (σ_y), yield strain (ε_y), and ultimate strength (σ_{ult}).

Above a certain stress level, the relationship between stress and strain in a linear elastic material ceases to be linear (Figure 5). These threshold stress and strain values define material properties called yield strength (σ_y) and yield strain (ε_y), respectively. If the applied stress or strain exceeds this threshold, irreversible damage occurs within the material. In bone, damage first occurs through the formation of microscopic cracks. Propagation of these microscopic cracks is hindered, to a certain degree, by heterogeneities in the bone microstructure. The ultimate strength (σ_{ult}) is the maximum

stress that a material can carry before final fracture. In bone, final fracture occurs when a larger crack propagates across the whole bone or specimen. The amount of energy per unit volume required to fracture the bone is referred to as toughness, and it can be estimated as the area under the stress-strain curve. Thus, toughness of a material is proportional to not only its ultimate strength, but it is also largely affected by how much strain occurs within the material within the post-yield region. For example, diamond is a very strong material, but it has very low toughness because it does not undergo any post-yield strain. A summary of key terms pertinent to mechanics of materials and their definition are presented in Table 1.

Table 1. Basic mechanics of materials terminology.

Term	Definition
Stress (σ)	Measure of internal force (per unit area) acting within a deformable body.
Strain (ε)	Normalized measure of a deformable body's internal deformation, i.e., change in size, under an applied force.
Elastic deformation	Deformation that is recoverable after the applied force is removed.
Yield	Onset of irrecoverable deformation.
Elastic modulus (E)	Material property describing the ability to resist elastic deformation under load.
Yield strength (σ_y)	Material property that describes the stress required to cause the onset of permanent deformation, i.e., stress value below which deformation is recoverable.
Yield stain (ε_y)	Material property that describes the maximum internal deformation that is fully recoverable.
Ultimate strength (σ_{ult})	Material property describes the stress required to cause fracture.
Toughness	Measure of a material's resistance to fracture; energy absorbed by the material up to the point of fracture.
Hardness	Measure of a material's resistance to deformation by indentation and scratching.

For many materials such as metals, the properties are the same in all directions. These materials are described as having isotropic behavior. Bone, however, is not an isotropic material. Its microstructure has preferential orientations, which result in anisotropic (directionally dependent) properties. In the shafts of long bones, elastic modulus and strength are higher along the length of the bone (longitudinally), than in the plane transverse to the long bone axis. Typical values reported for the longitudinal tensile elastic modulus of adult human cortical bone range from 16 to 18 GPa

in the femur and from 19 to 29 GPa in the tibia.[3-5] In the plane transverse to the long bone axis, modulus typically ranges from 9 to 14 GPa in adult cortical bone.[4]

MATERIAL BEHAVIOR OF BONE IN OI

Fundamental abnormalities in collagen biochemistry and bone mineralization have been measured in OI. Studies have reported that the diameters of type I collagen fibrils differ from typical bone in OI, although there have been conflicting observations as to whether the fibrils were thinner or thicker than normal.[6,7] Bone mineral crystals are also affected, since the folding and spacing of collagen influences hydroxyapatite deposition. Crystal size tends to be smaller than in typical bone, and this size appears to be affected by OI severity.[8,9] The mineral crystals do not conform to a normal plate-like shape, and they appear to be poorly organized relative to the collagen fibrils.[8] Bone mineralization density in OI is usually higher than in typical bone,[2,10,11] and is even higher in individuals with OI type III than in those with type I.[10] Finally, the calcium-phosphate ratio tends to be lower in OI bone than in typical bone.[12]

These abnormalities in collagen and mineral crystals suggest that bone material properties are compromised in individuals with OI. Little data, however, is available to describe these properties; therefore the effects of this disorder on the intrinsic properties of bones are currently not well understood. The present section offers a summary of studies pertaining to bone material properties in OI.

Mouse Models

Mouse models have been used to study how OI affects the mechanics of bones. While the material properties of mouse bones differ from those of human bones, mouse models of OI have indicated that bone properties are affected by OI. For example, *Mov13* mice, which bear similarities to mild OI in humans, have lower cortical bone elastic modulus, yield strength, yield strain, and ultimate strength than wild-type controls.[13] A mouse model of severe OI, the *oim/oim* mouse, has lower ultimate cortical bone strength and toughness, but tends to have a higher elastic modulus than their wild-type littermates.[14-17] Another model, the *Brtl* mouse for OI type IV, was found to exhibit bone material properties that vary with age.[18] Little data, however, is

yet available to confirm whether these trends in bone material properties hold true for humans with this disorder.

Nanoindentation

A few studies have used nanoindentation to characterize bone material properties in biopsy and osteotomy specimens from children with OI.[11,19-21] In nanoindentation tests, a sharp indenter is pressed into the surface of a specimen creating a very small indent, and two material properties are determined from the load-displacement data: elastic modulus and hardness, a property representing the material's resistance to deformation by indentation or scratching.

In preparation for nanoindentation tests, bone specimens are dehydrated using ethanol solutions, embedded in a polymer, and their surface is polished. During the test, a diamond-tip indenter is pressed into the polished surface, creating an indentation a few hundred nanometers deep. Force and displacement are measured during the indentation, and this data is used to calculate local elastic modulus and hardness.

Because of its small scale, nanoindentation lends itself well to the testing of small specimens such as biopsies and osteotomies. Use of this technique to characterize bone tissue, nonetheless, has limitations. This test provides an estimate of elastic modulus at the site of indentation. Local elastic modulus varies within different regions of the bone microstructure.[22-24] These values further do not take into account vascular pores, which result in lower average elastic modulus at larger scales. Calculation of elastic modulus from nanoindentation involves the assumption that the specimen has isotropic properties, which, as discussed earlier, is not quite true for bone. Assumptions must also be made regarding the specimen's Poisson's ratio[†], a property that can vary both between and within bone specimens. Moreover, several experimental factors have been shown to affect the properties measured by nanoindentation in bone specimens. Therefore, bone

[†] When a deformable body is subjected to axial tension, it tends to contract in the directions perpendicular to the load. Similarly, when it is compressed, it tends to expand in the directions perpendicular to the applied compressive load. Poisson's ratio is a material property describing the ratio of the strain occurring perpendicularly to the applied load to that occurring in the direction of the load. For bone, Poisson's ratio ranges between 0.2 and 0.6. Since bone is a heterogenous and anisotropic material, Poisson's ratio is likely to exhibit local and directional variations.

properties obtained with this technique should not be interpreted as absolute values. Nonetheless, nanoindentation provides a valuable means of comparing modulus and hardness between groups of specimens.

Results of published nanoindentation studies in OI bone are summarized in Tables 2 and 3. At the nanoindentation scale (submicrostructural scale), elastic modulus and hardness at were found to be higher in children with severe OI than in age-matched controls.[11] This observation is similar to those made in studies of the *oim/oim* mouse model of severe OI.[15-17] No significant differences were seen between OI types III and IV.[20,21] However, bone elastic modulus was found to be slightly higher in children with OI type I than in those with type III,[22] indicating that bone modulus is also higher in mild OI than in normal bone. This observation diverges from the study of *Mov13* mouse model for mild OI, in which these mice were found to have lower bone modulus than wild-type controls.[13]

Interestingly, no significant difference in elastic modulus was found by nanoindentation between the longitudinal and transverse directions in specimens from children with severe OI.[11,19] This observation is in sharp contrast to normal tissue, where modulus measured by nanoindentation is approximately 40% lower in the transverse vs. longitudinal direction.[25-27] This observation has led to speculation that OI bone material properties may not display as much anisotropy than typical bone, at least at the submicrostructural scale.

Effect of Age

Bone material behavior varies as a person ages. In typical tissue, pediatric bones are more flexible and have lower elastic modulus and strength, but higher strain to failure and toughness than do adult bones.[28] Age, however, was not found to be a predicting factor for elastic modulus and hardness in nanoindentation studies of bone specimens from children with OI.[20,22] Nonetheless, no data is yet available to describe bone material properties in adults with OI.

Table 2. Published results for intrinsic elastic modulus (E) in OI bone tissue. Results in GPa. Means (SD).

Study	OI Type	Cortical	Trabecular	Observations
[19]	III	L: 15.2 (1.9)[a]	13.6 (3.4)	No difference between L and T directions.
		T: 13.9 (2.8) [a]		No significant difference between cortical and trabecular regions.
[11]	Controls	18.8 (1.1)		E was higher in OI type III than in controls.
	III, before pamidronate	21.3 (1.5)		E did not change after 2-3 years of pamidronate treatment.
	III, after pamidronate	22.1 (2.0)		
[21]	III	19.7 (2.8)[b]	19.2 (2.0)[b]	No significant difference between OI types III and IV.
	IV	19.2 (2.4)[b]	18.2 (2.8)[b]	
[22]	I	I: 17.7 (1.8)[c]		E was slightly higher in OI type I than in type III.
		H: 16.1 (1.1)[c]		E was greater in interstitial regions than within secondary osteons.
	III	I: 17.3 (1.3)[c]		
		H: 15.2 (0.9)[c]		

a: L and T denote modulus along the longitudinal axis of the bone and in the transverse plane, respectively.
b: The authors did not indicate whether the values in parentheses represent standard deviation or standard error.
c: I and H denote results from interstitial and Haversian bone regions, respectively.

Table 3. Published results for bone hardness (H) in OI. Results in GPa. Means (SD).

Study	OI Type	Cortical	Trabecular	Observations
[19]	III	L: 0.42 (0.04)[a]	0.42 (0.06)	No difference in between L and T directions.
		T: 0.42 (0.05)[a]		No difference between cortical and trabecular regions.
[11]	Controls	0.67 (0.05)		H was higher in OI type III than in age-matched controls.
	III, before pamidronate	0.81 (0.08)		H did not change after 2-3 years of pamidronate treatment.
	III, after pamidronate	0.83 (0.11)		
[21]	III	0.70 (0.17)[b]	0.65 (0.12)[b]	No significant difference was found between OI types III and IV.
	IV	0.66 (0.13)[b]	0.62 (0.14)[b]	
[22]	I	I: 0.59 (0.05)[c]		H was slightly higher in OI type I than in type III.
		H: 0.59 (0.08)[c]		Greater in interstitial regions than within Haversian bone.
	III	I: 0.61 (0.04)[c]		
		H: 0.54 (0.05)[c]		

a: L and T denote modulus along the longitudinal axis of the bone and in the transverse plane, respectively.
b: The authors did not indicate whether the values in parentheses represent standard deviation or standard error.
c: I and H denote results from interstitial and Haversian bone regions, respectively.

Bisphosphonate Effect

Bisphosphonate treatments have become common as a means to reduce fracture risk in children with OI. It was found that elastic modulus and hardness as measured by nanoindentation were not significantly affected after two to three years of bisphosphonate treatments.[11] Similarly, in another nanoindentation study, no significant association was observed between these two properties and whether or not the subject had a history of bisphosphonate treatments prior to specimen donation.[29] It should be emphasized, however, that these studies did not measure bone material strength or toughness. Therefore, we caution that it should not be concluded, based on those results, that bisphosphonate treatments have no effect on bone material properties. By inhibiting osteoclasts, bisphosphonates influence the bone remodeling process, which may adversely affect the material strength and toughness of the bone tissue. Nevertheless, as suggested by Weber et al.,[11] the reduction in fracture incidence after pamidronate treatment is likely to be attributed to an increased bone mass and volume rather than to changes in bone material properties.

Ongoing Work

Fracture risk can be assessed by calculating stress and strain distributions within a loaded structure and comparing these results to threshold values. As discussed earlier, onset of damage in a linear elastic material occurs when the applied local stresses exceeds the yield strength, and final fracture occurs when the stress reaches the ultimate strength. While the yield strength, ultimate strength and toughness of typical human bones have been studied using cadaveric bone specimens, little data is yet available to describe these properties in individuals with OI. An ongoing study at Shriners Hospital–Chicago and Marquette University is focused on characterization of cortical bone material properties in children with OI. In this study, small bone specimens are collected during routine corrective osteotomy surgeries. Although their limited size renders them unsuitable for most mechanical test protocols, in which specimens are typically a few centimeters long, a small-scale three-point bending test methodology (Figure 6) has recently been developed and validated to characterize these small bone specimens.[30] Preliminary results indicate that, much like typical bones tissue, OI bones exhibits clear anisotropic material properties,[31] although their properties appear to differ from those of normal bone tissue. Specifically, bone material strength and elastic modulus results in specimens from children with OI[30,32] were lower than values for typical pediatric bones.[33] Further research is

warranted to investigate how these properties are affected by factors such as: age, genotype, level of mobility, and bisphosphonate treatments. Finally, comparing the strength and toughness of bone tissues from individuals with and without OI would help to further our understanding of the mechanical basis of bone fragility associated with this disorder.

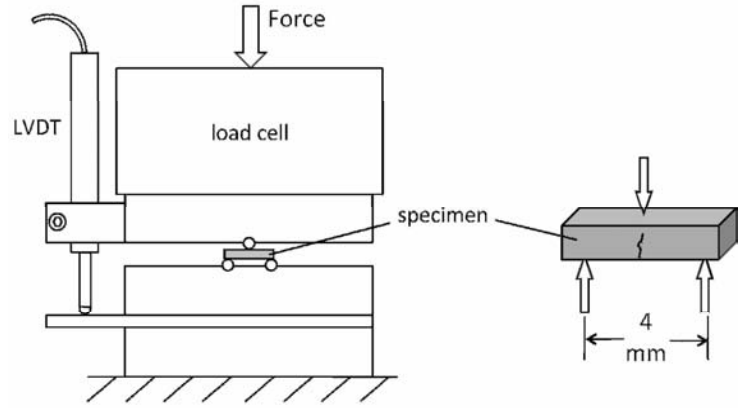

Figure 6. Three-point bending test configuration for characterization of the flexural properties of small bone specimens. A compressive force is applied with a materials testing machine bending the specimen to the point of fracture. Deflection of the specimen is measured with a linear variable differential transformer (LVDT). Bending strength is calculated from the force and deflection data.

Fracture toughness, a measure of resistance to crack growth within a material, has not yet been measured in OI bone. Future studies characterizing bone fracture toughness in OI would be valuable in understanding how this disorder affects the ability of the bone material to resist fracture propagation.

Trabecular bone is a porous structure and its effective macroscopic properties are affected by its porosity. The effective modulus and effective strength of trabecular bone both decrease with an increase in porosity.[34] While the intrinsic properties of individual trabeculae reflect the quality of the bone material itself, effective properties better reflect the capacity of trabecular bone as a structure to carry loads. Although no data is yet available to describe the effective modulus and strength of trabecular bone in OI, these values are likely to increase with bisphosphonate treatment as a result of increased trabecular bone mass. Future work to characterize the effective properties of trabecular bone in OI would be useful in structural analyses aiming to predict fractures.

CONCLUSION

The structural strength of bones, i.e., their ability to bear loads without fracturing, depends on their structure (i.e., size and geometry) as well as on the material properties of the bone tissue itself. In OI, bone structure is affected: individuals with OI tend to have small, narrow bones and low bone mass, and this is especially true in moderately severe and severe OI. Significant bowing of long bone shafts is also common in individuals with moderately severe and severe OI. These structural abnormalities can contribute to the increased fracture risk by increasing local stress levels within the bone material under a given load. The decreased incidence of fractures observed following bisphosphonate treatments in individuals with OI is likely attributed to the resulting increase in bone mass rather than to changes in material properties of the bone tissue. Although little data is yet available to describe bone material properties in humans with OI, murine models of this disorder have indicated that bone material properties are indeed compromised. Nanoindentation studies of pediatric OI bone specimens have indicated that elastic modulus tends to be increased at the microstructural scale. Conversely, preliminary findings from three-point bending characterization of surgical pediatric bone specimens indicate that bone material strength and elastic modulus at the mesoscale are lower than normal in children with OI. Finally, further research is necessary toward understanding the effects of several parameters such as age, genotype, level of mobility, gender, anatomic site, and bisphosphonate treatments on bone strength.

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ABBREVIATIONS

A	Specimen cross-sectional area
F	Force applied
L	Longitudinal direction, i.e., along the long bone axis
$L_{initial}$	Initial gage length of specimen
L_{final}	Final gage length of specimen
OI	Osteogenesis imperfecta
T	Transverse direction, i.e., transverse to the long bone axis
ε	Strain
ε_y	Yield strain
σ	Stress
σ_{ult}	Ultimate strength
σ_y	Yield strength

REFERENCES

1. Rauch F, Travers R, Parfitt AM, Glorieux FH. Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. *Bone.* Jun 2000;26(6):581-589.
2. Roschger P, Fratzl-Zelman N, Misof BM, Glorieux FH, Klaushofer K, Rauch F. Evidence that abnormal high bone mineralization in growing children with osteogenesis imperfecta is not associated with specific collagen mutations. *Calcif Tissue Int.* Apr 2008;82(4):263-270.
3. Burstein AH, Reilly DT, Martens M. Aging of bone tissue: Mechanical properties. *Journal of Bone and Joint Surgery Am.* 1976;57(7):956-966.
4. Reilly DT, Burstein AH. The elastic and ultimate properties of compact bone tissue. *J Biomech.* 1975;8(6):393-405.
5. Darmana R, Hobatho MC, Ashma RB, Morucci JP. Optimization of the size sample in the elastic moduli measurement of human cortical bone. Paper presented at: Engineering in Medicine and Biology Society, 14th AnnualConference of the IEEE; Oct 29 - Nov 1, 1992; Paris, France.
6. Stoss H, Freisinger P. Collagen fibrils of osteoid in osteogenesis imperfecta: Morphometrical analysis of the fibril diameter. *American Journal of Medical Genetics.* 1993;45:257.
7. Cassella JP, Barber P, Catterall AC, Ali SY. A morphometric analysis of osteoid collagen fibril diameter in osteogenesis imperfecta. *Bone.* May-Jun 1994;15(3):329-334.
8. Traub W, Arad T, Vetter U, Weiner S. Ultrastructural studies of bones from patients with osteogenesis imperfecta. *Matrix Biol.* Aug 1994;14(4):337-345.
9. Vetter U, Eanes ED, Kopp JB, Termine JD, Robey PG. Changes in apatite crystal size in bones of patients with osteogenesis imperfecta. *Calcif Tissue Int.* Oct 1991;49(4):248-250.
10. Boyde A, Travers R, Glorieux FH, Jones SJ. The mineralization density of iliac crest bone from children with osteogenesis imperfecta. *Calcif Tissue Int.* Mar 1999;64(3):185-190.

11. Weber M, Roschger P, Fratzl-Zelman N, et al. Pamidronate does not adversely affect bone intrinsic material properties in children with osteogenesis imperfecta. *Bone.* Sep 2006;39(3):616-622.
12. Cassella JP, Ali SY. Abnormal collagen and mineral formation in osteogenesis imperfecta. *Bone Miner.* May 1992;17(2):123-128.
13. Jepsen KJ, Schaffler MB, Kuhn JL, Goulet RW, Bonadio J, Goldstein SA. Type I collagen mutation alters the strength and fatigue behavior of Mov13 cortical tissue. *J Biomech.* Nov-Dec 1997;30(11-12):1141-1147.
14. McCarthy EA, Raggio CL, Hossack MD, et al. Alendronate treatment for infants with osteogenesis imperfecta: demonstration of efficacy in a mouse model. *Pediatr Res.* Nov 2002;52(5):660-670.
15. Misof BM, Roschger P, Baldini T, et al. Differential effects of alendronate treatment on bone from growing osteogenesis imperfecta and wild-type mouse. *Bone.* Jan 2005;36(1):150-158.
16. Miller E, Delos D, Baldini T, Wright TM, Pleshko Camacho N. Abnormal mineral-matrix interactions are a significant contributor to fragility in oim/oim bone. *Calcif Tissue Int.* Sep 2007;81(3):206-214.
17. Rao SH, Evans KD, Oberbauer AM, Martin RB. Bisphosphonate treatment in the oim mouse model alters bone modeling during growth. *J Biomech.* Dec 5 2008;41(16):3371-3376.
18. Kozloff KM, Carden A, Bergwitz C, et al. Brittle IV mouse model for osteogenesis imperfecta IV demonstrates postpubertal adaptations to improve whole bone strength. *J Bone Miner Res.* Apr 2004;19(4):614-622.
19. Fan Z, Smith PA, Eckstein EC, Harris GF. Mechanical properties of OI type III bone tissue measured by nanoindentation. *J Biomed Mater Res A.* Oct 2006;79(1):71-77.
20. Fan Z, Smith PA, Harris GF, Rauch F, Bajorunaite R. Comparison of nanoindentation measurements between osteogenesis imperfecta Type III and Type IV and between different anatomic locations (femur/tibia versus iliac crest). *Connect Tissue Res.* 2007;48(2):70-75.
21. Fan Z, Smith PA, Rauch F, Harris GF. Nanoindentation as a means for distinguishing clinical type of osteogenesis imperfecta. *Composites Part B: Engineering.* 2007;38(3):411-415.
22. Albert C, Jameson J, Toth JM, Smith P, Harris G. Bone properties by nanoindentation in mild and severe osteogenesis imperfecta. *Clin Biomech (Bristol, Avon).* 2013;28(1):110-116.
23. Hoffler CE, Guo XE, Zysset PK, Goldstein SA. An application of nanoindentation technique to measure bone tissue lamellae properties. *J Biomech Eng.* Dec 2005;127(7):1046-1053.
24. Rho JY, Zioupos P, Currey JD, Pharr GM. Microstructural elasticity and regional heterogeneity in human femoral bone of various ages examined by nano-indentation. *J Biomech.* Feb 2002;35(2):189-198.
25. Fan Z, Swadener JG, Rho JY, Roy ME, Pharr GM. Anisotropic properties of human tibial cortical bone as measured by nanoindentation. *J Orthop Res.* Jul 2002;20(4):806-810.
26. Rho JY, Roy ME, 2nd, Tsui TY, Pharr GM. Elastic properties of microstructural components of human bone tissue as measured by nanoindentation. *J Biomed Mater Res.* Apr 1999;45(1):48-54.
27. Turner CH, Rho J, Takano Y, Tsui TY, Pharr GM. The elastic properties of trabecular and cortical bone tissues are similar: results from two microscopic measurement techniques. *J Biomech.* Apr 1999;32(4):437-441.

28. Currey JD, Butler G. The mechanical properties of bone tissue in children. *J Bone Joint Surg Am.* Sep 1975;57(6):810-814.
29. Albert C, Jameson J, Toth J, Smith P, Harris G. Intrinsic modulus of bone in osteogenesis imperfecta - a nanoindentation study. Paper presented at: 17th Biannual Canadian Society for Biomechanics Conference; June 6-9, 2012, 2012; Burnaby, BC.
30. Albert C, Jameson J, Harris G. Design and validation of bending test method for characterization of miniature pediatric cortical bone specimens. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine.* 2013;227(2):105-113.
31. Albert C, Smith P, Harris G. Decreased bone material strength in severe osteogenesis imperfecta (OI). Paper presented at: Proceedings of the 37th annual meeting of the American Society of Biomechanics; September 4-7, 2013, 2013; Omaha, NE.
32. Albert C, Jameson J, Smith P, Harris G. Reduced diaphyseal strength associated with high intracortical vascular porosity within long bones of children with osteogenesis imperfecta. *Bone* 2014; 66:121-130.
33. Currey JD. The effects of strain rate, reconstruction and mineral content on some mechanical properties of bovine bone. *J Biomech.* Jan 1975;8(1):81-86.
34. Gibson LJ. The mechanical behaviour of cancellous bone. *J Biomech.* 1985;18(5):317-328.

12 ROLE OF MICRO-CT IN THE VISUALIZATION, MEASUREMENT, AND QUANTIFICATION OF BONE STRUCTURE IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Even though bone and skeletal disorders are primary symptoms of osteogenesis imperfecta (OI), relatively few attempts have been made to estimate OI bone morphometric indices, determine how OI weakens the osseous tissue architecture, or quantitatively stratify risk of fracture. Currently, there is little biomechanical data on OI bone. The majority of characterization studies have used simple measures of bone quantity, such as bone mineral density (BMD), to provide an estimate of bone integrity. However, the mechanical properties and performance of bone depend on many factors in addition to the quantity of bone present including the quality of existing material and the three-dimensional trabecular architecture.[1-3] New methods of analysis, such as imaging, in particular micro-Computed Tomography (micro-CT), offer a novel, non-destructive technique for analyzing bone specimens and developing better biomechanical models for determining fracture risk assessment and clinical management approaches.[1,4-6]

Micro-CT Instrumentation and Specimen Scanning

Micro-CT offers the capacity to three-dimensionally (3-D) image bone structures down to the trabecular level and smaller. In order to capture and properly quantify trabecular morphology, micro-CT imaging systems must have the ability to resolve features in the tens of microns range or smaller. Currently, few imaging systems with this capability, especially those used for *in vivo* scanning, have been designed or are available on the market. More so, virtually none are approved and available for doing *in vivo* studies in humans. In recent years, several instrumentation manufacturers have introduced micro-CT imaging systems primarily for research applications and 'non-destructive' analysis of excised or isolated samples, in some cases under *in vitro* conditions. Many of the imaging systems provide more than acceptable results when scanning bone, since its material composition supplies relatively high contrast within the energy range of typical X-ray sources implemented. All commercially available imaging systems employ polychromatic X-ray sources with wide energy spectrums (at least tens of keVs). Since the attenuation coefficient of materials being studied is a strong function of the incident X-ray energy, there are inherent artifacts, such as beam hardening (caused by non-uniform attenuation of photons with those in the lower energy ranges being selectively filtered out), in the resulting images. A polychromatic energy source combined with a detector that cannot discriminate the energy of incident photons also prohibits performing material composition. Select systems have the ability to resolve structures as small as several microns, although there is generally a trade-off in increased scan time as resolution increases. For example, high-resolution scans (< 10 microns) may take a number of hours to complete for a sample that is only a few centimeters long. In addition, depending on spatial resolution, grayscale resolution (i.e., the bit depth of the individual volume element or voxel), sample size, and field of view required or obtained, the resultant data sets can easily be in excess of several gigabytes. These large data set sizes evoke their own unique challenges such as file storage, file management, and data analysis. As a result, in depth guidelines for the assessment of bone microstructure in rodents using micro-CT have been developed.[7]

Data Analysis

Simple dimensional measurements such as lengths, cross sectional areas, cortical thickness, etc. can be easily determined with most standard image analysis software as long as spatial information about voxel sizes are either

embedded in the image file or input as part of the file import/loading procedure. Complex morphometric parameters analysis of micro-CT bone data is more involved and requires specialized software tools or algorithms. In addition, a preprocessing step is required where a threshold based segmentation algorithm is used to identify and isolate bone from any other materials present within the imaged volume. One automated thresholding technique often used for bone segmentation is the clustering-based Otsu method.[8] Once the image volume has been segmented the data can be binarized, such that voxels identified as 'bone' are assigned the value of 1 and all others are assigned 0, or the grayscale value of bone voxels is retained and all other voxels set to an arbitrary, non-overlapping value. Although most current bone morphometry algorithms are designed to use binary data, some novel approaches are capable of processing grayscale data.

Trabecular bone samples from vertebrae tend to be more rod-like, whereas bone from femoral head tends to be more plate-like. In trabecular bone analysis it is not appropriate to apply model assumptions often used in 2-D analysis, since the "plate-like" or "rod-like" character of trabecular bone can change both between bone samples and from one end of a volume of interest (VOI) to the other. Therefore, most contemporary 3-D analysis software is model-independent and will measure morphometric parameters directly without the need for addressing shaped-based assumption.

Bone Morphology, Morphometry, Microstructure, and Quantitative Parameters

This section describes the quantitative morphometric parameters that are typically calculated and made available by analyzing micro-CT data. Advanced CT bone imaging, formulation of morphometric parameters, and in depth discussion of their practical implementation can be found in many sources.[5,7,9-12] Here we provide a succinct overview and definitions as background. A summary of the parameters can be found in Table 1.

Table 1. Summary of bone indices.

Index	Abbreviation	Description	Standard unit
Total (Tissue) Volume	TV	Volume of volume of interest	mm^3
Bone Volume	BV	Volume of region segmented as bone	mm^3
Bone volume density	BV/TV	Ratio of BV to the TV	%
Trabecular Thickness	Tb.Th	Mean thickness of trabeculae	mm
Trabecular Spacing	Tb.Sp	Mean distance between trabeculae	mm
Trabecular Number	Tb.N	Average number of trabeculae per unit length	1/mm
Bone Surface	BS	Surface area of region segmented as bone	mm^2
Specific Bone Surface	BS/BV	Ratio of BS to the BV	1/mm
Cross Sectional Area	CSA	Area of cross sectional slice of bone specimen	mm^2
Cortical Thickness	Ct.Th	Thickness of cortical bone	mm
Tissue Mineral Density	TMD	Total mineral mass in the region segmented as bone	mg/cm^3
Bone Mineral Content	BMC	Total mineral mass in the VOI	mg
Bone Mineral Density	BMD	BMC normalized by the volume of the VOI	mg/cm^3
Connectivity Density	Conn.D	A measure of the connectivity of the trabeculae divided by TV	$1/ mm^3$
Degree of Anisotropy	DA	Length of longest divided by the shortest mean intercept length vector	*
Structure Model Index	SMI	Indicator of the structure of the trabeculae	*

* Dimensionless variable

Bone volume density, often represented as BV/TV, is one of the most common and often reported micro-CT parameters that represents the fraction of a given VOI, total volume, or tissue volume (TV) that is occupied by bone (BV) and is usually reported as a percentage value. BV/TV can be used to evaluate relative changes in bone volume present from one time point to another or before and after a given treatment, for example after treatment with common anti-resorptive drugs such as bisphosphonates.

Unfortunately, BV/TV, like many morphometrics parameters, will vary if the selected VOI is different from one scan to another or when the same data is analyzed using different VOIs. Furthermore, if another material is present in the VOI, such as metal hardware, the artifacts present will result in segmentation errors and anomalous estimation of values. Likewise, comparative analysis between samples will not be possible if different scanner settings have been used or if there are inconsistencies in specimen preparation.

Trabecular thickness (Tb.Th) and trabecular spacing (Tb.Sp) are measures of the 3-D structure of cancellous or spongy bone. As the names imply, these parameters characterize the thickness of the trabecular columns and the spacing in between, respectively. These parameters are often reported as a mean, for example mean thickness of the structure calculated as the volume weighted average of the local thicknesses. We can imagine that these scalar measures are not able to describe all structural attributes, i.e., the same value may be obtained in a case where the struts are of uniform thickness compared to one where the struts taper considerably. Therefore, it may be more useful and informative to represent the thickness and spacing parameter on a continuum for the VOI as a histogram of the values. Trabecular number (Tb.N) is taken as the inverse of the mean distance between the mid-axes of the structure to be examined. The mid-axes are assessed using a 3-D distance transformation and extracting the center points of 'non-redundant' spheres set to fill the structure completely. The mean distance is calculated as the average separation between the mid-axes and the Tb.N determined.

Bone surface (BS) and specific bone surface (BS/BV) can be calculated by tessellating or creating a two-dimensional plane using repeated geometric shapes (usually triangles) with no overlaps and no gaps utilizing the segmented portion of the image data that has been identified as bone. The typical approach to calculate these parameters is to create a polygonal mesh

that represents the surface of the object. The Volumetric Marching Cubes algorithm is usually used to place tetrahedrons (or hexahedrons) on the surface of the object.[13] A better representation of the surface is typically obtained by smoothing the mesh before summing the total area of all polygons to estimate the bone surface (BS) of the identified structure. An additional benefit to creating these meshes is that they can be used as input files for finite element simulations. The BV computation becomes the volume within the tessellated surface and the BS/BV follows as a measure for the bone surface per given bone volume. This parameter is used because it provides a measure of how many bone-lining cells cover a given volume of bone.

Bone mineral content (BMC) is the total of all mineral mass in a VOI or the amount of mineral matter within the sampled volume. Bone mineral density (BMD) is derived by normalizing BMC by the volume of the VOI. Tissue mineral density (TMD) is the total mineral mass in the region within the VOI that has been segmented as bone. Whereas BMD measures the average quantity of bone mass in a representative volume, TMD measures the density of the bone material in that volume.

Simple dimensional parameters that are used to quantify cortical bone include cross-sectional area (CSA), which determines the area of cortical bone contained within a selected cross-section defined for analysis and cortical thickness (Ct.Th), the thickness of the cortex measured in a region at a selected cross-section.

Several other parameters have been used to characterize cancellous bone. Connectivity density (Eu.Conn.D or Conn.D) exploits Euler analysis and provides a measure of the connectivity of the trabecular network, indicating the number of redundant connections between trabecular structures per unit volume. The degree of anisotropy (DA) provides a measure of the directional dependence of trabeculae and is equal to the length of the longest divided by shortest mean intercept length vector (DA is 1 for ideally isotropic conditions, while this number is increasingly larger when the bone is more anisotropic). Finally, structure model index (*SMI*) describes the degree to which the trabecular network follows common plate-like or rod-like structural models (SMI will be 0 for parallel plates and 3 for cylindrical rods).[14]

MOUSE MODEL OF OI BONE MORPHOLOGY

OI is a genetic bone fragility syndrome commonly characterized by mutations in the genes that code for type I collagen and its associated structural proteins. Type I collagen and hydroxyapatite (HA) are the most prevalent organic and inorganic components in bone, respectively, and these components contribute significantly to its mechanical properties.[15] Most symptoms of OI can be attributed to altered collagen synthesis and assembly. Clinically, OI patients are currently classified into eight groups, Type III being the most severe form compatible with life. Due to limited availability and the small size of excised human OI specimens, animal models have been developed for research purposes. Murine models, typically with defective collagen synthesis abnormalities, have become standard surrogates for research in OI.[16-18] One common mouse model of Type III OI is the homozygous oim B6C3Fe a/a-Col1a2oim/J strain (oim/oim).[19] Although a number of studies have addressed determining bone morphometric parameters using micro-computed tomography (micro-CT),[1,9-12,20] the goal of the work presented here was to gather baseline data and validate a micro-CT system for the evaluation of murine models of OI and human OI bone samples.

Methods

Animals

All studies were performed under approval of an Institutional (Medical College of Wisconsin and Zablocki Veterans Affairs Medical Center) Animal Care and Use Committee (IACUC) protocol. Mice were obtained from Jackson Laboratory (Bar Harbor, ME). Ten male mice were anesthetized and euthanized, after which five oim/oim and five wild-type (+/+) femora were harvested and fresh frozen at -70°C until micro-CT evaluation. Average ages of the oim/oim and +/+ mice at tissue dissection were 9 and 10 weeks, respectively.

Imaging

Scans were performed using a custom-built micro-CT system designed and developed at the Zablocki Veterans Affairs Medical Center (Milwaukee, WI). The system has a simple cone beam geometry composed of a FeinFocus 100.50 X-ray source (3-μm focal spot; Comet North America, Stamford, CT), an AI-5830-HP image intensifier (North American Imaging, Camarillo, CA) coupled to a Silicon Mountain Design SMD1M-15 CCD camera (Teledyne

DALSA, Billerica, MA), and a specimen micromanipulator stage, mounted on a precision rail as described in previous reports.[21-23] Femora were thawed, placed in 1.5-mL Eppendorf tubes filled with saline, mounted on the specimen stage, and scanned using continuous rotation (33 kVp, 242 μA, 7-frame average) at two magnifications. Reconstructions were performed using a standard Feldkamp reconstruction algorithm,[24] with resulting isotropic voxel sizes of 17 and 34 μm, corresponding to high and low magnification, respectively.

Analysis

Image visualization, VOI selection, and morphometric parameter estimation were performed using ImageJ (v1.42; NIH) and MicroView (v2.1.2; GE Healthcare, Waukesha, WI). VOIs in each specimen were determined and analyzed for several locations in cortical and trabecular bone. Femoral length was measured using the line tool within MicroView. Longitudinal cortical regions were selected from the low-magnification scans. These cortical VOIs extended distally 2.5 mm from the femoral midpoint and were used to measure CSA and Ct.Th. Measurements of Ct.Th were made at the mid-diaphysis and each value reported is an average of 10 measurements taken all around the cross-section. Cylindrical shaped trabecular regions were isolated from high-magnification data volumes, proximal and adjacent to the distal femoral growth plate, extending proximally 1.5 mm with a diameter of 1 mm. A local threshold (determined using MicroView's auto-threshold option) was used to segment and isolate trabecular VOIs, and these regions were subsequently evaluated for BV/TV, Tb.N, Tb.Th, and Tb.Sp.

Statistical analysis

Data from each genotype was pooled and compared for statistical significance using an unpaired student's t-test.

Results

Femoral length was not significantly different between femurs from oim/oim and wild-type mice. However, cortical and trabecular indices were generally inferior for oim/oim mice compared to controls (Table 2). Figure 1A shows an example of a surface-shaded rendering of a micro-CT image of a normal mouse femur. In Figure 1B renderings of example portions of a femur and trabecular bone ROI from a normal and oim/oim mouse are presented for visualization. The qualitative visual appearance of the oim/oim cortical cross-sectional geometry was more flattened and ellipsoidal in appearance

than seen in the wild-type mice (Figure 1B). Mid-shaft oim/oim cortices showed a 16% reduction in CSA, suggesting decreased resistance to bending loads. These observations are in agreement with findings from a previous study.[25] The oim/oim trabecular network appeared more rarefied (Figure 1B), which was confirmed by significantly reduced BV/TV and Tb.N, as well as a corresponding increase in Tb.Sp (Table 2).

Table 2. Summary of calculated bone parameters.

Genotype	Morphometric Parameters					
	CSA (mm^2)	*Ct.Th* (*mm*)	*BV/TV*	*Tb.N* (mm^{-1})	*Tb.Th* (*mm*)	*Tb.Sp* (*mm*)
Control (+/+)	0.87 ± 0.15	0.20 ± 0.03	0.25 ± 0.05	6.89 ± 1.71	0.036 ± 0.006	0.12 ± 0.04
Oim/oim	0.73 ± 0.10*	0.19 ± 0.01	0.14 ± 0.03†	3.67 ± 1.03†	0.038 ± 0.005	0.28 ± 0.09†

* $p < 0.06$ between +/+ and *oim/oim*.
† $p < 0.05$ between +/+ and *oim/oim*.

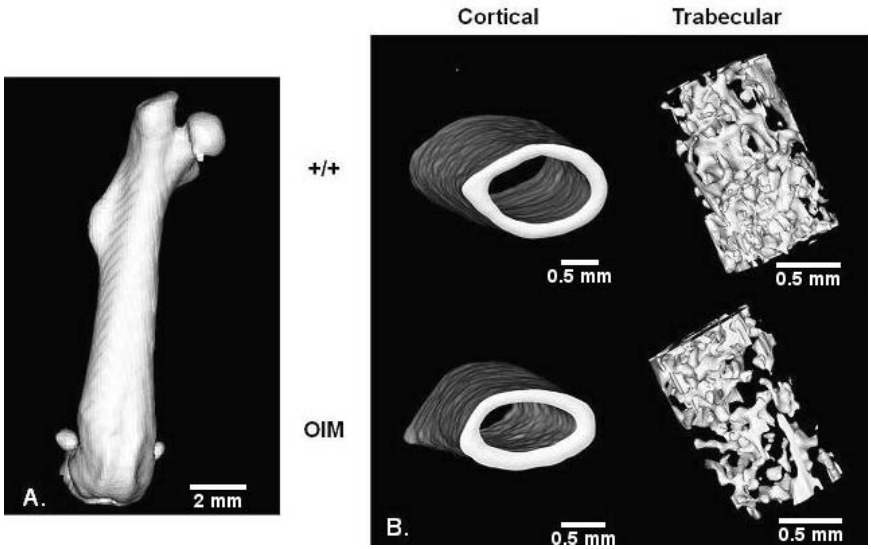

Figure 1. Representative surface-shaded renderings of mouse femora from μCT data. (A) Whole femur from a normal wild-type mouse. (B) Cortical and trabecular VOIs.

Discussion

The results support prior findings reporting that OI mice have a decrease in trabecular tissue and reduced mechanical integrity.[25,26] The resolution achieved (isotropic voxel size of 17 μm) for our trabecular analysis is sufficient for mouse bone specimens and the resulting indices estimated agreed well with values previously reported in the OI mouse literature.[25-27] The study confirms that the scanning and analysis methods employed can be applied to murine bone samples and that these techniques enable examination of differences in bone structure between OI mouse models and their wild-type counterparts.

STUDY OF HUMAN OI SAMPLES

In the clinical setting, bone mineral and structural parameters are typically determined using 2-D techniques including dual-energy X-ray absorptiometry (DEXA) and histology. Although these methods have become accepted clinical standards,[28,29] they provide only limited data and are inadequate for developing better quantitative analysis of fracture risk and therapeutic intervention. DEXA integrates mineral information into 2-D data providing only mean values across the sample volume. Three-dimensional information that may be fundamentally important to understanding bone mechanical properties is lost and the ability of DEXA alone to accurately predict fracture is questionable, especially in the growing skeleton.[30] In addition, DEXA scans subject patients to ionizing radiation, and although the radiation dose is relatively small, this raises safety concerns for OI patients who routinely undergo multiple annual X-ray scans (e.g. for fractures, deformity mapping, follow-ups, etc.). Fan et al. have used a novel nanoindentation method to characterize OI bone.[31-33] However, histological and nanoindentation evaluation require destructive excision and morphometric parameters derived from histology rely on geometric and material distribution assumptions to extrapolate 3-D properties from 2-D slides. Therefore, where conventional radiography and histological analysis has been the mainstay of fracture assessment, micro-CT may allow for a large improvement in characterizing the degree of underlying bone fragility, the progression of fracture healing, and for monitoring interventional therapies.[1-3]

Micro-CT affords straightforward 3-D analysis of BMD and bone microstructure.[34] Although high-resolution CT and micro-CT are relatively new to the clinical arena, scanners have been recently developed and made commercially available allowing examination of human limbs *in vivo* and providing qualitative and quantitative assessment of bone microstructure.[35-38] Micro-CT can be particularly useful for OI research because patients routinely undergo corrective surgeries that involve removal of small bone fragments. After establishing agreement with studies reported for murine models, we applied our methods to human OI bone specimen. The study[39] was aimed to investigate micro-CT as a method to characterize OI bone architecture in several of these excised fragments, and to compare the results to previous reports. Correlations were also performed to determine possible relationships among the different parameters.

Methods

A total of 8 fragments were collected from lower extremity long bones (femur or tibia) of 5 children with OI (sex: 2M, 3F; age range: 1.5-11.5 years) under written informed consent/assent and Institutional Review Board (IRB) approval during routine osteotomy surgical procedures (Shriners Hospitals for Children, Chicago, IL). All patients were diagnosed with moderate or severe OI (types IV or III, respectively), and 3 of the 5 patients had received at least one round of bisphosphonate therapy to increase bone mass. The specimens were stored in a freezer at -70°C prior to scanning. The bone fragments were scanned using the Keck micro-CT system described previously. Specimens were thawed and scanned in saline in continuous mode (33 kVp, 231 μA, 360 views, 7-frame average) to obtain 35-μm isotropic voxel resolution. As a preprocessing step, a ring artifact reduction algorithm was implemented on the projection images prior to reconstruction to decrease artifacts caused by detector limitations and to improve the ability of the segmentation procedure to correctly isolate the bone from its surroundings.[40] After the data was reconstructed with a Feldkamp algorithm, attenuation intensity values were converted to Hounsfield units (HU). Trabecular VOIs were identified from the resulting grayscale image volumes and analyzed for several structural parameters in MicroView (v2.1.2; GE Healthcare, Waukesha, WI). Cubic VOIs (2-mm side length) were segmented by applying a local threshold determined using the Auto-Threshold option in MicroView, which utilizes an Otsu cluster thresholding algorithm.[8] Each VOI was examined using the Bone Analysis tool, which directly measures BV/TV and BS/BV and then calculates Tb.Th, Tb.N, Tb.Sp, and Eu.Conn.D. Highly

connected tissues (such as healthy trabecular bone) have large, negative Euler numbers.

After the specimens were analyzed, 3-D surface-shaded renderings were produced using the MicroView Isosurface Tool for visualization purposes. BMD measurements are widely used for diagnostic purposes and evaluation and treatment efficacy.[3,5,10] We also performed several common bone densitometry measurements on the trabecular VOIs in MicroView including volumetric BMD, TMD, and BMC. BMC was calculated first by using a phantom (Image Analysis, Inc., Columbia, KY) with various hydroxyapatite (HA) concentrations (0, 75, and 150 mg-HA/cm^3) to convert the grey value (in HU) for each voxel in the VOI to an equivalent mass of mineral (in mg-HA). Volumetric BMD was then calculated by normalizing BMC by the total volume of the VOI. Finally, volumetric TMD was calculated by summing the BMC of only those voxels whose grey values were above a minimum bone threshold, then normalizing by the volume of all included voxels (Figure 2). This ensures exclusion of non-bone background material (e.g., air, water, marrow), which can greatly affect density calculations.

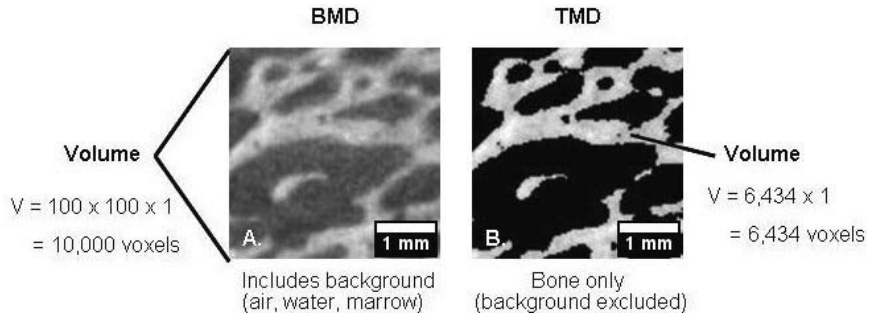

Figure 2. Description of methods applied to calculate BMD and TMD. A: All voxels are used for BMD, and the calculation is independent of any threshold; B: Only voxels with grey values greater than or equal to the bone threshold are counted in the calculation.

Results

General Morphology

Visualization of the rendered VOIs demonstrated that the trabeculae had general plate-like structure, common for lower extremity long bones (Figure 3). Unlike healthy bone, the OI trabecular plates did not appear to display a preferential orientation, suggesting less organized architectural characteristic, as is sometimes observed in diseased or deteriorating

cancellous bone structures, such as due to aging.[14] Samples from one of the severe (type III) OI patients appeared to follow characteristics found in the parallel plate bone model (Figure 3, G-H). Structural changes due to factors such as drug treatment, harvest site, gender, and OI (genetic) type were not evident or easily distinguishable.

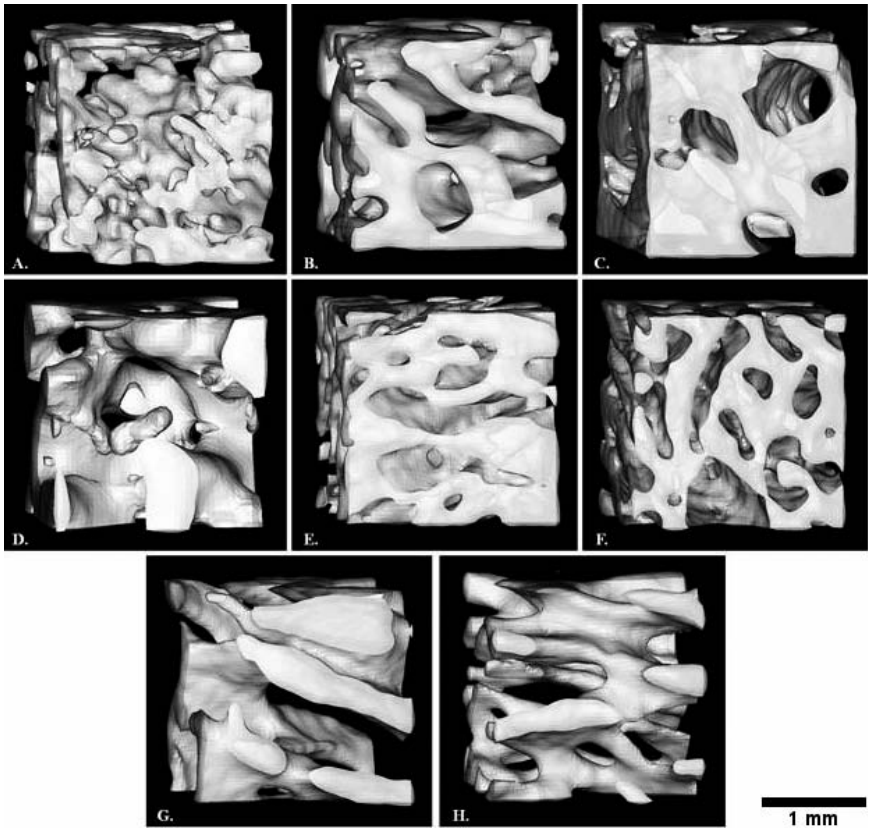

Figure 3. Surface-shaded renderings of trabecular VOIs. A*: Patient 1 (specimen 1-A, female, 8 yrs, type IV, tibia); B*: Patient 1 (specimen 1-B); C*: Patient 2 (specimen 2, female, 6.5 yrs, type III, tibia); D: Patient 3 (specimen 3, male, 10.5 yrs, type III, tibia); E*: Patient 4 (specimen 4-A, female, 1.5 yrs, type III/IV moderate, femur); F*: Patient 4 (specimen 4-B, 1.8 yrs, tibia); G: Patient 5 (specimen 5-A, male, 11.5 yrs, type III, femur). H: Patient 5 (specimen 5-B). *Indicates patient received bisphosphonate treatment.

Bone Morphometry

Results from the structural analysis are summarized in Table 3. Although parameters tended to display moderate heterogeneity across the sample population, both Eu.Conn.D and Tb.N were highly correlated with each other

(R^2=0.81) and these parameters tended to be related to severity of OI (R^2=0.51 and 0.50, respectively). Type III specimens also tended to have fewer trabeculae and lower connectivity than those from either type IV or III/IV patients. Several indices including BV/TV, Tb.N, and Eu.Conn.D were elevated in specimens from patients who had received at least one round of a bisphosphonate prior to harvesting. One patient who received such treatments between the first (4-A) and second (4-B) specimen collections exhibited modest increases in BV/TV and Tb.Th, but decreases in the other parameters.

Table 3. Bone morphometric parameters.

Specimen	OI type	BV/TV	BS/BV (1/mm)	Tb.Th (mm)	Tb.N (1/mm)	Tb.Sp (mm)	Eu.Conn.D ($1/mm^3$)
1-A*	IV	0.41	13.54	0.15	2.77	0.21	21.74
1-B*	IV	0.48	9	0.22	2.18	0.24	7.98
2	III	0.64	5.6	0.36	1.78	0.2	4.86
3*	III	0.43	8.34	0.24	1.79	0.32	7.13
4-A*	III/IV	0.41	14.52	0.14	2.98	0.2	18.02
4-B*	III/IV	0.58	9.35	0.21	2.73	0.15	10.78
5-A	III	0.28	9.37	0.21	1.33	0.54	1.84
5-B	III	0.26	13.19	0.15	1.74	0.42	3.84
Median (range):		0.42 (0.37)	9.36 (8.92)	0.21 (0.22)	1.99 (1.65)	0.23 (0.38)	7.56 (19.9)

*Patient received bisphosphonate treatment prior to specimen harvesting.

BMD

Results from the BMD tests are summarized in Table 4. This analysis did not reveal any clear relationships between OI severity and bone mineral metrics. Yet, patients who received drug therapy tended to have increased BMD and BMC compared to untreated peers, and like the results of the structural analysis, the patient who underwent drug treatment between specimen collections exhibited substantial increases in all mineral parameters (Table 4, specimens 4-A and 4-B).

Table 4. BMD calculations.

Specimen	OI Type	BMD (mg/cm^3)	TMD (mg/cm^3)	BMC (mg)
1-A*	IV	232.3	564.6	1.87
1-B*	IV	411.6	831.2	3.25
2	III	558.1	868.3	4.48
3*	III	400.0	907.3	1.36
4-A*	III/IV	278.6	661.9	2.24
4-B*	III/IV	470.6	806.8	3.78
5-A	III	228.9	791.4	1.84
5-B	III	200.8	759.2	1.61
Median (Range):		339.3 (357.2)	799.1 (342.7)	2.05 (3.13)

*Patient received bisphosphonate treatment prior to specimen harvesting.

Discussion

Several historic studies have used standard histomorphometric methods to examine small OI populations,[41-43] however, there is surprisingly little data on how OI affects bone and its development. While McCarthy et al.[42] focused on adult populations and the Baron and Ste-Marie studies tested relatively small clinical populations (n<10), Rauch et al., in the most extensive study to date, used histomorphometric methods to characterize bone specimens from 70 children with OI and 27 age-matched controls.[44] The Rauch study, in which individuals having undergone pharmacological therapy were excluded, found significantly decreased BV/TV, Tb.N, and Tb.Th in individuals with OI and minimal differences in trabecular parameters between types III and IV in the OI population.

In our current study, Micro-CT was used to quantitate measures of trabecular microstructure and mineralization in pediatric bone specimens from children with a range of moderate to severe OI. Morphometric indices determined were generally higher than those reported in the histomorphometric studies. These differences may be explained by the following factors. These previously published histological studies tested bone biopsies from the iliac crest, while specimens in the current study were collected from lower extremity long bones. As previous mentioned, histological studies rely on model assumptions to extrapolate structural 3-D parameters from thin 2-D specimens. These limitations can lead to more

conservative parameter estimates. Furthermore, most of the specimens in our study came from patients who also received drugs targeted to enhance bone mass, effectively increasing indices. These drugs affect bone structure and mineral composition. Our analysis was able to detect the augmented effects despite a small sample size.

One interesting observation from our study was that Eu.Conn.D and Tb.N were highly correlated and related to the severity of OI. Detecting differences in these indices could prove to be important differential diagnostic procedure for assessment and distinguishing OI types. As an example, although one of the patients within the study was diagnosed with type III/IV OI based on clinical observations, indices determined through micro-CT analysis suggest the patient's bone characteristics are more similar to other type IV patients.

Simple linear regression analyses suggest strong correlations between the morphometric and mineral parameters (Figure 4). The strongest structural correlations occurred between BMD, TMD, and BMC with BV/TV, BS/BV, and BV/TV, respectively. The finding that BV/TV was strongly related to two mineral content parameters underscores the importance of considering both structure and bone mass when analyzing trabecular bone.[3,45]

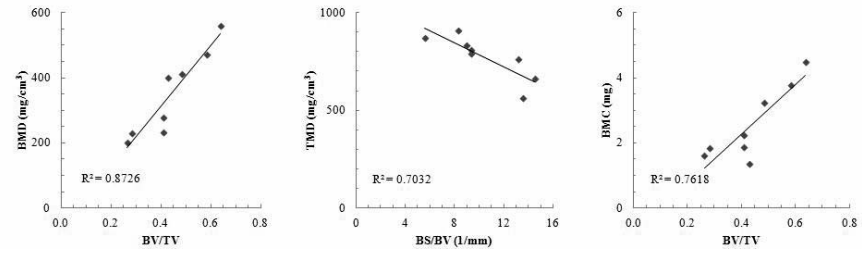

Figure 4. Correlations between architectural and mineral parameters.

The results of the current study present some of the first quantitative micro-CT data on human OI bone, and provide intriguing evidence for the use of micro-CT analysis in OI bone. Nonetheless, we must acknowledge factors that potentially confound the study. These include the fact that specimens tested came from different sites within femora and tibia and the exact site of excision was not rigorously documented.

FUTURE OF BONE QUANTIFICATION AND CHARACTERIZATION OF OI

With the advent of high-resolution micro-CT systems available for clinical evaluation and research, *in vivo* scanning of OI may become a valuable clinical tool. To achieve this, several technical challenges must be addressed. These challenges include improving algorithms to more systematically and/or automatically determine the volume of interest, minimizing radiation dose (a goal more broadly addressed by projects like that found at imagegently.org and imagewisely.org), and developing applicable standardized imaging protocols to address consistency and repeatability. Current scanners allow for the examination of extremitie,[35-38] which may be ideal for evaluation and analysis of OI patients with symptomatic expression in legs or arms, however, with the current geometry of the scanners relatively proximal scans are likely to be difficult if not impossible. Unfortunately, the use of orthopedic hardware such as screws and rods in the clinical management of OI cause image artifacts that complicate and in some cases undermine the use of CT imaging and analysis methods. New techniques for removing these artifacts will be required to avoid this practical drawback.

Fragments of bone that are excised through surgical intervention for correcting deformities will still be available for *ex vivo* research and analysis, but a more likely scenario is that presurgical *in vivo* scanning will have already been performed for bone assessment and pre-operative planning.

The current state of fracture risk assessment and bone biomechanical models, especially those in OI or that incorporate structural and material properties measured through imaging, is still in its relative infancy.[1-4,6,27,46] Methods and protocols for maintaining consistent imaging geometries and analytical techniques require standardization and optimization. In addition, more studies in which intact bones are imaged, modeled, and mechanically tested are greatly needed. Finite element analysis techniques derived from micro-CT data are also likely to become chief methods of bone analysis.[1,10,47] The biomechanical competence of bone is a function of its geometrical and material properties. Links between bone microstructure, composition, and mechanical characteristics are recently becoming better understood.[1-3,5,10] Increasingly it is becoming evident that bone strength and risk of fracture is only partially determined by bone mineralization and that bone architecture has considerable influence.

Currently, the technique of analyzing volumetric imaging data is relatively tedious and requires substantial computer processing capacity. Automated algorithms and protocols must be developed to improve throughput, reproducibility, and to reduce user bias that is inherently introduced. With some semi-automated techniques becoming available, such as those found in BoneJ (a plug-in for the open source image processing software platform ImageJ),[48] consensus on standards for analytical implementations are sure to soon follow.

Although not practical for *in vivo* or clinical use, synchrotron source micro-CT[1,7,49-51] provides advantages over standard X-ray micro-CT, such as higher spatial resolution, alternative contrast techniques, fewer artifacts, and a nearly monochromatic energy source, driving research that aims to better understand and characterize minute bone features and more precise distribution of material composition. With its superior resolution, synchrotron source imaging applied to bone will aid in the assessment of microdamage, capturing features such as the orientation and geometry of microcracks and secondary osteon, that plays a role in initiating or dissipating energy and regulating the repair process, ultimately impacting bone quality and fracture healing.

Recent advances in micro-CT imaging, morphometric analysis, and biomechanical modeling are creating new opportunities to study and understand bone biology, architecture, fracture risk, and the effects of pharmacotherapy. These combined methods are gaining more widespread acceptance and are quickly becoming incorporated into clinical trials. Although currently the techniques entail specialized equipment, exposure to modest amounts ionizing radiation, and require non-standardized image analysis, they provide information about BMD, macrostructure, and microstructure. Furthermore, there is a high likelihood that these technical limitations will soon be reduced or eliminated. Advanced techniques in micro-CT, FEM, and bone modeling are certainly poised to improve our understanding of bone biomechanics, fracture propensity, and clinical management of OI.

ABBREVIATIONS

2-D	Two-dimensional
3-D	Three-dimensional
+ -	Wild-type
BMD	Bone mineral density
CCD	Charge-coupled device
cm	Centimeter
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
FEM	Finite element method
GE	General Electric
HA	Hydroxyapatite
HU	Hounsfield units
keVs	Kiloelectron-volts
kVp	Peak kilovoltage
OI	Osteogenesis imperfecta
oim	Osteogenesis imperfecta murine (mouse) model
mg	Milligram
micro-CT	Micro-computed tomography
mL	Milliliter
mm	Millimeter
NIH	National Institutes of Health
ROI	Region of interest
uA	Microamp
uL	Microliter
um	Micrometer
VOI	Volume of interest
voxel	Volume element

REFERENCES

1. Ito M. Assessment of bone quality using micro-computed tomography (micro-CT) and synchrotron micro-CT. *J. Bone Miner. Metab.* 2005; 23 Suppl: 115-21.
2. Liebschner MA, Muller R, Wimalawansa SJ, et al. Testing two predictions for fracture load using computer models of trabecular bone. *Biophys. J.* 2005; 89(2): 759-67.
3. Jiang Y, Zhao J, Liao EY, et al. Application of micro-CT assessment of 3-D bone microstructure in preclinical and clinical studies. *J. Bone Miner. Metab.* 2005; 23 Suppl: 122-31.
4. Yeni YN, Brown CU, Wang Z, et al. The influence of bone morphology on fracture toughness of the human femur and tibia. *Bone*. 1997; 21(5): 453-9.

5. Ito M, Ikeda K, Nishiguchi M, et al. Multi-detector row CT imaging of vertebral microstructure for evaluation of fracture risk. *J. Bone Miner. Res.* 2005; 20(10): 1828-36.
6. Engelke K, Song SM, Gluer CC, et al. A digital model of trabecular bone. *J. Bone Miner. Res.* 1996; 11(4): 480-9.
7. Bouxsein ML, Boyd SK, Christiansen BA, et al. Guidelines for assessment of bone microstructure in rodents using micro-computed tomography. *J. Bone Miner. Res.* 2010; 25(7): 1468-86.
8. Sezgin M, Sankur B. Survey over image thresholding techniques and quantitative performance evaluation. *J. Electron. Imaging.* 2004; 13(1): 146-65
9. Muller R, Van Campenhout H, Van Damme B, et al. Morphometric analysis of human bone biopsies: a quantitative structural comparison of histological sections and micro-computed tomography. *Bone*. 1998; 23(1): 59-66.
10. Genant HK, Engelke K, Prevrhal S. Advanced CT bone imaging in osteoporosis. *Rheumatology* (Oxford). 2008; 47 Suppl 4: iv9-16.
11. Ito M, Nishida A, Nakamura T, et al. Differences of three-dimensional trabecular microstructure in osteopenic rat models caused by ovariectomy and neurectomy. *Bone*. 2002; 30(4): 594-8.
12. Ito M, Nakamura T, Matsumoto T, et al. Analysis of trabecular microarchitecture of human iliac bone using microcomputed tomography in patients with hip arthrosis with or without vertebral fracture. *Bone*. 1998; 23(2): 163-9.
13. Muller R, Ruegsegger P. Three-dimensional finite element modelling of non-invasively assessed trabecular bone structures. *Med. Eng. Phys.* 1995; 17(2): 126-33.
14. Hildebrand T, Ruegsegger P. Quantification of Bone Microarchitecture with the Structure Model Index. *Comput Methods Biomech Biomed Engin.* 1997; 1(1): 15-23.
15. Fung YC. Mechanical properties of living tissues. *Biomechanics*. New York: Springer-Verlag; 1993. p. 500-36
16. Pereira R, Khillan JS, Helminen HJ, et al. Transgenic mice expressing a partially deleted gene for type I procollagen (COL1A1). A breeding line with a phenotype of spontaneous fractures and decreased bone collagen and mineral. *J. Clin. Invest.* 1993; 91(2): 709-16.
17. Chipman SD, Sweet HO, McBride DJ, Jr., et al. Defective pro alpha 2(I) collagen synthesis in a recessive mutation in mice: a model of human osteogenesis imperfecta. *Proc. Natl. Acad. Sci. USA.* 1993; 90(5): 1701-5.
18. Bonadio J, Saunders TL, Tsai E, et al. Transgenic mouse model of the mild dominant form of osteogenesis imperfecta. *Proc. Natl. Acad. Sci. USA.* 1990; 87(18): 7145-9.
19. Camacho NP, Hou L, Toledano TR, et al. The material basis for reduced mechanical properties in oim mice bones. *J. Bone Miner. Res.* 1999; 14(2): 264-72.
20. Gasser JA, Ingold P, Grosios K, et al. Noninvasive monitoring of changes in structural cancellous bone parameters with a novel prototype micro-CT. *J. Bone Miner. Metab.* 2005; 23 Suppl: 90-6.
21. Karau KL, Johnson RH, Molthen RC, et al. Microfocal X-ray CT imaging and pulmonary arterial distensibility in excised rat lungs. *Am J Physiol Heart Circ Physiol.* 2001; 281(3): H1447-57.
22. Karau KL, Molthen RC, Dhyani A, et al. Pulmonary arterial morphometry from microfocal X-ray computed tomography. *Am J Physiol Heart Circ Physiol.* 2001; 281(6): H2747-56.

23. Molthen RC, Karau KL, Dawson CA. Quantitative models of the rat pulmonary arterial tree morphometry applied to hypoxia-induced arterial remodeling. *J. Appl. Physiol.* 2004; 97(6): 2372-84; discussion 54.
24. Feldkamp LA, DAVIS LC, KRESS JW. Practical cone-beam algorithm. *Journal of the Optical Society of America A.* 1984; 1(6): 612-9.
25. Misof BM, Roschger P, Baldini T, et al. Differential effects of alendronate treatment on bone from growing osteogenesis imperfecta and wild-type mouse. *Bone*. 2005; 36(1): 150-8.
26. Uveges TE, Kozloff KM, Ty JM, et al. Alendronate treatment of the brtl osteogenesis imperfecta mouse improves femoral geometry and load response before fracture but decreases predicted material properties and has detrimental effects on osteoblasts and bone formation. *J. Bone Miner. Res.* 2009; 24(5): 849-59.
27. McBride DJ, Jr., Shapiro JR, Dunn MG. Bone geometry and strength measurements in aging mice with the oim mutation. *Calcif. Tissue Int.* 1998; 62(2): 172-6.
28. Muller R, Hahn M, Vogel M, et al. Morphometric analysis of noninvasively assessed bone biopsies: comparison of high-resolution computed tomography and histologic sections. *Bone.* 1996; 18(3): 215-20.
29. Interdisciplinary treatment approach for children with osteogenesis imperfecta. Chiasson RM, Munns C, Zeitlin L, editors: Shriners Press; 2004.
30. Petit MA, Beck TJ, Kontulainen SA. Examining the developing bone: What do we measure and how do we do it? *J Musculoskelet Neuronal Interact.* 2005; 5(3): 213-24.
31. Fan ZF, Smith P, Rauch F, et al. Nanoindentation as a means for distinguishing clinical type of osteogenesis imperfecta. *Composites Part B: Engineering.* 2007; 38(3): 411–5.
32. Fan Z, Smith PA, Harris GF, et al. Comparison of nanoindentation measurements between osteogenesis imperfecta Type III and Type IV and between different anatomic locations (femur/tibia versus iliac crest). *Connect. Tissue Res.* 2007; 48(2): 70-5.
33. Fan Z, Smith PA, Eckstein EC, et al. Mechanical properties of OI type III bone tissue measured by nanoindentation. J Biomed Mater Res A. 2006; 79(1): 71-7.
34. Kalpakcioglu BB, Morshed S, Engelke K, et al. Advanced imaging of bone macrostructure and microstructure in bone fragility and fracture repair. *J. Bone Joint Surg. Am.* 2008; 90 Suppl 1: 68-78.
35. Firoozabadi R, Morshed S, Engelke K, et al. Qualitative and quantitative assessment of bone fragility and fracture healing using conventional radiography and advanced imaging technologies--focus on wrist fracture. *J. Orthop. Trauma.* 2008; 22(8 Suppl): S83-90.
36. Boutroy S, Bouxsein ML, Munoz F, et al. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J. Clin. Endocrinol. Metab.* 2005; 90(12): 6508-15.
37. Khosla S, Melton LJ, 3rd, Achenbach SJ, et al. Hormonal and biochemical determinants of trabecular microstructure at the ultradistal radius in women and men. *J. Clin. Endocrinol. Metab.* 2006; 91(3): 885-91.
38. Burghardt AJ, Issever AS, Schwartz AV, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* 2010; 95(11): 5045-55.
39. Jameson J, Albert C, Molthen R, et al., editors. Micro-CT characterization of human trabecular bone in osteogenesis imperfect. *Medical Imaging: Biomedical*

Applications in Molecular, Structural, and Functional Imaging; 2011 February 13-17, 2011; Lake Buena Vista, FL: SPIE, Bellingham, WA.
40. Rivers. M. L., Sutton S. Geoscience applications of X-ray computed microtomography. *Proceedings of SPIE*, Developments in X-ray Tomography II. 1999; 3772: 78-86.
41. Baron R, Gertner JM, Lang R, et al. Increased bone turnover with decreased bone formation by osteoblasts in children with osteogenesis imperfecta tarda. *Pediatr. Res.* 1983; 17(3): 204-7.
42. McCarthy EF, Earnest K, Rossiter K, et al. Bone histomorphometry in adults with type IA osteogenesis imperfecta. *Clin Orthop Relat Res*. 1997; (336): 254-62.
43. Ste-Marie LG, Charhon SA, Edouard C, et al. Iliac bone histomorphometry in adults and children with osteogenesis imperfecta. *J. Clin. Pathol.* 1984; 37(10): 1081-9.
44. Rauch F, Travers R, Parfitt AM, et al. Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. *Bone*. 2000; 26(6): 581-9.
45. Cointry GR, Capozza RF, Chiappe MA, et al. Novel experimental effects on bone material properties and the pre- and postyield behavior of bones may be independent of bone mineralization. *J. Bone Miner. Metab.* 2005; 23 Suppl: 30-5.
46. Yeni YN, Brown CU, Norman TL. Influence of bone composition and apparent density on fracture toughness of the human femur and tibia. *Bone*. 1998; 22(1): 79-84.
47. Dragomir-Daescu D, Op Den Buijs J, McEligot S, et al. Robust QCT/FEA models of proximal femur stiffness and fracture load during a sideways fall on the hip. *Ann. Biomed. Eng.* 2011; 39(2): 742-55.
48. Doube M, Klosowski MM, Arganda-Carreras I, et al. BoneJ: Free and extensible bone image analysis in ImageJ. *Bone*. 2010; 47(6): 1076-9.
49. Larrue A, Rattner A, Peter ZA, et al. Synchrotron radiation micro-CT at the micrometer scale for the analysis of the three-dimensional morphology of microcracks in human trabecular bone. *PLoS One.* 2011; 6(7): e21297.
50. Cooper DM, Erickson B, Peele AG, et al. Visualization of 3D osteon morphology by synchrotron radiation micro-CT. *J. Anat.* 2011; 219(4): 481-9.
51. Matsumoto T, Nishikawa K, Tanaka M, et al. In vivo CT quantification of trabecular bone dynamics in mice after sciatic neurectomy using monochromatic synchrotron radiation. *Calcif. Tissue Int.* 2011; 88(5): 432-41.

13 QUANTITATIVE ASSESSMENT OF CHILDREN WITH OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Assessments of children with Osteogenesis Imperfecta (OI) are typically limited to a physical exam and observations from a clinician during a hospital visit. Often quantitative information such as bone mineral density and outcome questionnaires is obtained, but with the increasing prevalence of motion analysis and other performance type laboratories, there are many other tools available, which could be beneficial to this patient population. These laboratories can provide data supplementary to morphologic and radiographic data that is helpful in tracking changes in the patient's functional abilities, recovery from fracture, and treatment outcomes. This chapter will cover some useful evaluation methods for children with the most commonly seen types of OI and provide some examples of their test results.

METHODOLOGY – EVALUATION TOOLS

It is important to first identify areas of pain and eliminate patients with fractures from being asked to perform functional assessments. Those individuals with minimal-to-no-pain and no fractures could benefit from a

variety of assessments such as a thorough physical examination that includes joint range of motion (ROM) measurements and strength testing. Plantar pressures provide a quick evaluation of foot mechanics and can identify biomechanical deformities like pes valgus. Gait analysis quantifies temporal-spatial parameters (i.e. walking speed), joint motion (kinematics), joint forces (kinetics) and muscle activity (electromyography). Postural control testing is useful in ensuring the safety of these patients by identifying standing instability and it also plays a role in the development and completion of gross motor skills. Combined, these tools provide a quantitative assessment of the physical abilities as part of a comprehensive functional evaluation of children with OI. This information can assist in making the best treatment decisions and track patient progress over time.

Pain Assessment

The Faces Pain Scale-Revised[1] is a commonly used tool to have the patient indicate their level of pain on a scale of 0 – 10. Establishing the level of pain is important prior to proceeding with any functional assessment. If pain levels are above the 0 – 1 range certain tests may not produce accurate results.

Physical Exam

A lower extremity physical exam performed by a physical therapist or orthopaedic physician is useful in providing joint range of motion (ROM) and strength measurements. The Minimum Standardized Gait Analysis Protocol (MSGAP)[2] can be used for collecting measurements bilaterally of the subject's hips, knees and ankle joints. Table 1 shows an example of a typical physical exam of a patient with OI type I. Note the abnormal knee hyperextension and ankle hypermobility as well as the hindfoot valgus and some asymmetry.

Table 1. Physical exam measures of a 9 year old female with type I OI.

Physical exam: 9 year old female with OI type I		
LEFT ROM	JOINT MOTION	RIGHT ROM
	HIP	
130	Flexion 0-125°	130
0	Extension (supine, Thomas test) 0°	0
75	Abduction (flexed) 0-45°	75
45	Abduction (extended) 0-45°	48
20	Adduction 0-20°	20
60	Internal Rotation (prone) 0-45°	60
40	External Rotation 0-45°	40
	KNEE	
150	Flexion (supine) 0-140°	150
145	Flexion (prone) 0-140°	145
10 Hyper	Extension 0° (Note Hyperextension)	8 Hyper
10	Popliteal Angle (op extended) 25°	10
80	Straight Leg Raise 0-90°	80
	ANKLE	
50	Dorsiflexion (knee flexed) 0-20°	45
40	Dorsiflexion (knee extended) 0-10°	35
45	Plantarflexion 0-45°	50
45	Adduction (post tib) 0-40°	40
40	Abduction (peroneals) 0-30°	30
	STATIC TRANSVERSE/CORONAL ALIGNMENT	
10° AV	Femoral Anteversion (Ryder)	10° AV
2° Evert	Thigh Foot Angle	14° Evert
5° Invert	Transmaleolar Axis	18° Evert
	STATIC FOOT ALIGNMENT – WEIGHT BEARING	
8° Valgus	Hindfoot	15° Valgus
Decreased	Midfoot (Arch)	Decreased
Neutral	Forefoot	Neutral
Neutral	Great Toe	Neutral

To break the cycle of fracture leading to immobility, leading to weakness, leading to fracture in children with OI, it is helpful to quantify baseline levels of strength and monitor them for deficits in order to maintain the highest level of functional ability. Due to bone fragility, strength assessments must be performed with the utmost concern for the patient's safety. Tests that apply forces or initiate resistance are often avoided in this patient

population. Strength can still be assessed by having the patient perform tests without manual resistance, where they initiate the force instead of tests where forces are applied to them. Strength testing methods include:

a) Manual Muscle Test — where the therapist or physician does not apply manual resistance;

b) Functional Assessments of Strength – measure the maximum number of repetitions of movements:
   - Single leg heel rise test[3,4] assigns a plantarflexion strength score based on how many heel rises can be completed out of 20 (Example in Table 2).
   - Lateral/Frontal step ups
   - Sit to stand;

c) Dynamometry – can be used to quantify the strength of isometric muscle contractions. There are hand held devices or larger systems that a patient is seated in and positioned to isolate certain muscle groups. Table 2 displays the results of a single patient's strength represented by the single leg heel rise test score and plantarflexor strength measured using a Biodex System III (Shirley, New York).

Table 2. Strength measures for a 9 year old female with type I OI.

Test	Left	Right	Controls
Heel Rises	20	11	20
Plantarflexion* (PKTQ/BW)%	66.1	63.9	101.7
Dorsiflexion* (PKTQ/BW)%	47.7	47.7	45.5

*PKTQ/BW: This is the peak torque generated during the duration of the trial and divided by the subject's body weight so the value is reported as a percentage of total body weight.

Previous research, as well as the data in Table 2, shows that weakness is prevalent in the OI population. Common areas of weakness include the plantarflexors, shoulder abductors, hip flexors, ankle dorsiflexors and grip strength.[5-7] This weakness may affect exercise tolerance and high level gross motor activities, which results in functional skills ranging from very limited to highly functional depending on disease severity. Weakness does not appear to be progressive. This is similar to Engelbert et al., 2004, who reported that muscle strength did not change significantly over time in

children with OI.[8] They found that as children aged, from ~7 years old to ~11 years old, the ability to care for themselves improved along with their overall functional ability.

Pedobarography

Pedobarography is a timely way to quantify foot mechanics during gait. Due to the characteristic ligament laxity in the OI population, pes valgus and decreased medial arches are often seen during static standing and the stance phase of gait. Flatfoot is typically a deformity created by malalignment of several adjacent joints. According to Mosca, "the anatomic characteristics of a flatfoot are excessive eversion of the subtalar complex during weight bearing with plantarflexion of the talus, plantarflexion of the calcaneus in relation to the tibia, a dorsiflexed and abducted navicular and supinated forefoot."[9] Jameson et al. have developed a pedobarographic technique that helps in the identification of poor foot mechanics, or flexible lever arm dysfunction.[10] This is accomplished by tracing the relative movement of the center of pressure across the plantar surface of the foot during the stance phase of gait. By identifying the medial-lateral location of the center of pressure progression (COPP), you can determine if the hindfoot, midfoot and/or forefoot are varus, valgus or neutral. It is hypothesized that improper foot positioning during loading may lead to inadequate shock absorption during initial foot contact and loading response, and it has been found that poor foot mechanics in OI type I can lead to reduced ankle push off power generation during forward propulsion.[11] Figure 1 displays the plantar pressures of a patient with OI next to that of a typically developing child. Notice the increased surface area in contact with the floor at the midfoot and the decreased time spent loading the forefoot.

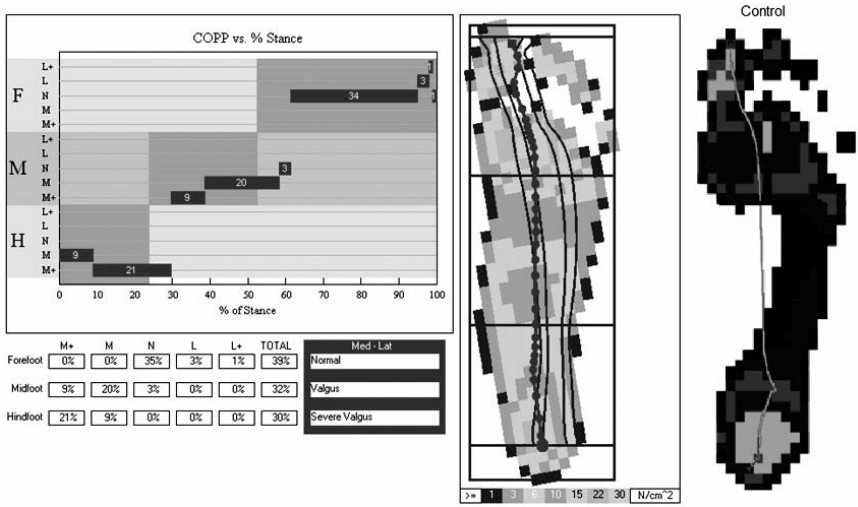

Figure 1. Pedobarography Sample Report. The top left graph shows the % of stance phase that the Center of Pressure Progression (COPP) is within the hindfoot (H), midfoot (M) and forefoot (F). Below the graph shows the % of stance phase that the COPP is normal (N), medial by 2+ std. deviations (M+), medial by one std. dev (M), lateral (L) or lateral by 2+ std. deviations (L+). Next to that is a display that summarizes the COPP location. This subject has a severe valgus hindfoot, valgus midfoot and normal forefoot COPP position, but reduced % of stance on the forefoot.

Gait Analysis

Gait analysis is another tool often used to quantify functional ability by measuring the three dimensional motion of body segments during gait. It can be used to collect data longitudinally and measure changes over time, pre and post intervention, and then compare data to a typically developing individual's gait pattern to identify deficits. Analysis of gait typically involves an observational component including video and photographs, as well as quantitative three-dimensional motion capture data. Useful parameters such as temporal spatial values (i.e. walking speed, step/stride length and foot contact time), kinematics (ankle, knee and hip joint angles/rotations), kinetics (joint forces/moments and powers) and electromyography (muscle activity) can be recorded simultaneously during walking. The recording and analysis of this information can be helpful in evaluating children with OI especially due to the disorder's heterogeneity, even within types.

Gait disturbances in OI are typically caused by underlying bony deformities or by weakness in the musculoskeletal system. These children are not known to have any neurologic conditions associated with the disease. Some individuals with OI are observed using an antalgic gait pattern to minimize

the application of forces to weakened or compromised areas, while others may vault or circumduct to accommodate other problems. Gait analysis can help to identify or dissociate between primary gait deviations due to structural deformities that cause biomechanical abnormalities and the compensatory strategies used to maximize ambulatory capacity. Typically, a gait analysis will discover gait abnormalities that then need to be sorted and pieced together to uncover the primary problems. Some examples of this can be seen in Table 3.

Table 3. Gait Abnormalities and their associated problems in children with OI.

Gait Abnormality	Description and secondary gait abnormalities	Primary Problem
Increased Hip Abduction	Increased coronal plane pelvic/trunk motion (Trendelenberg pattern) Attempts to diminish forces generated by muscles that typically stabilize the hip	Gluteal weakness
Fixed Pelvic Obliquity	Vaulting on one side/circumducting on the other Flexed hip or knee	Leg length discrepancy
Decreased Peak Ankle Power Generation	Increased hip and/or knee power generation Prolonged stance phase Excessive ankle dorsiflexion due to ligament laxity	Plantar flexor weakness and/or pes valgus
Knee Hyperextension	Increased power absorption Prolonged stance phase	Ligament laxity and plantar flexor weakness

Temporal Spatial Parameters

Treatment strategies for OI should improve functional abilities, which may in turn affect some time dependent activities such as navigating a crosswalk and keeping up with peers in the community. Analysis of gait can provide insight into the level of these abilities. Table 4 shows examples of these parameters for someone with OI types I, III and IV, all of whom have reduced walking speed compared to typically developing individuals. All groups also show increased time with the foot in contact with the ground, or a delay in their foot off.

Table 4. Temporal spatial parameters for three individuals with OI.

Parameter	Type I	Type III	Type IV	Typically Developing
Walking Speed (m/s)	0.97	0.27	0.69	1.21
Cadence (steps/min)	126	65.7	95.6	122.9
Foot Off (%GC)	63.1	75.0	65.4	60.3
Double Support (%GC)	27.8	48.9	35.2	21.5
Single Support (%GC)	36.5	25.2	33.7	38.8
Step Length (m)	0.47	0.25	0.40	0.6
Stride Length (m)	0.92	0.52	0.85	1.1

Kinematics

Kinematic analysis describes joint angles during the gait cycle. Once the angular position can be calculated, the functional ability of the corresponding muscles and bones that cause that motion can be described in regards to gait. The kinematic analysis of these individuals with OI types I, III and IV reveals several trends that can be seen in the OI population (Figure 2). In these examples, the type I pattern is quite similar to a typically developing pattern, while the type III pattern is distinctly different with many gait deficits. The type IV pattern can be quite variable and in this example falls between the types I and III as far as quality of gait. Gait patterns typically correspond to the severity of the disease in these individuals. Even with the type I pattern, there are several characteristics different from the typically developing group. Here are some other common gait characteristics:

a) Type I common kinematic gait characteristics:
- Similar to typically developing children
- Increased knee hyperextension in midstance
- Increased ankle dorsiflexion throughout the gait cycle
- Reduced peak ankle plantarflexion during push off

b) Type III common kinematic gait characteristics:
- Increased anterior pelvic tilt throughout the gait cycle
- Reduced hip ROM and peak hip extension
- Reduced knee ROM with increased flexion throughout the gait cycle
- Reduced peak ankle plantarflexion during push off

- Variable rotational profiles at hip, shank or foot due to bone deformities

c) Type IV common kinematic gait characteristics:
- Variable gait pattern that can range in quality from that of type I to type III
- Variable rotational profiles at hip, shank or foot due to bone deformities
- Increased knee hyperextension in midstance
- Increased ankle dorsiflexion throughout the gait cycle
- Reduced peak ankle plantarflexion during push off

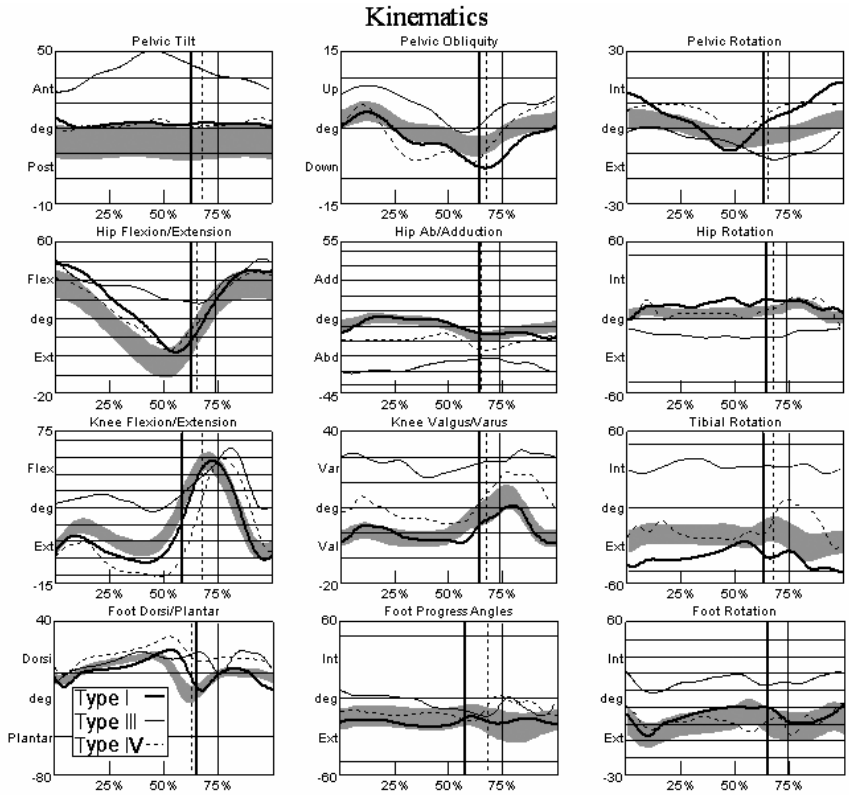

Figure 2. Gait Kinematics for 3 individuals with OI. Gray band is Typically Developing (TD) gait pattern, thick black line is an individual with type I, thin line is type III and the dotted line is type IV. The types I and IV are independent ambulators and the type III subject uses lofstrand crutches.

Kinetics

Kinetic analysis of the lower extremities during gait is somewhat limited by current technology due to the fact that the forceplate must be struck "cleanly", or by one whole foot at a time. This is difficult for individuals who use assistive devices and/or take small steps, which is the case especially in the OI type III population. However, the use of force transducer instrumented crutches, walkers or wheelchairs allows for upper extremity kinetic analysis. Of those who do "cleanly" strike the forceplates, typically individuals with types I and IV, we are able to understand in greater detail the causes of gait deviations seen in the lower extremity kinematic data. Calculating joint moments helps to explain how the body responds to external loading and the changing position of the ground reaction force during gait. Joint power is calculated by measuring the work done over time. The analysis of power data can be viewed as a summary of gait findings because it has components from the kinematic data (joint angular velocity) and the moment data, and provides a description of muscle activity (concentric or eccentric contraction). Kinetic analysis demonstrates that children with OI do typically exhibit several deficits from typically developing kinetic gait patterns (Figure 3):

a) Type I kinetic gait characteristics:
   - Similar to typically developing
   - Decreased plantar flexor demand
   - Decreased peak ankle power generation
   - Increased hip power generation as compensation for reduced ankle power

b) Type III kinetic gait characteristics:
   - Often limited to upper extremity analysis using instrumented assistive devices

c) Type IV kinetic gait characteristics:
   - Similar to type I but may exhibit greater deficits depending on severity
   - Increased knee flexor demand due to knee hyperextension in midstance.

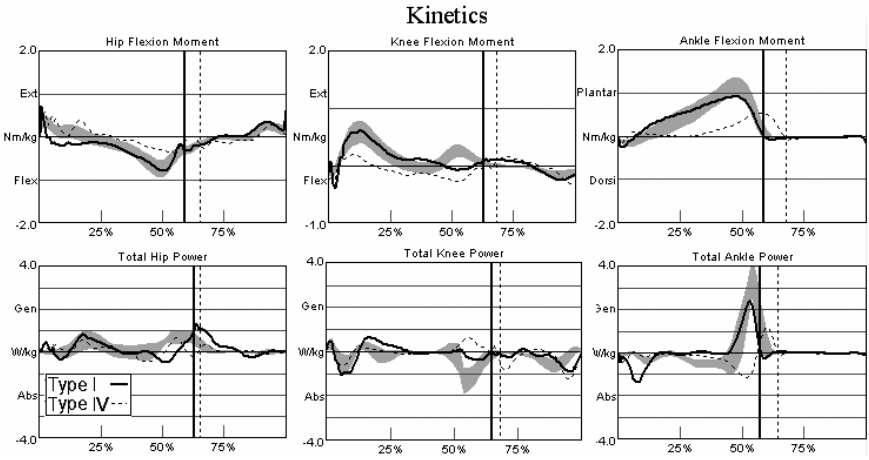

Figure 3. Gait kinetics for two individuals with OI. The Gray band is typically developing, the thick black line is an individual with type I OI and the dotted is type IV. There is no data for type III because all subjects used assistive devices causing inaccurate force plate data.

Postural Control

With a high risk of fracture in the OI population, balance and stability is of the utmost importance. Static and dynamic balance is vital for patient safety but is often difficult to assess in a clinical setting. Many individuals with OI will walk with a gait pattern that increases the duration of stance phase or delay the time until foot off to increase the time both feet are on the ground, thereby increasing stability. Static balance can be effectively evaluated using a system such as the Neurocom® SMART EquiTest® (Natus Medical, Inc., Pleasanton, CA). Postural stability is discussed further in a subsequent chapter.

Energy Efficiency

Many motion analysis laboratories now have systems capable of analyzing expired CO_2/O_2 as a measure of energy efficiency. This information is useful for objectively quantifying and differentiating the gait efficiency of children with OI compared with typically developing individuals. Takken et al. found that fatigue often limits patients with OI during activities of daily living and exercise. This may be a result of hypoactivity, and thus leads to detraining[5] and increase in the fracture cycle. Their findings confirm that OI has a large impact on functional ability depending on severity with common findings of decreased muscle strength and exercise ability.

The Cosmed K4B[2] (Rome, Italy) is an example of a device used to assess cardiopulmonary fitness. It is a wireless, portable system that allows the subject to walk and move at their desired pace making within-subject comparisons possible. There are several parameters that can be generated during the analysis of expired gases that may be useful in treating children with OI including heart rate (HR), energy expenditure (EE), VO_2, energy efficiency index (EEI)[12] and net non-dimensional (NN) scheme outputs.[13] The EEI determines efficiency of movement using HR and walking speed. The NN was introduced as a method to reduce the variability in energy expenditure due to age and stature by appropriate non-dimensionalization,[14] which makes it useful for children with OI. Table 5 and Figure 4 show the results for a 10 year old male with type IV OI during resting, walking and on an ergometer. This individual has a higher heart rate, but is nearly normal in walking efficiency compared to typically developing individuals.

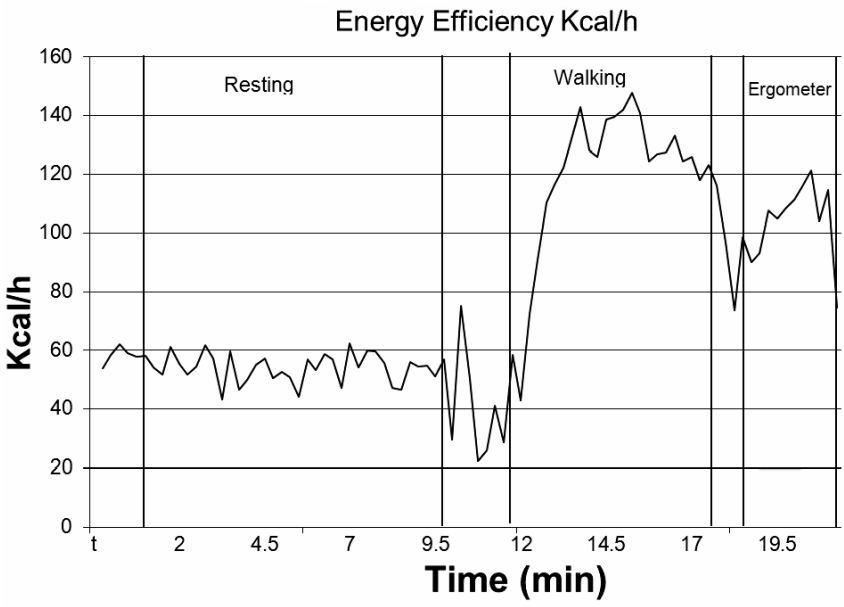

Figure 4. Energy efficiency (Kilocalories/hour) over time for roughly 10 minutes of resting, 6 minutes of walking and 3 minutes of ergometer use.

Table 5. Energy efficiency parameters for a 10 year old male with type IV OI.

Parameter	HR (beats/min)	Eehour (Kcal/h)	VO2 (ml/min)	EEI (beats/min)	Nncost
Resting (10min)	102.6	54.1	179.6	-	-
Walking (6min)	131.4	128.0	440.3	0.70	0.26
Ergometer (3min)	126.6	109.1	366.6	0.62	0.29

Assistive Devices

Assistive devices such as walkers, lofstrand crutches and wheelchairs are often used by children with severe cases of OI. It has been reported by Engelbert et al. that the severity of the collagen defect is the greatest predictor of ambulatory ability in this patient population.[15] Out of 70 children with OI all with type I were able to ambulate and 85% of those walked independently without assistive devices. Individuals with OI types III and IV had a lower chance of walking than those with type I. Rodding of the lower extremities also limited ambulation. It was found that with an increase in the number of rods inserted into the long bones there was a reduction in the subject's walking ability. Children dependent upon assistive devices prove more difficult to evaluate, but still benefit greatly from functional evaluation.

As previously mentioned, it is possible to assess upper extremity joint kinetics using walker or crutch handles that are instrumented with six-degree-of-freedom force transducers in conjunction with a kinematic model. Examples of the use of this technology can be seen in a subsequent chapter.

CLINICAL IMPLICATIONS

Motion analysis laboratories have several tools that may be helpful in assessing the functional ability of children with OI. Prior to performing any tests that require physical activity it is important to consider the classification of OI of the patient. The classification is helpful in understanding disease related characteristics specific to each class and allows for more accurate patient comparisons and expectations. Several studies have determined that strength, functional ability and prognosis for walking are closely associated with the type of OI.[3,5,8,15,16] Sillence et al. reported that rehabilitation should focus on strategies to achieve community

walking in type I, exercise or household walking in type III and household or community walking in type IV. Determining the appropriate assessment tools and treatment options may also depend on the classification keeping in mind the wide range of variability in the disease (Table 6). Individuals with OI type I typically are independent ambulators with normal stature and few visible physical abnormalities that would limit function. Upon closer examination however, some characteristics may become apparent such as joint hypermobility and muscle weakness. Ligament laxity could cause knee hyperextension, excessive ankle dorsiflexion and flatfeet. Muscle weakness could be a limiting factor in high level gross motor activities. The short stature and limb deformities prevalent in individuals with type III OI may limit mobility to a wheelchair or necessitate the use of an assistive device to ambulate. If that is the case, upper extremity evaluation tools can be used such as a walker, crutches or a wheelchair instrumented with force transducers to assess loading of the bones and joints during gait. These tools are discussed further in other sections of this book. With the heterogeneous nature of OI type IV, and physical changes that occur with age in these individuals, functional assessment is very useful, though careful consideration needs to be taken in testing selection. These individuals could be administered the same protocol as for type I or type III, depending on their severity.

Table 6. Recommended evaluation tools for types of OI.

OI Type	Evaluations Tools
I,III,IV	Pain Scale
I, III, IV	Physical Exam – ROM, static alignment
I, III, IV	Strength (Manual Muscle Test without resistance
I, IV	Strength (Dynamometer Test — isometric)
I, III, IV	Pedobarography
I, III, IV	Gait Temporal Spatial Parameters
I, III, IV	Gait Kinematics
I,IV	Gait Kinetics
I, IV	Postural Control
III, IV	Instrumented Walker/Crutches/Wheelchair
I, III, IV	Energy Efficiency

The treatment of OI has improved in many ways with advancements in surgical rodding, gene and drug therapy. With increasing treatment options it is important to be able to thoroughly assess these patients in order to focus treatment in the most appropriate areas and to use the most effective methods available. The fundamental variability of this disease also

necessitates the use of evaluation tools capable of measuring the abilities of children with a range of body types and functional levels, while still providing the capacity to track changes over time. These methods described in this chapter allow for both quantitative intra- and inter-patient comparison, and therefore lend themselves well to use in a clinical setting as well as for research studies.

ABBREVIATIONS

BW	Body weight
COPP	Center of pressure progression
EE	Energy expenditure
HR	Heart rate
NN	Net non-dimensional
OI	Osteogenesis imperfecta
PKTQ	Peak torque
ROM	Range of motion
TD	Typically developing
%GC	Percent gait cycle

REFERENCES

1. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain.* Aug 2001;93(2):173-183.
2. Davis R DJ, Gorton G, Aiona M, Scarborough N, Oeffinger D, Tylekowski C, Bagley A. A Minimum Standardized Gait Analysis Protocol: Development and Implementation by the Shriners Motion Analysis Laboratory Network (SMALnet). In: Harris G SP, ed. *Pediatric Gait A New Millennium Clinical Care and Motion Analysis Technology*. Piscataway: IEEE; 2000:1-7.
3. Lunsford BR, Perry J. The standing heel-rise test for ankle plantar flexion: criterion for normal. *Phys Ther.* Aug 1995;75(8):694-698.
4. Hislop HJ MJ. *Muscle Testing: Techniques of manual examination*. 6th ed. Philadelphia: W.B. Saunders Company; 1995.
5. Takken T, Terlingen HC, Helders PJ, Pruijs H, Van der Ent CK, Engelbert RH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. *J Pediatr.* Dec 2004;145(6):813-818.
6. Montpetit K, Plotkin H, Rauch F, et al. Rapid increase in grip force after start of pamidronate therapy in children and adolescents with severe osteogenesis imperfecta. *Pediatrics.* May 2003;111(5 Pt 1):e601-603.
7. Caudill A, Flanagan A, Hassani S, et al. Ankle strength and functional limitations in children and adolescents with type I osteogenesis imperfecta. *Pediatr Phys Ther.* Fall 2010;22(3):288-295.
8. Engelbert RH, Uiterwaal CS, Gerver WJ, van der Net JJ, Pruijs HE, Helders PJ. Osteogenesis imperfecta in childhood: impairment and disability. A prospective study with 4-year follow-up. *Arch Phys Med Rehabil.* May 2004;85(5):772-778.

9. Mosca VS. The child's foot: principles of management. *J Pediatr Orthop.* May-Jun 1998;18(3):281-282.
10. Jameson EG, Davids JR, Anderson JP, Davis RB, 3rd, Blackhurst DW, Christopher LM. Dynamic pedobarography for children: use of the center of pressure progression. *J Pediatr Orthop.* Mar 2008;28(2):254-258.
11. Krzak J GA, Flanagan A, Caudill A, Smith P, Harris G. Analysis of Push-Off Power During Locomotion in Children with Type I Osteogenesis Imperfecta. *Journal of Experimental and Clinical Medicine.* 2011;3(5):195-199.
12. Rose J, Gamble JG, Lee J, Lee R, Haskell WL. The energy expenditure index: a method to quantitate and compare walking energy expenditure for children and adolescents. *J Pediatr Orthop.* Sep-Oct 1991;11(5):571-578.
13. Schwartz MH, Koop SE, Bourke JL, Baker R. A nondimensional normalization scheme for oxygen utilization data. *Gait Posture.* Aug 2006;24(1):14-22.
14. Baker R, Hausch A, McDowell B. Reducing the variability of oxygen consumption measurements. *Gait Posture.* May 2001;13(3):202-209.
15. Engelbert RH, Uiterwaal CS, Gulmans VA, Pruijs H, Helders PJ. Osteogenesis imperfecta in childhood: prognosis for walking. *J Pediatr.* Sep 2000;137(3):397-402.
16. Sillence DO, Morley K, Ault JE. Clinical management of osteogenesis imperfecta. *Connect Tissue Res.* 1995;31(4):S15-21.

14 MULTISEGMENTAL FOOT AND ANKLE MODELING:
HISTORY, DEVELOPMENT, AND IMPLICATIONS IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Gait analysis is an established clinical tool for treatment planning (both surgical and non-surgical methods), as well as outcomes assessment and longitudinal studies of maintenance and progress. Three-dimensional motion analysis techniques used in gait analysis have been shown to have good repeatability in a clinical setting,[1-3] and lower extremity motion analysis during gait is a frequently used tool in pre-operative planning for patients with cerebral palsy.[4-8] When used as an assessment tool in treatment planning, gait analysis can alter surgical decision making,[9-12] and can reduce cost of care by limiting the number of subsequent surgical or other interventions.[13,14] Motion analysis methods provide a quantitative description of the gait cycle which complement and augment standard observational analysis.

UNDERLYING PRINCIPLES

In general, motion analysis involves the tracking of anatomical segments in space. Most clinically relevant motion analysis is conducted in three dimensions, and requires the tracking of planar segments that can be described with local three-dimensional axis systems. Depending on the type of system technology being used for the analysis, segments may be tracked directly, or they may be constructed from tracked anatomic landmarks. For instance, the pelvis can be tracked using a three-dimensional transducer placed on the pelvic brim, or can be constructed from tracked markers placed on the ASIS and PSIS bilaterally.

Given the three-dimensional orientation of multiple segment axis systems in space, relative angles between segments can be calculated using a number of different methods. The Euler/Cardan angle approach is used most frequently in clinical settings;[2] other methods include helical (screw) axes, direction cosines, and the floating axis method described by Grood and Suntay.[15] Common to all these methods is a means of reporting the motions of segments in a clinically relevant manner. This is usually a description of the position of a distal segment relative to a proximal segment, with a common point of articulation (a "joint"), and rotations expressed in clinically relevant terms of sagittal, coronal, and transverse plane motion.

CURRENT TECHNOLOGY

To calculate joint kinematics (and subsequent kinetics), the information provided by these systems regarding position and/or orientation in space is processed through a biomechanical model. In theory, any number of biomechanical models could be used to calculate limb orientation in space. Individual research studies and pathology-specific clinical protocols often require customized models tailored to the specific application. For clinical assessment using optical systems, three different modeling approaches are prevalent. Anthropometric models use positions of body-mounted markers to calculate the locations of virtual joint centers based on previously established regression equations.[16-18] Cluster models rely on groups of rigidly fixed markers mounted on body segments. While placement of the clusters requires less precision than anthropometric models, a technical-anatomical calibration is required to reference anatomical landmarks and segment axes to associated marker clusters. OJC (optimized joint center) models can be based on a number of different marker placement schemes; their common element is reliance on data from extensive calibration trials for an optimized estimate of joint center location.

FOOT/ANKLE GAIT ANALYSIS

Classic Representation of the Foot

As the first link in the kinetic chain between the floor and the load-bearing lower extremity, the foot is subject to a great deal of clinical scrutiny. However, due to technical restrictions and the feasibility of clinical implementation, classic lower extremity models for gait have represented the foot as a rigid segment with a single articulation at the ankle. Instrumentation is non-invasive, and can be completed in a short amount of

time by a trained technician. Some models even do away with a three-dimensional measure of foot motion, dealing only with a linear segment capable of plantar/dorsiflexion and internal/external rotation.

A great deal of data are still available from such a model, as long as they are appreciated in the context of the model's limitations. A wide range of published studies have used this simplified approach for characterization and follow-up studies involving orthopaedic surgery,[19-23] neurosurgery,[24] and physiatry,[25] as well as investigations of orthotic intervention[26,27] and prosthetic design.[28,29] None of these studies purported to completely describe the motion of the foot during gait, and most commented on the need for more refined measures in follow-up investigations.

Even some studies of foot pathology have made use of the single rigid segment foot model. Brodsky et al. evaluated a series of 12 patients who underwent tendon substitution and MDCO (medial displacement calcaneal osteotomy) for stage II posterior tibial tendon dysfunction (PTTD).[30] Single segment foot and ankle kinematics were evaluated with a five-camera motion analysis system. Preoperative gait analysis was performed and analysis was also repeated one year postoperatively. Cadence, step length and velocity were reduced when compared to controls, and ankle push-off power was also reduced. However, the characteristic symptoms of PTTD (excessive hindfoot valgus and forefoot abduction) were not adequately represented by the model used, leaving a number of questions unanswered. A modified version of the single segment foot model was employed by Thomas et al. in an investigation of patients following ankle arthrodesis.[31] They constructed a forefoot segment by adding markers at the heads of metatarsals I and V and a point midway between their bases, and assumed this segment was neutrally aligned during comfortable stance. Their investigation revealed reduced ranges of motion in the foot segments of the arthrodesis patients compared to a group of controls, but could not discern any positional differences between the groups.

Multisegmental Representation of the Foot

There is a clear trade-off between clinical ease-of-use and accurate assessment of foot motion. When a single rigid segment is used to represent the foot, the multiple articulations that take place distal to the ankle joint complex (talocrural and subtalar joints) are not appropriately represented. Relative motion between the tibia and foot segments is represented as "ankle

motion", and motions between the intrinsic bones of the foot are disregarded altogether. In patients who present with foot pathology or deformity, calculations of ankle motion can actually be corrupted by motion of the distal tarsals and metatarsals, and the very motions that characterize their pathology are masked by the simplifications inherent in the model. An example, as described by Davis et al., is the effect of sagittal plane deformity (e.g. flatfoot) on measures of sagittal plane motion, in which the model calculates exaggerated measures of dorsiflexion which do not in fact exist.[32]

Early obstacles to tracking multiple segments of the foot fell within the realm of technical and clinical feasibility. Improvements in sensor technology have allowed the tracking of smaller and more numerous segments. For instance, higher video resolutions in camera-based systems allow the tracking of smaller spherical markers on the foot, and more markers can be placed with less concern for marker masking or merging. Concurrent improvements in calibration and instrumentation routines and increased clinical interest in detailed foot motion have also contributed to the appeal of multisegmental foot analysis.

Multisegmental Foot Modeling

An accurate representation of multisegmental foot/ankle motion is necessary for extending the full capabilities of gait analysis to populations with foot pathology. Numerous models have been proposed to more accurately calculate motion distal to the ankle joint complex. This text cannot adequately describe the full body of work in this field; the reader is referred to a recent review of multisegmental foot models authored by Rankine et al.[33] Rather, this text will attempt to highlight developments of significance and milestones in multisegmental foot modeling.

Early work in foot and ankle motion analysis examined relative gross spatial motion between the foot and tibia. Wright et al. provided one of the earliest reports of such modeling efforts, using synchronous data collection from several electrogoniometers to describe multiplanar movement at the ankle.[34] Dul and Johnson used external markers to determine talocrural (plantar/dorsiflexion) and subtalar (inversion/eversion) axes, and generated a 4x4 transformation matrix to describe the position of a foot coordinate system relative to a shank (tibial) coordinate system.[35] This work failed to address any functional motion of the foot, but did provide one of the earliest demonstrations of quantified foot motion.

Lundberg et al. provided a series of reports on foot/ankle kinematics which used radio-opaque markers in live subjects.[36-39] Roentgen stereophotogrammetry techniques were used to assess motion in all three planes during passive rotation under weightbearing conditions. Lundberg's work paid particular attention to the contributions of each joint to out-of-plane motions; for example, the talocrural joint was found to account for most transverse plane rotation during dorsiflexion, but the joints of the arch also contributed when the foot was in a plantarflexed position. In addition, Lundberg verified that the talocrural joint axis moves continuously during motion, with the center of rotation near the midpoint of the bimalleolar axis. These works represent a rigorous investigation of foot/ankle kinematics; however, the use of implanted markers and radiographs contrasts sharply with standard noninvasive techniques.

One of the confounding factors in evaluating foot motion is the separation of the talocrural and subtalar joints. The common bone for each is the talus; at the talocrural joint (also known as the "true" ankle joint) the talus articulates with the tibia and fibula, while at the subtalar joint it articulates with the calcaneus. Noninvasive techniques make tracking of the talus during gait very difficult, as there is no reliable point for instrumentation that is not affected by soft tissue motion during ambulation.

A number of approaches have been reported for addressing these difficulties. Kepple et al. investigated the generally accepted method of combining motion at both joints into a single 3DOF articulation, effectively creating a single-segment foot which articulated with the tibia/fibula.[40] They measured mean error < 0.4° and standard deviations < 0.2° for all axes, and found this technique to be reliable for evaluating stance phase motion in live subjects with a video-based motion analysis system. However, their model did not examine motion distal to the calcaneus, and did not deal with swing phase at all.

More recent work on foot/ankle modeling has built on the preceding models, with attempts made to augment information with joint kinetics and data from the full gait cycle. Scott and Winter developed a model comprised of eight rigid segments and eight 1DOF joints, with viscoelastic properties for each of the seven segments of plantar soft tissue.[41] Their results suggested extension of the longitudinal arch during forefoot loading, followed by flexion during toe-off, with joint moment magnitudes largely dependent on plantar pressure distributions. While sophisticated, their model required a

data collection session of unsatisfactory duration and complexity, and was not feasible for incorporation into a clinical assessment. Also of note were limiting assumptions regarding locations of bones distal to the calcaneus.

Buczek et al. incorporated measures of joint translation into an evaluation of power at a 6DOF ankle joint.[42] Using the lumped ankle joint simplification, they measured foot and tibial kinematics and kinetics during normal ambulation, and found translational joint velocities peaking below 10% of the mean walking velocity. Leardini approached the problem from a purely mechanical perspective, developing a four-bar linkage model to describe sagittal plane motion at the ankle joint, based on observations from stereophotogrammetric tracking of calcaneal motion in cadaver specimens.[43] This established the single DOF behavior of the ankle joint during passive motion, with minimal motion at the subtalar joint and a nonstationary talocrural axis of rotation. Leardini's model lent support to the idea that complex ankle kinematics were dependent only on the articular surfaces and ligamentous constraints. A subsequent report on subtalar joint mobility noted that subtalar motion only occurred when perturbations applied to the calcaneus caused deviations from the passive flexion ROM; these subtalar motions followed a repeatable path, with two distinct axes of rotation (inversion and eversion), and full recovery was observed with the cessation of perturbation.[44] Leardini inferred that the subtalar joint complex behaved as a flexible structure, with motion occurring only during periods of ligamentous lengthening or articular surface indentation (i.e., during periods of applied loading).

In assessing the relative motion of anatomical segments, a key component of the analysis is the basis for the neutral or "zero" alignment. When the orientation of a distal segment is measured relative to a more proximal segment, a measure of zero in all three planes indicates that the segments are perfectly aligned. When considering the multiple segments of the foot, a clear definition of the neutral position becomes especially important, as the orientations of the segments are not clearly apparent from visual inspection of the foot. Some previous reports have defined the neutral position based on a patient's comfortable standing position;[45,46] others have used an imposed position such as subtalar neutral[47] or vertical tibia.[48,49] However, the ability of these models to adequately represent deformities such as calcaneal valgus or collapsed longitudinal arch has been questioned.[48,50]

Referencing to the orientation of the underlying bony anatomy allows the calibration of neutral positions based on absolute bony alignment. Standard weightbearing radiographs (antero-posterior, lateral, and coronal plane views) can be used to measure the angles between specific bony segments. If the weightbearing position is duplicated during calibration trials with a motion analysis system, the system-based orientation of segments (i.e. calculated from anatomical markers or sensors) can be correlated with orientations based on radiographs. A transformation matrix can be calculated to convert from system-based orientations to anatomy-based orientations, and this transformation can be applied to ensuing motion trials to effectively measure multisegmental foot motion at the bony level.

Examples of each type of referencing are described in the following sections. The Milwaukee and Oxford Foot Models are each well-represented in a series of technical papers establishing their repeatability and reliability, as well as series of clinical papers describing their use in assessing specific patient populations.

Milwaukee Foot Model

The Milwaukee Foot Model (MFM) was originally developed at Marquette University and the Medical College of Wisconsin. The MFM characterizes the foot/ankle complex as four rigid bodies (tibia, hindfoot, forefoot, and hallux), [51] using nine reflective markers placed on the skin surface, and a marker triad is fixed to the first phalanx of the hallux (Figure 1). The twelve markers (three per segment) are tracked using standard video-based motion analysis techniques during ambulation, and three-dimensional kinematic results are reported for both stance and swing phases of a single stride. Kinematics are calculated using classic techniques, with Euler angles reported for all segments (each segment relative to next most proximal segment, and tibia relative to global). The model was originally developed for use in adults,[51-53] and a subsequent validation established its validity in assessing pediatric populations.[54]

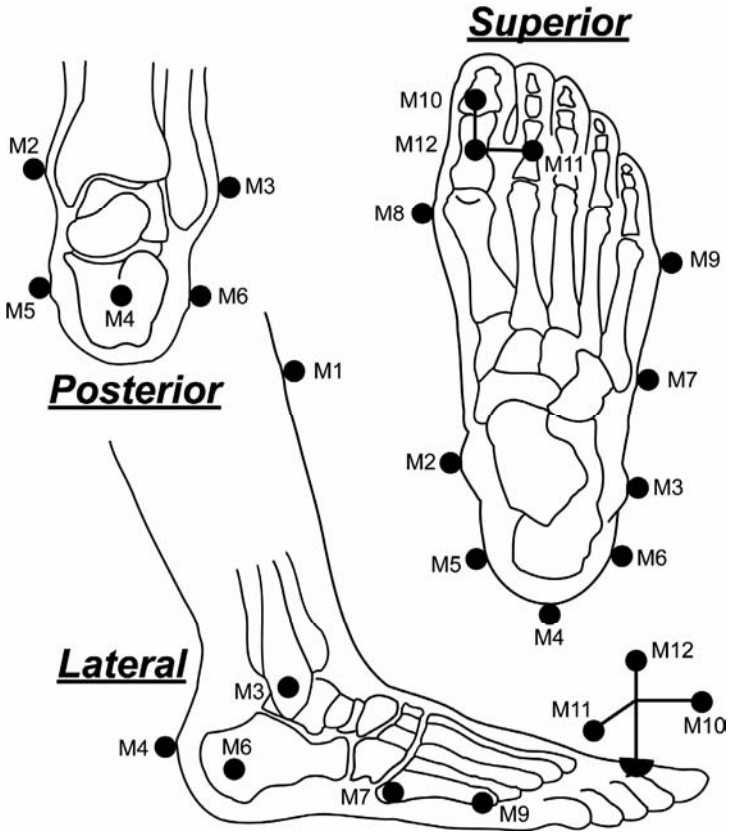

Figure 1. Anatomical marker placement for the Milwaukee Foot Model. From Kidder et al. (© 1996 IEEE)[51]

An added dimension of the MFM is its ability to reference angular motion of the marked segments to underlying bony motion, based on weightbearing radiographs collected from the patient at the time of the assessment. Standard A/P and lateral views are required of each foot being tested, as well as a modified coronal plane view which utilizes a foot positioning template to align the patient's foot for the radiograph[55] (Figure 2). The weightbearing orientation of each segment relative to the next most proximal segment can be measured from these three views. This information is used by the model to create a transformation matrix which converts marker-based kinematic values to anatomically based kinematic values, and the sensitivity of this model to these radiographic parameters has been established.[56] Since its initial development, the MFM has been used in tandem with a series of clinical studies in evaluating adult patients with foot/ankle pathology,[57-63]

and more recent work has explored its use in a multicenter design[64] and its integration into a lower extremity model.[65]

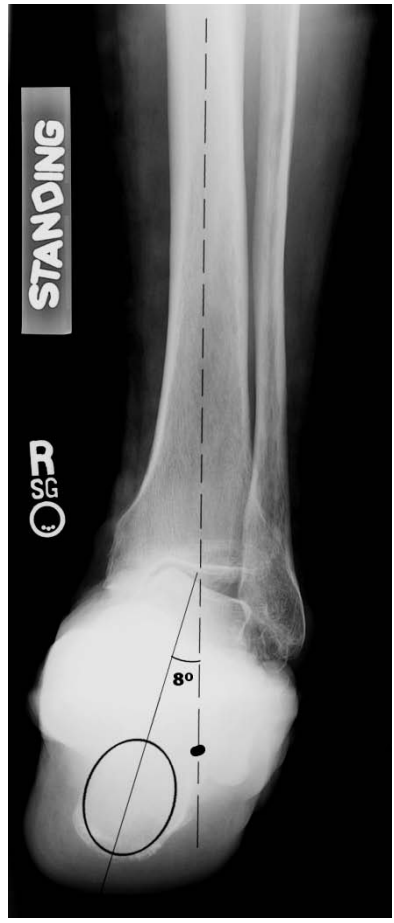

Figure 2. Modified coronal plane radiograph of the foot and ankle (Milwaukee view). Note ellipse highlighting the posterior aspect of the calcaneus, providing a reference for the alignment of the calcaneus relative to the tibia.

Oxford Foot Model

The Oxford Foot Model (OFM) was originally developed at Oxford University in collaboration with Nuffield Orthopaedic Centre. Validation of the OFM was detailed in a report by Carson et al.,[48] and its validity in pediatric populations was established by Stebbins et al.[66] Since its original description, the model has undergone some modifications to improve repeatability, incorporating

conventional knee and ankle joint centers and referencing angular measurements to a standard neutral position.

This model uses a set of reflective markers (similar to those used for the MFM) in conjunction with a video-based tracking system. Like the MFM, it includes four segments (tibia, hindfoot, forefoot, and hallux); unlike the MFM, it makes use of more than three markers per segment. The tibia, for example, is defined coronally by the plane through the fibular head and the intramalleolar axis, and sagittally by the malleolar midpoint and the tibial tubercle. The model also incorporates a subset of virtual markers, with different marker sets for static and dynamic trials. Other differences include the use of an alignment jig for maintaining vertical tibial position during the static trial, and the dorsal mounting of markers on the metatarsal heads (in anticipation of significant skin motion artifact). This model has been used clinically to describe motion in patient populations including rheumatoid arthritis,[67] hallux valgus,[68] pediatric forefoot varus,[69] flatfoot,[70] and cerebral palsy.[66]

Intra-rater reliability of the model has been established,[71] with differences attributed mainly to variability in marker placement. Hallux motion was more variable; the authors attributed this to a combination of high accelerations at toe contact and toe-off, and relative motion between the hallux markers due to equipment failure. All repeatability measures were conducted using Confidence Interval testing methods; correlations to bony motion were not performed. The Oxford Foot Model does not use radiographic indexing, although the authors acknowledge that the system would require some type of offset method to accommodate patients with hindfoot pathology or deformity. The repeatability of the modified version of the model has also been established, with the highest reliability found in hindfoot and forefoot angles when referenced to neutral stance (reliability ICC $\geq$ 0.83, error $\leq$2.45°).[72]

PRIORITIZATION AND STANDARDIZATION: GCMAS FOOT AND ANKLE SYMPOSIUM

A 2003 symposium of the Gait and Clinical Movement Analysis Society addressed the current state of the art in foot modeling from a combined clinical and technical perspective.[73] A major outcome of this symposium was the identification of the hindfoot, forefoot, and hallux as individual segments of key interest to both clinicians and researchers. As prior research studies

had identified foot segments of interest based on the research team's focus, this consensus on which segments were of particular interest provided a clear direction to future endeavors in multisegmental modeling. A second outcome of the symposium was the development of consensus terminology for describing the motion of each segment in each plane (Table 1). Prior research groups had used a range of vocabulary in describing these motions; agreement on appropriate vocabulary provided another clear benchmark in the development of multisegmental foot modeling standards.

Table 1. Consensus terminology for motion of key segments in three planes of motion. Adapted from Rankine et al.[33]

	Motion Plane		
Segment	Sagittal	Coronal	Transverse
Hindfoot	Dorsiflexion Plantarflexion	Inversion Eversion	Internal Rotation External Rotation
Forefoot	Dorsiflexion Plantarflexion	Inversion Eversion	Abduction Adduction
Hallux	Dorsiflexion Plantarflexion	Inversion Eversion	Abduction Adduction

IMPLICATIONS IN OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI) is a congenital heritable bone fragility disorder characterized by skeletal deformities and increased bone fragility.[74] It is frequently caused by aberrations in the genes producing type 1 collagen. In addition to increased risk of bony fracture, the presence of type I collagen in ligaments means that persons with OI often demonstrate joint hypermobility and pes planus. Symptoms of more severe forms of OI may include bowing of the long limbs and spinal deformities (kyphosis and/or scoliosis). Engelbert et al. have reported on the prognosis for walking in patients with OI, and concluded that the likelihood of walking was most strongly related to the underlying type of OI.[75]

The role of multisegmental foot-ankle modeling in OI is best appreciated in the context of the biomechanical implications of the disease. In particular, the prevalence of pes planus in these patients clarifies the need for understanding the effect of the disease on a tarsal level. The body of literature focused on the ambulatory characteristics of these patients is not large, and the most recent work in the area was performed by Graf et al. in

an investigation of ten pediatric patients with OI.[76] Major findings included prolonged double limb support and longer stance phases of gait in the OI population when compared with healthy controls, as well as reduced overall ankle range of motion (ROM) and reduced peak plantarflexion at toe-off. Peak ankle push-off power was also significantly reduced and delayed. This ensemble of results points to a prolonged period of loadbearing in which the foot demonstrates significant impairments in its ability to act as both a pliant support structure and a rigid lever for toe-off. Concurrent physical findings of increased hindfoot valgus and diminished midfoot arch point toward the pes planus common in patients with OI. However, the effect of this deformity on the ambulatory pattern is incompletely captured due to the group's use of a single rigid foot segment in modeling the gait mechanics.

While no study to date has characterized multisegmental foot motion in patients with OI, the findings of Graf et al. can be considered along with those of other investigators who have provided valuable information on biomechanical parameters directly affecting the multiple segments of the foot. Most of these investigations have focused on areas other than the foot; Aarabi reported on coxa vara in patients with OI and noted that the deformity was not rare, and especially prevalent in more severe forms of the disease.[77] Patients demonstrating coxa vara had concurrent limitations in hip abduction and internal rotation, and demonstrated a Trendelenburg gait pattern. While Aarabi's interest stemmed from a focus on femoral rodding, the inverse dynamics approach makes it clear that motion patterns at the foot and ankle will have a direct effect on the knee; when the joint system is complicated by a coronal plane deformity, an understanding of these tarsal mechanics becomes even more crucial. Similarly, Losa Iglesias et al. reported on the prevalence of intoeing in OI type I, attributed to either torsional deformity or metatarsal adductus.[78] Like the coxa vara deformity noted by Aarabi, this intoeing pattern warrants further detailed study to determine the relationship between the multiple articulations of the foot and motion patterns (and possible injury risk) at more proximal articulations.

CONCLUSION

The development of multisegmental foot and ankle models has accelerated over the past 15 years due to improvements in tracking technology and progress in modeling methods. The development of research priorities and the establishment of a common vocabulary point the way toward standardization of practice, which will promote and direct further

development. The integration of this technology and these methods into patient populations has been well established in persons with explicit foot/ankle pathology, and initial groundwork has been laid to do the same for patients with osteogenesis imperfecta. Further study in this group is warranted to investigate the implications of pes planus in combination with bony fragility on tarsal biomechanics.

ABBREVIATIONS

A/P	Anteroposterior
ASIS	Anterior superior iliac spine
DOF	Degree(s) of freedom
ICC	Intraclass correlation coefficient
MDCO	Medial displacement calcaneal osteotomy
MFM	Milwaukee Foot Model
OFM	Oxford Foot Model
OI	Osteogenesis imperfecta
OJC	Optimized joint center
PSIS	Posterior superior iliac spine
PTTD	Posterior tibial tendon dysfunction
ROM	Range of motion

REFERENCES

1. Kadaba MP, Ramakrishnan HK, Wootten ME, Gainey J, Gorton G, Cochran GV. Repeatability of kinematic, kinetic, and electromyographic data in normal adult gait. *J Orthop Res.* 1989;7(6):849-860.
2. Kadaba MP, Ramakrishnan HK, Wootten ME. Measurement of lower extremity kinematics during level walking. *J Orthop Res.* May 1990;8(3):383-392.
3. Ramakrishnan HK, Kadaba MP. On the estimation of joint kinematics during gait. *J Biomech.* 1991;24(10):969-977.
4. Gage JR, Fabian D, Hicks R, Tashman S. Pre- and postoperative gait analysis in patients with spastic diplegia: a preliminary report. *J Pediatr Orthop.* Nov 1984;4(6):715-725.
5. Gage JR, Novacheck TF. An update on the treatment of gait problems in cerebral palsy. *J Pediatr Orthop B.* Oct 2001;10(4):265-274.
6. Etnyre B, Chambers CS, Scarborough NH, Cain TE. Preoperative and postoperative assessment of surgical intervention for equinus gait in children with cerebral palsy. *J Pediatr Orthop.* Jan-Feb 1993;13(1):24-31.
7. Cook RE, Schneider I, Hazlewood ME, Hillman SJ, Robb JE. Gait analysis alters decision-making in cerebral palsy. *J Pediatr Orthop.* May-Jun 2003;23(3):292-295.
8. DeLuca PA, Davis RB, 3rd, Ounpuu S, Rose S, Sirkin R. Alterations in surgical decision making in patients with cerebral palsy based on three-dimensional gait analysis. *J Pediatr Orthop.* Sep-Oct 1997;17(5):608-614.

9. Chang FM, Seidl AJ, Muthusamy K, Meininger AK, Carollo JJ. Effectiveness of instrumented gait analysis in children with cerebral palsy—comparison of outcomes. *J Pediatr Orthop.* Sep-Oct 2006;26(5):612-616.
10. Cook RE, Schneider I, Hazlewood ME, Hillman SJ, Robb JE. Gait analysis alters decision-making in cerebral palsy. *J Pediatr Orthop.* May-Jun 2003;23(3):292-295.
11. DeLuca PA, Davis RB, 3rd, Ounpuu S, Rose S, Sirkin R. Alterations in surgical decision making in patients with cerebral palsy based on three-dimensional gait analysis. *J Pediatr Orthop.* Sep-Oct 1997;17(5):608-614.
12. Kay RM, Dennis S, Rethlefsen S, Skaggs DL, Tolo VT. Impact of postoperative gait analysis on orthopaedic care. *Clin Orthop Relat Res.* May 2000(374):259-264.
13. Davis RB, Ounpuu S, Bell KJ, DeLuca PA. A long-term follow-up of the effects of rectus femoris, hamstring and gastrocnemius surgery on the knee in persons with cerebral palsy. *Gait Posture.* 1996;4(2):183-183.
14. Ounpuu S, DeLuca P, Davis R, Romness M. Long-term effects of femoral derotation osteotomies: an evaluation using three-dimensional gait analysis. *J Pediatr Orthop.* Mar-Apr 2002;22(2):139-145.
15. Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. *J Biomech Eng.* May 1983;105(2):136-144.
16. Bell AL, Pedersen DR, Brand RA. Prediction of hip joint center location from external markers. *Human Movement Science.* 1989;8(1):3-16.
17. Bell AL, Pedersen DR, Brand RA. A comparison of the accuracy of several hip center location prediction methods. *J Biomech.* 1990;23(6):617-621.
18. Davis RB, 3rd, Ounpuu S, Tyburski D, Gage JR. A gait analysis data collection and reduction technique. *Human Movement Science.* 1991;10(5):575-587.
19. Rigoldi C, Galli M, Tenore N, Crivellini M, Albertini G. Gait alteration of a teenager with Down's syndrome: a 5-year follow-up before and after surgery. *J Pediatr Orthop B.* Jan 2007;16(1):73-75.
20. Lindemann U, Becker C, Unnewehr I, et al. Gait analysis and WOMAC are complementary in assessing functional outcome in total hip replacement. *Clin Rehabil.* May 2006;20(5):413-420.
21. Pedersen ENG, Alkjaer T, Soballe K, Simonsen EB. Walking pattern in 9 women with hip dysplasia 18 months after periacetabular osteotomy. *Acta Orthop.* Apr 2006;77(2):203-208.
22. Hemo Y, Macdessi SJ, Pierce RA, Aiona MD, Sussman MD. Outcome of patients after Achilles tendon lengthening for treatment of idiopathic toe walking. *J Pediatr Orthop.* May-Jun 2006;26(3):336-340.
23. Ristanis S, Stergiou N, Patras K, Tsepis E, Moraiti C, Georgoulis AD. Follow-up evaluation 2 years after ACL reconstruction with bone-patellar tendon-bone graft shows that excessive tibial rotation persists. *Clin J Sport Med.* Mar 2006;16(2):111-116.
24. Deltombe T, Detrembleur C, Hanson P, Gustin T. Selective tibial neurotomy in the treatment of spastic equinovarus foot: a 2-year follow-up of three cases. *Am J Phys Med Rehabil.* Jan 2006;85(1):82-88.
25. Molenaers G, Desloovere K, Fabry G, De Cock P. The effects of quantitative gait assessment and botulinum toxin a on musculoskeletal surgery in children with cerebral palsy. *J Bone Joint Surg Am.* Jan 2006;88(1):161-170.
26. Desloovere K, Molenaers G, Van Gestel L, et al. How can push-off be preserved during use of an ankle foot orthosis in children with hemiplegia? A prospective controlled study. *Gait Posture.* Oct 2006;24(2):142-151.

27. Radtka SA, Oliveira GB, Lindstrom KE, Borders MD. The kinematic and kinetic effects of solid, hinged, and no ankle-foot orthoses on stair locomotion in healthy adults. *Gait Posture.* Oct 2006;24(2):211-218.
28. Goujon H, Bonnet X, Sautreuil P, et al. A functional evaluation of prosthetic foot kinematics during lower-limb amputee gait. *Prosthet Orthot Int.* Aug 2006;30(2):213-223.
29. Chow DHK, Holmes AD, Lee CKL, Sin SW. The effect of prosthesis alignment on the symmetry of gait in subjects with unilateral transtibial amputation. *Prosthet Orthot Int.* Aug 2006;30(2):114-128.
30. Brodsky JW. Preliminary gait analysis results after posterior tibial tendon reconstruction: a prospective study. *Foot Ankle Int.* Feb 2004;25(2):96-100.
31. Thomas R, Daniels TR, Parker K. Gait analysis and functional outcomes following ankle arthrodesis for isolated ankle arthritis. *J Bone Joint Surg Am.* Mar 2006;88(3):526-535.
32. Davis RB, Jameson E, Davids JR, Christopher LM, Rogozinski B, Anderson JP. The Design, Development, and Initial Evaluation of a Multisegment Foot Model for Routine Clinical Gait Analysis. In: Harris GF, Smith PA, Marks RM, eds. *Foot and Ankle Motion Analysis: Clinical Treatment and Technology*: CRC Press; 2008:425.
33. Rankine L, Long J, Canseco K, Harris GF. Multisegmental foot modeling: a review. *Crit Rev Biomed Eng.* 2008;36(2-3):127-181.
34. Wright DG, Desai SM, Henderson WH. Action of the Subtalar and Ankle-Joint Complex during the Stance Phase of Walking. *J Bone Joint Surg Am.* Mar 1964;46:361-382.
35. Dul J, Johnson GE. A kinematic model of the human ankle. *J Biomed Eng.* Apr 1985;7(2):137-143.
36. Lundberg A, Svensson OK, Nemeth G, Selvik G. The axis of rotation of the ankle joint. *J Bone Joint Surg Br.* Jan 1989;71(1):94-99.
37. Lundberg A, Goldie I, Kalin B, Selvik G. Kinematics of the ankle/foot complex: plantarflexion and dorsiflexion. *Foot Ankle.* Feb 1989;9(4):194-200.
38. Lundberg A, Svensson OK, Bylund C, Goldie I, Selvik G. Kinematics of the ankle/foot complex—Part 2: Pronation and supination. *Foot Ankle.* Apr 1989;9(5):248-253.
39. Lundberg A, Svensson OK, Bylund C, Selvik G. Kinematics of the ankle/foot complex—Part 3: Influence of leg rotation. *Foot Ankle.* Jun 1989;9(6):304-309.
40. Kepple TM, Stanhope SJ, Lohmann KN, Roman NL. A video-based technique for measuring ankle-subtalar motion during stance. *J Biomed Eng.* Jul 1990;12(4):273-280.
41. Scott SH, Winter DA. Biomechanical model of the human foot: kinematics and kinetics during the stance phase of walking. *J Biomech.* Sep 1993;26(9):1091-1104.
42. Buczek FL, Kepple TM, Siegel KL, Stanhope SJ. Translational and rotational joint power terms in a six degree-of-freedom model of the normal ankle complex. *J Biomech.* Dec 1994;27(12):1447-1457.
43. Leardini A, O'Connor JJ, Catani F, Giannini S. A geometric model of the human ankle joint. *J Biomech.* 1999;32(6):585-591.
44. Leardini A, Stagni R, O'Connor JJ. Mobility of the subtalar joint in the intact ankle complex. *J Biomech.* Jun 2001;34(6):805-809.
45. Ringleb SI, Kavros SJ, Kotajarvi BR, Hansen DK, Kitaoka HB, Kaufman KR. Changes in gait associated with acute stage II posterior tibial tendon dysfunction. *Gait Posture.* 2007;25(4):555-564.
46. MacWilliams BA, Cowley M, Nicholson DE. Foot kinematics and kinetics during adolescent gait. *Gait & Posture.* Jun 2003;17(3):214-224.

47. Tome J, Nawoczenski DA, Flemister A, Houck J. Comparison of foot kinematics between subjects with posterior tibialis tendon dysfunction and healthy controls. *J Orthop Sports Phys Ther.* Sep 2006;36(9):635-644.
48. Carson MC, Harrington ME, Thompson N, O'Connor JJ, Theologis TN. Kinematic analysis of a multi-segment foot model for research and clinical applications: a repeatability analysis. *J Biomech.* Oct 2001;34(10):1299-1307.
49. Woodburn J, Helliwell PS, Barker S. Three-dimensional kinematics at the ankle joint complex in rheumatoid arthritis patients with painful valgus deformity of the rearfoot. *Rheumatology (Oxford).* Dec 2002;41(12):1406-1412.
50. Simon J, Doederlein L, McIntosh AS, Metaxiotis D, Bock HG, Wolf SI. The Heidelberg foot measurement method: Development, description and assessment. *Gait Posture.* 2006;23(4):411-424.
51. Kidder SM, Abuzzahab FS, Jr., Harris GF, Johnson JE. A system for the analysis of foot and ankle kinematics during gait. *IEEE Trans Rehabil Eng.* Mar 1996;4(1):25-32.
52. Johnson JE, Kidder SM, Abuzzahab FS, Jr., Harris GF. Three-dimensional motion analysis of the adult foot and ankle. In: Harris GF, Smith PA, eds. *Human motion analysis : current applications and future directions*. New York, NY: IEEE Press; 1996:351-369.
53. Abuzzahab FS, Jr., Harris GF, Kidder SM. Foot and ankle motion analysis system: Instrumentation, calibration, and validation. In: Harris GF, Smith PA, eds. *Human motion analysis : current applications and future directions*. New York, NY: IEEE Press; 1996:152-166.
54. Myers KA, Wang M, Marks RM, Harris GF. Validation of a mutlisegment foot and ankle kinematic model for pediatric gait. *IEEE Trans Rehab Eng.* March 2004 2004;12(1):122-130.
55. Johnson JE, Lamdan R, Granberry WF, Harris GF, Carrera GF. Hindfoot coronal alignment: a modified radiographic method. *Foot Ankle Int.* Dec 1999;20(12):818-825.
56. Long JT, Wang M, Winters JM, Harris GF. A multisegmental foot model with bone-based referencing: sensitivity to radiographic input parameters. *Conf Proc IEEE Eng Med Biol Soc.* 2008;2008:879-882.
57. Canseco K, Rankine L, Long J, Smedberg T, Marks RM, Harris GF. Motion of the multisegmental foot in hallux valgus. *Foot Ankle Int.* Feb 2010;31(2):146-152.
58. Marks RM, Long JT, Ness ME, Khazzam M, Harris GF. Surgical reconstruction of posterior tibial tendon dysfunction: prospective comparison of flexor digitorum longus substitution combined with lateral column lengthening or medial displacement calcaneal osteotomy. *Gait Posture.* Jan 2009;29(1):17-22.
59. Canseco K, Long J, Marks R, Khazzam M, Harris G. Quantitative motion analysis in patients with hallux rigidus before and after cheilectomy. *J Orthop Res.* Jan 2009;27(1):128-134.
60. Ness ME, Long J, Marks R, Harris G. Foot and ankle kinematics in patients with posterior tibial tendon dysfunction. *Gait Posture.* Feb 2008;27(2):331-339.
61. Canseco K, Long J, Marks R, Khazzam M, Harris G. Quantitative characterization of gait kinematics in patients with hallux rigidus using the Milwaukee foot model. *J Orthop Res.* Apr 2008;26(4):419-427.
62. Khazzam M, Long JT, Marks RM, Harris GF. Kinematic changes of the foot and ankle in patients with systemic rheumatoid arthritis and forefoot deformity. *J Orthop Res.* Mar 2007;25(3):319-329.
63. Khazzam M, Long JT, Marks RM, Harris GF. Preoperative gait characterization of patients with ankle arthrosis. *Gait Posture.* Aug 2006;24(1):85-93.

64. Long JT, Eastwood DC, Graf AR, Smith PA, Harris GF. Repeatability and sources of variability in multi-center assessment of segmental foot kinematics in normal adults. *Gait Posture.* Jan 2010;31(1):32-36.
65. Long JT, Wang M, Harris GF. A Model for the Evaluation of Lower Extremity Kinematics with Integrated Multisegmental Foot Motion. *Journal of Experimental & Clinical Medicine.* 2011;3(5):239-244.
66. Stebbins J, Harrington M, Thompson N, Zavatsky A, Theologis T. Gait compensations caused by foot deformity in cerebral palsy. *Gait Posture.* Jun 2010;32(2):226-230.
67. Woodburn J, Nelson KM, Siegel KL, Kepple TM, Gerber LH. Multisegment foot motion during gait: proof of concept in rheumatoid arthritis. *J Rheumatol.* Oct 2004;31(10):1918-1927.
68. Deschamps K, Birch I, Desloovere K, Matricali GA. The impact of hallux valgus on foot kinematics: a cross-sectional, comparative study. *Gait Posture.* May 2010;32(1):102-106.
69. Alonso-Vazquez A, Villarroya MA, Franco MA, Asin J, Calvo B. Kinematic assessment of paediatric forefoot varus. *Gait Posture.* Feb 2009;29(2):214-219.
70. Levinger P, Murley GS, Barton CJ, Cotchett MP, McSweeney SR, Menz HB. A comparison of foot kinematics in people with normal- and flat-arched feet using the Oxford Foot Model. *Gait Posture.* Oct 2010;32(4):519-523.
71. Curtis DJ, Bencke J, Stebbins JA, Stansfield B. Intra-rater repeatability of the Oxford foot model in healthy children in different stages of the foot roll over process during gait. *Gait Posture.* Jul 2009;30(1):118-121.
72. Wright CJ, Arnold BL, Coffey TG, Pidcoe PE. Repeatability of the modified Oxford foot model during gait in healthy adults. *Gait Posture.* Jan 2011;33(1):108-112.
73. Pediatric and Adult Foot and Ankle Workshop: New Horizons in Clinical Treatment and Innovative Technology; November 15, 2003, 2003; Washington, D.C.
74. Byers PH, Steiner RD. Osteogenesis imperfecta. *Annu Rev Med.* 1992;43:269-282.
75. Engelbert RH, Uiterwaal CS, Gulmans VA, Pruijs H, Helders PJ. Osteogenesis imperfecta in childhood: prognosis for walking. *J Pediatr.* Sep 2000;137(3):397-402.
76. Graf A, Hassani S, Krzak J, et al. Gait characteristics and functional assessment of children with type I osteogenesis imperfecta. *J Orthop Res.* Sep 2009;27(9):1182-1190.
77. Aarabi M, Rauch F, Hamdy RC, Fassier F. High prevalence of coxa vara in patients with severe osteogenesis imperfecta. *J Pediatr Orthop.* Jan-Feb 2006;26(1):24-28.
78. Losa Iglesias ME, Becerro de Bengoa Vallejo R, Salvadores Fuentes P. In-toeing in children with type I osteogenesis imperfecta: an observational descriptive study. *J Am Podiatr Med Assoc.* Jul-Aug 2009;99(4):326-329.

15 MOTION ANALYSIS STRATEGY APPROPRIATE FOR 3D KINEMATIC ASSESSMENT OF CHILDREN AND ADULTS WITH OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Human motion analysis provides a quantitative means of assessing whole body and segmental motion of subjects with musculoskeletal pathologies. This chapter describes a low cost motion analysis appropriate for complete three-dimensional (3D) assessment of upper and lower extremity kinematics. The system has been designed to support lower cost outreach efforts that require accuracy and resolution on the order of classical fixed lot systems such as Vicon. The focus of this work addresses the assessment needs typically seen in adults and children with osteogenesis imperfect (OI) experiencing ambulatory and upper extremity challenges.

Fundamental Approach

The general method used for quantitative motion assessment defines a segmental model of the skeletal region of interest with intersegmental joints. Quantitative description of the tri-axial joint motion requires a mathematical model of the system and a series of external markers that are visible to the

motion capture system and in proximity to key anatomical landmarks. An example would be the Helen-Hayes marker set where the body is broken up into seven segments; three segments for each leg as well as a segment describing the pelvis.[1] Each segment is created by three or more markers to define a plane such that tri-axial rotation is fully defined. The preference is to employ a Cartesian coordinate system embedded into each body segment for calculation of intersegmental joint angles. Optical cameras are widely used to record the position of the external markers in space as the subject ambulates through a predetermined capture volume. At least two cameras must simultaneously view each marker in order to determine its 3D coordinates. Most systems are redundant with multiple cameras because some markers can be obstructed from the view of cameras during arm swing and with the use of assistive devices, such as Lofstrand crutches and walkers. All cameras are synchronized to record marker position at the same time using a frame rate typically between 50 and 250 frames per second depending on the application. Once the marker positions have been located in 3D space, associated labels are applied to each marker to define anatomic location, i.e. RASIS: Right Anterior Superior Iliac Spine.

Biomechanical modeling software is then used to determine joint orientation and motion between segments. In lower extremity gait analysis, this would include motion at the pelvis, hip, knee, and ankle in all three anatomic planes. The analytical software usually incorporates algorithms and filters to better estimate joint orientation, angular velocity, and angular acceleration.[1]

Typical Applications

Motion analysis systems have been used in the clinical setting for pre- and post-treatment assessment of subjects with upper and lower extremity pathologies. Almost any pathology affecting the musculoskeletal system can be assessed using motion analysis. Depending on the area of focus for a particular patient, motion analysis can be used to describe broad motion such as hip, knee, and ankle or can be more specific when looking at motion of the hindfoot, midfoot, and hallux.[3-11] This can be similarly done when examining the upper extremities while trying to focus on motion at the torso, shoulder, elbow, and wrist.[12-15] With the ability to assess both upper and lower extremities using motion analysis, disabilities can be described within all three anatomic planes of motion that may have been more difficult to assess previously by observation only.

Osteogenesis imperfecta (OI) is a pathology that has received more recent attention within the motion analysis community. A study by Graf et al. compared gait characteristics in children with type 1 OI to those of age-matched controls. The results from the study showed that the OI group demonstrated increased double limb support, delayed foot off, and decreased ankle range of motion and plantar flexion during the third rocker.[16] Joint angle characteristics between controls and subjects with OI are shown in Figure 1. One specific aim of this study was to assess push-off power at the ankle during gait. The study found that, due to weaker plantar flexors, the children with OI had a reduced ankle power production and decreased ankle angle velocity in the sagittal plane.[17] The authors noted that results could be used to gain a better understanding of OI and to help improve treatment planning and overall quality of life.

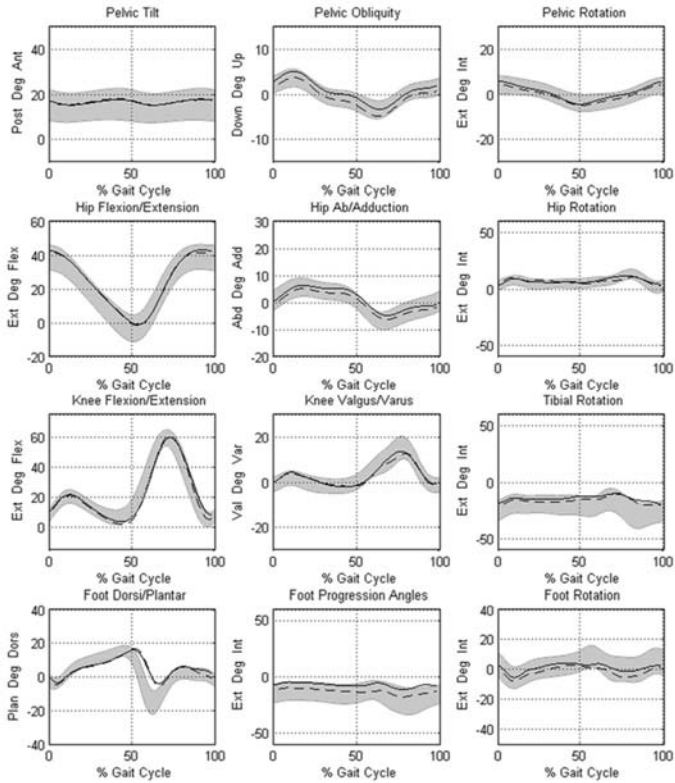

Figure 1. Joint kinematic comparison between normal and OI populations. The band represents the average of the normal population and the solid and dashed lines represent the average left and right sides of the OI population, respectively.

Kinetics has also been incorporated into assessment of persons with OI. A study by Fritz et al. quantified loading conditions at the femoral head and condyles along the femur. The authors wanted to determine the risk of femoral fracture for a subject with OI type I during normal ambulation. Findings included the OI modeled femur showing no risk of fracture during normal gait and that the highest stress level occurred during the mid-stance and loading response phases of gait.[13]

Motion Analysis Systems

There are a wide variety of motion analysis systems available on the market today. The most prevalent systems will be discussed here. Vicon (Vicon Motion Systems, Oxford, England) is one of the most traditional systems currently being used in the clinical setting. The system captures and tracks motion using passive markers, and offers standard components typically used by researchers or clinicians during gait analysis. The system utilizes Nexus software to record movement data along with synchronized signals from other measurement devices including EMG (electromyography) and force plates. Vicon Nexus offers several features to automate processing including automatic marker labeling and event detection (i.e. foot strike and foot off). Vicon's Polygon software allows post processing to display joint kinematics, kinetics, and EMG data.[18]

Another system is the Optotrak Certus (Northern Digital Inc, Ontario, Canada). Optotrak incorporates a "Smart Marker" system of active markers. Battery powered strobes eliminate the need for wires. Up to 50 strobes can be used at a time per battery system. The Optotrak software allows for incorporation of force plates, EMG, eye-trackers, and other third-party instrumentation. The Optotrak motion analysis system is compatible with other software including Visual3D (C-Motion, Germantown, MD), which is used for higher level data processing by multiple vendors.[19]

Motion Analysis Corporation (MAC) (Santa Rosa, CA) is another company that provides motion analysis systems used for gait analysis. Much like the Vicon system, MAC uses passive markers. The main motion capture software called Cortex is used for all phases of recording including calibration, tracking, and post processing. These systems also allow simultaneous analog data input from force plate and EMG sources. Cortex is used to calculate and display kinematic, kinetic, and EMG data. SIMM (MusculoGraphics, Inc., Santa Rosa, CA) is software supplied by MAC which is used for monitoring changes

in muscle length and muscle moment arms during gait.[20] This software can also be used with various gait analysis systems, including Vicon.

Systems can also be developed by combining hardware, data capture, and processing software. A recent development described here is a combination of Optitrack Cameras (NaturalPoint, Inc., Corvallis, OR) and Visual3D and AMASS (C-Motion Inc., Germantown, MD) software. The Optitrack cameras were originally designed to be used for video game motion analysis, but using them for clinical applications is also possible. The Optitrack hardware includes V100:R2 motion capture cameras that are much smaller than the standard Vicon or MAC cameras. The AMASS software is used for capturing and labeling marker data while Visual3D software is used for kinematic analysis and external signal synchrony (EMG, force plate).[21] Other cameras are also available from Naturalpoint, Inc. that can be incorporated with the C-motion, Inc. software. One in particular would be the Flex 13 cameras which are the same size as the V100:R2 cameras and only a few hundred dollars more but provide three times greater resolution than the V100:R2 cameras.

New Horizons in Motion Analysis Technology

Two independent factors to consider when developing a system are cost and performance. Listed below is a comparison of performance characteristics of all systems described herein (Table 1). The first three systems have been tested for accuracy, precision, and/or resolution.[22-24] Traditionally, motion analysis system cost can range from $50k - $300K, which may not be affordable for some clinics and hospitals, particularly those in underdeveloped countries. The combination of Optitrack cameras and C-motion software may provide a less expensive alternative with the hardware and software priced at less than $50K. The static and dynamic calibration of the cameras and kinematic comparison to Vicon will be discussed further with respect to its potential use for a less expensive, yet reliable, motion analysis system. If successful, this combination system will allow a broader population to undergo gait analysis and whose ability to ambulate could be greatly improved from the information surgeons and physicians obtain from these assessments. In particular, it can be applied to benefit children and adults with OI in clinics that could not otherwise afford motion analysis technology.

Table 1. Motion analysis system performance parameters.

	Markers	Sampling Rate (frames/sec)	System Resolution (mm)	Precision (mm)	System Accuracy (%)
Optitrack	Passive	50-100	0.63	-	94.82
Vicon	Passive	120-250	1.49	-	98.3
Optotrack	Active	50	-	0.03	98.44
Cortex (MAC)	Passive	200	-	-	-

METHODS

Instrumentation

An eight-camera Optitrack V100:R2 (Naturalpoint Inc., Corvallis, OR) motion capture system was used to acquire marker data at 100 frames per second (fps) with markers measuring 15.9 mm in diameter. ARENA motion capture software (Naturalpoint Inc., Corvallis, OR), which came with the Optitrack cameras, was used to acquire the 3D marker data. A Styrofoam cone was used for static testing while a combination of the Styrofoam cone and a bar were used for dynamic testing represented by Figure 2A and Figure 3A, respectively.

For angular dynamic testing, a Biodex System III (Biodex, Biodex Medical Systems, Shirley, NY) was employed to generate a constant angular velocity for a desired angular range. The Biodex system was used for angular dynamic testing since the system can be programmed to rotate in multiple planes.[22]

Kinematic joint angle data was obtained using ten Optitrack V100:R2 cameras in collaboration with AMASS and Visual3D software (C-Motion, Inc. Germantown, MD).

Camera Validation Protocol

Accuracy and resolution of the Optitrack motion capture system were determined statically and dynamically.[22,23,25,26] For static linear testing, three markers were placed on the Styrofoam cone at measured distances associated with typical foot marker placements (Figure 2A).[22,23] The short foot and long foot distances measured 57.5 mm and 140.6 mm, respectively. The short foot marker distance was selected as a representative constraint

for potential foot models. The Styrofoam cone was placed along the Cartesian coordinate axes and positioned to face the center of the capture volume at the five locations seen in Figure 2B. A 3-second trial was recorded at each of the five locations along all three primary axes. Marker data was processed by performing marker labeling and exported for statistical analysis in MATLAB.

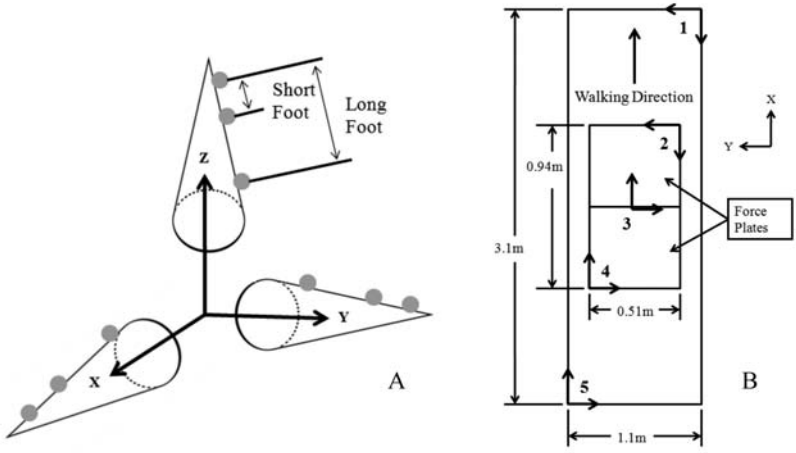

Figure 2. (A) Calibration cone used for static testing. (B) Locus for static calibration within capture volume.

For linear dynamic testing, the Styrofoam cone and leg bar were fixed to each other to represent a leg with typical marker placement used for whole body lower extremity gait (Figure 3A). Five markers were located on the leg bar at 205.3 mm, 417.8 mm, 181.6 mm, and 397.2 mm, representing the approximate distances for hip to mid-thigh, hip to knee, knee to mid-calf, and knee to ankle, respectively. These marker locations are also analogous to those used for upper extremity analysis (walker, crutch, cane, and wheelchair).[27] Marker distances used for the Styrofoam cone were identical to those of the static testing. The entire lower extremity system (foot and leg segment) was then translated at a free walking speed through the capture volume in the positive and negative X-direction five times.

Angular dynamic testing employed the Biodex System III to rotate through a range of 305 degrees. Five markers were placed on the Biodex attachment arm at distances of 57.5 mm, 140.6 mm, 205.3 mm, and 417.8 mm (Figure 3B). The marker distances were analogous to those used in the linear dynamic testing. The Biodex was programmed to rotate through a range of 305 degrees at 90 deg/sec. Data were recorded for five trials in all three

planes of motion (XY, YZ, XZ) during clockwise and counterclockwise rotation. A 2-second portion, in which the angular velocity was calculated to be constant, was used for analysis.

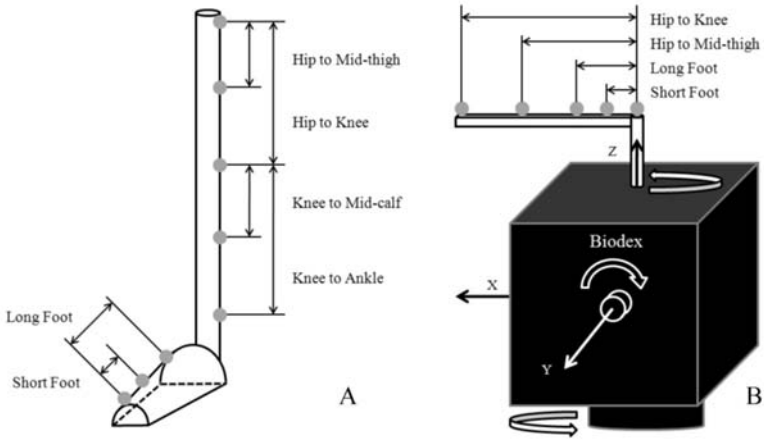

Figure 3. (A) Linear dynamic calibration frame. (B) Biodex with rotational dynamic calibration frame. Marker distances are representative of those used in human gait.

System resolution was calculated using the following equation:[22,23]

$$R = \left| D - \frac{1}{n}\sum_{i=0}^{n-1} d_i \right| \pm t\left(\frac{s}{\sqrt{n}} + \varepsilon_r + \varepsilon_m \right) \quad (1)$$

Where:

R	System resolution;
D	measured (empirical) distance;
n	total number of samples;
d_i	computed distance;
t	t-test coefficient [23];
s	sample standard deviation;
ε_r	round-off error = (5/10m);
ε_m	measurement error; based on micrometer resolution (±0.02 mm);
m	number of significant digits.

System accuracy was computed as:[22,23]

$$A = \left(1 - \frac{\left| x_w - \frac{1}{n} \sum_{i=0}^{n-1} d_i \right|}{\frac{1}{n} \sum_{i=0}^{n-1} d_i} \right) \times 100\% \qquad (2)$$

Where:

A	system accuracy as a percentage;
x_w	"worst" data point.

The average value of the computed distance was used as an estimate of the true distance between markers due to measurement error.[28]

Joint Kinematics

Kinematic joint angle data was obtained by applying 15 reflective markers (diameter = 14mm) along with knee alignment devices (KAD's) on 10 control patients with normal gait. Markers were placed such that the pelvis, thighs, shanks, and feet were represented by a plane made up of three markers. The pelvis was represented by markers located on the left and right ASIS as well as a sacral marker. The thigh was represented by an ASIS marker, thigh wand, and knee marker located on the lateral femoral epicondyle. The shank was represented by the knee marker, shank wand, and lateral malleolus marker. The foot was represented by the lateral malleolus, heel and toe marker located on the head of the 2nd metatarsal. The KAD's were used only during the static trial to more accurately describe the joint center of the knee. A series of required measurements were also taken including height, weight, inter-ASIS, ASIS to lateral malleolus, thigh radius, knee width, and ankle width.

Each subject stood still in the center of the capture volume for a static capture trial. For dynamic capture trials, the subject stood at one end of the capture volume and proceeded to ambulate across the volume at a free walking pace to the other end. Data were recorded at a rate of 100 fps. Ten-second trials were used to ensure sufficient time for the subject to ambulate across the capture volume within the designated time frame. A total of twelve trials were recorded where the subject started walking with their left foot for the first six trials, and started walking with their right foot for the second six trials. Three trials for each side of the body where chosen in which there was

the least amount of marker drop out. Using AMASS, the trials were then labeled and exported to c3d files for processing in Visual3D.

Visual3D software was then used for kinematic analysis. The static trial was used to apply the Helen-Hayes marker set model with KAD's.[1] This model is based off the plug-in-gait model used by Vicon, a clinical standard. Segments including a pelvis, thigh, shank, and foot were created with intersegmental joints to describe joint kinematics. Each segment is given a local coordinate system to help describe motion of that particular segment. To describe the joint kinematics at the hip, a segment is described with respect to a reference segment. In this case it would be the thigh segment coordinate system moving with respect to the pelvic coordinate system. This same process is performed for the knee, and ankle. Pelvic motion is described as the pelvis coordinate system moving with respect to the global coordinate system. Once the model was applied, the dynamic trials were implemented into Visual3D for processing. For each dynamic trial, foot strike and foot off were determined. The frame at which the heel marker no longer moved forward was deemed as foot strike and the frame at which the metatarsal marker initiated forward movement was deemed as foot off.

The joint angle data can then be plotted within Visual3D. The data was interpolated with a maximum gap of 10 frames using a 3rd order polynomial. Visual3D uses a Segmental Optimization or Global Optimization to interpolate gaps in the data due to marker drop out.[29,30] In addition, the data was filtered using a 6 Hz Butterworth filter.

The marker data collected in AMASS was also processed using Vicon's Nexus software. The "KAD PlugInGait (SACR)" model was attached to the marker data collected from AMASS. This model is the standard model for lower extremity kinematic analysis during gait when using Vicon. Each dynamic trial associated with each subject's static trial was opened and labeled. Foot strike and foot off were determined for each dynamic trial. In a similar fashion to Visual3D, foot strike was determined by looking at when the forward motion of the heel marker stopped, and foot off was determined by looking at when forward motion began for the 2nd metatarsal marker. Marker gaps were filled using direct pose estimation or global optimization.[29,30] A Woltring filter with a mean squared error of 10 was applied to the data. The dynamic model was then run to calculate the joint angle data for the pelvis, hip, knee, and ankle.

Statistics

For statistical analysis, a variance components model was used to compare the data between Visual3D and Nexus.[31,32] The joint angle values computed from Visual3D and Nexus include the maximum, minimum, and range values for the pelvis, hip, knee, and ankle in all three anatomic planes of motion. In addition, cadence, walking speed, step length, and stride length were compared. The model assumes four different sources of variability including the subject, side of the foot (left or right), which system was used to calculate the joint angles, and all other possible sources of variability aggregated in the error term. The main interest was to see if a system change, Visual3D or Nexus, showed a significant contribution to the total variability of the joint angle data. In addition, a paired t-test was used to compare the mean values from all of the subjects between the two systems. The associated p-values and confidence interval were determined when the two systems were compared. A p-value of 0.01 was used to determine significance in the variance components model and paired t-test.

RESULTS

Static and Dynamic Testing

The maximum and minimum accuracy and resolution values for the static and dynamic testing are shown in Table 2. The minimum accuracy for static testing was 99.31% for the short foot distance along the X-axis and the maximum accuracy was 99.90% for the long foot distance along the Z-axis. The minimum resolution for static testing was 0.63±0.15 mm for the long foot distance along the Y-axis and the maximum resolution was 0.04±0.15 mm for the short foot distance along the Z-axis.

The minimum accuracy for linear dynamic testing was 95.59% for the short foot distance going forward (+X direction) through the capture volume and the maximum accuracy was 99.77% for the knee to mid-calf distance going forward (+X direction) through the capture volume. The minimum resolution for linear dynamic testing was 0.37±0.23 mm for long foot distance walking in the –X-direction though the capture volume and the maximum resolution was 0.09±0.26 mm for the knee to ankle distance walking in the –X-direction through the capture volume.

The minimum accuracy for angular dynamic testing was 94.82% for the short foot distance along the XY-plane and the maximum accuracy was 99.68% for

the hip to knee distance along the XZ-plane. The minimum resolution was 0.61±0.31 mm for the hip to knee distance along the YZ-plane and the maximum resolution was 0.10±0.19 mm for the long foot distance along the XZ-plane. All of the resolution values are at the 0.05 level of significance.

Table 2. Maximum and minimum accuracy and resolution values for three different calibration methods.

Test Method	Maximum Accuracy (%)	Minimum Accuracy (%)	Maximum Resolution (mm)	Minimum Resolution (mm)
Static	99.90	99.31	0.04 ± 0.15	0.63 ± 0.15
Linear Dynamic	99.77	95.59	0.09 ± 0.26	0.37 ± 0.23
Angular Dynamic	99.68	94.82	0.10 ± 0.19	0.61 ± 0.31

Temporal Parameters and Joint Kinematics

The joint angle comparison between Visual3D and Nexus is shown in Figure 4. The solid line with the darker band represents the joint angle data provided by Visual3D and the dashed line with the lighter band represents the joint angle data calculated from Nexus. The plots display the mean from all subjects and one standard deviation for the joint angle with respect to percent gait cycle. This data represents the joint angles calculated for the right side of the body. The left side was compared in a similar fashion. When assessing both sides, no significant difference was seen between the two sets of data from Visual3D and Nexus except for tibial torsion as well as all of the data for the foot segment movement. Table 3 shows the maximum, minimum, and range of tibial torsion and foot kinematics that that showed significant difference when analyzed statistically. All of the temporal and stride parameters including step length, stride length, cadence, and walking speed showed no significant difference between systems. Visual3D calculated values of 112.42 steps/min, 1.200 m/s, 0.637 m, and 1.281 m for cadence, walking speed, step length, and stride length, respectively. Nexus calculated values of 112.73 steps/min, 1.198 m/s, 0.637 m, and 1.278 m for cadence, walking speed, step length, and stride length, respectively.

Table 3. Representation of maximum, minimum, and range values associated with joint angles where significant differences were seen.

	Maximum		Minimum		Range	
	Visual3D	Nexus	Visual3D	Nexus	Visual3D	Nexus
Right Tibial Rotation	18.13	14.56				
Left Tibial Rotation	13.37	11.25				
Right Foot Dorsi Plantar	14.92	15.3	-8.78	-12.9	23.71	28.21
Left Foot Dorsi Plantar	13.85	14.99	-11.64	-15.41	25.49	30.4
Right Foot Progression	-5.16	-1.72	-13.51	-11.43	8.36	9.72
Left Foot Progression	-2.74	-0.66	-11.48	-9.88	8.75	9.22
Right Foot Rotation	-11.31	-6.08	-24.78	-18.69		
Left Foot Rotation	-6.22	-0.57	-18.55	-16.55		

DISCUSSION

System Characterization

The static and dynamic calibration done to the V100:R2 cameras provides comparable results to studies reported by Kidder et al. and Myers et al. Kidder used a five camera Vicon motion tracking system. Static results showed a minimum accuracy of 99.4% and resolution of 0.6 ± 0.82 mm at the 0.05 level of significance. Dynamic results showed a minimum accuracy of 98.3% and resolution of 1.49 ± 0.1 mm at the 0.05 level of significance [23]. Myers used a fifteen-camera Vicon 524 motion tracking system. Static results showed a minimum accuracy of 99.88% and a resolution of 0.60 ± 0.14 mm at the 0.05 level of significance. Dynamic results showed a minimum accuracy of 99.18% and resolution of 2.96 ± 3.53 mm at the 0.05 level of significance [22]. The Optitrack cameras provided comparable results to those seen in the Kidder and Myers studies with a minimum static accuracy of 99.31% and resolution of 0.63 ± 0.15 mm at the 0.05 level of significance, and dynamic accuracy of 94.82% and resolution of 0.61 ± 0.31 mm at the 0.05 level of significance.

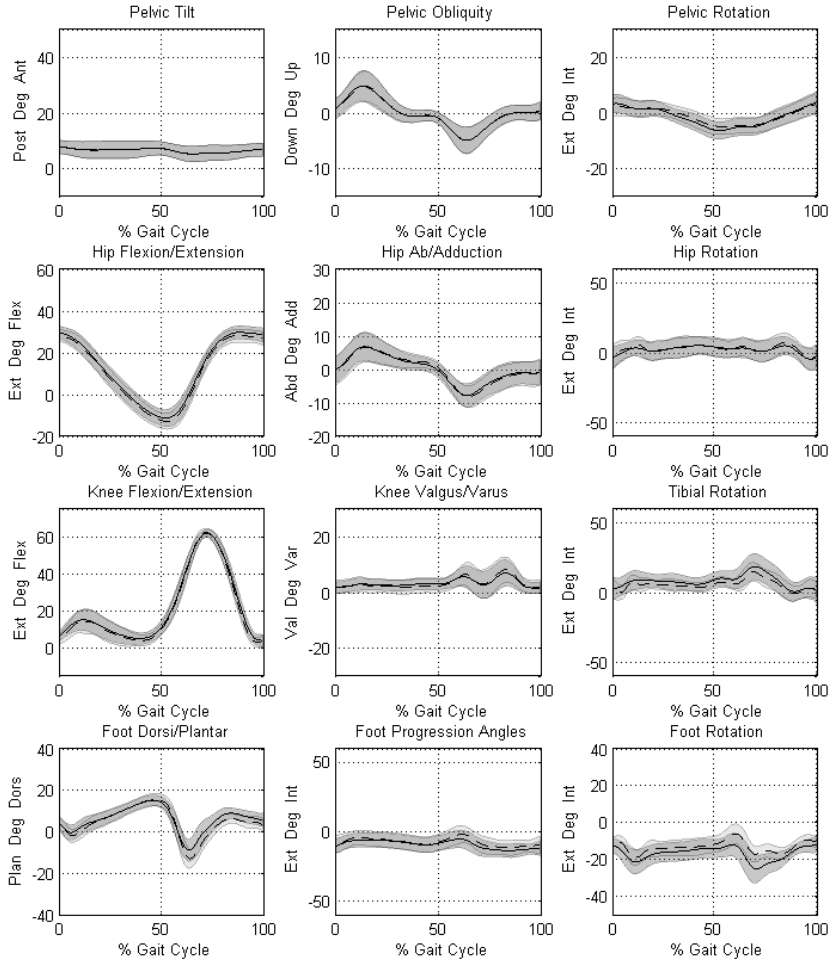

Figure 4. Joint angle kinematics for right side of body compared between Visual3D and Nexus. Visual3D is represented by a solid line and darker standard deviation band. Nexus is represented by a dashed line and lighter standard deviation band. Because there was significant overlap between the two data sets, some graphs may appear as one set of data when in fact there are two.

These values show that the V100:R2 Optitrack camera system can provide as accurate 3D marker data as that of current clinical standards at a fraction of the cost. The marker position data is essential in providing accurate motion analysis results. Any subtle deviation in the marker position data can result in a larger deviation when calculating joint angles. A study by Stagni et al. found that when trying to calculate hip joint centers, a mislocation of 30 mm of the marker placement resulted in an error of 22% in the hip flexion/extension moment.[33] Several other factors can play into the accuracy

of marker position data such as camera position, what view each camera has on the markers, pixel value, and number of cameras. With the advancement of technology and cost of equipment decreasing, the ability to collect accurate and reliable data at a cheaper price is becoming more of a reality.[36]

Kinematic and Temporal Findings

The lower cost system provides comparable results to that of clinically standard systems like Vicon. This can be seen in the temporal and stride parameters as well as the joint kinematic maximum, minimum, and range values for the pelvis, hip, knee, and ankle. No significant differences were seen in the three anatomic planes at the pelvis, hip, and knee with the exception of the maximum tibial rotation angle. Primary differences were found, however, at the ankle due to variations in the foot segment coordinate system with each model (Visual3D and Nexus). Temporal and stride parameters, including cadence, walking speed, stride length, and step length, showed no significant differences between the two systems.

Depending upon the similarity of applications, users should also be aware of more subtle differences in estimation algorithms and filtering.[34] Estimation algorithms are used to fill gaps from marker drop out while filters are set typically to reduce higher frequency noise and artifact signals.[29,30]

With the lower cost system, more hospitals and clinics can offer motion analysis services in the hope that more people can benefit from this technology including those in underserved areas.

Future Applications

With the cameras and biomechanical modeling software validated, several directions can be taken to expand the low cost system. Advancements in technology will allow cameras with increased resolution and accuracy to be used in replacement of the cameras validated in this chapter. The improved cameras will more closely approximate the system requirements of more expensive equipment. Recent hardware developments will also allow the integration of force plates and EMG systems. This will allow more complete characterization of mobility including full joint dynamics and muscle activity.

Access to this technology can now be offered to new populations of children and young adults with mobility challenges. New biomechanical models can be developed to assist these populations by analyzing upper extremity

pathologies, assisted mobility, and segmental distal extremity motion. The combined advances in technology and population outreach efforts will serve to significantly increase access to quantitative mobility assessment for those with musculoskeletal pathologies. This access will simultaneously offer new opportunities to clinicians and researchers interested in mobility assessment and improved patient care. The complex mobility needs of children and young adults with OI, and particularly those in underserved areas, can benefit significantly from these advances.

CONCLUSION

The Optitrack motion capture system was evaluated through static, linear dynamic, and angular dynamic trials. Joint angle data were compared between a standard Vicon system with Nexus software and the lower cost Optitrack system with C-motion software (AMASS and Visual3D). Joint angle maximum, minimum, and range values are not significantly different at the pelvis, hip, and knee, expect for the maximum angle of tibial rotation. There were significant differences due to system (model) variability for the ankle. This can be explained because of the variance in coordinate systems used for the foot segment in the two systems. Validation of the low cost system is a first step towards expansion of motion analysis to a broader clinical community, particularly those with OI and disabilities that restrict patients to a wheelchair or other assistive devices. Kinetic application will require further incorporation of force plates and EMG data. Lower cost system availability will increase opportunities for researchers and clinicians as they examine an ever increasing range of mobility challenges to persons with disabilities including OI.

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REFERENCES

1. Post DC. Gait Analysis Review. 2006. www.nd.edu/~dpost/IntSyst/ report1.pdf
2. Freeman, Miller. *Cerebral Palsy*. New York, NY: 2005. Print.
3. Cooper RA. Biomechanics of Mobility and Manipulation. R*ehabilitation Engineering: Applied to Mobility and Manipulation*. Philadelphia: IOP Publishing Ltd: 1995:69-154.
4. Kadaba MP, Ramakrishnan HK, Wootten ME Measurement of Lower Extremity Kinematics during Level Walking. *Journal of Orthopaedic Research*. 1990;8:383-392.
5. Gage JR, Novacheck TF. An Update on the Treatment of Gait Problems in Cerebral Palsy. *Journal of Pediatric Orthopaedics*. 2001;10:265-274.
6. Wiley ME, Damiano DL. Lower-extremity strength profiles in spastic cerebral palsy. *Developmental Medicine & Child Neurology*. 1998;40:100-107.
7. Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance Training improves gait kinematics in Persons with Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation*. 2005; 86:1824-1829.
8. El-Hawary R, Karol LA, Jeans KA, Richards BS. Gait Analysis of Children Treated for Clubfoot with Physical Therapy or the Ponseti Cast Technique. *Journal of Bone and Joint Surgery*. 2008;90(7):1508-1516.
9. Canseco K, Rankine L, Long J, Smedburg T, Marks R, Harris GF. Motion of the Multisegmental Foot in Hallux Valgus. *Foot and Ankle International*. 2010; 31(2):146-152.
10. Canseco K, Long J, Marks R, Khazzam M, Harris GF. Quantitative Characterization of Gait Kinematics in Patients with Hallux Rigidus Using the Milwaukee Foot Model. *Journal of Orthopaedic Research.* 2008;26:419-427.
11. Myers KA, Long JT, Klein JP, Wertsch JJ, Janisse D, Harris GF. Biomechanical implications of the negative heel rocker sole shoe: Gait kinematics and kinetics. *Gait and Posture*. 2006;24:323-330.
12. Marks RM, Long JT, Ness ME, Khazzam M, Harris GF. Surgical Reconstruction of Posterior Tibial Tendon Dysfunction: Prospective Comparison of Flexor Digitorum Longus Substitution Combined with Lateral Column Lengthening or Medial Displacement Calcaneal Osteotomy. *Gait and Posture*. 2009;29:17-22.
13. Slavens BA, Sturm PF, Bajournaite R, Harris GF. Upper Extremity Dynamics during Lofstrand Crutch-Assisted Gait in Children with Myelomeningocele. *Gait and Posture*. 2009;30:511-517.
14. Strifling KM, Lu N, Wang M, Cao K, Ackman JD, Klein JP, Schwab JP, Harris GF. Comparison of Upper Extremity Kinematics in Children with Spastic Diplegic Cerebral Palsy Using Anterior and Posterior Walkers. *Gait and Posture*. 2008; 28:412-419.
15. Konop K, Strifling K, Wang M, Cao K, Eastwood D, Jackson S, Ackman J, Schwab J, Harris GF. A Biomechanical Analysis of Upper Extremity Kinetics in Children with Cerebral Palsy using Anterior and Posterior Walkers. *Gait and Posture*. 2009;30:364-369.
16. Graf A, Hassani S, Krzak J, Caudill A, Flanagan A, Bajorunaite R, Harris G, Smith P. Gait Characteristics and Functional Assessment of Children with Type I Osteogenesis Imperfecta. *Journal of Orthopaedic Research*. 2009;27:1182-1190.
17. Krzak JJ, Graf A, Flanagan A, Caudill A, Smith P, Harris GF. Analysis of Push-Off during Locomotion in Children with Type 1 Osteogenesis Imperfecta. *Journal of Experimental and Clinical Medicine.* 2011;3(5):195-199.

18. "Gait Analysis Rehabilitation." Vicon. Web. 3 Jan 2012. www.vicon.com /applications/gait_analysis.html.
19. "Optotrak Certus Motion Capture System." Northern Digital Inc. Web. 3 Jan 2012. www.ndigital.com/lifesciences/certus-software.php.
20. "Gait Analysis." Motion Analysis: The Industry Leader for 3D Passive Optical Motion Capture. Web. 3 Jan 2012. www.motionanalysis.com/html/ movement/gait.html
21. "3D Biomechanics Research Software – Visual3DTM." C-Motion Research Biomechanics. Web. 3 Jan 2012. www.c-motion.com.
22. Myers KA, Wang M, Marks RM, Harris GF. Validation of a Multisegment Foot and Ankle Kinematic Model for Pediatric Gait. *IEEE/TNSRE.* 2004;12(1):122-130.
23. Kidder SM, Abuzzahab FS, Harris GF, Johnson JE. A system for the analysis of foot and ankle kinematics during gait *IEEE/TNSRE*. 1996;4:25-32.
24. Schmidt J, Berg DR, Ploeg HL. Precision, repeatability and accuracy of Optotrak optical motion track systems. *International Journal of Experimental and Computational Biomechanics*. 2009;1(1):114-127.
25. Kadaba MP, Wooten ME, Ramakrishnan HK, Hurwitz D, Cochran GV. Assessment of human motion with VICON. *ASME Biomechanical Symposium*. 1989;84:335-338.
26. Van den Bogart AJ, Smith GD, Nigg BM. In vivo determination of the anatomical axes of the ankle joint complex: An optimization approach. *Journal of Biomechanics*. 1994;27(12):1477-1488.
27. Wiley ME, Damiano DL. Lower-extremity strength profiles in spastic cerebral palsy. Developmental Medicine & Child Neurology 1998;40:100-107.
28. Nachtigal CH. *Instrumentation and Control: Fundamentals and Applications*. New York: Wiley; 1990: p. 62.
29. Hofmann M. Multi-view 3D human pose estimation combining single-frame recovery, temporal integration and model adaption. *IEEE conference on Computer Vision and Pattern Recognition*. 2009:2214-2221.
30. Lu T, O'Connor J. Bone position estimation from skin marker co-ordinates using global optimization with joint constraints. *Journal of Biomechanics*. 1999;32: 129-134.
31. Cleophas T, Zwinderman A. Random effects models in clinical research. *International Journal of Clinical Pharmacology Therapy.* 2008;46(8):421-427.
32. DerSimonian R. Kacker R. Random-effects model for meta-analysis of clinical trials: An update. *Contemporary Clinical Trials*. 2007;28:105-114.
33. Stagni R, Leardini A, Cappozzo A, Benedetti M, Cappello A. Effects of hip joint centre mislocation on gait analysis results. *Journal of Biomechanics*. 2000;33: 1479-1487.
34. Woltring H. A FORTRAN package for generalized, cross-validatory spline smoothing and differentiation. *Advances in Engineering Software*. 1986;8(2): 104-113.
35. Rankine L, Long J, Canseco K, Harris GF. Multisegmental Foot Modeling: A Review. C*ritical Reviews in Biomedical Engineering*. 2008;36(2-3):127-181.
36. Kertis J, Fritz J, Long J, Harris GF. Static and Dynamic Calibration of an Eight-Camera Optical System for Human Motion Analysis. *Critical Reviews in Physical and Rehabilitation Medicine*. 2010;22(1):49-59.

16 FLUOROSCOPIC METHODS AND THEIR APPLICATIONS IN STEOGENESIS IMPERFECTA

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INTRODUCTION

Dynamic assessment of skeletal kinematics is necessary for understanding normal joint function, in addition to effects of injury or disease.[1,2] Orthopaedic disorders, such as osteogenesis imperfecta (OI), cerebral palsy, or myelomeningocele, often require lower extremity orthoses for ambulation. Gait analysis to determine the joint kinematics and kinetics cannot typically be performed with conventional optical methods while wearing braces, orthotics, or modified footwear. Fluoroscopy offers a valuable complement to conventional motion analysis by providing dynamic weight-bearing intra-articular motion measurements that are otherwise difficult to achieve. Fluoroscopic methods can potentially enable gait analysis with orthoses, which may aid in orthoses design and surgical planning.

Fluoroscopy is an imaging technique that obtains a sequence of x-ray images of a joint as it performs a dynamic motion. Fluoroscopy can be performed using one fluoroscope (i.e., single plane fluoroscopy), or two fluoroscopes (i.e., biplane fluoroscopy). The images acquired by the fluoroscope are processed to eliminate distortions created by the imaging hardware. Software algorithms are then used to estimate the positions and orientations of the bones to determine the joint kinematics. The ability to directly analyze the bones and joints within the body to attain reliable *in vivo* kinematics is beneficial for research in several fields. This chapter will review skin motion artifact in conventional gait analysis and present fluoroscopy as an alternative imaging technique with higher accuracy. The chapter will review the basic hardware, calibration, and software methods for fluoroscopic gait analysis followed by a summary of published studies. Finally, the chapter will

discuss future work using fluoroscopy, including the application of fluoroscopic methods to OI research and treatment.

SKIN MOTION ARTIFACT IN CONVENTIONAL GAIT ANALYSIS

Conventional methods of motion analysis track skin-mounted optical markers with motion cameras to determine joint kinematics and kinetics of the underlying bones.[3] While these methods are simple, easy to implement and appropriate for various clinical and research related applications, it has been found that the most significant source of error in gait analysis is skin movement artifacts.[3,4] Skin movement artifacts (SMA) are due to the relative movement between markers and underlying bone. These movements can be caused by the non-rigid attachment of skin to bone, muscle contractions underneath skin, and inertial effects.[3] If the kinematics determined from skin markers are combined with musculoskeletal models to estimate dynamic loads in joints, even errors as small as 1 mm may be unacceptable.[1]

Various invasive and non-invasive methods have been used to directly measure in vivo skeletal motion in an effort to eliminate SMA. These methods include bone pins,[5-8] external fixation devices,[3] percutaneous skeletal tracker,[9] and fluoroscopy.[4,10] Studies using intra-cortical bone pins attached to bones in the lower extremities have found significant differences in angular displacements about all axes of rotation and displacements of skin markers relative to underlying bone of up to 20 mm.[6,7] A study that used external fracture fixation devices at the femur or tibia found skin marker displacements with respect to underlying bone ranged from a few millimeters up to 40 mm.[3] These invasive methods may expose the subjects to pain during the procedure, causing alteration of otherwise painless motions, and have a risk of infection.[7]

Fluoroscopy can be used to simultaneously visualize skin markers and bone motion during activity with relatively low radiation dose.[4,8,10] In a study involving the foot and ankle, the two malleoli markers showed the largest artifact with the mean displacement between skin markers and bones varying from 2.7 to 14.9 mm.[8]

ALTERNATIVE IMAGING TECHNIQUES

Imaging methods that allow direct 3D imaging of *in vivo* joint morphology, such as computed tomography (CT) and magnetic resonance (MR) imaging, have been used to study various joints.[11,12] These techniques are expensive and restrict the joint to one position during the CT or MR scan, preventing the quantification of full motion kinematics during various functional activities.[11] Also, CT and MR images are generally not acquired under weight-bearing conditions and may be distorted in the presence of metal implants.[13]

Roentgen stereophotogrammetric analysis (RSA) involves static x-ray imaging of joint implants or markers attached to bones to determine their positions.[14] Single plane RSA used in studying hip and knee prostheses had an accuracy of 0.7 – 0.9 mm.[15,16] In a study of knee prostheses, biplane RSA was found to have accuracy as high as 10-250 μm.[17] While RSA has demonstrated accurate determination of positioning, it exposes the patient to high radiation dosage compared to x-ray fluoroscopy.[18,19]

Whereas RSA acquires bi-plane x-ray images at one time point, x-ray fluoroscopy acquires a time sequence of images.[15] Single plane fluoroscopy allows direct visualization of underlying bones and has been used to track bone movements in animals,[20] the forearm,[21] fingers,[22] spine,[23] the natural and artificial knee[13,24-29] and the ankle.[11] While fluoroscopy is limited to a single joint at a time and has extensive image data processing, it is minimally invasive and provides complete 3-dimensional (3D) analysis of joints with reduced SMA. An average testing procedure of 20 seconds has a radiation exposure of 80 μSv, which is equivalent to the approximate solar radiation exposure received on a 12 hour flight from London to Tokyo.[30] In the United States, the average person is exposed to 3.0 mSv every year from natural background radiation.[31] Figure 1 is an x-ray image of the ankle acquired from a single plane fluoroscopy system. Single plane fluoroscopy uses a 3D to 2-dimensional (2D) registration technique to match 3D models with x-ray images.[21] The six kinematic parameters, three rotations and three translations, can be estimated for each frame. Single plane fluoroscopy is limited to 2D evaluation and is susceptible to out-of-plane errors and motion blur.[1] The assessment of out-of-plane translations is unreliable and the accuracy for measuring out-of-plane translations is poor relative to accuracy for measuring in-plane translations.[13,32] Single plane fluoroscopy lacks the ability to capture accurate 3D motion during dynamic functional loading and should not be used to study joints that have combined motions in different planes.[31]

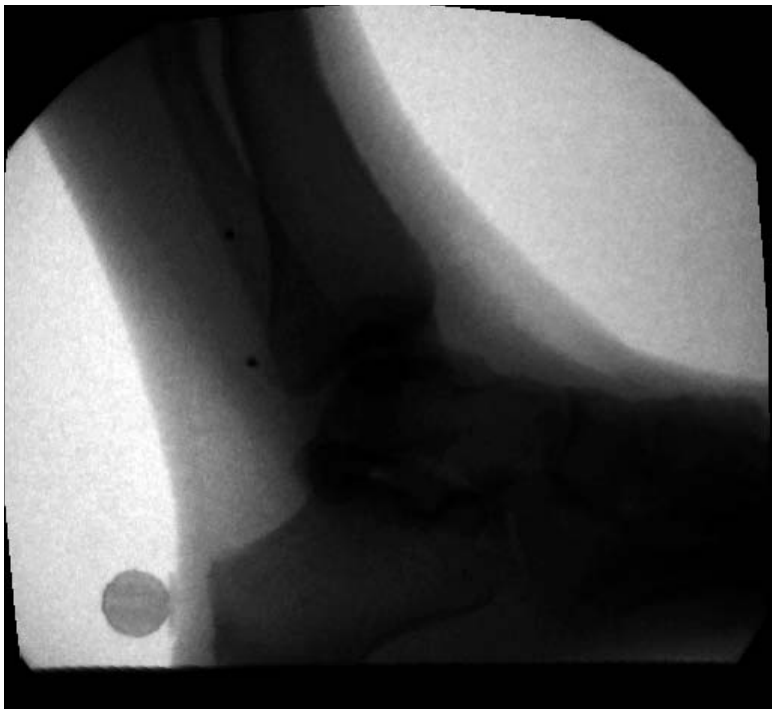

Figure 1. Single plane fluoroscopic X-ray image of ankle joint complex (Image courtesy of Ben McHenry, Marquette University).

In biplane fluoroscopy, radiographic images are captured in two different planes, allowing for assessment of 3D joint motion. It has the potential to quantify six degrees of freedom (DOF) joint motion with high accuracy and has important applications to a wide range of problems in orthopaedics, sports medicine, and bioengineering.[19] Biplane fluoroscopy has been used to determine joint motion in animals,[1,2,33] the shoulder,[34,35] spine,[31,36,37] hip,[38] the natural and artificial knee[39-42] and the ankle.[43,44] Figure 2 presents a diagram of a biplane fluoroscopy system. The two fluoroscopy gantries are separated by angle θ, allowing 3D localization in the region irradiated by both systems. A walkway containing a force plate enables kinetic analysis as well. Kinematic data from biplane fluoroscopy, along with patient specific models, can be used to calculate stress distributions and assess deformation to joint structures.[45]

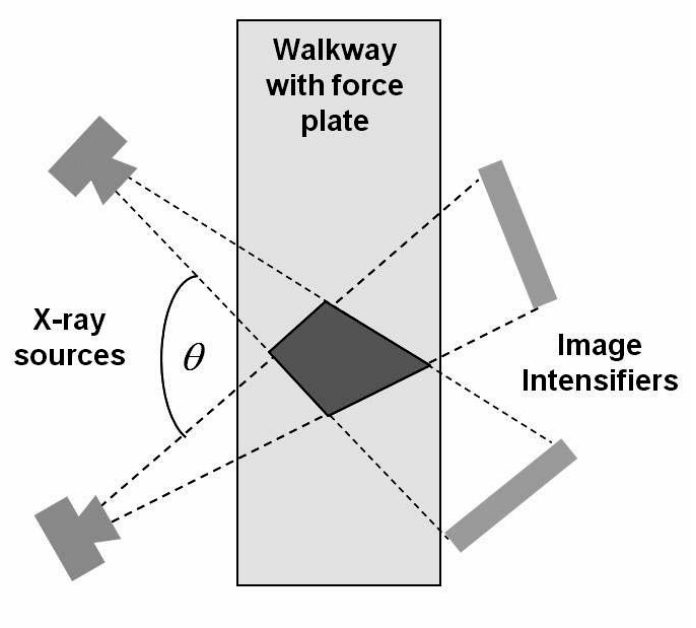

Figure 2. Diagram of biplane X-ray fluoroscopy system.

GAIT ANALYSIS WITH FLUOROSCOPY

Four components are required to perform fluoroscopic gait analysis: 1) a hardware system for acquiring x-ray images; 2) software algorithms for tracking bones or markers; 3) a 3D model, generated from a CT or MR scan, for markerless tracking; 4) a set of kinematic equations for determining joint motion.

Hardware

Depending on the study, either one or two x-ray fluoroscopes with an image intensifier coupled to a high-speed video camera are typically used to acquire images. The fluoroscopes can be used in the standard C-arm configuration or a custom build gantry. High-speed cameras are typically shuttered and sampled at 250 frames per second to reduce motion blur when recording joint motion.[19] The settings for x-ray tube current (mA) and kilovoltage (kV) vary depending on the investigated joint and surrounding soft tissue. X-ray currents between 3 and 5 mA are generally sufficient for marker-based fluoroscopy studies.[33] Because signal-to-noise ratio increases with tube current, there is a tradeoff between image quality and the amount of x-ray

exposure.[46] Lead vests or aprons are typically worn during testing to cover areas not being studied. Image quality is also affected by the beam energy, subject size, image intensifier size, and the distance from the patient to image intensifier.[46] Positioning the patient closer to the image intensifier reduces the air gaps and may reduce image blur.[19]

Calibration

The image intensifier introduces distortion on the order of 10% that must be corrected to minimize 3D tracking errors.[1,32] Distortion can be corrected by acquiring calibration images with a calibration frame attached to the face of the image intensifier. Calibration frames contain lead beads on a Plexiglass sheet or a perforated metal sheet. The distortion correction algorithm compares the spacing between the beads or holes of the calibration frame in the fluoroscope image with the true spacing and calculates a transformation matrix for correcting the images.[33] Each x-ray image undergoes calibration using the distortion correction algorithm prior to joint motion analysis. Positioning the anatomy of interest in the center of the image intensifier also helps minimize distortion.

In biplanar studies, a 3D calibration object is needed to calibrate the imaging volume so that the relationship between the 3D coordinates of the bones and the projected 2D image coordinates can be determined. The calibration object is typically acrylic, either a cube or triangle, with beads implanted in known locations. Software using the direct linear transformation method calculates the position of each bead to determine the configuration of the biplane system relative to the global reference coordinate system.[1, 2]

Marker-based Fluoroscopy

In marker-based fluoroscopy, tantalum beads implanted in bones are used to track and calculate kinematics. A minimum of three beads per bone segment are required for 3D analysis.[33] This is an invasive procedure that is limited to subjects who are undergoing a surgical procedure at the same time as implantation.[34] To extract the marker coordinates from biplane x-ray images, four steps are required. First, the images are corrected with the distortion correction algorithm. Next, the 3D space is calibrated using the calibration object and required parameters. Then, the marker positions are tracked in the x-ray images. Finally, the 3D coordinates of the markers are used to calculate the rigid body motions of each bone segment. In addition to being invasive, some trials can be lost due to the beads becoming obstructed when

aligned with implanted joint prostheses, screws or rods. Also, a bead must be simultaneously visible in both fluoroscopy images in order to calculate the 3D bead position.[36] Marker-based studies are typically used as the "gold standard" when evaluating the accuracy and validating model-based tracking methods and software.

Model-based Fluoroscopy

Model-based or markerless fluoroscopy has been developed because of the invasiveness and limitations of implanting beads into living subjects. The model-based method determines bone positions and orientations by comparing a 3D bone model, obtained with CT or MR, to the acquired biplane fluoroscopic images. The 3D model is typically created from CT images by identifying and segmenting the anatomy of interest using various available software packages. Once surface 3D CT bone models are created, a local coordinate system is assigned to each model so that the orientation and positions of the models can be determined within the calibrated space using standard rigid-body transformations.

The model pose is defined by the six DOF position and orientation of the model's local coordinate system relative to the global coordinate system.[18] Two techniques to estimate the pose of the 3D model are currently used: feature-based or intensity-based. The feature-based methods rely on identifying features in the image, such as bony landmarks and contour information. The prosthesis or bone models are projected as a 2D silhouette over the images to determine the position and orientation.[13] The bony landmarks and contours assist in aligning the projection over the image for optimal placement of the model. This method has been effective for assessing *in vivo* kinematics of both joint prosthesis[13,18,25-27] and natural joints.[37,47] Due to the smooth, rounded corners of bones, feature detection in natural joints may be difficult using this technique. This method also requires manual identification of the landmarks on each frame of fluoroscopy images.

The intensity-based method is performed by comparing digitally reconstructed radiographs (DRRs) with the acquired x-ray images. DRRs are x-ray images created by computer simulation using virtual models of the fluoroscopy system and subject anatomy. Using the calibration object data, the 3D locations and orientations of the x-ray sources and high-speed cameras are modeled within a computer program so that a virtual configuration identical to the actual biplane fluoroscopy system is created.[19,38] The 3D CT bone models created from the CT images are placed

within the virtual configuration so that a pair of DRRs can be generated by ray-tracing projections through the bone models.[32] The DRRs change accordingly as the CT models are translated and rotated within the virtual space, resulting in simulated 2D images (DRRs) from the 3D geometry of the modeled bones. The similarity between the modeled DRRs and the acquired biplane x-ray images is calculated, and the positions of the bone models are optimized to find the positions which yield the highest similarity between the simulated DRRs and the acquired images.[18, 34] Various similarity metrics and optimization algorithms have been proposed, including: Euclidean distance between contours extracted from the DRRs and measured x-ray images,[13] root mean square distance between projection lines and model surface,[25] similarity measures between the x-ray image and DRRs,[47] downhill Simplex optimization,[2] and optimization by simulated annealing.[26] Once the bone model and biplane x-ray images are optimally aligned for each frame in the sequence, the joint position and orientation are obtained directly from the model using inverse kinematics.[19] While intensity-based methods are computationally more expensive than feature-based methods, they have been used successfully to asses *in vivo* joint kinematics of the spine,[48] shoulder,[34] and knee.[2,40,41] An overview of the markerless method is presented in Figure 3.

STUDIES USING FLUOROSCOPY

Single and biplane fluoroscopy methods have been used to study total knee replacement kinematics,[13,18,24-27,29,39] natural knee kinematics,[28,40,50] patellofemoral joint motion,[41] and knee kinematics after anterior cruciate ligament reconstruction.[42] Figure 4 shows a biplane system for analyzing the knee. Table 1 compares the accuracy of studies performed on the knee joint. Typically, the accuracy of biplane fluoroscopy is higher compared to single plane, with both types of fluoroscopy systems having substantially higher accuracy compared to skin marker techniques. A direct comparison between studies is difficult due to differences in techniques, testing conditions, and software packages.

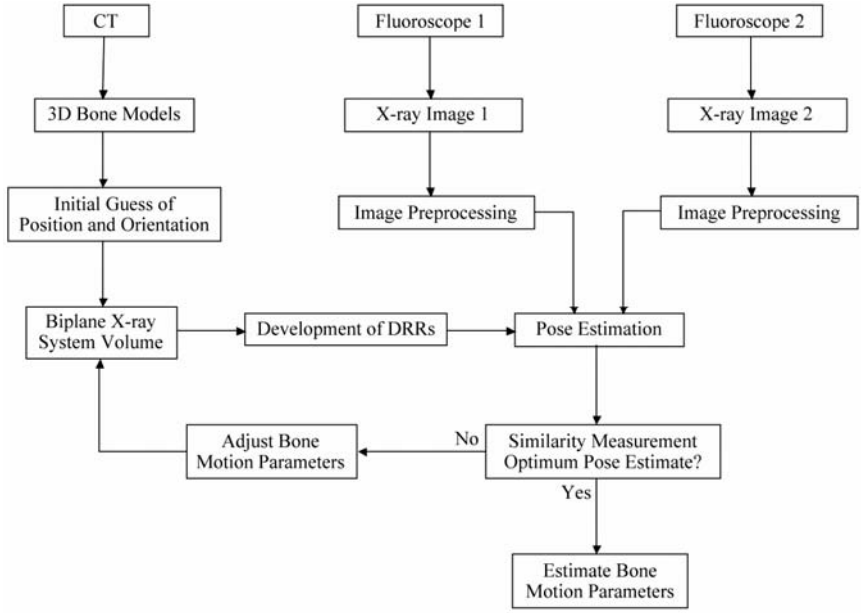

Figure 3. Flow chart of process used by model-based tracking software to estimate bone's optimal motion parameters from biplane fluoroscopy system.

Figure 4. Biplane system for knee analysis (Image courtesy of Scott Tashman, Ph.D., Director of the Biodynamics Laboratory, University of Pittsburgh Department of Orthopaedic Surgery).

Table 1. Comparison of Accuracy in Knee Joint Studies for Kinematic Measurement Systems.

Ref	Type of System	Type of Joint	Rotational Accuracy (°)	Translational Accuracy (mm)
Indirect Joint Kinematics				
49	6 DOF electromagnetic tracker	Artificial knee	1.5	6.4
Single Plane Fluoroscopy Kinematics				
13	Computer modeling	Artificial knee	0.3	0.2 (in-plane) 2.0 (out-of-plane)
	In vitro	Artificial knee	1.1	0.5 (in-plane) 6.6 (out-of-plane)
24	*In vitro*	Artificial knee	0.35	0.5
25	*In vitro*	Artificial knee	1.5	1.5
26	*In vitro*	Artificial knee	1.5	0.7
28	Computer modeling	Natural knee	1.5	2.0
29	*In vivo*	Artificial knee	1.57	0.2 (in-plae) 3.25 (out-of-plane)
Biplane Fluoroscopy Kinematics				
39	*In vivo*	Artificial knee	0.57	0.17
41	*In vivo*	Natural knee	0.987	0.455
50	*In vivo*	Natural knee	0.16	0.24
40	*In vivo*	Natural knee	0.94	0.74

While the majority of fluoroscopy studies have been on the major weight-bearing joints, studies using model-based methods were successfully performed for the shoulder, spine and ankle. A biplane study of the shoulder found a dynamic accuracy of ±0.4 mm for translation and ±0.5° for rotation.[34] Another biplane study had precision values of 0.4 mm for translation and 1.1° for rotation in the cervical spine.[31] Fluoroscopy using model-based tracking also had extremely high repeatability in the spine with 0.02 mm in translation and 0.06° in rotation.[31] A study using single plane fluoroscopy found the accuracy and reproducibility of tracking a total ankle replacement to be within 0.2 mm for in plane translation and 0.6° for rotations.[11]

Fluoroscopic analysis may be beneficial in the foot and ankle joint complex. Conventional motion analysis methods often make assumptions of these segments due to the numerous small bones and several joints involved. Also, the absence of external landmarks on the talus limits the ability of skin-mounted markers to measure the ankle joint complex kinematics accurately.[11] Due to the close proximity of the bones and multiplanar joint motion, biplane fluoroscopy may provide better precision by decreasing the overlapping of bones in the projections.

APPLICATIONS TO OSTEOGENESIS IMPERFECTA

Children with OI present with a variety of clinical problems that often result in reduced mobility and other functional activities.[51] With no cure for OI, several treatment options are available, including braces, assistive devices and physical therapy. Stainless steel rods may also be implanted into the intramedullary canals of long bones to assist in correction of bony deformities, facilitate fracture rehabilitation, and to prevent future breaks.[52] Fluoroscopic analysis could be performed to evaluate rod placement and motion, along with determining the effect on joint forces and torques.

Patients with OI types III or IV are often prescribed braces to assist in ambulation.[51] Leg bracing is recommended to support weak muscles, reduce motion and pain, control joint alignment, and promote upright balance. Hip-knee-ankle-foot-orthoses (HKAFO), fabricated using lightweight thermoplastic, may increase pelvic stability, while controlling knee recurvatum and severe hindfoot valgus.[51] A more in-depth analysis of the effects of leg braces, as is possible with fluoroscopic gait analysis, could lead to advances in orthoses design and an increase in ambulation and functional activities.

Gait analysis on children with OI found significantly less mean peak ankle plantar flexion and significantly less overall ankle range of motion during stance when compared to a control group.[52] In the same study, kinetic analysis showed children with OI had significantly reduced peak ankle push off power and minimum peak power during stance versus the control group. Due to the complex nature of the foot and its role in the gait cycle, it is essential to quantify the kinematics of the joints involved. Biplanar fluoroscopic analysis of the foot and ankle complex may provide better understanding of the ankle, subtalar, midfoot and forefoot kinematics in patients with OI. With the development of fluoroscopy analysis combined

with multi-sensor force plate technology, a better understanding of the foot kinetics could also be obtained.

FUTURE OF FLUOROSCOPY SYSTEMS

Determining accurate 3D kinematics from fluoroscopic images has shown to be a useful tool in several research studies. While techniques have evolved and improved, fluoroscopic analysis can be further enhanced to improve results and facilitate translation into routine clinical use. Many fluoroscopy studies are limited by small sample sizes and lack of age-matched control groups. While validation studies using animal, cadaver specimens or simulated conditions may provide high accuracy, these results often cannot be obtained *in vivo*. Future work is required to validate fluoroscopic methods with larger sample sizes while performing dynamic, muscle driven motions to provide more reliable results of the systems accuracy.

Modifying the gantry design may improve visualization and reduce ambulation limitations. For example, a current challenge of x-ray fluoroscopy is capturing joint motion in the narrow field of view of the image intensifier. This small volume area limits the number of joints and types of motions that can be analyzed. This limitation may be overcome by a horizontally translating fluoroscopy system that allows tracking of a joint during level walking, which may improve measurement accuracy for gait analysis. Automatic control of when the radiation is initiated and terminated would reduce the radiation exposure to the patient. Future studies may also replace conventional x-ray image intensifiers with dynamic solid-state image detectors. These detectors use less x-ray power, have a substantially greater field of view, larger spatial resolution, do not exhibit geometric distortion, and are lighter and less bulky than x-ray image intensifier systems.[53]

The pose estimation in model-based systems is accurate and reliable, but is currently operator-dependent and may be time consuming for large sequences of images. Further development of image segmentation and registration algorithms are needed to reduce image processing time and potentially provide software for real-time measurement of joint kinematics to advance fluoroscopy into clinical practice. An assumption for both marker-based and model-based fluoroscopy is that the bones are rigid. This assumption may introduce errors for diseases that affect the rigidity of bones, such as OI. Future work is required to develop software algorithms for deformable tissues.

CONCLUSIONS

Several research studies are currently using fluoroscopy methods to quantify dynamic motion patterns in joints, and to characterize joint function, articular wear, implant performance and joint replacement failure mechanisms. Biplane fluoroscopy is an accurate, non-invasive method for quantifying *in vivo* dynamic joint motion. Results from fluoroscopy studies may lead to improved implant design, optimal implant placement and reduced health care costs due to fewer revision surgeries. Fluoroscopy techniques also provide dynamic motion measurements beneficial in research of orthopaedic gait disorders that are difficult to otherwise obtain, for example when using orthoses. Further improvements to fluoroscopic hardware and software methods will enhance the understanding of *in vivo,* dynamic joint motion.

ABBREVIATIONS

CT	Computed tomography
MR	Magnetic resonance
OI	Osteogenesis imperfecta
SMA	Skin movement artifacts
RSA	Roentgen stereophotogrammetric analysis
3D	3-dimensional
2D	2-dimensional
DOF	Degrees of Freedom
DRRS	Digitally Reconstructed Radiographs
HKAFO	Hip-Knee-Ankle-Foot-Orthoses

REFERENCES

1. Tashman S, Anderst W. In-vivo measurement of dynamic joint motion using high speed biplane radiography and CT: application to canine ACL deficiency. *J Biomech Eng.* 2003;125(2):238-245.
2. You BM, Siy P, Anderst W, Tashman S. In vivo measurement of 3-D skeletal kinematics from sequences of biplane radiographs: Application to knee kinematics. *Medical Imaging, IEEE Transactions.* 2001;20(6):514-525.
3. Cappozzo A, Catani F, Leardini A, Benedetti M, Della Croce U. Position and orientation in space of bones during movement: experimental artefacts. *Clin Biomech.* 1996 3;11(2):90-100.
4. Leardini A, Chiari L, Croce UD, Cappozzo A. Human movement analysis using stereophotogrammetry: Part 3. Soft tissue artifact assessment and compensation. *Gait Posture*. 2005 2;21(2):212-225.

5. Reinschmidt C, van den Bogert AJ, Lundberg A, Nigg BM, Murphy N, Stacoff A, et al. Tibiofemoral and tibiocalcaneal motion during walking: external vs. skeletal markers. *Gait Posture.* 1997 10;6(2):98-109.
6. Benoit DL, Ramsey DK, Lamontagne M, Xu L, Wretenberg P, Renström P. Effect of skin movement artifact on knee kinematics during gait and cutting motions measured in vivo. *Gait Posture*. 2006 10;24(2):152-164.
7. Fuller J, Liu LJ, Murphy MC, Mann RW. A comparison of lower-extremity skeletal kinematics measured using skin- and pin-mounted markers. *Human Movement Science*. 1997 4;16(2-3):219-242.
8. Shultz R, Kedgley AE, Jenkyn TR. Quantifying skin motion artifact error of the hindfoot and forefoot marker clusters with the optical tracking of a multi-segment foot model using single-plane fluoroscopy. *Gait Posture.* 2011 5;34(1):44-48.
9. Holden JP, Orsini JA, Siegel KL, Kepple TM, Gerber LH, Stanhope SJ. Surface movement errors in shank kinematics and knee kinetics during gait. *Gait Posture.* 1997 6;5(3):217-227.
10. Akbarshahi M, Schache AG, Fernandez JW, Baker R, Banks S, Pandy MG. Non-invasive assessment of soft-tissue artifact and its effect on knee joint kinematics during functional activity. *J Biomech.* 2010 5/7;43(7):1292-1301.
11. Yamaguchi S, Tanaka Y, Kosugi S, Takaura Y, Sasho T, Banks SA. In vivo kinematics of two-component total ankle arthroplasty during non-weightbearing and weightbearing dorsiflexion/plantarflexion. *J Biomech*. 2011;44:995-1000.
12. Arnold AS, Salinas S, Asakawa DJ, Delp SL. Accuracy of muscle moment arms estimated from MRI-based musculoskeletal models of the lower extremity. *Computer Aided Surgery.* 2000;5(2):108-119.
13. Banks SA, Hodge WA. Accurate measurement of three-dimensional knee replacement kinematics using single-plane fluoroscopy. *Biomedical Engineering, IEEE Transactions.* 1996;43(6):638-649.
14. Kedgley AE, Birmingham T, Jenkyn TR. Comparative accuracy of radiostereometric and optical tracking systems. *J Biomech.* 2009 6/19;42(9):1350-1354.
15. Ioppolo J, Börlin N, Bragdon C, Li M, Price R, Wood D, et al. Validation of a low-dose hybrid RSA and fluoroscopy technique: Determination of accuracy, bias and precision. *J Biomech.* 2007;40(3):686-692.
16. Yuan X, Ryd L, Tanner KE, Lidgren L. Roentgen single-plane photogrammetric analysis (RSPA): A new approach to the study of musculoskeletal movement. *J Bone Joint Surg Br.* 2002 August 1;84-B(6):908-914.
17. Short A, Gill HS, Marks B, Waite JC, Kellett CF, Price AJ, et al. A novel method for in vivo knee prosthesis wear measurement. *J Biomech.* 2005 2;38(2):315-322.
18. Bingham JT, Li G. An optimized image matching method for determining in-vivo TKA kinematics with a dual-orthogonal fluoroscopic imaging system. *J Biomech E.* 2006;128(4):588-595.
19. Ackland DC, Keynejad F, Pandy MG. Future trends in the use of x-ray fluoroscopy for the measurement and modelling of joint motion. *Proc IMechE.* 2011;225:1-13.
20. Bauman JM, Chang Y. High-speed X-ray video demonstrates significant skin movement errors with standard optical kinematics during rat locomotion. *J Neurosci Methods.* 2010 1/30;186(1):18-24.
21. Matsuki KO, Matsuki K, Mu S, Sasho T, Nakagawa K, Ochiai N, et al. In vivo 3D kinematics of normal forearms: Analysis of dynamic forearm rotation. *Clin Biomech.* 2010 12;25(10):979-983.

22. Rash GS, Belliappa PP, Wachowiak MP, Somia NN, Gupta A. A demonstration of the validity of a 3-D video motion analysis method for measuring finger flexion and extension. *J Biomech.* 1999 12;32(12):1337-1341.
23. Auerbach JD, Wills BP, McIntosh TC, Balderston RA. Evaluation of Spinal Kinematics Following Lumbar Total Disc Replacement and Circumferential Fusion Using In Vivo Fluoroscopy. *Spine.* 2007;32(5):527-536.
24. Hoff WA, Komistek RD, Dennis DA, Gabriel SM, Walker SA. Three-dimensional determination of femoral-tibial contact positions under in vivo conditions using fluoroscopy. *Clin Biomech.* 1998 10;13(7):455-472.
25. Zuffi S, Leardini A, Catani F, Fantozzi S, Cappello A. A model-based method for the reconstruction of total knee replacement kinematics. *Medical Imaging, IEEE Transactions.* 1999;18(10):981-991.
26. Mahfouz MR, Hoff WA, Komistek RD, Dennis DA. A robust method for registration of three-dimensional knee implant models to two-dimensional fluoroscopy images. *Medical Imaging, IEEE Transactions.* 2003;22(12):1561-1574.
27. Yamazaki T, Watanabe T, Nakajima Y, Sugamoto K, Tomita T, Yoshikawa H, et al. Improvement of depth position in 2-D/3-D registration of knee implants using single-plane fluoroscopy. *Medical Imaging, IEEE Transactions.* 2004;23(5):602-612.
28. Fregly BJ, Rahman HA, Banks SA. Theoretical accuracy of model-based shape matching for measuring natural knee kinematics with single-plane fluoroscopy. *J Biomech E.* 2005;127(4):692-699.
29. Zihlmann MS, Gerber H, Stacoff A, Burckhardt K, Székely G, Stüssi E. Three-dimensional kinematics and kinetics of total knee arthroplasty during level walking using single plane video-fluoroscopy and force plates: A pilot study. *Gait Posture.* 2006 12;24(4):475-481.
30. Bottollier-Depois J, Chau Q, Bouisset P, Kerlau G, Plawinski L, Lebaron-Jacobs L. Assessing Exposure to Cosmic Radiation during Long-Haul Flights. *Radiat Res.* 2000 May;153(5, Part 1):pp. 526-532.
31. Anderst WJ, Baillargeon E, Donaldson III WF, Lee JY, Kang JD. Validation of a Noninvasive Technique to Precisely Measure In Vivo Three-Dimensional Cervical Spine Movement. *Spine.* 2011;36(6):E393-E400.
32. Penney GP, Weese J, Little JA, Desmedt P, Hill DLG, hawkes DJ. A comparison of similarity measures for use in 2-D-3-D medical image registration. *Medical Imaging, IEEE Transactions.* 1998;17(4):586-595.
33. Brainerd EL, Baier DB, Gatesy SM, Hedrick TL, Metzger KA, Gilbert SL, et al. X-ray reconstruction of moving morphology (XROMM): precision, accuracy and applications in comparative biomechanics research. *J Exp Zool Part A: Ecol Gen Physi.* 2010;313A(5):262-279.
34. Bey MJ, Zauel R, Brock SK, Tashman S. Validation of a new model-based tracking technique for measuring three-dimensional, in vivo glenohumeral joint kinematics. *J Biomech E.* 2006;128(4):10.1115/ 1.2206199.
35. Bey MJ, Kline SK, Zauel R, Lock TR, Kolowich PA. Measuring dynamic in-vivo glenohumeral joint kinematics: Technique and preliminary results. *J Biomech.* 2008;41(3):711-714.
36. Anderst WJ, Vaidya R, Tashman S. A technique to measure three-dimensional in vivo rotation of fused and adjacent lumbar vertebrae. *Spine J.* 2008 12;8(6):991-997.
37. Xia Q, Wang S, Kozanek M, Passias P, Wood K, Li G. In-vivo motion characteristics of lumbar vertebrae in sagittal and transverse planes. *J Biomech.* 2010 7/20;43(10):1905-1909.

38. Martin DE, Greco NJ, Klatt BA, Wright VJ, Anderst WJ, Tashman S. Model-Based Tracking of the Hip: Implications for Novel Analyses of Hip Pathology. *J Arthroplasty.* 2011 1;26(1):88-97.
39. Hanson GR, Suggs JF, Freiberg AA, Durbhakula S, Li G. Investigation of in vivo 6DOF total knee arthoplasty kinematics using a dual orthogonal fluoroscopic system. *J Ortho Res.* 2006;24(5):974-981.
40. Anderst WJ, Zauel R, Bishop J, Demps E, Tashman S. Validation of three-dimensional model-based tibio-femoral tracking during running. *Med Eng Phys.* 2009 1;31(1):10-16.
41. Bey MJ, Kline SK, Tashman S, Zauel R. Accuracy of biplane x-ray imaging combined with model-based tracking for measuring in-vivo patellofemoral joint motion. *J Ortho Surg Res. 2008*;3(38):10.1186/1749-799X-3-38.
42. Abebe ES, Utturkar GM, Taylor DC, Spritzer CE, Kim JP, Moorman III CT, et al. The effects of femoral graft placement on in vivo knee kinematics after anterior cruciate ligament reconstruction. *J Biomech.* 2011 3/15;44(5):924-929.
43. de Asla RJ, Wan L, Rubash HE, Li G. Six DOF in vivo kinematics of the ankle joint complex: Application of a combined dual-orthogonal fluoroscopic and magnetic resonance imaging technique. *J Ortho Res.* 2006;24(5):1019-1027.
44. Wan L, de Asla RJ, Rubash HE, Li G. In vivo cartilage contact deformation of human ankle joints under full body weight. *J Ortho Res.* 2008;26(8):1081-1089.
45. Fernandez JW, Pandy MG. Integrating modelling and experiments to assess dynamic musculoskeletal function in humans. *Experi Physi.* 2006 March 01;91(2):371-382.
46. Geise RA. Fluoroscopy: Recording of Fluoroscopic Images and Automatic Exposure Control. *Radiographics.* 2001 January 01;21(1):227-236.
47. Tersi L, Fantozzi S, Stagni R. 3D Elbow Kinematics with Monoplanar Fluoroscopy: *In Silico* Evaluation. *EURASIP J Adv Signal Proc.* 2010;2010:doi:10.1155/2010/142989.
48. Bifulco P, Sansone M, Cesarelli M, Allen R, Bracale M. Estimation of out-of-plane vertebra rotations on radiographic projections using CT data: a simulation study. *Med Eng Phys.* 2002 5;24(4):295-300.
49. An KN, Jacobsen MC, Berglund LJ, Chao EYS. Application of a magnetic tracking device to kinesiologic studies. *J Biomech*. 1988;21(7):613-620.
50. Li G, Van de Velde SK, Bingham JT. Validation of a non-invasive fluoroscopic imaging technique for the measurement of dynamic knee joint motion. *J Biomech.* 2008;41(7):1616-1622.
51. Gerber LH, Binder H, Berry R, Siegel KL, Kim H, Weintrob J, et al. Effects of withdrawal of bracing in matched pairs of children with osteogenesis imperfecta. *Arch Phys Med Rehabil.* 1998 1;79(1):46-51.
52. Graf A, Hassani S, Krzak J, Caudill A, Flanagan A, Bajorunaite R, et al. Gait characteristics and functional assessment of children with Type I Osteogenesis Imperfecta. *J Ortho Res.* 2009;27(9):1182-1190.
53. Cowen AR, Davies AG, Sivananthan MU. The design and imaging characteristics of dynamic, solid-state, flat-panel x-ray image detectors for digital fluoroscopy and fluorography. *Clin Radiol.* 2008 10;63(10):1073-1085.

17 FLUOROSCOPIC SYSTEM FOR ASSESSMENT OF *IN VIVO* HINDFOOT KINEMATICS DURING GAIT: CONTROL DATA AND APPLICATIONS IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Literature suggests that the children with type I osteogenesis imperfecta (OI) suffer from a variety of abnormal gait characteristics which include a reduction in power generation during push off.[1,2] This reduction is of interest clinically because 80% of the power associated with normal ambulation is derived from push off, and is often the gold standard used in defining a normal gait pattern. The exact biomechanical reasons for this reduction in push off power seen in patients with type I OI are not well understood, but a fluoroscopic *in vivo* assessment of the foot may reveal some clues.

Historically, *in vivo* lower extremity modeling has been accomplished by defining a system of segments in which the most distal segment is a rigid representation of the entire foot.[3-7] This rigid representation of the foot fails to account for the known articulations within the foot, and can lead to errors in gait analysis, especially when applied to the deformed foot.[8,9] To overcome the shortcomings of defining the foot as a single rigid segment, several multi-

segmental foot models are described in the literature. These models use externally placed markers on the skin to break the foot into multiple segments, ranging from as few as two to as many as nine segments.[10-16] While these multi-segmental foot models provide a more accurate representation of the motion of the deformed foot, they have shortcomings associated with external marker use and rigid segment assumptions.

Any human locomotion model using external markers attached to the skin to track underlying bone has potential error associated with soft tissue artifacts (STA). These artifacts arise because superficial muscle and skin are free to move relative to the underlying bony anatomy, making it difficult to reliably measure the bony movement of interest. A recent hindfoot study using single-plane fluoroscopy reported translational soft tissue artifact at the calcaneus ranging from 5.9 ± 7.3 mm at heel strike to 12.1 ± 0.3 mm at toe off.[17] Several additional studies have attempted to quantify and reduce this source of error, but none have demonstrated a reliable way to do it.[18-21] In general, STA are: (1) dependent on the anatomic location of interest, (2) dependent on the task being measured, (3) different between subjects, and (4) of a frequency content similar to the movement of interest, such that they cannot be filtered out.[22]

In addition to STA, marker placement repeatability errors arise in current multi-segmental foot models and can be directly attributed to the use of external markers. Marker locations are usually used in conjunction with anthropomorphic data to mathematically determine anatomic locations or to define local coordinate systems. Because of this, external marker placement becomes critical in the evaluation of the model. Most models use easily palpable landmarks as locations to place external markers, though a number of studies have quantified errors associated with finding them. Della Croce et al. measured the precision with which lower limb anatomic locations could be repeatedly determined and reported values at the foot as high as 10.3mm and 21.5 mm for intra and inter-examiner precision respectively.[23] A similar study done by Rabuffetti et al. reported inter-examiner precision values at the lateral malleolus and fifth metatarsal head of 9.2 mm and 7.0 mm respectively.[24] These misplacement errors propagate through the kinematic model and end up affecting the reported results. Della Croce et al. estimated intra- and inter-examiner precision of ankle joint angles during upright posture as high as 3.9° and 10.9° respectively.[23]

The reliability of marker placement has a direct effect on joint kinematics. In joints that undergo small ranges of motion (such as those intra-foot), the error associated with marker misplacement can be considerable.[25] As the distance between external markers decreases (e.g., when defining multiple segments in the small volume occupied by the foot), error associated with marker placement repeatability can increase, resulting in angle definition sensitivity.[26]

In addition to the errors associated with STA and marker placement, multi-segmental foot models make rigid body assumptions in segments containing multiple bones. The validity of these rigid body assumptions (i.e., the question of whether the bones within the segment move with respect to each other) directly affects the kinematic data resulting from these segments. There is a risk of attributing motion to a joint where it is not actually taking place, or of missing a motion entirely. Nester et al. reported specifically on the error associated with rigid body violations of mid and forefoot segments and concluded that there was clear evidence of how different bone groupings influenced a segment's kinematics.[27] The only way to correct for this is to subdivide the segment into more segments; for a marker-based model, this requires the use of more markers, which may be affixed either externally or internally (i.e. by invasive means). Internally fixed bone-anchored markers, for example, are often regarded as a solution to the rigid body assumption. However, because of their invasive nature and potential for altering gait, they are rarely used for clinical assessment.

To address these limitations, the aim of this study was to develop a multi-segmental hindfoot model that used fluoroscopy to define bony segment position. The planar fluoroscopic images obtained from the described system were used to determine talocrural and subtalar kinematics in the sagittal plane. These kinematics compare favorably to those reported by more invasive means.

METHODS

Participants

The right feet of five subjects were tested after institutional review approval and informed consent (5 Male; 22.8 ± 4.0 years of age). All subjects demonstrated normal lower extremity function and had no prior lower extremity injuries.

Protocol

Each subject underwent standard barefoot gait analysis with simultaneous fluoroscopic image collection at 120Hz. Following dynamic data collection, subjects were escorted to a nearby x-ray suite where a single limb support barefoot x-ray was taken of their right foot placed at the same foot progression angle observed during dynamic image collection. The developed multi-segmental hindfoot model was then applied to the collected data.

Gait Analysis

Motion data was collected at 120Hz using a 14 camera motion capture system (Vicon Motion Systems, Inc., Lake Forest, CA) while subjects walked across a raised six meter long walkway. Reflective markers were placed at specific anatomic landmarks and were used to define a tibial coordinate system, foot progression angle, and global referencing points for each of the collected fluoroscopic images (Table 1). Subjects were asked to walk at a self-selected pace for a maximum of five trials of fluoroscopic exposure.

Table 1. External marker locations. Markers M1 and M2 are used to define the foot progression angle (β) in Equation 2. Markers M3-M6 are used to define the axes of the tibial coordinate system.

Marker Name	Marker Location
M1	Calcaneal tuberosity
M2	Head of the 2nd metatarsal
M3	Medial malleolus
M4	Lateral malleolus
M5	Medial femoral epicondyle
M6	Lateral femoral epicondyle

Fluoroscopic Imaging

Fluoroscopic images were collected at 120 fps using a Basler Aviator avA1000km camera (Basler Vision Technologies, Ahrensburg, Germany), XCAP imaging software (XCAPTM, Buffalo Grove, IL), and a reconfigured OEC 9000 C-arm fluoroscopy unit (GE, Fairfield, CT). Ground reaction force data was collected using a multi-axis AMTI OR6-5-1 force plate (AMTI, Watertown, MA) embedded in a raised walkway. Figure 1 illustrates the system configuration. The image intensifier was placed flush with the force plate (global XZ plane) and slightly below the raised walkway to allow the best view of the stance phase of gait. Because both the gait analysis motion data and fluoroscopic images were collected at 120Hz, the fluoroscopic

images could be synchronized to the motion data (during data processing) by use of the ground reaction force and a five-volt TTL pulse (emitted by the fluoroscopy unit when activated). In addition to synchronization, the fluoroscopic images underwent a linearization process to correct for the pincushion image distortion created by the tube nature of the image intensifier.[28]

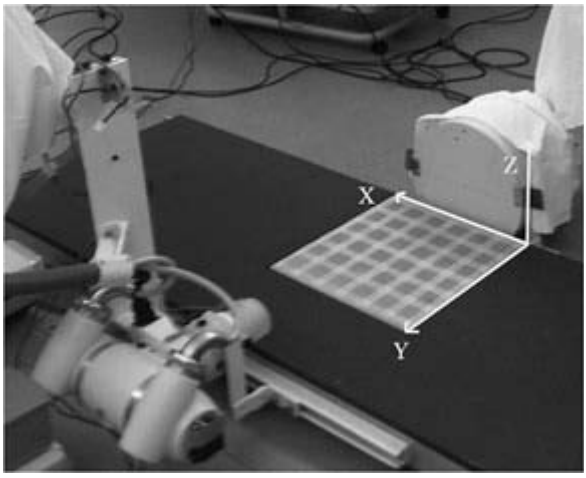


Figure 1. System configuration: Embedded force plate with global coordinate system, emitter (nearside), and image intensifier (far side).

Static X-Ray

After gait analysis motion data was collected, the average foot flat progression angle was calculated for all trials by using external markers. This average progression angle was used to position the foot for a lateral, single limb support x-ray. The foot was positioned for the x-ray such that it matched the position of foot flat during the walking trials.

Hindfoot Model

A three-segment rigid body model was developed to describe the kinematics of the hindfoot during the stance phase of gait. The segments were: (1) tibia, (2) talus, and (3) calcaneus. The tibial segment coordinate system was defined completely by external markers as it remained outside the image intensifier field of view for much of stance. The talar and calcaneal segment coordinate systems were defined by first locating virtual markers in the fluoroscopic images (i.e. image coordinates) and translating them into global coordinates by a method of global referencing. Because only one fluoroscopic

unit was used in this study virtual markers were translated into a 2D motion plane. The motion plane was the foot progression plane; or the plane that includes the M1 and M2 markers and is perpendicular to the global XY plane (see Figure 2). Translating virtual marker points of interest from image coordinates (POIx', POIz') to global coordinates (POIX, POIY, POIZ) within the motion plane required having a reference point and knowledge about the magnification of the foot in the images. The reference point must have coordinates that are known in both the image and global coordinate systems and must also be contained within the motion plane. For the fluoroscopic images, marker M1 is used as the reference point because it is contained by the motion plane and has known image and global coordinates ((Hx', Hz') and (HX, HY, HZ) respectively). The magnification of the foot in the fluoroscopic images is determined by adhering two radiographic markers to the subject's ankle 30mm from each other. The pixel distance between these markers is then determined in the fluoroscopic images and a constant pixels per millimeter (ppm) variable is calculated. Equations 1-3 (Table 2) are used to translate points of interest from image coordinates to global coordinates within the motion plane. Figure 3 shows a typical fluoroscopic image where several parameters in equations 1-3 are defined (note: only parameters θ and ppm are constants for each trial, all other parameters are calculated for each fluoroscopic image).

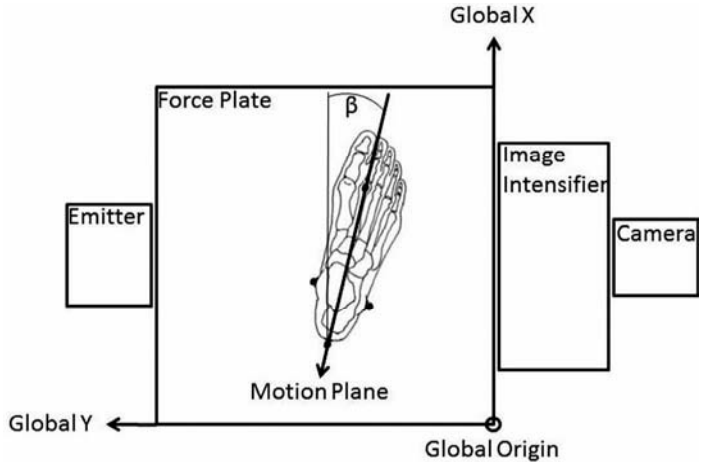


Figure 2. Motion plane. The plane of motion is perpendicular to global XY plane through markers on the calcaneal tuberosity and the superior head of the second metatarsal.

Table 2. Global referencing equations.

$$POIX = HX + \left[\left[\frac{POIx' - Hx'}{ppm}\right]\cos\theta + \left[\frac{POIz' - Hz'}{ppm}\right]\sin\theta\right] \quad \text{(Eq. 1)}$$

$$POIY = HY + \left[\left[\frac{POIx' - Hx'}{ppm}\right]\cos\theta + \left[\frac{POIz' - Hz'}{ppm}\right]\sin\theta\right]\tan\beta \quad \text{(Eq. 2)}$$

$$POIZ = HZ + \left[-\left[\frac{POIx' - Hx'}{ppm}\right]\sin\theta + \left[\frac{POIz' - Hz'}{ppm}\right]\cos\theta\right] \quad \text{(Eq. 3)}$$

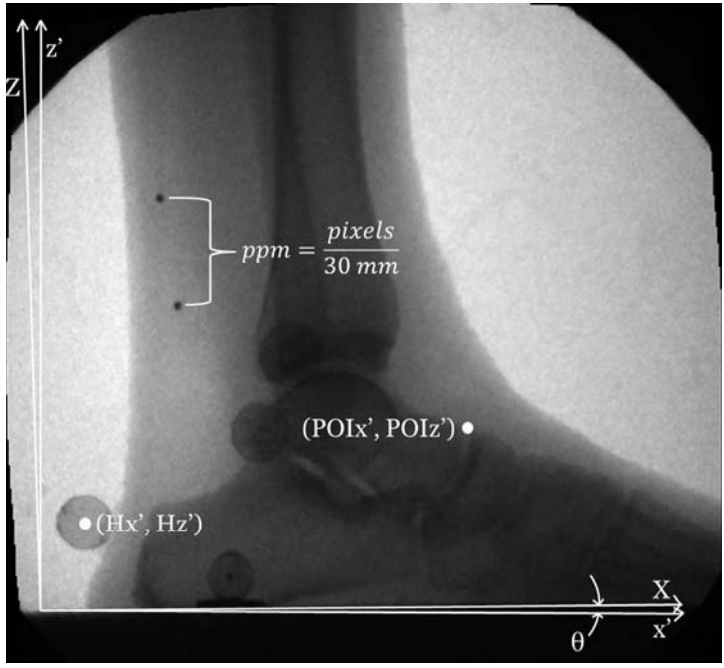
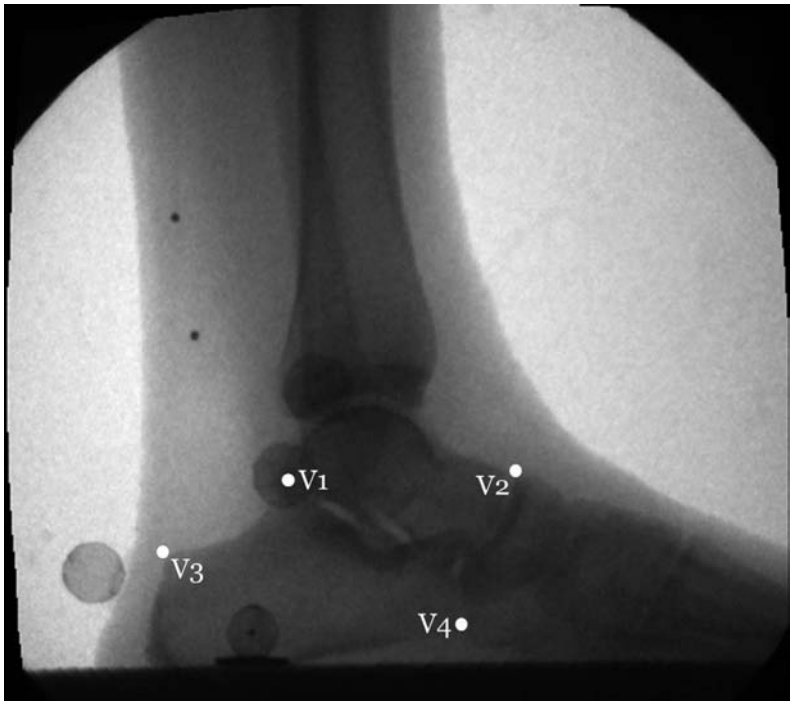


Figure 3. Typical fluoroscopic image. POI locations are translated from image coordinates (POIx', POIz') to global (POIX, POIY, POIZ) using an external marker's image (Hx', Hz') and global (HX, HY, HZ) coordinate locations, as well as the image pixels per millimeter (ppm) magnification, subject foot progression angle (β, calculated from external markers), and the camera's angular rotation from global (θ).

Two virtual markers for the talus (V1, V2) as well as two for the calcaneus (V3, V4) (Figure 4) were globally referenced (Table 2) for each of the fluoroscopic images. These virtual marker locations were subject specific and were chosen because they were easily identified in all fluoroscopic

images. After virtual marker locations were translated to global coordinates via global referencing, they were used in conjunction with external skin marker locations to define the local coordinate axes of the tibial, talar and calcaneal coordinate systems (Table 3).

Once coordinate systems were defined for all three segments the anatomical joint angles for the talocrural and subtalar joint were determined using the Joint Coordinate Method.[29] as described by Vaughn et al.[30] After the anatomical joint angles were determined, they were compared to the angles of quiet standing (quiet standing angles were determined by applying the developed model to the static x-ray image for each subject). The measured angles during quiet standing are used for clinical reference and represent neutral position for reported kinematics.



Figures 4. Virtual marker locations. V1 and V2 represent typical virtual marker locations for the talus, while V3 and V4 represent typical virtual marker locations for the calcaneus.

Table 3. Segment coordinate system axes definition. Virtual markers have prefix V, external markers have prefix M. All marker locations (virtual and external) are defined in global coordinates.

Segment	i-axis	j-axis	k-axis
Calcaneus	$\frac{(V3-V4)}{\lvert(V3-V4)\rvert}$	$\frac{(k_{axis}\times i_{axis})}{\lvert(k_{axis}\times i_{axis})\rvert}$	$\frac{(i_{axis}\times(0,0,1))}{\lvert(i_{axis}\times(0,0,1))\rvert}$
Talus	$\frac{(V1-V2)}{\lvert(V1-V2)\rvert}$	$\frac{(k_{axis}\times i_{axis})}{\lvert(k_{axis}\times i_{axis})\rvert}$	$\frac{(i_{axis}\times(0,0,1))}{\lvert(i_{axis}\times(0,0,1))\rvert}$
Tibia	$\frac{\left(\frac{M5+M6}{2}\right)-\left(\frac{M3+M4}{2}\right)}{\left\lvert\left(\left(\frac{M5+M6}{2}\right)-\left(\frac{M3+M4}{2}\right)\right)\right\rvert}$	$\frac{\left(\left(M3-\left(\frac{M3+M4}{2}\right)\right)\times i_{axis}\right)}{\left\lvert\left(\left(M3-\left(\frac{M3+M4}{2}\right)\right)\times i_{axis}\right)\right\rvert}$	$\frac{(i_{axis}\times j_{axis})}{\lvert(i_{axis}\times j_{axis})\rvert}$

RESULTS

Figure 5 shows the talocrural and subtalar sagittal plane kinematics for a single subject and demonstrates the repeatability of the model to measure hindfoot kinematics trial to trial. Figure 6 shows the talocrural and subtalar kinematics for all five subjects combined. The X axis on Figures 5 and 6 represents the % Stance Phase of gait, with 0% representing heel strike and 100% representing toe off. Because the calcaneus and talus are no longer in the fluoroscopic field of view at toe off, most trials do not have data through 100% of the gait cycle, which manifests with missing data towards the end of Stance Phase. Table 4 shows the mean peak plantar and dorsiflexion values for the talocrural and subtalar kinematics, respectively, for all five subjects combined.

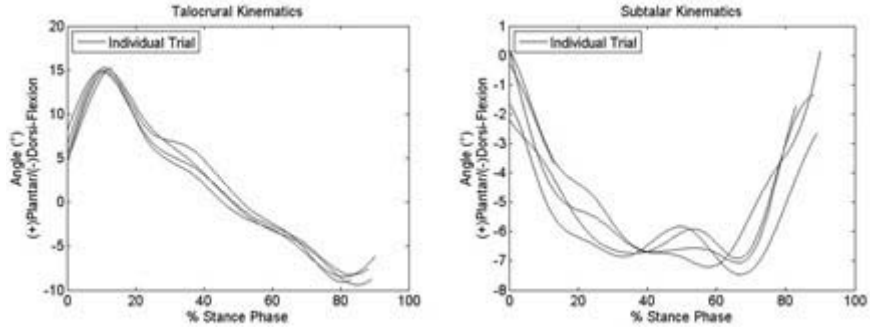


Figure 5. Sagittal plane kinematic results. Black lines represent individual trials for a single subject.

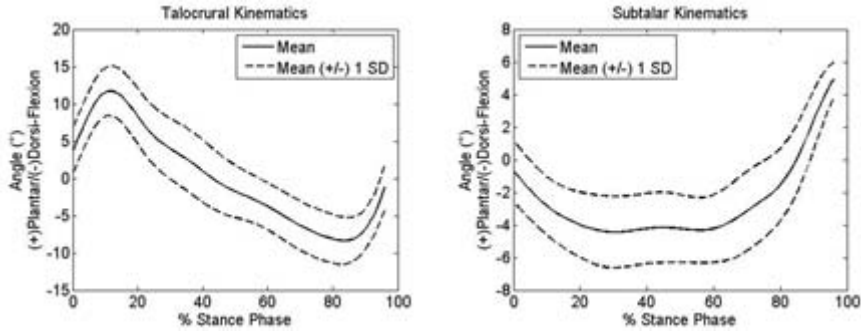


Figure 6. Sagittal plane kinematic results. Solid line represents mean angle of all five subjects combined. Dashed lines represent mean ± 1 SD.

Table 4. Kinematic statistics.

TALOCRURAL JOINT MOTION		
Peak Plantar Flexion	11.70°	@ 12% of Stance Phase
Peak Dorsiflexion	8.36°	@ 83% of Stance Phase
Range	20.06°	
SUBTALAR JOINT MOTION		
Peak Plantar Flexion	5.45°	@ 96% of Stance Phase
Peak Dorsiflexion	4.44°	@ 30% of Stance Phase
Range	9.89°	

DISCUSSION

Talocrural joint motion starts in a neutral position and slopes towards plantar flexion during heel strike, reaching peak plantar flexion around 12% of stance (Figure 6). After foot flat occurs, the tibia rolls over the talus forcing the talocrural joint into dorsiflexion which lasts until about 83% of stance. As push off occurs, the talocrural joint once again moves towards plantar flexion. Talocrural range of motion (ROM) for the five subjects combined is 20.06° (Table 4). As shown in Figure 6, subtalar motion is primarily in dorsiflexion during stance phase, moving into plantar flexion around 84% of stance. Subtalar ROM for the five subjects combined is 9.89° as reported in Table 4.

Other than the fluoroscopic method described in the current study, only bone anchored marker studies report both talocrural and subtalar motion during the entire stance phase of gait. These studies rely on intra-cortical pins to be surgically inserted into the various bones of the foot/ankle. Attached to the

ends of these pins is a cluster of markers whose motion is captured using stereophotogrammetry. The advantages of using bone pins is that STA is no longer present, and bones with few palpable landmarks can be tracked directly (not combined with other bones). A study by Arndt et al. tested three subjects using surgically inserted intra-cortical pins and reported both talocrural and subtalar motion.[31,32] The results of the Arndt study compared to the fluoroscopic talocrural and subtalar results are shown in figures 7 and 8 respectively.

As shown in figure 7, the shape and pattern of talocrural joint motion in both studies is quite similar. Peak plantar flexion for both studies occurs between 10-15% of gait, and peak dorsiflexion occurs between 80-85%. Figure 8 shows similar results in subtalar motion between the studies, with peak plantar flexion occurring between 20-30% of stance, and peak dorsiflexion occurring between 95-100%. The major differences in the kinematics of the two studies is seen in overall ROM, with the fluoroscopic study subjects combined averaging 20.1° and 9.9° for talocrural and subtalar motion respectively, and the Arndt study subjects combined averaging 11.7° and 2.8° respectively.[31,32] Reasons for the reduced ROM seen in the Arndt study compared to the fluoroscopic study may be attributed to methodological differences between studies. The Arndt study uses intra-cortical pins to avoid STA and muti-bone segment rigidity assumptions. While the intra-cortical pins are effective in these areas, their use is considered invasive and studies need to be undertaken to quantitatively ensure they do not alter normal gait function. The fluoroscopic study is 2D in nature and is dependent on the clinician to locate the virtual markers in every collected fluoroscopic frame. While requiring the clinician to locate virtual markers in every frame is a good way of self-correcting marker location frame to frame, any out of plane motion which appears to alter in-plane marker placement will not be noticed by the clinician, and out of plane motion could be falsely reported as occurring in plane. In addition, the fluoroscopic study group consisted of younger individuals (22.8 years) than the bone pin kinematic studies (39.3 years).[31,32] Oberg et al. has described differences in gait kinematics with aging for 233 healthy subjects aged 10-79 years.[33] While these differences are small, the effects of age upon *in vivo* bony kinematics of the foot and ankle have not been studied.

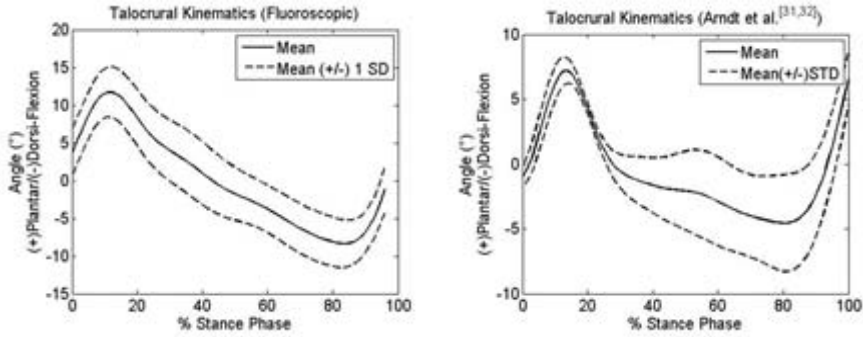


Figure 7. Sagittal plane talocrural kinematics. Solid line represents mean angle of all subjects combined. Dashed lines represent mean ± 1 SD. The fluoroscopic study consisted of 5 subjects, while the Arndt et al. study consisted of 3 subjects.[31,32]

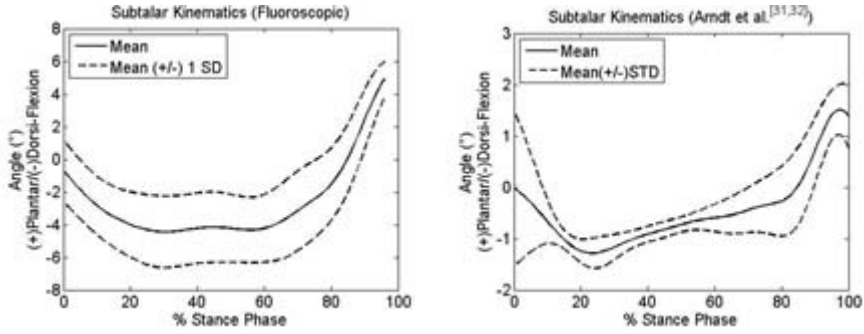


Figure 8. Sagittal plane subtalar kinematics. Solid line represents mean angle of all subjects combined. Dashed lines represent mean ± 1 SD. The fluoroscopic study consisted of 5 subjects, while the Arndt et al. study consisted of 3 subjects.[31,32]

CONCLUSION

The use of fluoroscopy shows promise in the foot and ankle motion analysis. Unlike current multi-segment foot models, fluoroscopic models do not suffer from assumptions made about STA, marker placement repeatability, or segment rigidity, and are completely non-invasive. In addition to the mentioned advantages, the radiographic nature of fluoroscopy would allow for the described model to be easily applied to the shod foot (which would be nearly impossible using external or bone anchored markers) and since most of human ambulation occurs in the shod condition, knowledge of how the bones of the foot and ankle move within a shoe would be of great clinical significance.

Study limitations include a narrow sample of adult male subjects aged 18 to 28 with no reported gait deficiencies or prior bony foot injury. The current study is also limited to a single plane (sagittal) analysis of hindfoot motion components. A further limitation is the use of ionizing radiation with current levels estimated at 10 μSv/trial. According to the USNRC, whole body annual occupational limits are 5 rems (50,000 μSv).

ACKNOWLEDGEMENTS

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REFERENCES

1. Graf, A., et al., Gait characteristics and functional assessment of children with type I osteogenesis imperfecta. *J Orthop Res* 2009;27(9):1182-90.
2. Krzak, J.J., et al., Analysis of Push-Off Power During Locomotion in Children with Type 1 Osteogenesis Imperfecta. *Journal of Experimental and Clinical Medicine* 2011;3(5):195-199.
3. Apkarian, J., S. Naumann, and B. Cairns, A three-dimensional kinematic and dynamic model of the lower limb. *J Biomech* 1989;22(2):143-55.
4. Cappozzo, A., T. Leo, and A. Pedotti, A general computing method for the analysis of human locomotion. *J Biomech* 1975;8(5):307-20.
5. Kadaba, M.P., H.K. Ramakrishnan, and M.E. Wootten, Measurement of lower extremity kinematics during level walking. *J Orthop Res* 1990;8(3):383-92.
6. Ounpuu, S., J.R. Gage, and R.B. Davis, Three-dimensional lower extremity joint kinetics in normal pediatric gait. *J Pediatr Orthop* 1991;11(3):341-9.
7. White, S.C., H.J. Yack, and D.A. Winter, A three-dimensional musculoskeletal model for gait analysis. Anatomical variability estimates. *J Biomech* 1989;22(8-9):885-93.
8. Davis, R.B., et al., The Design, Development, and Initial Evaluation of a Multisegment Foot Model for Routine Clinical Gait Analysis, in *Foot and Ankle Motion Analysis: Clinical Treatment and Technology*, G.F. Harris, P.A. Smith, and R.M. Marks, Editors. 2008, CRC Press. p. 425-444.
9. Harris, G.F., Analysis of Ankle and Subtalar Motion During Human Locomotion, in *Inman's Joints of the Ankle*, J.B. Stiehl, Editor. 1991, Williams & Wilkins. p. 75-84.
10. Hunt, A.E., et al., Inter-segment foot motion and ground reaction forces over the stance phase of walking. *Clin Biomech* 2001;16(7):592-600.
11. Hwang, S.J., H.S. Choi, and Y.H. Kim, Motion analysis based on a multi-segment foot model in normal walking. *Conf Proc IEEE Eng Med Biol Soc* 2004;7:5104-6.

12. Jenkyn, T.R. and A.C. Nicol, A multi-segment kinematic model of the foot with a novel definition of forefoot motion for use in clinical gait analysis during walking. *J Biomech* 2007;40(14):3271-8.
13. Kidder, S.M., et al., A system for the analysis of foot and ankle kinematics during gait. *IEEE Trans Rehabil Eng* 1996;4(1):25-32.
14. Leardini, A., et al., Rear-foot, mid-foot and fore-foot motion during the stance phase of gait. *Gait Posture* 2007;25(3):453-62.
15. Leardini, A., et al., An anatomically based protocol for the description of foot segment kinematics during gait. *Clin Biomech* 1999;14(8):528-36.
16. MacWilliams, B.A., M. Cowley, and D.E. Nicholson, Foot kinematics and kinetics during adolescent gait. *Gait Posture* 2003;17(3):214-24.
17. Shultz, R., A.E. Kedgley, and T.R. Jenkyn, Quantifying skin motion artifact error of the hindfoot and forefoot marker clusters with the optical tracking of a multi-segment foot model using single-plane fluoroscopy. *Gait Posture* 2011;34(1):44-8.
18. Okita, N., et al., An objective evaluation of a segmented foot model. *Gait and Posture* 2009;30(1):27-34.
19. Shultz, R., A.E. Kedgley, and T.R. Jenkyn, Quantifying skin motion artifact error of the hindfoot and forefoot marker clusters with the optical tracking of a multi-segment foot model using single-plane fluoroscopy. *Gait and Posture* 2011;34(1):44-48.
20. Tranberg, R. and D. Karlsson, The relative skin movement of the foot: a 2-D roentgen photogrammetry study. *Clin Biomechs* 1998;13(1):71-76.
21. Wrbaskic, N. and J.J. Dowling, An investigation into the deformable characteristics of the human foot using fluoroscopic imaging. *Clin Biomech* 2007;22(2):230-238.
22. Leardini, A., et al., Human movement analysis using stereophotogrammetry: Part 3. Soft tissue artifact assessment and compensation. *Gait and Posture* 2005;21(2):212-225.
23. della Croce, U., A. Cappozzo, and D.C. Kerrigan, Pelvis and lower limb anatomical landmark calibration precision and its propagation to bone geometry and joint angles. *Med Biol Eng Comput* 1999;37(2):155-61.
24. Rabuffetti, M., et al., Self-marking of anatomical landmarks for on-orbit experimental motion analysis compared to expert direct-marking. *Human Movement Science* 2002;21(4):439-455.
25. Della Croce, U., et al., Human movement analysis using stereophotogrammetry: Part 4: assessment of anatomical landmark misplacement and its effects on joint kinematics. *Gait and Posture* 2005;21(2):226-237.
26. Della Croce, U., et al., Human movement analysis using stereophotogrammetry: Part 4: assessment of anatomical landmark misplacement and its effects on joint kinematics. *Gait and Posture* 2005;21(2):226-237.
27. Nester, C., et al., Error in the description of foot kinematics due to violation of rigid body assumptions. *Journal of Biomechanics* 2010;43(4):666-672.
28. Karau, K.L., et al., Microfocal X-ray CT imaging and pulmonary arterial distensibility in excised rat lungs. *Am J Physiol Heart Circ Physiol* 2001;281(3):H1447-57.
29. Grood, E.S. and W.J. Suntay, A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. *Journal of Biomechanical Engineering* 1983;105(2):136.
30. Vaughan, C.L., B.L. Davis, and J.C. O'Connor, Dynamics of human gait. Vol. 2. 1992: Human Kinetics.

31. Arndt, A., et al., Ankle and subtalar kinematics measured with intracortical pins during the stance phase of walking. *Foot Ankle Int* 2004;25(5):357-64.
32. Arndt, A., Personal Communication 2012.
33. Oberg, T., A. Karsznia, and K. Oberg, Joint angle parameters in gait: reference data for normal subjects, 10-79 years of age. *J Rehabil Res Dev* 1994;31(3):199-213.

18 WHEELED MOBILITY DEVICES

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BACKGROUND

Over 3.3 million persons with disabilities in the United States of America use some form of wheeled mobility devices to perform activities of daily living, live independently, and actively participate in their community.[1] Mobility remains an important aspect of everyday function and contributes substantially to the independence and self-care of an individual. An individual may need to travel within the home environment, in the community, and/or for employment. Traditionally, the primary purpose of wheeled mobility devices has been to assist with mobility, however, the current state of wheelchair science has gone beyond addressing mobility issues to explore how wheelchairs can assist with medical necessities such as muscle tone and spasticity, and with other activities of daily living to improve the quality of life of an individual with a disability. Wheeled mobility devices can be classified into four major types: manual wheelchairs, pushrim activated power assisted wheelchair, electric power wheelchairs, and power operated vehicles (or scooters).[2]

Individuals with Osteogenesis Imperfecta (OI) may use a number of assistive technologies for mobility purposes, such as a cane, a walker, and/or a wheelchair.[3] In this chapter, we focus on aspects of wheeled mobility devices that help individuals with OI to meet their mobility and functional needs. The approach we follow in discussing the principles of wheeled mobility devices

is influenced by that of the International Classification of Functioning, Disability and Health (ICF), which takes into account the body, the individual, and society.

International Classification of Functioning, Disability and Health

ICF is a classification created by the World Health Organization (WHO) to provide a unified and standard language and framework for the description of health and health-related domains.[4] Health and health-related domains are classified from the body, individual, and societal perspectives using two basic criteria: 1) body functions and structure, and 2) domains of activity and participation. The classification of the domains describes changes in the body function and structure in an individual with a disease or disorder in both a standard environment as well as in their usual environments. "Functioning" in ICF refers to all body functions of an individual, as well as the individual's activities and participation in the community. "Disability" in ICF is an umbrella term for impairments, activity limitations and participation restrictions. ICF also lists environmental factors that affect an individual's functioning and disability.

ICF complements WHO's International Classification of Diseases 10th revision (ICD-10), which contains information on diagnosis of diseases, disorders and other health conditions. WHO states that combining ICF and ICD-10, information on diagnosis and functioning can provide a more meaningful picture regarding the health of an individual, thus informing health care providers' decision-making process. The WHO's ICF and ICD-10 influence the research, evidence-based practice of wheelchair provision, existing technology, funding policies, testing standards, and future developments in the field of wheeled mobility devices.

OI AND WHEELED MOBILITY

Individuals with OI use wheeled mobility devices for independence, self-care and mobility purposes. In the following sections we discuss the service delivery of wheeled mobility devices, biomechanical aspects related to wheeled mobility, various types of wheeled mobility devices, seating systems, and funding for wheeled mobility devices in order to provide an overview of the related technologies.

Service Delivery of Wheeled Mobility Devices

Assistive technology (AT) provision and delivery for clients with disabilities requires a multi-disciplinary team approach that works both with the clients and their families to identify needs and to recommend appropriate wheeled mobility devices.[5] When working with individuals with OI, it is most important to focus on their particular abilities, strengths, and weaknesses rather than on their OI type.

Role of the Multi-disciplinary Team

The Center for Assistive Technology at the University of Pittsburgh Medical Center has developed a model for service delivery of AT. The model used by the multi-disciplinary team includes an assessment of the following aspects: medical history, physical and motor assessment, performance of activities of daily living (ADL) or instrumental activities of daily living (IADL), current use of AT, living situation or life roles, personal goals, environment (home, work or school and community), transportation, and funding.[5] Accordingly, the multi-disciplinary team should consist of the following professionals:[6]

- Physiatrists, i.e. Doctors of Medicine or Doctors of Osteopathic Medicines who have a background in physical medicine and rehabilitation. Physiatrists first assess and address the medical needs of a person with OI before guiding them through the decision making process of the technology selection. As part of the assessment, the physiatrists should consult the orthopedic surgeons treating individuals with OI to obtain information regarding the type of OI, fracture history, and surgeries prior to the provision of technology.
- Occupational and physical therapists analyze the clients' needs and help them with selecting the appropriate technology. In addition, the therapists can provide training on how to use the wheeled mobility device.
- Rehabilitation engineers and engineering technologists act to develop, modify and customize the wheeled mobility devices to suit the clients' needs. Assistive technology professionals help with purchasing and servicing the AT.
- Vocational rehabilitation counselors assist in the social, vocational and school integration of clients with OI.

Therapists and rehabilitation engineers can obtain certification from programs offered by the Rehabilitation Engineering and Assistive Technology Society of North America (RESNA) including Assistive Technology Professional, Seating and Mobility Specialist, and Rehabilitation Engineering Technologist.[7] These certification programs allow the service

providers to analyze the needs of their clients, assist in the selection of the appropriate assistive technology, and provide training to use the selected technology.

Biomechanics During Wheeled Mobility Use

This section discusses the major aspects of biomechanics related to wheeled mobility use: wheelchair propulsion, transfers, and whole body vibration.

Wheelchair Propulsion

Manual wheelchair propulsion involves repetitive use of upper extremities among wheelchair users, which increases their risk of upper extremity pain and injury.[8] Research by Boninger *et al.* has found that propelling a manual wheelchair with lower stroke frequencies may prevent wheelchair users from developing median nerve injuries,[9,10] and that spending more time on the pushrim during the push phase allows the forces to be distributed over a longer distance, thus potentially minimizing high impact forces on the upper limbs.[9] The authors recommend using a semicircular motion of propulsion, which is associated with reduced repetitive use of upper extremities and more efficient propulsion.[10]

Transfers

Individuals using wheeled mobility devices transfer multiple times to and from their assistive device during their activities of daily living and travel. These transfers can be performed by caregivers or the individuals themselves based on their upper arm strength. Research has shown that the surface to which the individuals transfer should be at equal height or slightly lower height than the surface from which individuals transfer.[8] Transferring to a higher surface leads to an increase in friction, forces, and effort required on the upper limbs of wheelchair users.[11] The *Preservation of Upper Limb Function Following Spinal Cord Injury*, a clinical practice guideline for health-care professionals, has provided the following recommendations for wheelchair users: a) perform level transfers when possible, b) avoid placing either hand on a flat surface when a handgrip is possible during transfers, c) avoid positions of impingement when possible, and d) vary the transfer technique used and the arm that leads.[8] In individuals with OI appropriate transfer methods, including transfer boards, hoyer lifts, or caregivers, should be used to transfer the individuals to and from the wheeled mobility devices based on the severity of OI.

Whole Body Vibration Exposure

Wheeled mobility device users are subjected to whole body vibrations on a daily basis as they travel in community environments traversing obstacles such as curb drops and potholes or cracks in the sidewalks. Sustained exposure to whole body vibrations in individuals with certain types of OI may lead to secondary injuries and bone fractures. As a preventive measure, these individuals can use appropriate seating technology, including cushions and wheeled mobility devices specific to their medical needs.

Research by Wolf *et al.* analyzed whether wheelchair cushions altered potentially harmful whole-body vibrations transferred from wheeled mobility device to manual wheelchair users.[12] The results of the study in 32 manual wheelchair users showed that the Invacare Pindot (contoured foam) and the Varilite Solo (air bladder with a foam base) cushions were the most effective in reducing whole-body vibrations. In another study, Kwarciak *et al.* evaluated the ability of suspension manual wheelchairs to reduce the seat accelerations which contributed towards whole body vibrations during curb descents of various heights (5 cm, 10 cm and 15 cm).[13] Their research showed that suspension manual wheelchairs, such as the Quickie XTR, transmitted significantly lower peak seat accelerations than folding wheelchairs during 5 cm curb descents, and significantly lowered frequency-weighted peak seat accelerations during 5 cm and 10 cm curb descents. However, the researchers caution that even though the suspension manual wheelchairs reduced whole body vibration during curb descents, their limitations should be taken into account when prescribing a wheelchair for everyday use.

Wheeled Mobility Devices

The major types of wheeled mobility devices available – including manual wheelchairs, electric power wheelchairs, and power-operated vehicles (scooters) – are presented in the following section. In addition, we also discuss pushrim activated power assisted wheelchairs, which are manual wheelchairs with certain additional features.

Manual Wheelchairs

Manual wheelchairs can be classified into several categories based on their cost, function, adjustability, and weight. The most common types of manual wheelchairs include standard, heavy duty, bariatric, high-strength lightweight, and ultra-lightweight (ultralight). The use of a standard or

lightweight manual wheelchair is contraindicated in individuals with OI as they are at high risk of acquiring fractures. Oftentimes an ultra lightweight manual wheelchair is the most effective for active and full-time users due to its adjustability and ease of transportability (Figure 1). The features of an ultralight manual wheelchair are: very light weight (between 12-30 lbs); a fully adjustable frame; and a quick release axle. The adjustable frame of the ultralight wheelchair is either non-foldable (box and cantilever) or foldable (side-folding and front-folding).[14] The rear wheels of an ultralight wheelchair can be easily removed during transportation by using a quick release. Table 1 shows a case study in which a custom ultralight manual wheelchair was recommended to a young individual with OI.

Figure 1. An ultralight manual wheelchair.

Table 1. A case study of a young individual with OI who was recommended a custom ultralight manual wheelchair by the multi-disciplinary team at the Center for Assistive Technology at the University of Pittsburgh.

Diagnosis: Osteogenesis Imperfecta [756.51]
Type of current mobility assistive equipment: Ti-lite Custom Problems with current mobility assistive equipment: worn and in disrepair Age: 23, Height: 3'9", Weight: 60 lbs. Transportation: Oldsmobil-Alero equipped with hand controls Education/Employment: Accounting Executive Living Situation: Lives with parents in a multi story home, 14 steps to ascend/descend, independent by scooting down, needs assistance to carry the w/c up/down
Recommendation: Our multi-disciplinary team assessment of the client's seating and mobility needs determined that a custom 13" wide and 10" deep Quickie Ti with custom footrest and Corbee cushion was the most reasonable and cost effective alternative in meeting this client's needs. The multi-disciplinary team chose this equipment because the client preferred the operation and maneuverability of the device as compared to other devices tried. This equipment is needed for the following reasons: • The client is unable to ambulate even with the use of assistive devices due to skeletal hip deformities associated with the client's diagnosis of Osteogenesis Imperfecta • The client is a very active wheelchair user who enjoys college and sports activities. • The client utilizes a manual wheelchair for all mobility activities within his home and in the community. Research has found that manual wheelchair propulsion causes excessive strain onto the shoulder, elbow and wrist joints; however, peer reviewed research has also found that reducing the weight of the wheelchair in combination with appropriate wheel alignment can significantly reduce the risk of these injuries. An ultra light weight wheelchair not only weighs less than a standard wheelchair, but it also provides adjustable features to fit the wheelchair biomechanical most favorable to the user and therefore can prevent and significantly reduce the risk of repetitive strain injuries. • The Ultralight manual wheelchair is light and durable enough to accommodate this client's lifestyle. • A custom frame is required to accommodate the client's small body-frame and to ensure that positioning and wheel alignment is biomechanical appropriate for safe, functional and effective self-propulsion of this chair.

Manual wheelchair users propel their wheelchairs by pushing on the rims of the rear wheels (pushrims). The rims come in two common designs: the less expensive traditional simple metal hoop (rim) and the ergonomically designed hand rims such as the Natural-Fit[15] and FlexRim[16] which are circular rims with coatings of vinyl and foam rubber, respectively, to increase friction and thereby improve wheelchair propulsion. Manual wheelchair

setup and customization is discussed in a later section entitled Wheelchair Customization and Fitting.

Pushrim Activated Power Assisted Wheelchair

The use of a manual wheelchair may be feasible when travelling short distances. However, users may have difficulty propelling over uneven terrains, inclined surfaces, or during long distance travel, especially users with weak upper extremities and limited cardiovascular capacity. The Pushrim Activated Power Assisted Wheelchair (PAPAW) is a manual wheelchair to help such users. It is propelled by hub motors in the wheel that are controlled from the pushrims. The PAPAW's novel sensing and control technology amplifies the force applied by the user to the pushrims to propel or brake the wheelchair,[17] thereby decreasing the amount of force, stroke frequency, and range of motion during propulsion.[18] The PAPAW has the advantages of putting less stress on the arm joints and offering some of the aerobic exercise benefits of manual wheelchair propulsion.[19]

Electric Power Wheelchairs

Electric power wheelchairs (EPWs) are wheeled mobility devices that consist of a power base and/or a power seating system are useful for individuals unable to use a manual wheelchair due to motor impairments or problems with fatigue when traveling long distances or across uneven terrain. Whereas the basic power base includes an electric motor, a battery, and an electronic controller for the mobility aspects related to wheeled mobility devices, the advanced power base (Figure 2) also encompasses power seating options to accommodate medical necessities (discussed in the section Power Seat Functions in Electric Power Wheelchairs). EPWs are classified into three drive categories: 1) mid-wheel, which tend to be very stable, 2) front-wheel, which are good at climbing obstacles, and 3) rear-wheel, which usually have good traction. EPWs have two drive motors that are driven by an electronic controller that interprets signals obtained from an input device such as a joystick or a switch. Table 2 shows a case study in which an elderly individual with OI was recommended an EPW, because this client was no longer able to perform safe ambulation and had already used an EPW in the past.

Table 2. A case study where an elderly individual with OI was recommended an EPW.

Diagnoses: Osteogenesis Imperfecta [756.51]; Diabetes with neurological manifestations adult onset [250.60] Osteogenesis imperfecta, diabetes mellitus, hypertension, chronic lymphedema, cellulitis, obesity, osteoporosis, congestive heart failure, heterotopic ossification following total knee replacement on the right side, asthma.
Type of current mobility assistive equipment: Currently owns a Nutron power wheelchair that is 18" x 16" and has a 19.5" front seat to floor height. It is equipped with a right joystick, swing-away footrests, sling upholstery with no cushion, desk length height adjustable armrests. Problems with current mobility assistive equipment: Chair is extremely old, in poor condition, and too small. Seat upholstery is extremely slung out. The client reports pain in her buttocks and low back, whenever seated in this wheelchair. Moreover, the client is unable to utilize a cushion as the chair is too tall for transfers with a cushion. The client reports a history of the chair tipping forward when travelling on downhill terrains. Age: 77, Height: 4'6", Weight: 242 lbs. Transportation: ACCESS transportation Education/Employment: N/A Living Situation: Resides alone in a two bedroom apartment located on the 4th floor of an elevator accessible apartment. The rooms in the apartment are average in size and the floor surfaces are partially carpeted.
Recommendation: Our multi-disciplinary team assessment of the client's seating and mobility needs determined that the Q614 power wheelchair with 20" wide and 18"deep captain style seat was the most reasonable and cost effective alternative in meeting the client's needs. This equipment was chosen over other alternatives because the client preferred the operation and maneuverability of the device as compared to other devices tried. This equipment is needed for the following reasons: • The client is unable to independently, safely, or functionally ambulate for completion of mobility related activities of daily living, even with the use of assistive devices, secondary to the inability to tolerate weight bearing through her legs, strength impairments, balance impairments, tendency to easily fracture, nonfunctional endurance, and nonfunctional speed. • The client is unable to independently self-propel a manual wheelchair of any style, secondary to strength and range of motion impairments in her arms. • The client is unable to transfer to a scooter, nor does a scooter provide sufficient postural support or ability to maneuver within her home. • The client is independent with all functional mobility with the use of client's existing power wheelchair; however, this wheelchair is no longer meeting the client's seating and mobility needs. The client also reports a history of the chair tipping forward when travelling on downhill terrains. • After a thorough assessment the client does not want any power seat functions at this time. The client may require power seat functions at a future date, and we are therefore, recommending a group 3 power wheelchair with electronics that will support this upgrade, if necessary. The client prefers a contoured seat at this time.

Figure 2. An electric power wheelchair.

One EPW model, the Permobil K450MX, may be especially suitable for persons with OI of short stature.[20] Classified as a pediatric wheelchair, this model is suitable for individuals weighing less than 125 lbs and who need a 10-16 inch adjustable seat. The K450MX wheelchair also has an additional power function that lowers the power seat from an upright position at 26 inches down to the floor to allow easy access to the floor and easier transfer to other surfaces.

Power Operated Vehicles or Scooters

Power operated vehicles or scooters are becoming common among the elderly and persons with less severe disabilities (cardiovascular and pulmonary conditions) due to their low cost, ease of driving, and societal acceptance.[21,22] However, the disadvantages of using these technologies include fixed seating, lack of any power seat functions, poor turning radius, and compromised lateral stability. The lack of stability may cause tips and

falls while driving and turning on inclined surfaces, due to their high centers of gravity compared to wheelchairs. Therefore, the use of scooters in individuals with OI should be limited. Scooters also require an individual to have the ability to transfer independently. In addition, scooters are designed for individuals of standard arm length, making them unsuitable for individuals with OI with shorter upper arm lengths compared to the general adult population.

Seating Systems

The seating and positioning of an individual are important aspects of wheeled device delivery because of their impact on function and mobility. An individual must reposition themselves several times over the day to assist in function, comfort, stability and balance, range of motion, muscular flexibility, and tone or spasticity or reflexes.[5,23] The primary aim of clinicians during wheeled mobility device provision is to accommodate medical problems, prevent secondary problems, and promote function.

Sitting in a wheeled mobility device for long durations with pressure on sacrum, pubis symphysis, and ischial tuberocity leads to posterior pelvic tilt, anterior pelvic tilt, and pelvic obliquity. These sitting postures in turn lead to a number of unintended spinal postures including kyphosis, lordosis, scoliosis, and windswept deformity. These modified sitting postures negatively impact function, comfort, and vital organ functions. Appropriate seating and positioning can prevent joint contractures and bone malformations, and can assist an individual with disability to achieve smooth joint function, a wide range of motions, and efficient use of muscles.

Seating systems are classified into three types: 1) prefabricated, 2) either modular or adjustable, and 3) custom molded/contoured. The prefabricated systems comprise basic options of linear seating systems and general contoured systems which are suitable for high functioning individuals who may be able to independently perform pressure relief. Modular seating systems may be chosen to prevent postural deformities. Custom molded/contoured seating systems may be used to address the severe fixed or the semi-fixed postural deformities discussed previously. The seating system selection for manual wheelchairs focuses on the cushion as it can provide pressure relief and the backrest, which unobtrusively supports wheelchair propulsion. The cushion choice is influenced by the following requirements: the transfer assistance it can provide, the cushion's comfortability, light weight, stability and pressure relief. There are several

types of cushions available on the market, ranging from simple foam cushions to sophisticated air bladders with a foam base (air-foam) or gel based cushions. Research showed that air foam cushions are the most effective in reducing whole-body vibrations.[12] Moreover, clinical experience demonstrated that air-foam cushions are a good choice for individuals with IO who are exposed to a higher risk of fractures.

The multi-disciplinary team interviews and observes the client's use of the seating and the mobility system. Many AT provision clinics also use pressure mapping and SmartWheel tools to objectively evaluate the seating pressure distribution and the propulsion pattern, respectively. Objective measurements performed by the pressure mapping and the SmartWheel can play a major role in writing documentation and funding reimbursements necessary for purchasing the wheeled mobility device and the seating system.

A number of assistive device options, such as manual wheelchairs, EPWs with fixed seats, and scooters, exist for individuals who have upper arm strength and can independently perform daily functions and transfers. However, individuals with severe disabilities who may not be able to perform transfers, weight shifts, and ADLs/IADLs need dynamic wheeled mobility devices, such as seat elevator function for transfer and tilt and recline functions for pressure relief.

Power Seat Functions in Electric Power Wheelchairs

Individuals with OI can maximize their strength and function as well as meet medical needs by using various power seat functions throughout the day. Power seat functions in EPWs include tilt in space, seat recline, legrest elevation, seat elevation, lateral tilt, and standing.[23,24] The advantages of various power seat functions are discussed below:

- Tilt in space: enables postural stability, relief of pressure and weight redistribution to counter the effects of gravity, provides comfort, and helps prevent sliding out of the chair.
- Recline: accommodates limited hip flexion; used in combination with tilt allows pressure relief and increase in comfort; allows adjustment to fluctuation in muscle tone; and assists with activities of daily living such as catheterization and dressing. The recline feature also alters the load on postural musculature, improves blood circulation and facilitates respiration. This feature is beneficial to an individual who cannot achieve or maintain an upright seated position due to poor trunk mobility, fatigue, pain, or postural deformities. Besides

decreasing seating pressure, Nachemson *et al.* found that the tilt and recline functions could decrease inter-vertebral disc pressure by reclining the back of the seat from 80 to 130 degrees.[25]

- Elevating legrests: accommodates casts or braces on EPWs, assists with management of lower extremity edema, assists with curb clearance, and adjusts for fluctuation in muscle tone. Moreover, the use of power elevating legrests in combination with tilt in space or recline while lowering the torso can improve venous return and decrease fluid pooling in the lower extremities.
- Seat elevation: accommodates limited use of upper extremities, ADLs, IADLs, reach, transfers, and social interaction.
- Lateral tilt: prevents leaning, increases comfort, and provides pressure relief.

Even though the power seat functions alleviate a number of medical problems, the multi-disciplinary team must take care to provide extensive documentation regarding the AT assessment and how the power seat function can meet medical necessity. Failure to do so may result in non-approval of the power seat functions by insurance providers, which can limit the client's function and independence. Table 3 shows a case study where a middle-aged individual with OI was recommended an EPW with tilt-in space function.

Table 3. A case study where a middle age individual with OI was recommended an EPW with tilt-in-space function.

Diagnoses: Osteogenesis imperfecta [756.51]; Carpal tunnel syndrome [354.0], Rotator cuff syndrome [726.10]
Type of current mobility assistive equipment: Invacare Tracer IV manual wheelchair. Problems with current mobility assistive equipment: The client cannot propel it a functional distance. She gets fatigued. The seat rubs on her right shorter leg. Height: 5'1 1/2", Weight: 245 lbs. Transportation: Client's son drives the client in his Caravan minivan. Education/Employment: The client has General Education Development degree. The client was a stay at home mom and is now on Social Security's Supplemental Security Income. Living Situation: The client lives alone in a trailer.
Recommendation: Our multi-disciplinary team assessment of the client's seating and mobility needs determined that the Pride Quantum 600 power wheelchair endowed with the power tilt-in-space function was the most reasonable and cost effective alternative in meeting the client's needs. This equipment was chosen over other alternatives because the client preferred the

operation and maneuverability of the device as compared to other devices tried. This equipment is needed for the following reasons:

- The client cannot ambulate even with the use of an assistive device due to minimal weight bearing through the right leg, decreased strength in her left leg, and bilateral carpal tunnel.
- The client does not have sufficient upper extremity function to self-propel an optimally configured manual wheelchair due to right shoulder pain, bilateral carpal tunnel, and her body weight.
- The client is not a candidate for a scooter as the client needs the mobility device for both inside and outside of her house. A scooter has limited function inside the house because it requires an increased turning radius and increased time and effort to rotate the seat in order to get close to surfaces such as sinks, counters, and tables.
- The use of a powered mobility device will significantly improve the client's ability to participate in mobility related activities of daily living and the client has expressed interest in using such a device.
- The client is not a candidate for a Group 1 power wheelchair as she will use the device continuously throughout the day as well as on surfaces that a Group 1 power wheelchair is not designed for.
- A Group 3 single power wheelchair is recommended as the client has a mobility limitation due to failed total hip and numerous fractures when she was young.
- Power tilt-in-space is necessary as the client has chronic back pain and repeated cellulitis resulting in open wounds.
- The client meets the criteria for power features per the Rehabilitation Engineering & Assistive Technology Society of North America's (RESNA) Position Papers.

Wheelchair Customization and Fitting

The multi-disciplinary team customizes and fits the wheeled mobility device for an individual with OI considering the various aspects discussed in the previous sections.

Manual Wheelchair Customization

Many physical features of an individual with OI such as shortened extremity length need to be considered to assure adequate seated support as well as effective wheelchair propulsion. Studies have shown that manual wheelchair propulsion efficiency varies between 5% and 18% depending upon the style of the wheelchair and the chair's fit to the user.[26-28] This lack of efficiency can significantly affect the wheelchair user's abilities to complete their ADLs. Customization of a manual wheelchair for clients with OI may include the following adjustments:[8]

- The axle position may be adjusted to improve manual wheelchair users' propulsion and stability. Considerations include the further back from the users' center of mass the axle is, the more stable the chair, but the more difficult it becomes to propel as access to the pushrim is reduced and wheelchair castors are weighed down. Between 25% to 80% of long term manual wheelchair users are reported to have injuries to the wrist, elbow or shoulder.[29,30] The *Preservation of Upper Limb Function Following Spinal Cord Injury* recommends that the axle position of the wheelchair should be as forward as possible without compromising the controlled stability of manual wheelchair users.[8] This will allow the user with increased access (desired at 100°) to the pushrim, shift the center of gravity in anterior or posterior direction by adjusting the weight distribution , and off load the wheelchair castors to negotiate small obstacles reducing the risk of forward falls.
- The backrest height and angle and the seat dump affect both the balance and the ability to propel the wheelchair. A backrest that is too high may reduce the range of motion of the scapula and limit the reach and access to the pushrim needed for functional propulsion; however, if the backrest is not high enough, it will not provide adequate support.
- The floor to seat height is an important consideration in regards to transfers as well as access to wheelchair user's environment. If an individual performs independent stand pivot transfers, then the wheelchair must have a lower seat to floor height to allow for continued independence. However, a lower seat to floor height may interfere with peer interaction and limits access to various surface heights in the wheelchair user's home, school, and community.
- The legrest height is adjusted to provide appropriate support and stability.
- The anti-tippers are applied for stability and safety until a new wheelchair user has completed wheelchair skills training program.
- The seating system is incorporated for alleviating medical issues.

All components must be carefully considered and modified by a RESNA trained assistive technology professional to create and fit the device which best suits the individual.

Electric Power Wheelchair Customization

Customization of a power wheelchair can allow for incorporating and adjusting the seating system to improve posture, adjusting the speed profiles of power wheelchairs to allow safe indoor and outdoor navigation, and adjusting legrest height to improve sitting posture [23]. The majority of EPW

customization and delivery includes training EPW users to drive safely and to use various power seat functions.

Wheelchair Skills Program

The Wheelchair Skills Program (WSP) is an important aspect of wheelchair delivery and use of wheeled mobility devices.[31] The WSP includes two modules: the Wheelchair Skills Test (WST)[32] or the questionnaire version of the WST (WST-Q) and the Wheelchair Skills Training Program (WSTP).[33] The wheelchair should be customized for the user prior to the WST and WSTP. The WST and WST-Q are standardized evaluation methods used by clinicians to objectively and inexpensively test and document wheelchair skills required for manual wheelchair or EPW use. Research by Kirby *et al.* has shown that the WST is safe, practical, reliable, valid, and useful.[32] The WST's key elements are: general instructions on how to use the WST, general considerations for the WST-Q and tests of individual skills for manual wheelchair and EPW use. Some of the individual skills for WST include: propelling forward and backward; maneuvering through hinged doors, sideways, side-slopes and soft surfaces; 90° turns while propelling and 180° turn in place; ascending and descending inclines, curbs (15 cm), level changes (5 cm) and stairs; performing 30 seconds of stationary wheelies; performing weight relief and transfers; folding and unfolding wheelchair; and reaching a high object and picking an object on the floor.[34] The WSTP uses the results from the WST and evidence based training methodology to improve wheelchair skills performance in wheelchair users. Research by Coolen *et al.* showed that the WSTP improved the wheelchair skills performance of wheelchair users two to threefold over standard care.[33]

SmartWheel Propulsion Training

The SmartWheel is a clinical tool used to assess: the average force it takes to propel a wheelchair; propulsion cadence; and smoothness of propulsion. Clinicians can use the SmartWheel to provide appropriate propulsion training (Figure 3) to reduce the risk of upper arm injury.[10,35] The SmartWheel is a result of many years of research and development at the Human Engineering Research Laboratories (HERL) at the University of Pittsburgh in Pittsburgh, Pennsylvania.[36,37]

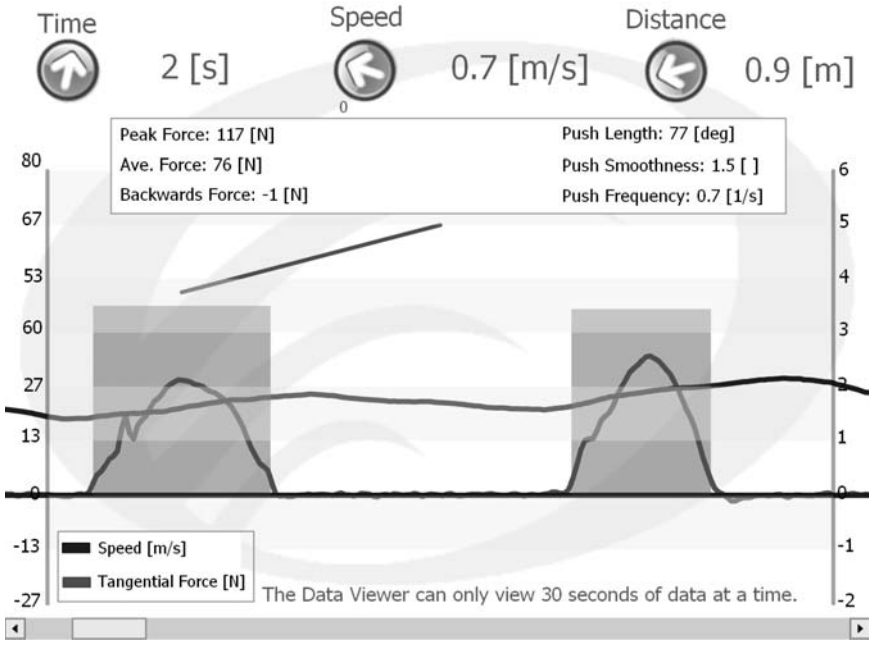

Figure 3. Clinician using the SmartWheel software to obtain wheelchair propulsion data for a new manual wheelchair user. The results can be used to provide visual feedback to wheelchair users to train and improve their propulsion techniques.

Pressure Mapping System

A pressure mapping system is a clinical tool used to assess the seating and appropriate fit of a wheelchair. Pressure mapping provides information regarding relative peak pressure points and variation in pressure distribution for different cushions. This mapping tool can be used to customize and set-up wheelchairs, measure and correct postural abnormality, and provide weight shifting interventions. The pressure mapping system can also be used to provide pressure relief training, which is crucial in preventing wheeled mobility device users from developing pressure ulcers. The pressure relief training may include appropriate and effective weight shift activities, and use of power seat functions in electric power wheelchairs.[8]

Funding for Wheeled Mobility Devices

Funding for AT and its associated services allows individuals with OI to obtain the AT appropriate for them. The cost of AT devices may vary from less than $100 for a simple pick-up-gripper to more than $20,000 for an EPW.

Some of the avenues for funding of wheeled mobility devices include: Medicaid; Children's Health Insurance Program (CHIP); School districts; and organizations such as Shriners Hospitals for Children. Medicaid provides health coverage for children from low-income families in the United States.[38] CHIP provides health coverage for children from families with incomes too high to qualify for Medicaid, but who are still unable to afford private coverage.[39] The funding of AT and associated services may vary depending on the individual's state of residence in the USA.

Taking these funding options into consideration, the multi-disciplinary team works with the clients to obtain the best wheeled mobility device. Position papers published by RESNA can aid the multi-disciplinary team in obtaining funding to enable the user to purchase the device appropriate for them.[40] These position papers (available on RESNA's website at www.resna.org) formulate the medical and functional necessity for specific wheeled mobility devices and assistive technology services and can guide the multi-disciplinary team in their decision making process.[40]

TESTING STANDARDS FOR WHEELED MOBILITY DEVICES

Wheeled mobility devices must meet the International Standards Organization (ISO) or the American National Standards Institute (ANSI/RESNA) requirements to ensure their safety and quality. A number of stakeholders benefit from these standards, including wheelchair users and their families, caregivers, clinicians prescribing AT, AT suppliers, Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (which classifies wheelchair devices as medical devices), and wheeled mobility manufactures, designers, and researchers.[41]

To comply with the ANSI/RESNA standards in the USA, all wheeled mobility devices have to meet the requirements and test methods for: static stability; wheelchair and seat dimensions; static, impact, and fatigue strength testing; flammability; test dummy specifications; and set-up procedures and vocabulary used for testing.[41] In addition, electric power wheelchairs and scooters have to meet the requirements and test methods for; dynamic stability; brake effectiveness; energy consumption; maximum speed, acceleration and deceleration; obstacle climbing ability; climatic testing; power and control system; and electromagnetic compatibility.[41]

Wheelchair Testing at the Human Engineering Research Laboratories

Research at HERL has shown that testing wheeled mobility devices by independent research centers is essential in evaluating the durability, reliability, and safety of these devices. Perlman *et al*. performed a study to determine the reliability and durability of low-cost power wheelchairs. In this study, only 3 out of 12 economical power wheelchairs passed the ANSI/RESNA durability tests for static, impact and fatigue strength testing.[42] Research also showed that the design features of some of these wheelchairs made them dynamically unstable and prone to wiring failures. In another study, Liu *et al*. evaluated the durability of aluminum ultralight folding wheelchairs compared to titanium ultralight rigid wheelchairs.[43] Their research found that there were no significant differences between the two wheelchair models for various ANSI/RESNA tests including static stability, braking effectiveness, brake fatigue, impact and static strength, and chair fatigue. These results showed that the frame material did not affect the failure modes, frames or components. However, researchers suggested that tire pressure, tube-wall thickness, and tube manufacturing did affect wheelchair durability.[43] Researchers have also evaluated the durability and performed a cost analysis of three common suspension manual wheelchairs from three different manufacturers, and compared the results with previously tested lightweight and ultra-lightweight folding-frame wheelchairs.[44] The results showed that the suspension manual wheelchairs did not provide any advantage in terms of durability or value over standard lightweight and ultra-lightweight folding-frame wheelchairs.

CURRENT DEVELOPMENTS IN TECHNOLOGIES

PerMMA

The Personal Mobility and Manipulation Appliance (PerMMA) is a robotic mobility and manipulation device for power wheelchair users (Figure 4) with severe disabilities and limited motor function.[45,46] PerMMA uses two coordinated arms to manipulate the objects in a person's environment. The robotic arms supplement the power wheelchair's functions to allow a wheelchair user to independently perform activities of daily living. In addition, the device's innovative interface is designed to be operated by the wheelchair user, remotely by an assistant via the internet, or by the user and the remote assistant together to perform a complex function or an activity. Currently, power wheelchair users are in the process of evaluating the

PerMMA and providing feedback.[46] Further, researchers at HERL are working on the next generation of PerMMA (PerMMA 2.0), which can climb curbs and intelligently drive through different terrains.

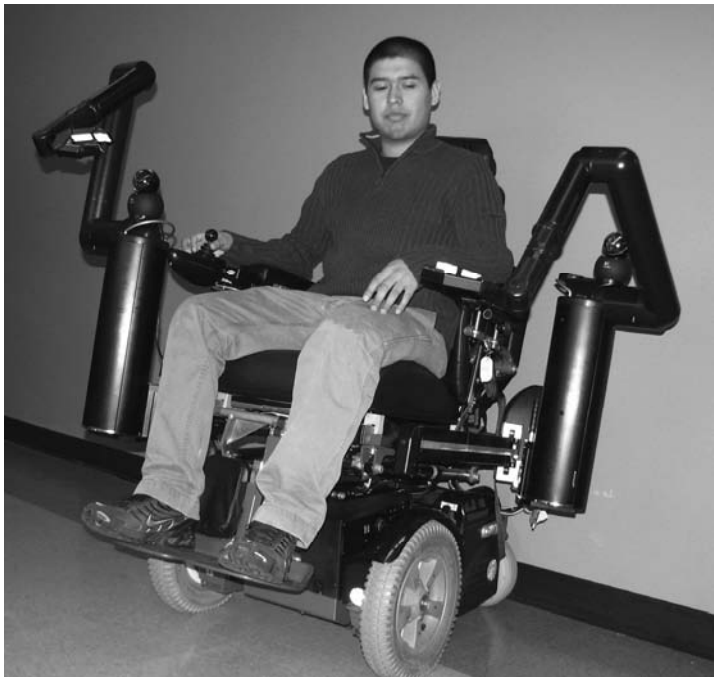

Figure 4. Investigator using the PerMMA. PerMMA is a robotic mobility and manipulation device consisting of two coordinated arms to manipulate the objects in a power wheelchair user's environment allowing individuals with severe disabilities to independently perform activities of daily living.

Virtual Coach

In our previous section on power seat functions in electric wheelchairs, we discussed how elevation, tilt, and recline can help increase function, reduce the risk of pressure ulcers, manage muscle tone, and reduce edema. However, many power wheelchair users may not use these functions effectively: they may not tilt far enough, or they may use an unsafe sequence of power seat functions. To prevent such problems, HERL researchers have developed a Virtual Seating Coach (Figure 5). The virtual coach system can be incorporated into a power wheelchair to assist in appropriate use of power seat functions. This instrumented power wheelchair has multiple sensors to detect the wheelchair user's current status and provide real time feedback to the user through a portable screen.[47,48]

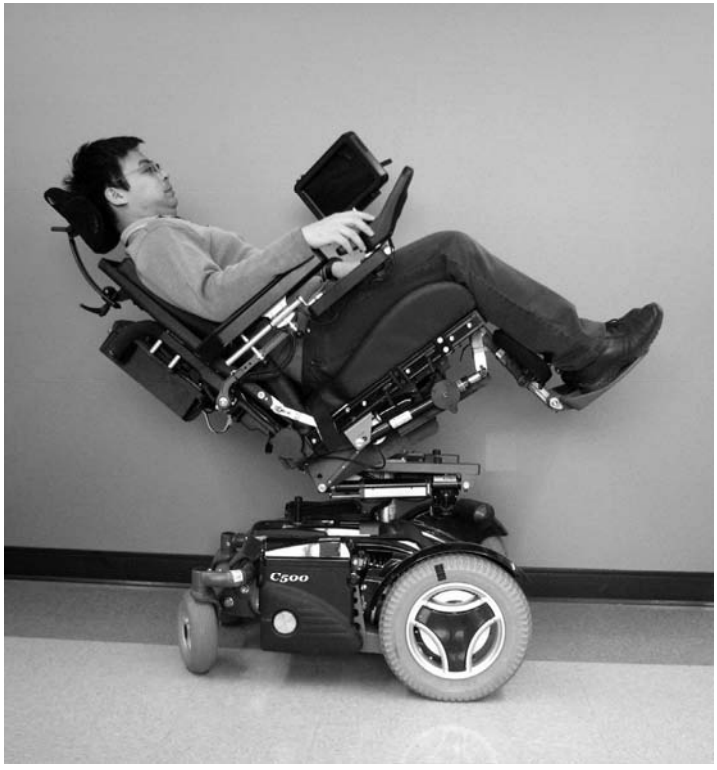

Figure 5. Investigator using the wheelchair instrumented with Virtual Seating Coach. The Virtual Seating Coach is an instrumented power wheelchair that has multiple sensors to detect and provide real time feedback to wheelchair users to appropriately use power seat functions.

Physical Activity Monitoring System

A physical activity monitoring system is a technology that researchers use to detect and estimate physical activity in manual wheelchair users. Regular physical activity in wheelchair users is associated with health benefits such as increased aerobic capacity, muscular strength and endurance, and flexibility, and decreased risk for chronic diseases and secondary complications.[49,50] However, there is a lack of valid tools for measuring physical activity objectively in this population to motivate them to perform optimal regular physical activity. Researchers have used wheel rotation dataloggers and activity monitors to detect and estimate wheelchair based physical activities in manual wheelchair users.[51-53] Researchers at the HERL are further developing a new type of physical activity monitoring system (PAMS), consisting of a wheel rotation datalogger (PAMS-DL) and a wearable

accelerometer (wocket), which provides real-time feedback regarding manual wheelchair users' physical activity levels via smart phone (Figure 6). The application running on the smart phone combines the information from the PAMS-DL and wocket to detect cadence (propulsion strokes per minute), travelled distance, and duration of wheelchair use. This objective information about wheelchair use can assist clinicians in recommending interventions to prevent injuries and increase the evidence-based practice of wheelchair service delivery.

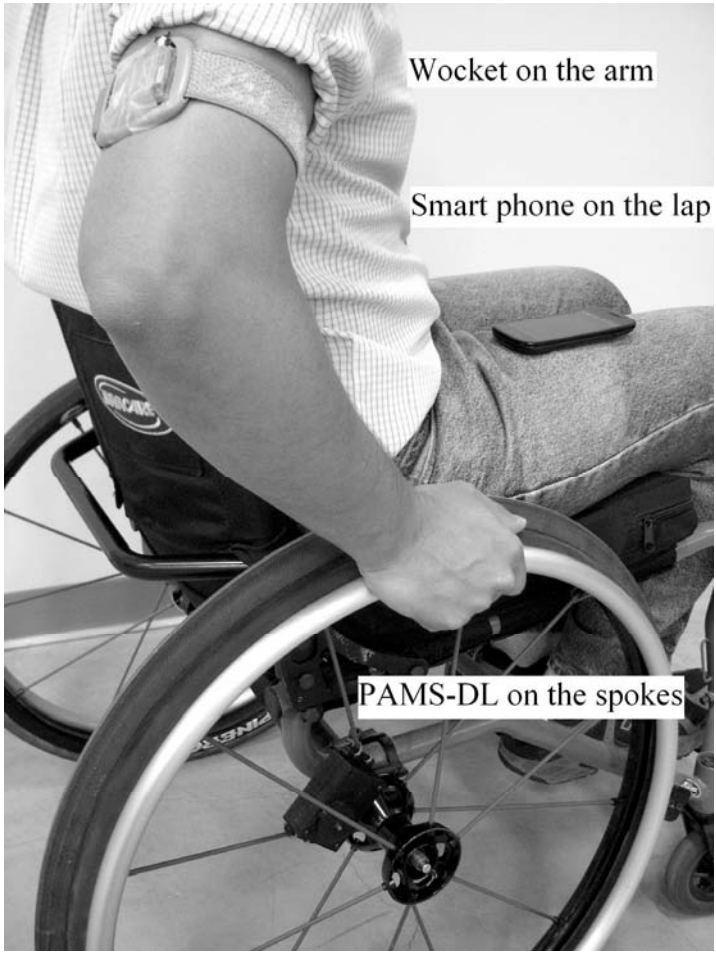

Figure 6. Investigator using the Physical Activity Monitoring System (PAMS). PAMS consists of a wheel rotation datalogger and a wearable accelerometer to detect wheelchair user's physical activity levels and provide real-time feedback via smart phone.

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ABBREVIATIONS

ADL	Activities of daily living
ANSI	American National Standards Institute
AT	Assistive technology
CHIP	Children's Health Insurance Program
CMS	Centers for Medicare and Medicaid Services
EPWs	Electric power wheelchairs
HERL	Human Engineering Research Laboratories
IADL	Instrumental activities of daily living
ICD-10	International Classification of Diseases 10th revision
ICF	International Classification of Functioning, Disability and Health
ISO	International Standards Organization
OI	Osteogenesis imperfecta
PAMS	Physical activity monitoring system
PAMS-DL	Physical activity monitoring system's wheel rotation datalogger
PAPAW	Pushrim activated power-assisted wheelchair
PerMMA	Personal mobility and manipulation appliance
Pushrims	Rims of the rear wheels
RESNA	Rehabilitation Engineering and Assistive Technology Society of North America
Ultralight	Ultra-lightweight
WHO	World Health Organization
WSP	Wheelchair Skills Program
WST	Wheelchair Skills Test
WST-Q	Questionnaire version of the Wheelchair Skills Test
WSTP	Wheelchair Skills Training Program

REFERENCES

1. Greer N, Brasure M, Wilt TJ. Wheeled Mobility (Wheelchair) Service Delivery. Technical Brief No. 9. AHRQ Publication No. 11(12)-EHC065-EF. Rockville, MD: Agency for Healthcare Research and Quality. 2012.
2. Koontz A, Pearlman J, Impink B, Cooper RA, Wilkinson M. Wheelchairs, in An Introduction to Rehabilitation Engineering, RA Cooper, H Ohnabe, and DA Hobson, Editors. 2007, Taylor & Francis Group: New York. 129-156.
3. King MM. Personal care for lifelong independence, in Growing Up with OI: A Guide for Caregivers and Families, EP Dollar, Editor. 2001, Osteogenesis Imperfecta Foundation: Gaithersburg, MD. 87-130.
4. World Health Organization. International Classification of Functioning, Disability and Health: ICF. Geneva, Switzerland: World Health Organization; 2001.
5. Arledge S, Armstrong W, Babinec M, et al. RESNA Wheelchair Service Provision Guide. 2011, Rehabilitation Engineering & Assistive Technology Society of North America: Arlington, VA.
6. A Team Approach at the Center for Assistive Technology (CAT). [cited 2012 February 29]; Available from: http://www.upmc.com/Services/rehab/rehab-institute/services/cat/Pages/team.aspx.
7. Rehabilitation Engineering & Assistive Technology Society of North America. RESNA Certification Programs: Arlington, VA.
8. Paralyzed Veterans of America Consortium for Spinal Cord Medicine. Preservation of Upper Limb Function Following Spinal Cord Injury: A Clinical Practice Guideline for Health-Care Professionals. J Spinal Cord Med, 2005; 28(5): 434–470.
9. Boninger ML, Koontz AM, Sisto SA, et al. Pushrim biomechanics and injury prevention in spinal cord injury: Recommendations based on CULP-SCI investigations. J Rehabil Res Dev, 2005; 42(3 S1): 9-20.
10. Boninger ML, Souza AL, Cooper RA, Fitzgerald SG, Koontz AM, Fay BT. Propulsion patterns and pushrim biomechanics in manual wheelchair propulsion. Arch Phys Med Rehabil, 2002; 83: 718-723.
11. Wang YT, Kim CK, H T Ford III, H.T. Ford Jr. Reaction force and EMG analyses of wheelchair transfers. Perceptual & Motor Skills, 1994; 79: 763-766.
12. Wolf EJ, Cooper RA, DiGiovine CP, Boninger ML, Guo S. Using the Absorbed Power Method to Evaluate Effectiveness of Vibration Absorption of Selected Seat Cushions During Manual Wheelchair Propulsion. Med Eng Phys, 2004; 26: 799-806.
13. Kwarciak AM, Cooper RA, Fitzgerald SG. Curb descent testing of suspension manual wheelchairs. J Rehabil Res Dev, 2008; 45(1): 73-84.
14. Olson JJ. Redesign, clinical testing and evaluation of the endeavor folding wheelchair. Master's Thesis, University of Pittsburgh, 2008.
15. Three Rivers Holdings LLC. The Natural-Fit. [cited 2012 April 6]; Available from: http://www.out-front.com/naturalfit_overview.php.
16. Max Mobility. FlexRim. [cited 2012 April 6]; Available from: http://max-mobility.com/products/flexrim.
17. Cooper RA, Fitzgerald SG, Boninger ML, et al. Evaluation of a pushrim activated power assisted wheelchair. Arch Phys Med Rehabil, 2001; 82(5): 702-708.
18. Corfman TA, Cooper RA, Boninger ML, Koontz AM, GFitzgerald S. Range of Motion and Stroke Frequency Differences between Manual Wheelchair Propulsion and Pushrim Activated Power Assisted Wheelchair Propulsion. J Spinal Cord Med, 2003; 26(2): 135-140.

19. Arva J, Fitzgerald SG, Boninger RACML. Mechanical efficiency and user power reduction with a pushrim activated power assisted wheelchair. Med Eng Phys, 2001; 23(10): 699-705.
20. Permobil. Permobil K450MX pediatric power wheelchair. [cited 2012 March 20]; Available from: http://www.permobil.com/USA/Products/Pediatric/K450-MX/.
21. Karmarkar AM, Dicianno BE, Cooper R, et al. Demographic profile of older adults using wheeled mobility devices. Journal of Aging Research, 2011; Epub.
22. Hubbard SL, Fitzgerald SG, Reker DM, Boninger ML, Cooper RA, Kazis LE. Demographic characteristics of veterans who received wheelchairs and scooters from Veterans Health Administration. J Rehabil Res Dev, 2006; 43(7): 831-844.
23. Dicianno BE, Arva J, Lieberman JM, et al. RESNA Position on the Application of Tilt, Recline, and Elevating Legrests for Wheelchairs. Assist Technol, 2009; 21(1): 13-22.
24. Arva J, Schmeler MR, Lange ML, Lipka DD, Rosen LE. RESNA Position on the Application of Seat-Elevating Devices for Wheelchari Users. Assist Technol, 2009; 21(2): 69-72.
25. Nachemson A. Towards a better understanding of low back pain: A review of the mechanics of the lumbar disc. Rheumatology Rehabilitation, 1975; 14: 129-143.
26. Bayley JC, Cochran TP, Sledge CB. The weight-bearing shoulder: the impingement syndrome in paraplegics. Journal of Bone & Joint Surgery - American, 1987; 69(5): 676-678.
27. Curtis KA, Roach KE, Applegate EB, et al. Development of the Wheelchair User's Shoulder Pain Index (WUSPI). Paraplegia, 1995; 33(5): 290-293.
28. Nichols PJ, Norman PA, Ennis JR. Wheelchair user's shoulder? Shoulder pain in patients with spinal cord lesions. Scand J Rehabil Med, 1979; 11: 29-32.
29. Boninger ML, Towers JD, Cooper RA, Dicianno BE, Munin MC. Shoulder Imaging Abnormalities in Individuals with Paraplegia. J Rehabil Res Dev, 2001; 38(4): 401-408.
30. Boninger ML, Cooper RA, Baldwin MA, Shimada SD, Koontz A. Wheelchair pushrim kinetics: weight and median nerve function. Arch Phys Med Rehabil, 1999; 80(8): 910-915.
31. Dalhousie University. Wheelchair skills program. [cited 2012 March 20]; Available from: http://www.wheelchairskillsprogram.ca/eng/4.1/WSP_General_Introduction.pdf.
32. Kirby RL, Dupuis DJ, MacPhee AH, et al. The Wheelchair Skills Test (version 2.4): measurement properties. Arch Phys Med Rehabil, 2004; 85: 794-804.
33. Coolen AL, Kirby RL, Landry J, et al. Wheelchair skills training program for clinicians: a randomized controlled trial with occupational therapy students. Arch Phys Med Rehabil, 2004; 85: 1160-1167.
34. Kirby RL, Smith C, Parker K, et al. Wheelchair Skills Test (WST)© Version 4.1 Manual. 2012 [cited 2012 April 6]; Available from: www.wheelchairskillsprogram.ca/eng/testers.php.
35. Cowan RE, Boninger ML, Sawatzky BJ, Mazoyer BD, Cooper RA. Preliminary Outcomes of the SmartWheel Users Group Database: A Proposed Framework for Clinicians to Objectively Evaluate Manual Wheelchair Propulsion. Arch Phys Med Rehabil, 2008; 89: 260-268.
36. Asato KT, Cooper RA, Robertson RN, Ster JF. SmartWheels: development and testing of a system for measuring manual wheelchair propulsion dynamics. IEEE Transactions on Bio-medical Engineering, 1993; 40: 1320-1324.

37. Cooper RA, Boninger ML, VanSickle DP, Robertson RN, Shimada SD. Uncertainty Analysis for Wheelchair Propulsion Dynamics. IEEE Trans Rehabil Eng, 1997; 5: 130-139.
38. Centers for Medicare & Medicaid Services. Medicaid and CHIP program information. [cited 2012 March 10]; Available from: http:// www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Population/ Children/Children.html.
39. Centers for Medicare & Medicaid Services. Children's Health Insurance Program (CHIP). [cited 2012 March 10]; Available from: http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/ Childrens-Health-Insurance-Program-CHIP/Childrens-Health-Insurance-Program-CHIP.html.
40. Rehabilitation Engineering & Assistive Technology Society of North America. Position Papers and Guides. [cited 2012 March 1]; Available from: http://www.resna.org/resources/position_papers.dot.
41. Rehabilitation Engineering & Assistive Technology Society of North America. Wheelchair Standards. [cited 2012 March 1]; Available from: http://resna.org/atStandards/standards.dot.
42. Pearlman JP, Cooper RA, Karnawat J, Cooper R, Boninger ML. Economical (K0010) power wheelchairs have poor reliability and important safety problems: An ANSI/RESNA wheelchair standards comparison study. Proceedings 28th Annual RESNA Conference, Atlanta, Georgia., 2005.
43. Liu H, Pearlman J, Cooper R, et al. Evaluation of aluminum ultralight rigid wheelchairs versus other ultralight wheelchairs using ANSI/RESNA standards. J Rehabil R D, 2010; 47(5): 441-456.
44. Kwarciak AM, Cooper RA, Ammer WA, Fitzgerald SG, Boninger ML, Cooper R. Fatigue testing of selected suspension manual wheelchairs using ANSI/RESNA standards. Arch Phys Med Rehabil, 2005; 86: 123-129.
45. Grindle GG, Wang H, Salatin BA, Vazquez JJ, Cooper RA. Design and development of the Personal Mobility and Manipulation Appliance. Assist Technol, 2011; 23(2): 81-92.
46. Human Engineering Research Laboratories. The Personal Mobility and Manipulation Appliance (PerMMA). [cited 2012 March 3]; Available from: http://www.herl.pitt.edu/permma.
47. Human Engineering Research Laboratories. The virtual seating coach. [cited 2012 March 3]; Available from: http://www.herl.pitt.edu/virtual-seating-coach.
48. Liu H-Y, Cooper R, Cooper RA, et al. Seating virtual coach: A smart reminder for power seat function usage. Technology and Disability, 2010; 22(1-2): 53-60.
49. Tawashy AE, Eng JJ, Lin KH, Tang PF, Hung C. Physical activity is related to lower levels of pain, fatigue and depression in individuals with spinal-cord injury: a correlational study. Spinal Cord, 2009; 47(7): 301-306.
50. Glaser RM, Janssen TWJ, Suryaprasad AG, Gupta SC, Mathews T. The Physiology of Exercise, in Physical Fitness: A Guide for Individuals with Spinal Cord Injury, DF Apple, Editor. 1996, Department of Veterans Affairs: Washington, DC.
51. Hiremath SV, Ding D, Farringdon J, Cooper RA. Predicting energy expenditure of manual wheelchair users with spinal cord injury using a multi-sensor based activity monitor. Arch Phys Med Rehabil, In Review.
52. Hiremath SV, Ding D. Evaluation of activity monitors in manual wheelchair users with paraplegia. J Spinal Cord Med, 2011; 34(1): 110-117.
53. Tolerico ML, Ding D, Cooper RA, et al. Assessing mobility characteristics and activity levels of manual wheelchair users. J Rehabil R D, 2007; 44(4): 561-572.

19 WALKER DESIGN FOR KINETIC ASSESSMENT OF UPPER EXTREMITY JOINT DEMANDS IN CHILDREN WITH OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Osteogenesis imperfecta (OI) is a congenital disease caused by a defect in the gene that produces type 1 collagen. One of the main effects is extremely fragile bones. OI affects 1 in 10,000 individuals in the United States.[1] There are eight types of OI, with type I being the most common and mildest form. Type II and type III are quite severe, while type IV is known as moderately severe OI. Type V and type VI are clinically similar to type IV, with histologic differences. Type VII is autosomal recessive and type VIII is very severe.

People with OI are encouraged to exercise as much as possible to promote muscle and bone strength. Walking is an excellent form of exercise for those with OI. Many children with various types of OI walk using mobility aids.[2]

Walking aids, such as walkers, crutches, or canes can allow a person to achieve weight bearing ambulation when their lower extremities (LEs) are not able to support the entire weight of their body. Walking aids allow some of the load to be distributed to the upper extremities (UEs). Since the UEs of bipeds are not accustomed to the magnitude and repetition of the loads

associated with gait, it is important to quantify the dynamic loads placed on them.

Motion analysis is an important biomechanical tool for evaluating the movement of body segments over time. Motion analysis is widely used to study LE gait, but has seen limited application to the UEs. Because of the range of UE activities studied, and lack of repeatable activity such as gait for the LEs, several types of UE kinematic models have been developed, and the results are not easily comparable. Work has been done by the International Society of Biomechanics to standardize UE models in terms of reference frames and reporting methods.[3]

This study will examine how the use of an instrumented walker, along with motion analysis, can provide information on the loads experienced by the UE joints during aided ambulation.

PREVIOUS WORK

Studies have been done to characterize forces internal to the walker structure (walker forces), where most examine walker leg loads and moments.[4–8] These methods do not allow for bilateral distinction of UE loading, and are insufficient for the determination of internal joint reaction forces and moments.

Our group developed an instrumented walker system that was able to detect contact forces and moments from the left and right hands separately. The initial design by Bachschmidt et al. included 24 resistive foil strain gages (six four-arm strain gage bridges) epoxied directly to each walker handle.[9,10] The strain gages were positioned in such a way to sense bending loads in the transverse and sagittal planes (sections AA and CC in Figure 1), as well as torsional and axial loads (section BB in Figure 1). Disadvantages of this system included potential for error in the mounting process and the inability to be applied easily to other devices.

A subsequent design was developed in conjunction with Advanced Medical Technology, Incorporated (AMTI). Custom dynamometers (model MCW-6-500, AMTI, Watertown, MA) that mounted to removable handle stems were created. They were 6-axis load cells, able to detect forces along three axes and moments about three axes, with a 500-pound capacity. The handle stems mounted to the walker with brackets allowing the height and angle to be

adjusted to the patients' needs. Positioning the load cells as close to the hands as possible minimized the cross-talk (less than 2%) from the statically indeterminate frame.[11] The non-linearity and hysteresis of the dynamometers were less than ±0.20%, and the lowest resonant frequency of a stand-alone load cell was 700 Hz.[12]

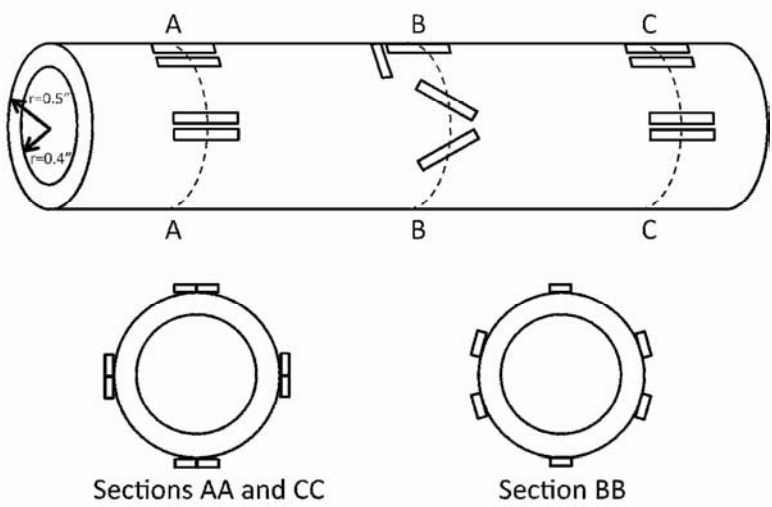

Figure 1. Diagram of strain gage configuration along walker handle.

The sensors consisted of a series of four-arm strain gage bridges. They were lightweight, with each load cell weighing about 100 grams. They were cylindrical, with a diameter of 38 millimeters and height of 60 millimeters. The load cells were tethered to two AMTI force plate amplifiers (model MSA-6) with 24-pin connector cables. Based on preliminary data analysis, the amplifier gains were set to 4000 for the vertical force channels, 2000 for the shear force channels, and 1000 for all of the moment channels.[12]

The instrumented handles were designed to be compatible with a variety of sizes and brands of walking frames, as well as anterior and posterior walker types. An anterior walker has a frame that is extended in front of the user, while a posterior walker's frame extends behind the user.

The instrumented walker handles, along with a unique biomechanical model, have been used to determine UE joint reaction forces and moments in healthy adults[10,13] and children with cerebral palsy.[11,12,14–17] This system is currently being used to test patients with cerebral palsy, OI, myelomeningocele, and spinal cord injury. This study presents internal joint

reaction force and moment data at the wrists, elbows and shoulders from one subject with OI and addresses the application of the system to the OI population.

METHODS

Kinematic Model

The UEs were modeled with seven rigid body segments: trunk, left and right upper arms, left and right forearms, and left and right hands). Sixteen passive reflective spherical markers were affixed to anatomical landmarks (Table 1, Figure 2) with double-sided tape and two were placed on the walker legs. Custom software was used for dynamic modeling.

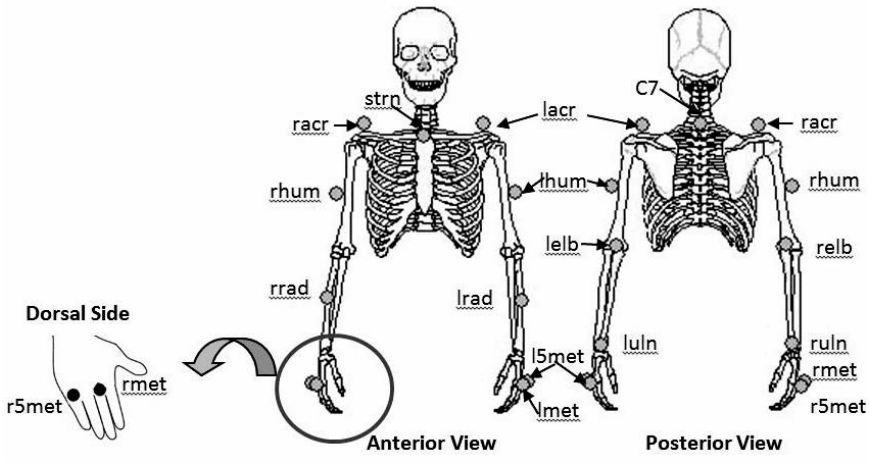

Figure 2. Marker configuration.

The body segment parameters used in this model were calculated based on Yeadon and Morlock's work in 1989.[18] Measurements of segment lengths and joint perimeters were used as inputs to equations used to calculate moments of inertia and masses of each segment. The center of gravity locations of each segment were calculated using equations from Chandler.[19] Although these equations were developed for adults, it has been shown that errors in body segment parameter estimations do not result in significant errors in the kinetic data.[20]

Table 1. Upper extremity (UE) marker locations.

Bony Landmark	Label	Marker Location
C7 vertebral process	C7	Most protruding vertebra on neck
Sternal notch	strn	Top of the sternum, between lowest part of the clavicles
Acromion process	lacr/racr	Top of shoulder
Mid-humerus	lhum/rhum	Mid-point of the lateral humerus
Olecranon	lelb/relb	Tip of the elbow
Radius	lrad/rrad	Mid-point of the radius
Ulnar styloid process	luln/ruln	Medial wrist bone
3rd metacarpal	lmet/rmet	Head of the middle finger
5th metacarpal	l5met/r5met	Head of the little finger

Segment Coordinate Systems

The current study reports the angles, forces, and moments in the reference system recommended by the International Society of Biomechanics (ISB). Positive x is anterior, positive y is superior, and positive z is directed laterally to the right. However, the model was developed under a different reference system convention in which positive x is anterior, positive y is directed laterally to the left and positive z is superior. A post-processing transformation was performed to allow the results to be reported in the ISB recommended system. The following description of the kinematic model will use the original reference system conventions.

Trunk

The trunk was modeled using the sternal notch, C7, and left and right anterior superior iliac spine (ASIS) markers from the LE marker set (Plug-In-Gait, Vicon, Oxford, UK). The z axis was defined using a vector from the pelvic center (midpoint between the ASIS markers) and the neck center (midpoint between the sternal notch and C7 markers). The y axis was defined by a vector from the left ASIS marker to the pelvic center. The x axis was the cross product of the y and z axes.

Upper Arm

The upper arm segments were modeled using the acromion process, mid-humerus, and olecranon markers. The origin was placed at the shoulder joint center (midpoint of the measured shoulder circumference). The z axis was defined using vectors connecting the shoulder joint center and the elbow joint center (midpoint of the elbow diameter). A temporary axis was constructed as a vector from the mid-humerus marker to the shoulder joint center. The x axis was defined as the cross product of the z axis and the temporary axis. The y axis was the cross product of the z and x axes.

Forearm

The forearm segments were modeled using the olecranon, mid-radius, and ulnar styloid process markers. The origin was placed at the elbow joint center. The z axis was defined as a vector from the wrist joint center (midpoint of the wrist diameter) to the elbow joint center. A temporary axis was constructed from the shoulder joint center to the elbow joint center. The y axis was defined as the cross product of the z axis and the temporary axis. The x axis was the cross product of the z and y axes.

Hand

The hand segments were modeled using the ulnar styloid process, third metacarpal and fifth metacarpal markers. The origin was placed at the wrist joint center. The z axis was defined as a vector from the third metacarpal joint to the wrist joint center. A temporary axis was constructed from the third metacarpal to the fifth metacarpal. The x axis was defined as the cross product of the z axis and the temporary axis. The y axis was the cross product of the z and x axes.

Rotation Sequence

The transformation matrix used to evaluate UE joint kinematics was computed using a sagittal-coronal-transverse rotation sequence, where α is the rotation in the sagittal plane, β is the rotation in the coronal plane, and γ is the rotation in the transverse plane (Equation 1).

$$[R] = \begin{bmatrix} \cos\alpha\cos\gamma + \sin\alpha\sin\beta\sin\gamma & \cos\beta\sin\gamma & -\sin\alpha\cos\gamma + \cos\alpha\sin\beta\sin\gamma \\ -\cos\alpha\sin\gamma + \sin\alpha\sin\beta\cos\gamma & \cos\beta\cos\gamma & \sin\alpha\sin\gamma + \cos\alpha\sin\beta\cos\gamma \\ \sin\alpha\cos\beta & -\sin\beta & \cos\alpha\cos\beta \end{bmatrix} \quad (1)$$

Angular velocities (ω_x, ω_y, ω_z) are given by Equation 2. Angular accelerations ($\dot{\omega}$) were calculated by taking the derivatives of the angular velocities.

$$\begin{aligned}\omega_x &= \dot{y}\sin(z)\cos(x) + \dot{x}\cos(z)\\ \omega_y &= \dot{y}\cos(z)\cos(x) - \dot{x}\sin(z)\\ \omega_z &= -\dot{y}\sin(x) + \dot{z}\end{aligned} \quad (2)$$

Kinetic Model

The kinetic calculations in this model follow the inverse dynamics equations based on the work of Vaughan and colleagues.[21] This method calculated the reaction force in the proximal joint ($\overline{F}_{\text{Joint}}$) using the mass-acceleration product (m = mass, $\bar{a}$ = acceleration, $\overline{g}$ = acceleration due to gravity) of the segment and the distal joint force contribution ($\overline{F}_{\text{Distal}}$), as shown in Equation 3. The rate of change of angular momentum ($\dot{H}$) is calculated using the mass moments of inertia (I_{XX}, I_{YY}, I_{ZZ}), angular velocities (ω_x, ω_y, ω_z), and angular accelerations ($\dot{\omega}_x$, $\dot{\omega}_y$, $\dot{\omega}_z$) as shown in Equation 4. The reaction moment in a joint of interest ($\overline{M}_{\text{Joint}}$) was calculated using the rate of change of angular momentum ($\dot{H}$) of the segment distal to it (Equation 4), the moment in the distal joint ($\overline{M}_{\text{Distal}}$), and the contributions of the forces ($\overline{F}_{\text{Proximal}}$, $\overline{F}_{\text{Distal}}$) crossed with the moment arms ($\bar{r}_{\text{proximal}}$, $\bar{r}_{\text{distal}}$) of the distal and proximal joints (Equation 5).[22]

$$\overline{F}_{\text{Joint}} = -m_{\text{DistalSegment}}(\bar{a}_{\text{DistalSegment}} + \bar{g}) + \overline{F}_{\text{Distal}} \quad (3)$$

$$\begin{aligned}\dot{H}_X &= I_{XX}\dot{\omega}_X - (I_{YY} - I_{ZZ})\,\omega_Z\,\omega_Y\\ \dot{H}_Y &= I_{YY}\dot{\omega}_Y - (I_{ZZ} - I_{XX})\,\omega_X\,\omega_Z\\ \dot{H}_Z &= I_{ZZ}\dot{\omega}_Z - (I_{XX} - I_{YY})\,\omega_Y\,\omega_X\end{aligned} \quad (4)$$

$$\overline{M}_{\text{Joint}} = \dot{H}_{\text{DistalSegment}} + \overline{M}_{\text{Distal}} - \left[\bar{r}_{\text{Proximal}} \times \overline{F}_{\text{Proximal}}\right] + \left[\bar{r}_{\text{Distal}} \times \overline{F}_{\text{Distal}}\right] \quad (5)$$

The most distal segment (hand) used the sensor outputs for $\overline{F}_{\text{Distal}}$ and $\overline{M}_{\text{Distal}}$. The center of mass of the hand was assumed to apply the load at the center of the handle. The distance from the center of the load cell to the center of the handle was factored in to the kinetic equations.

The axes were transformed to the ISB recommended system (x anterior, y superior, z lateral to the right). For the purposes of clinical reporting, adjustments were made to left side x and y angles so that adduction and internal rotation were positive for both left and right sides. Similarly, right side z forces were negated so that medial forces were always positive, and left side x and y moments were negated so that medial bending and internal rotation moments were always positive.

With these adjustments in mind, the following conventions apply to the results shown in this study. A positive joint reaction force (JRF) along the local y axis (superior) indicates compression of the joint. A positive JRF along the local x axis (anterior) indicates a posterior shearing force applied to the joint by the distal segment. A positive JRF along the z axis (medial) indicates a lateral shearing force applied to the joint by the distal segment. In a system with simplified force applications, pushing down on the walker handle would produce a superior (+y) JRF; pushing forward on the handle would produce a posterior (-x) JRF; and pushing outward on the handle would produce a medial (+z) JRF.[15]

The joint reaction moments (JRMs) reported with this model can be described in terms of the demands placed on the joints by the forces and moments applied to the joint. For example, a positive JRM about the segment's medial/lateral (z) axis indicates that there is a demand on the flexor muscles to keep the joint stable, while a negative JRM indicates a demand on the extensors. Moments about the anterior/posterior (x) axis describe the demands on the adductors and abductors, with abductors being positive. Finally, moments about the superior/inferior (y) axis describe the demands on the muscles that cause internal and external rotation, with internal rotation being positive.[23] These are similar to the conventions described in Winter et al.[24] See Table 2 for a summary of the coordinate system terminology and sign conventions.

Table 2. Coordinate system terminology.

Axis & Sense	Angle	Force	Moment
+x	Adduction	Anterior	Medial Bending
-x	Abduction	Posterior	Lateral Bending
+y	Internal Rotation	Superior	Internal Rotation
-y	External Rotation	Inferior	External Rotation
+z	Flexion	Medial	Flexion
-z	Extension	Lateral	Extension

The calculated joint reaction forces and moments were normalized in this study. The forces were divided by the subject's weight (N) to obtain a unitless "percent body weight" metric. This is a common method used by many researchers.[6,7,25] The moments were divided by the product of the subject's weight (N) and height (mm). This resulted in a unitless "percent body weight times height" metric. This method is also used elsewhere in literature; however some researchers only normalize moments to body weight.[25]

Subject Demonstration

After appropriate Institutional Review Board approval and subject consent and assent forms had been obtained, a subject (male, age: 15.5 years, weight: 27.7 kg, height: 1.19 m) with OI type III underwent gait testing. UE and LE body segment measurements were recorded. A standard lower body marker set (Plug-In-Gait) was applied to the LEs, and the custom UE marker set, described above, was applied to the upper body.

A pediatric walker (Sunrise Medical, Guardian Strider 07781, Longmont, CO) was fitted with handles instrumented with custom strain gage-based dynamometers (MCW-6-500, AMTI, Watertown, MA), described above (Figure 3). This type of walker was made of lightweight aluminum, had adjustable height legs, and could be used in the anterior or posterior configuration. The walker was used in the posterior configuration for this subject. The handle height was adjusted so that they reached the subject's ulnar styloid process when standing with arms relaxed, and the handle grips were positioned horizontally. A 14-camera motion analysis system (Vicon, Oxford Metrics, Oxford, UK), collecting data at 120 Hz, was used to capture the motion of the reflective markers in three dimensions. A Woltring filter with a mean-squared-error of 20 was applied to motion data.

A baseline trial with the unloaded walker alone was recorded. The force and moment values acquired from the baseline trial were used as an offset for the

motion trials. A static reference trial was collected with the subject standing in a comfortable position within the walker frame. This trial was used for marker labeling purposes. The subject then performed at least 10 walking trials, ensuring that at least 5 acceptable gait cycles were obtained. Three-dimensional load cell data was collected simultaneously at 1500 Hz.

Figure 3. Instrumented posterior walker.

RESULTS

Shoulder

The greatest forces seen at the shoulders were anterior shear forces. The left side saw greater forces (5.6 to 13.6 percent body weight (% BW)) than the right (4.8 to 11.8 % BW).

The greatest moments seen at the shoulders were flexion/extension moments. The left side experienced flexion moments ranging from 1.2 to 3.4 percent body weight times height (% BW*H). The right side experienced extension moments ranging from -1.6 to -3.3% BW*H. Shoulder angle, force, and moment plots are shown in Figure 4. Complete results are shown in Tables 3 and 4.

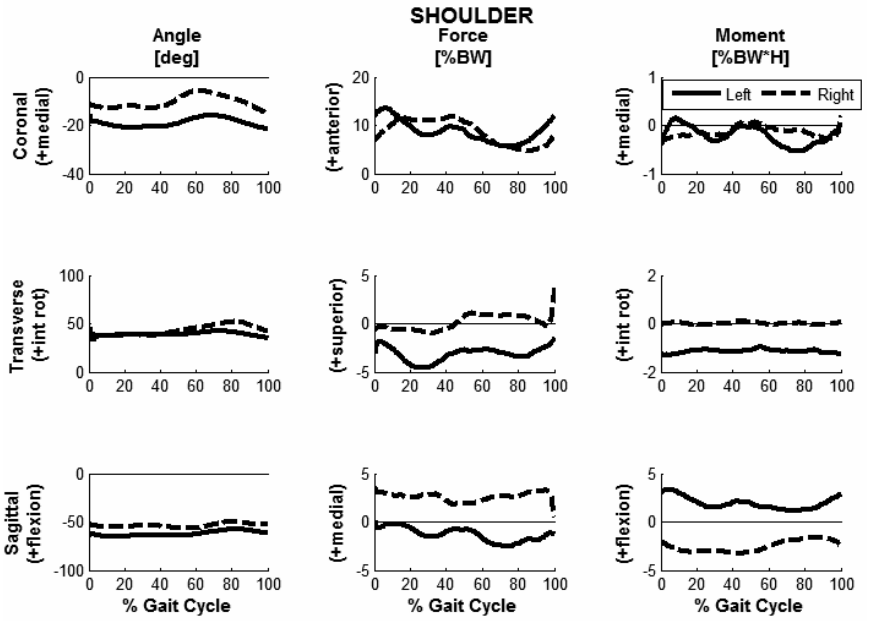

Figure 4. Bilateral shoulder (glenohumeral) joint angles, JRFs, and JRMs for a subject with OI in three planes.

Table 3. Joint reaction forces (%BW).

		Left			Right		
	(+/-)	min	max	range	min	max	range
Shoulder	M/L	-2.5	0.1	2.6	0.5	3.6	3.1
	S/I	-4.6	-1.4	3.2	-1.0	3.8	4.8
	A/P	5.6	13.6	8.0	4.8	11.8	7.0
Elbow	M/L	-1.9	1.2	3.1	4.3	7.9	3.6
	S/I	-9.6	-2.5	7.2	-5.8	-0.2	5.6
	A/P	-5.9	-3.9	2.0	-1.9	1.7	3.5
Wrist	M/L	3.3	5.6	2.3	-4.4	-2.3	2.2
	S/I	1.0	2.5	1.6	-0.9	0.9	1.8
	A/P	0.5	7.5	7.0	1.6	8.1	6.4

M/L = Medial/Lateral shear force, with medial being positive and lateral being negative.
S/I = Superior/Inferior force, with superior being positive and inferior being negative.
A/P = Anterior/Posterior shear force, with anterior being positive and posterior being negative.

Table 4. Joint reaction moments (%BW*H).

		Left			Right		
	(+/-)	min	max	range	min	max	range
Shoulder	M/L	1.2	3.4	2.3	-3.3	-1.6	1.7
	S/I	-1.3	-1.0	0.3	0.0	0.1	0.2
	A/P	-0.5	0.4	1.0	-0.4	0.2	0.6
Elbow	M/L	-0.5	0.0	0.5	-1.1	-0.9	0.2
	S/I	-0.3	0.0	0.3	0.0	0.1	0.1
	A/P	1.0	1.3	0.3	0.0	0.1	0.2
Wrist	M/L	1.0	1.8	0.8	0.8	1.7	0.8
	S/I	-0.7	-0.4	0.4	-0.3	-0.1	0.2
	A/P	0.4	0.7	0.3	0.2	0.4	0.2

F/E = Flexion/Extension moment, with flexion being positive and extension being negative.
I/E = Internal/External rotation moment, with internal rotation being positive and external rotation being negative.
M/L = Medial/Lateral bending moment, with medial bending being positive and lateral bending being negative.

Elbow

The greatest forces seen at the elbows were inferiorly directed forces. The left side saw greater forces (-2.5 to -9.6% BW) than the right side (-0.2 to -5.8% BW).

The greatest moments seen at the left elbow were medial bending moments (1.0 to 1.8% BW*H), while the greatest moments seen at the right elbow were extension moments (-0.9 to -1.1 %BW*H). Elbow angle, force, and moment plots are shown in Figure 5.

Wrist

The greatest forces seen at the wrists were anterior shear forces. The right side saw slightly greater forces (1.6 to 8.1% BW) than the left side (0.5 to 7.5% BW).

The greatest moments seen at the wrists were flexion moments. The left side experienced moments ranging from 1.0 to 1.8% BW*H, while the right side experienced moments ranging from 0.8 to 1.7% BW*H. Wrist angle, force, and moment plots are shown in Figure 6.

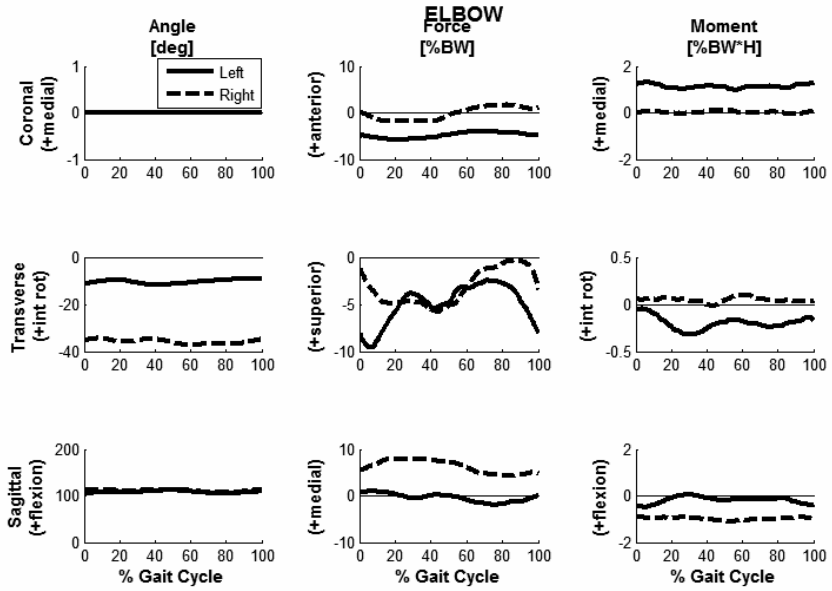

Figure 5. Bilateral elbow joint angles, JRFs, and JRMs for a subject with OI in three planes.

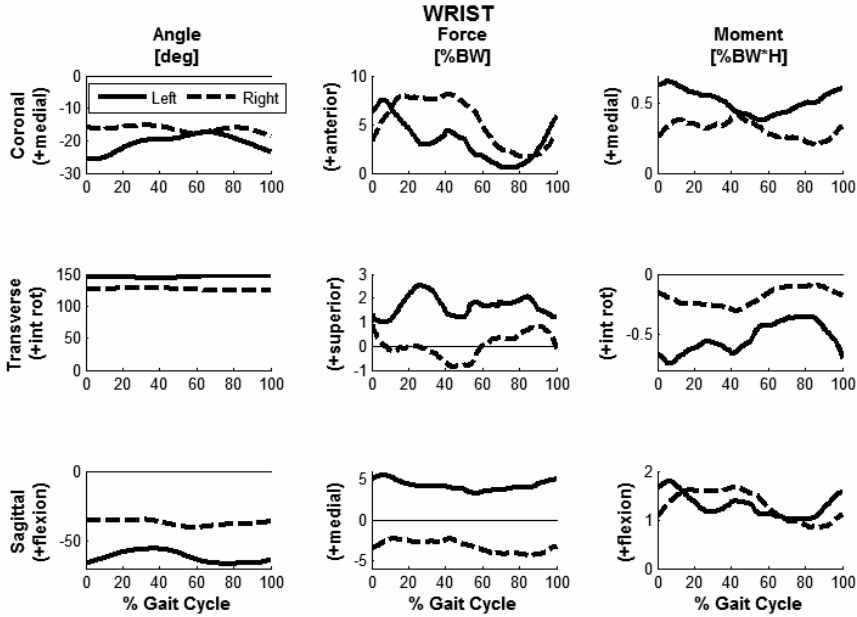

Figure 6. Bilateral wrist joint angles, JRFs, and JRMs for a subject with OI in three planes.

DISCUSSION

No previous studies have examined the UE dynamics during walker-assisted gait in the OI population. The results from the single subject analyzed here are not directly comparable to other studies, and there is no normal walker user population since all walker users have pathology. However, the general magnitudes and patterns can be compared and contrasted to other pediatric walker users. Our group has completed a study examining the JRFs and JRMs of 10 children with cerebral palsy (CP) during anterior and posterior walker use.[15] This study showed the greatest JRFs in the superior direction at the wrist (up to 6% BW), elbow (up to 7% BW), and shoulder (up to 4% BW). The current study shows the greatest JRFs in the shoulder and wrist to be anterior shear forces (up to 13.6% BW in the left shoulder; up to 8.1% BW in the right wrist). Anterior shear JRFs occur due to the extended posture of the shoulders throughout the gait cycle. The left elbow experienced inferior JRFs up to -9.6% BW. The CP study shows that the greatest JRMs occur in the shoulder (1.1% BW*H flexion). The current study also shows the greatest JRMs occurring in the shoulder joints, with left shoulder flexion moments up to 3.4% BW*H and right shoulder extension moments up to -3.3% BW*H.

The current results show generally higher absolute JRFs and JRMs than the CP study, however the results are reasonable. The CP study is an average of 10 subjects. Averaging data has the effect of attenuating peaks, which could account for the lower magnitude of the maximum and minimum values seen there. Other differences could be due to pathology, walking style and speed, and specific motion patterns exhibited by the current subject.

The results show several differences bilaterally. For example, the left shoulder experienced inferior JRFs and flexion JRMs over the entire gait cycle, while the right shoulder experienced mostly superior JRFs and all extension JRMs. This is not uncommon when dealing with pathology that affects each limb differently. The subject may favor one side due to pain, or experience musculoskeletal constraints that do not allow bilateral symmetry. Because of these differences, it is imperative that each side be examined separately, as with this instrumented walker system.

According to Wolff's law, bone adapts to the loads placed on it. Increase in load causes the trabeculae to undergo adaptive changes, followed by secondary changes to the cortical bone, making the bone denser and stronger. The converse is also true: decreased loading on a bone results in decreased bone density and therefore decreased strength and increased

fracture risk.[26] Therefore, it is important for children with OI to remain active, but it is also essential to monitor their activity to reduce fracture risk. Walking aids put added loads on the UEs, while relieving loads from the LEs. The lowered loading conditions on the LEs could mitigate fracture risk in the legs, and the increased loads on the UEs could help to maintain or even increase the strength of the UE bones. However, long-term walking aid use has been shown to have negative effects on the UE joints and soft tissue, including arthritis, shoulder rotator cuff injury, and carpal tunnel syndrome.[27,28] More research is needed to determine the optimal loading conditions to keep the bone healthy while also avoiding UE injury during aided ambulation.

We conclude that the instrumented walker system and UE model described here are useful for quantifying and analyzing UE kinematics and kinetics during walker-assisted gait in children with OI. The ability to evaluate and monitor the loads placed on the UE joints could be useful in decreasing the risk of UE injury through improved therapy and walking aid modifications.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

ASIS	Anterior superior iliac spine
CP	Cerebral palsy
C7	7th cervical vertebra
ISB	International society of biomechanics
JRF	Joint reaction force
JRM	Joint reaction moment
LE	Lower extremity
OI	Osteogenesis imperfecta
UE	Upper extremity
%BW	Percent body weight
%BW*H	Percent body weight times height

REFERENCES

1. Freemont A. The pathology of osteogenesis imperfecta. *J. Clin. Pathol.* 1996;49(8):618-619.

2. Marini JC. Osteogenesis imperfecta. In: *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Saunders Elsevier; 2011:692.
3. Wu G, van der Helm FCT, Veeger HEJD, et al. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion--Part II: shoulder, elbow, wrist and hand. *J Biomech*. 2005;38(5):981-992.
4. Fast A, Wang FS, Adrezin RS, et al. The instrumented walker: usage patterns and forces. *Arch Phys Med Rehabil*. 1995;76(5):484-491.
5. Finkel J, Fernie G, Cleghorn W. A guideline for the design of a four-wheeled walker. *Assist Technol*. 1997;9(2):116-129.
6. Melis EH, Torres-Moreno R, Barbeau H, Lemaire ED. Analysis of assisted-gait characteristics in persons with incomplete spinal cord injury. *Spinal Cord*. 1999;37(6):430-439.
7. Opila KA, Nicol AC, Paul JP. Forces and impulses during aided gait. *Arch Phys Med Rehabil*. 1987;68(10):715-722.
8. Pardo RD, Deathe AB, Winter DA. Walker user risk index. A method for quantifying stability in walker users. *Am J Phys Med Rehabil*. 1993;72(5):301-305.
9. Bachschmidt R, Harris G, Simoneau G. Development of an instrumented walker for measurement of unilateral hand loads. In: *Proceedings of the 1996 Fifteenth Southern Biomedical Engineering Conference*. Dayton, OH: Institute of Electrical and Electronics Engineers; 1996.
10. Bachschmidt RA, Harris GF, Simoneau GG. Walker-assisted gait in rehabilitation: a study of biomechanics and instrumentation. *IEEE Trans Neural Syst Rehabil Eng*. 2001;9(1):96-105.
11. Bachschmidt RA, Harris GF, Ackman J, et al. Development of a system for quantitative study of pediatric walker-assisted gait. In: *Proceedings of the 20th Annual Internation Conference of the IEEE Engineering in Medicine and Biology Society*.Vol 20(5). IEEE; 1998:2689-2692.
12. Bachschmidt RA, Harris GF. Quantitative Study of Walker-Assisted Gait in Children with Cerebral Palsy: Anterior versus Posterior Walkers. In: *Pediatric Gait: A New Millenium in Clinical Care and Motion Analysis Technology*. Piscataway, NJ: IEEE Press; 2000:217.
13. Simoneau GG, Hambrook G, Bachschmidt RA, Harris GF. Quantifying upper extremity efforts when using a walking frame. In: *Pediatric Gait: A New Millenium in Clinical Care and Motion Analysis Technology*. Piscataway, NJ: Institute of Electrical Engineers, Inc. 2000:210.
14. Baker KM, Wang M, Cao K, et al. Biomechanical System for the Evaluation of Walker-Assisted Gait in Children: Design and Preliminary Application. In: *Proceedings of the 25th Annual International Conference of the IEEE EMBS*. Cancun, Mexico; 2003:1851-1854.
15. Konop KA, Strifling KMB, Wang M, et al. A biomechanical analysis of upper extremity kinetics in children with cerebral palsy using anterior and posterior walkers. *Gait Posture*. 2009;30(3):364-369.
16. Konop KA, Strifling KMB, Wang M, et al. [Upper extremity kinetics and energy expenditure during walker-assisted gait in children with cerebral palsy]. *Acta Orthop Traumatol Turc*. 2009;43(2):156-164.
17. Konop KA, Strifling KMB, Krzak J, Graf A, Harris GF. Upper Extremity Joint Dynamics During Walker Assisted Gait: A Quantitative Approach Towards Rehabilitative Intervention. *Journal of Experimental & Clinical Medicine*. 2011;3(5):213-217.

18. Yeadon MR, Morlock M. The appropriate use of regression equations for the estimation of segmental inertia parameters. *J Biomech*. 1989;22(6-7):683-689.
19. Chandler FR. *Investigation of inertial properties of the human body*. Wright Patterson Air Force Base, OH: Army Medical Research Lab; 1975.
20. Bauer JJ, Pavol MJ, Snow CM, Hayes WC. MRI-derived body segment parameters of children differ from age-based estimates derived using photogrammetry. *J Biomech*. 2007;40(13):2904-2910.
21. Vaughan C, Davis B, O'Connor J. *Dynamics of Human Gait*. Champaign, IL: Human Kinetics Press; 1992.
22. Strifling. Anaylsis and modeling of upper and lower extremity dynamics in children with cerebral palsy using walkers. 2006.
23. Konop KA. A biomechanical analysis of upper extremity kinetics in children with cerebral palsy using anterior and posterior walkers. 2008.
24. Winter. *Biomechanics and motor control of human movement*. 3rd ed. Hoboken, NJ: John Wiley & Sons, Inc. 2005.
25. Ounpuu S, Davis RB, DeLuca PA. Joint kinetics: Methods, interpretation and treatment decision-making in children with cerebral palsy and myelomeningocele. *Gait*. 1996;4:62-78.
26. Wolff J. The Classic: On the Inner Architecture of Bones and its Importance for Bone Growth. *Clinical Orthopaedics and Related Research*®. 2010;468(4):1056-1065.
27. Kellner WS, Felsenthal G, Anderson JM, Hilton EB, Mondell DL. Carpal tunnel syndrome in the nonparetic hands of hemiplegics. Stress-induced by ambulatory assistive devices. *Orthop Rev*. 1986;15(9):608-611.
28. Klimaitis A, Carroll G, Owen E. Rapidly progressive destructive arthropathy of the shoulder--a viewpoint on pathogenesis. *J. Rheumatol.* 1988;15(12):1859-1862.

20 UPPER EXTREMITY INVERSE DYNAMICS MODEL FOR LOFSTRAND CRUTCH- ASSISTED GAIT IN CHILDREN WITH OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Our aim is to quantify upper extremity (UE) forces and moments during Lofstrand crutch-assisted gait to better predict skeletal loading during ambulatory and functional activities in children with osteogenesis imperfecta (OI). Approximately 566,000 crutch users live in the United States, of which among these are a population of children with OI.[1] Due to long-term assistive device usage, these children may be at an increased risk for developing UE pathologies. Literature has shown that longer-term crutch users experience altered UE joint loads, and may be at risk for development of musculoskeletal injury, early onset osteoarthritis, and carpal tunnel syndrome. Previous studies evaluating UE dynamics during assisted gait are limited. Our goal is to develop a three-dimensional (3-D) UE biomechanical model to quantify joint dynamics during Lofstrand crutch-assisted gait in children with OI. Our work recognizes that a pediatric biomechanical model may be a valuable tool for clinicians to characterize and better understand UE dynamics of crutch-assisted gait in children with OI.[2] While motion

analysis has been extensively used to study gait, limited work has been conducted to characterize UE dynamics during Lofstrand crutch-assisted gait.[3,4] Motion analysis is a noninvasive technique that allows evaluation of multi-planar motion during functional activities.[5,6] Improved motion analysis technology and modeling software has allowed more rapid development of complex biomechanical models, such as those needed to study UE kinematics and kinetics.

OI, a genetic disorder characterized by fragile bones, is a pediatric pathology associated with Lofstrand crutch use. It is caused by mutation in genes that affects the body's production of the collagen found in bones and other tissues.[7] In addition to fractures, people with OI often have muscle weakness, hearing loss, fatigue, joint laxity, curved bones, scoliosis, blue sclerae, dentinogenesis imperfecta (brittle teeth), and short stature.[8] OI has a prevalence of 1/5,000 to 1/10,000, with an estimated 20,000 to 50,000 cases in the U.S.[6,9] OI is divided into eight types (I, II, III, IV, V, VI, VII and VIII) based on clinical, radiographic and genetic characteristics.

OI type I is the mildest form of OI, and is also the most common type in this population. These children suffer from mild fractures and have frequent shoulder and elbow dislocations.[8] Children with OI type I commonly use assistive devices, such as Lofstrand crutches, for community ambulation (Figure 1). Those using Lofstrand crutches present a possibility of recurrent fractures due to repetitive, high forces placed on the UEs. These long-term crutch users may be at an increased risk for the development of UE joint pain and pathology.

Klimaitis and colleagues, as early as 1988, found that bearing weight through the upper limbs may hasten the development of degenerative arthritis in the shoulder, possibly by contributing to mechanical disruption of the rotator cuff.[10] In addition, multiple authors have reported that superiorly directed weight-bearing forces may potentially threaten glenohumeral joint integrity, as translation of the humeral head and subsequent impingement of subacromial structures may occur if these forces are not matched by an appropriate response of the rotator cuff and thoracohumeral depressor musculature.[11,12] The literature shows that long-term assistive device usage may result in upper limb pathologies, such as destructive shoulder arthropathy and degenerative arthritis of the shoulder.[13,14]

Figure 1. Patient with osteogenesis imperfecta (OI) using Lofstand crutches. She is instrumented with the UE marker system and is using the kinetic Lofstrand crutches.

With regard to more distal joints, an association between the development of carpal tunnel syndrome and the use of assistive devices has also been reported.[15-17] Repetitive impulse loading with prolonged wrist extension and with radial deviation have been identified as proposed risk factors for pathology.[16,17]

The inverse dynamics of Lofstrand crutch-assisted gait in the pediatric population has been reported only to a small extent.[3,4] Unlike lower extremity motion, UE motion does not follow a repeating pattern, thus making it difficult to standardize and compare data among different studies. The International Society of Biomechanics (ISB) has recently established

recommendations for modeling UE joint coordinate systems.[18] With this effort, communication among researchers and physicians has been enhanced through these modeling standards.

New efforts are underway to utilize instrumented Lofstrand crutches for characterization of UE dynamics during gait in children with OI. Tri-axial forces and moments occurring at the crutch cuff, handle, and tip can now be measured with the use of advanced sensor technology.[19] To our knowledge, these new endeavors are the upmost accurate and reliable presentation of UE kinetic data of the shoulder, elbow and wrist joints in children with OI using Lofstrand crutches. Applications of this system may offer valuable insight for crutch prescription, gait pattern selection, and long-term usage effects.

METHODS

Kinematic Model

The UEs were modeled using seven rigid body segments (i.e., thorax, upper arms, forearms, and hands) and 28 retro-reflective markers placed on bony landmarks and Lofstrand crutches.[19] Vicon BodyBuilder software (Vicon, Oxford, England) was used for dynamic modeling.

Joint Centers

Joint centers were calculated using subject specific anthropometric data.[19,20] The thorax model was based on the results of work done by Nyugen et al., for analyzing thorax kinematics in children with myelomeningocele.[21] The markers located at the clavicles ($\overline{m}_{rclav}$ and $\overline{m}_{lclav}$), C7 spinous process ($\overline{m}_{spc7}$) and xiphoid process ($\overline{m}_{xi}$) were used to define the thorax movement. The thorax center ($\overline{t}_c$) was located halfway between the center of the clavicles and the C7 spinous process.

The upper arm was defined using markers placed on the acromion processes ($\overline{m}_{racr}$ and $\overline{m}_{lacr}$), and right and left medial ($\overline{m}_{rme}$ and $\overline{m}_{lme}$) and lateral elbow epicondyles ($\overline{m}_{rle}$ and $\overline{m}_{lle}$). The radius of the shoulder joint was estimated by measuring the circumference of the shoulder. The shoulder joint center ($\overline{s}_c$) was computed by subtracting the distance equal to the radius of the marker

(7 mm) summed with the radius of the shoulder (*r*) from the acromion process marker in the negative Y direction ($\overline{Y}$).

The forearm segment was defined by the right and left medial ($\overline{m}_{rme}$ and $\overline{m}_{lme}$) and lateral elbow epicondyles ($\overline{m}_{rle}$ and $\overline{m}_{lle}$), and the radial ($\overline{m}_{rrad}$ and $\overline{m}_{lrad}$) and ulnar styloids ($\overline{m}_{ru\ln}$ and $\overline{m}_{lu\ln}$). The midpoint of the medial and lateral epicondyles was defined as the elbow joint center ($\overline{e}_c$).

Similarly, the wrist segment was defined bilaterally by the radial ($\overline{m}_{rrad}$ and $\overline{m}_{lrad}$) and ulnar styloids ($\overline{m}_{ru\ln}$ and $\overline{m}_{lu\ln}$), 3rd metacarpal ($\overline{m}_{rm3}$ and $\overline{m}_{lm3}$), and 5th metacarpal ($\overline{m}_{rm5}$ and $\overline{m}_{lm5}$). The midpoint of the radial and ulnar styloids was defined as the wrist joint center ($\overline{w}_c$).

Segment Coordinate Systems

Segment coordinate systems were developed for each of the seven segments of the upper body and for each of the six segments of the crutches.[20] The relative motion between two adjacent segments was used to define the joint angles. ISB recommendations were implemented for developing the axes of the segment coordinate systems.[18] All coordinate axes followed the right hand rule, where the X-axis was directed anteriorly, the Y-axis was directed superiorly, and the Z-axis was directed laterally to the right. The vectors used to evaluate the axes of the segment coordinate systems are described below.

Thorax

The thorax coordinate system was designed using a temporary coordinate system and a virtual point.[21,22] The temporary coordinate system had its origin at the xiphoid process ($\overline{m}_{xiph}$). This temporary coordinate system was represented as

$$\overline{Y}_{temp} = \frac{\overline{m}_{spc7} - \overline{m}_{xiph}}{\left|\overline{m}_{spc7} - \overline{m}_{xiph}\right|} \quad (1)$$

$$\overline{X}_{temp} = \frac{\left(\overline{m}_{rclav} + \overline{m}_{lclav}\right)/2 - \overline{m}_{xiph}}{\left|\left(\overline{m}_{rclav} + \overline{m}_{lclav}\right)/2 - \overline{m}_{xiph}\right|} \times \overline{Y}_{temp} \quad (2)$$

$$\overline{Z}_{temp} = \overline{X}_{temp} \times \overline{Y}_{temp} \quad (3)$$

The virtual point ($\bar{t}_{virtualpoint}$) was then computed by translating the thorax center 10 mm in the direction of the temporary X-axis.

$$\bar{t}_{virtualpoint} = \overline{t}_c + 0.01 \times \overline{X}_{temp} \quad (4)$$

The thorax center ($\overline{t}_c$) was the origin for the thorax coordinate system.

$$\overline{X}_{Thorax} = \frac{\left(\overline{m}_{rclav} + \overline{m}_{lclav}\right)/2 - \overline{m}_{spc7}}{\left|\left(\overline{m}_{rclav} + \overline{m}_{lclav}\right)/2 - \overline{m}_{spc7}\right|} \quad (5)$$

$$\overline{Y}_{Thorax} = \frac{\bar{t}_{virtualpoint} - \bar{t}_c}{\left|\bar{t}_{virtualpoint} - \bar{t}_c\right|} \times \overline{X}_{Thorax} \quad (6)$$

$$\overline{Z}_{Thorax} = \overline{X}_{Thorax} \times \overline{Y}_{Thorax} \quad (7)$$

Upper Arm

The shoulder joint center ($\overline{s}_c$) was the origin for the upper arm segment coordinate system. The vectors defining this segment coordinate system were

$$\overline{Y}_{Upperarm} = \frac{\bar{s}_c - \bar{e}_c}{\left|\bar{s}_c - \bar{e}_c\right|} \quad (8)$$

$$\overline{Z}_{Upperarm} = \frac{\overline{m}_{uln} - \bar{e}_c}{\left|\overline{m}_{uln} - \bar{e}_c\right|} \times \overline{Y}_{Upperarm} \quad (9)$$

$$\overline{X}_{Upperarm} = \overline{Z}_{Upperarm} \times \overline{Y}_{Upperarm} \quad (10)$$

Forearm

The elbow joint center ($\overline{e_c}$) was the origin for the forearm segment coordinate system. Varus and valgus was constrained by methods similar to those reported by Hingtgen, et al., Rab et al., and Schmidt et al.[23-25] The equations defining the axes of this segment coordinate system were

$$\overline{Y}_{Forearm} = \frac{\overline{e}_c - \overline{m}_{u\ln}}{\left|\overline{e}_c - \overline{m}_{u\ln}\right|} \tag{11}$$

$$\overline{X}_{Forearm} = \frac{\overline{m}_{u\ln} - \overline{m}_{rad}}{\left|\overline{m}_{u\ln} - \overline{m}_{rad}\right|} \times \overline{Y}_{Forearm} \tag{12}$$

$$\overline{Z}_{Forearm} = \overline{X}_{Forearm} \times \overline{Y}_{Forearm} \tag{13}$$

Hand

The hand coordinate system was set up using a temporary coordinate system and a virtual point. The temporary coordinate system had its origin at the ulnar styloid ($\overline{m}_{u\ln}$). This temporary coordinate system was

$$\overline{Y}_{temp} = \frac{\overline{m}_{u\ln} - \overline{m}_{m5}}{\left|\overline{m}_{u\ln} - \overline{m}_{m5}\right|} \tag{14}$$

$$\overline{X}_{temp} = \frac{\overline{m}_{u\ln} - \overline{m}_{rad}}{\left|\overline{m}_{u\ln} - \overline{m}_{rad}\right|} \times \overline{Y}_{temp} \tag{15}$$

$$\overline{Z}_{temp} = \overline{X}_{temp} \times \overline{Y}_{temp} \tag{16}$$

The virtual point ($\overline{h}_{virtualpoint}$) was computed by translating the third metacarpal marker in the direction of the temporary X-axis by a distance equivalent to half of the subject specific width of the hand ($w/2$) and radius of the marker (7 mm).

$$\overline{h}_{virtualpoint} = \overline{m_{m3}} + \left(\frac{w}{2} + 0.007\right) \times \overline{X}_{temp} \tag{17}$$

The wrist center ($\overline{w_c}$) was the origin for the hand coordinate system.[18,26] The 3-D hand coordinate system was calculated as

$$\overline{Y}_{Hand} = \frac{\overline{w}_c - \overline{h}_{virtualpoint}}{\left|\overline{w}_c - \overline{h}_{virtualpoint}\right|} \tag{18}$$

$$\overline{X}_{Hand} = \frac{\overline{m}_{u\ln} - \overline{m}_{rad}}{\left|\overline{m}_{u\ln} - \overline{m}_{rad}\right|} \times \overline{Y}_{Hand} \tag{19}$$

$$\overline{Z}_{Hand} = \overline{X}_{Hand} \times \overline{Y}_{Hand} \tag{20}$$

Crutch

Each Lofstrand crutch was divided into three segments: lower crutch, crutch handle, and crutch cuff (Figure 2).[19,20] The crutch was modeled as a rigid body segment. Thus, one main crutch segment was defined, which was then appropriately modified using spatial coordinate transformation for the computation of segmental kinematics.

Handle

The crutch handle segment consisted of the crutch handle, the upper load cell and the lower load cell. The crutch maker setup is shown in Figure 2. The origin of the handle segment ($\overline{lc}_c$) was defined as the midpoint of the lower load cell. The midpoint of the crutch tip was computed as a virtual point ($\overline{c}_{\text{virtualpoint}}$), which was then used for defining the segment coordinate system.[19]

$$\overline{lc}_c = \frac{(\overline{m}_{lateral} + \overline{m}_{medial})}{2} \tag{21}$$

$$\overline{c}_{virtualpo\,\text{int}} = \frac{(\overline{m}_{anterior} + \overline{m}_{posterior})}{2} \tag{22}$$

$$\overline{Y}_{Handle} = \frac{\overline{lc}_c - \overline{c}_{virtualpoint}}{\left|\overline{lc}_c - \overline{c}_{virtualpoint}\right|} \tag{23}$$

$$\overline{X}_{Handle} = \frac{\overline{m}_{medial} - \overline{m}_{lateral}}{\left|\overline{m}_{medial} - \overline{m}_{lateral}\right|} \times \overline{Y}_{Handle} \quad (24)$$

$$\overline{Z}_{Handle} = \overline{X}_{Handle} \times \overline{Y}_{Handle} \quad (25)$$

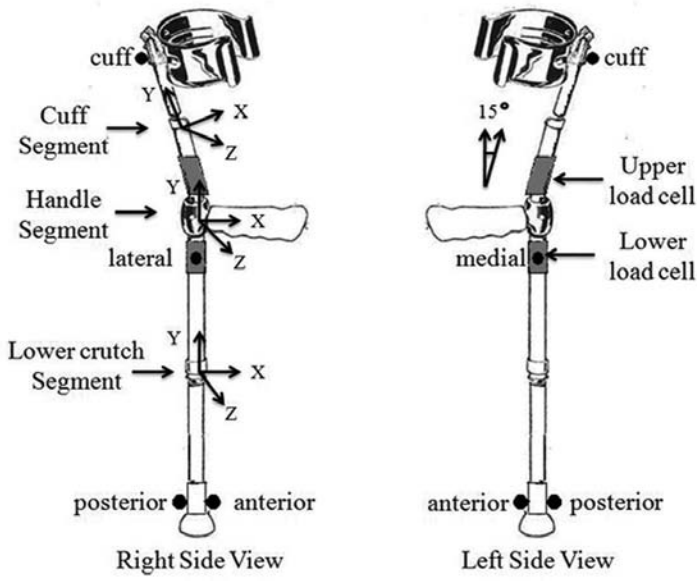

Figure 2. Crutch segment definitions and axes orientation. Each crutch segment consists of the handle, the lower crutch, and cuff segments. The coordinate systems of the segments follow x-axis: anterior, y-axis: superior, and z-axis: lateral. The cuff is offset from the lower crutch by a 15-degree angle. Markers were placed on the cuff segment, right and left sides of the lower load cell, and on the anterior and posterior crutch tip. (Reprinted from Journal of Biomechanics, 44 (11), Brooke A. Slavens, Neha Bhagchandani, Mei Wang, Peter A. Smith, and Gerald F. Harris, An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait, Copyright 2011, with permission from Elsevier.[19])

Lower crutch

The midpoint of the lower load cell ($\overline{lc}_c$) and the virtual point ($\overline{c}_{\text{virtualpoint}}$) was used to compute the origin for the crutch tip segment ($\overline{Ctip}_c$).[19]

$$\overline{Ctip}_c = \frac{(\overline{lc}_c + \overline{c}_{virtualpoint})}{2} \quad (26)$$

$$\overline{Y}_{LowerCrutch} = \frac{\overline{lc}_c - \overline{Ctip}_c}{\left|\overline{lc}_c - \overline{Ctip}_c\right|} \quad (27)$$

$$\overline{X}_{LowerCrutch} = \frac{\overline{m}_{medial} - \overline{m}_{lateral}}{\left|\overline{m}_{medial} - \overline{m}_{lateral}\right|} \times \overline{Y}_{LowerCrutch} \quad (28)$$

$$\overline{Z}_{LowerCrutch} = \overline{X}_{LowerCrutch} \times \overline{Y}_{LowerCrutch} \quad (29)$$

Cuff

To define the cuff coordinate system, a temporary segment was first designed, which was positively rotated along the Z-axis by an angle of 15 degrees. The 15-degree angle is attributed to the cuff being rotated 15 degrees with reference to the vertical shaft (Figure 2). To obtain the origin of the cuff segment, the midpoint of the upper load cell was estimated by translating the lower load cell midpoint by 9 cm in the Y direction of the temporary axis. The cuff segment had the same orientation as the temporary axis while the origin of this coordinate system was located at the midpoint of the upper load cell. The temporary axis definitions, origin of the cuff segment, and the axes of the coordinate system of the cuff segment are given below.[19]

$$\overline{Z}_{temp} = \overline{Z}_{Handle} \quad (30)$$

$$\overline{X}_{temp} = \overline{X}_{Handle} * \cos(15^o) - \overline{Y}_{Handle} * \sin(15^o) \quad (31)$$

$$\overline{Y}_{temp} = \overline{X}_{Handle} * \sin(15^o) + \overline{Y}_{Handle} * \cos(15^o) \quad (32)$$

$$\overline{cuff}_c = \left(\overline{lc}_c + 0.09\right) \times \overline{Y}_{temp} \quad (33)$$

$$\overline{Z}_{cuff} = \overline{Z}_{temp} \quad (34)$$

$$\overline{X}_{cuff} = \overline{X}_{temp} \quad (35)$$

$$\overline{Y}_{cuff} = \overline{Y}_{temp} \quad (36)$$

Euler Angle Sequence

The Z-X-Y Euler rotation sequence was used to evaluate the UE joint kinematics.[27]

$$R = \begin{bmatrix} -\sin(\theta_1)\sin(\theta_2)\sin(\theta_3)+\cos(\theta_1)\cos(\theta_3) & -\sin(\theta_1)\cos(\theta_2) & \sin(\theta_1)\sin(\theta_2)\cos(\theta_3)+\cos(\theta_1)\sin(\theta_3) \\ \cos(\theta_1)\sin(\theta_2)\sin(\theta_3)+\sin(\theta_1)\cos(\theta_3) & \cos(\theta_1)\cos(\theta_2) & -\cos(\theta_1)\sin(\theta_2)\cos(\theta_3)+\sin(\theta_1)\sin(\theta_3) \\ -\cos(\theta_2)\sin(\theta_3) & \sin(\theta_2) & \cos(\theta_2)\cos(\theta_3) \end{bmatrix} \quad (37)$$

Kinetic Model

Lofstrand crutches (Walk Easy, Inc., Delray Beach, FL) were instrumented with four six-degree-of-freedom, custom designed load cells (2 per crutch; AMTI, Watertown, MA). One transducer each was placed above and below the crutch handle to directly measure triaxial forces and moments. The analog data from the load cells were amplified using AMTI MSA-6 high gain amplifiers. The weight of each load cell and crutch was 0.10 kg and 0.43 kg, respectively.

Kinetic Equations

The kinetic equations were computed using the inverse dynamics Newton-Euler approach.[27] Reaction forces and moments from the two load cells in each crutch were used recursively to solve the kinetic equations one after the other, starting from the most distal segment. The proximal forces were computed from the known distal forces, mass, and acceleration of a segment. The proximal moments were computed from the known distal moments, rate of change of angular momentum of the segment, moment arms, and moment contribution of the distal and proximal forces. The free body diagrams for each segment are displayed (Figures 3-5). The kinetic equations for each segment were applied separately in the x, y and z directions.

Lower Crutch Segment

The lower crutch segment consisted of the lower load cell and the lower shaft of the crutch. The force and moment from the lower load cell were used to evaluate the force and moment contribution at the crutch tip (Figure 3) as

$$\overline{F}_{ctip} = -m_{ctip}(\overline{a}_{ctip} + \overline{g}) - \overline{F}_{lowerLC} \quad (38)$$

$$\overline{M}_{ctip} = \dot{H}_{ctip} - \overline{M}_{lowerLC} - \overline{r}_{dist} \times \overline{F}_{ctip} - \overline{r}_{prox} \times \overline{F}_{lowerLC} \quad (39)$$

where $\overline{F}_{ctip}$ and $\overline{M}_{ctip}$ are the unknown force and moment occurring at the crutch tip. m_{ctip} and $\bar{a}_{ctip}$ are the mass and the linear acceleration of the lower crutch segment. $\bar{g}$ is the acceleration due to gravity. $\overline{F}_{lowerLC}$ and $\overline{M}_{lowerLC}$ are the known force and moment at the lower load cell. $\dot{H}_{ctip}$ is zero since the angular velocities and accelerations are zero for a rigid body. $\bar{r}_{dist}$ is the distance from the crutch tip and $\bar{r}_{prox}$ is the distance from the center of the lower load cell to the center of mass (CoM) of the lower segment.[19]

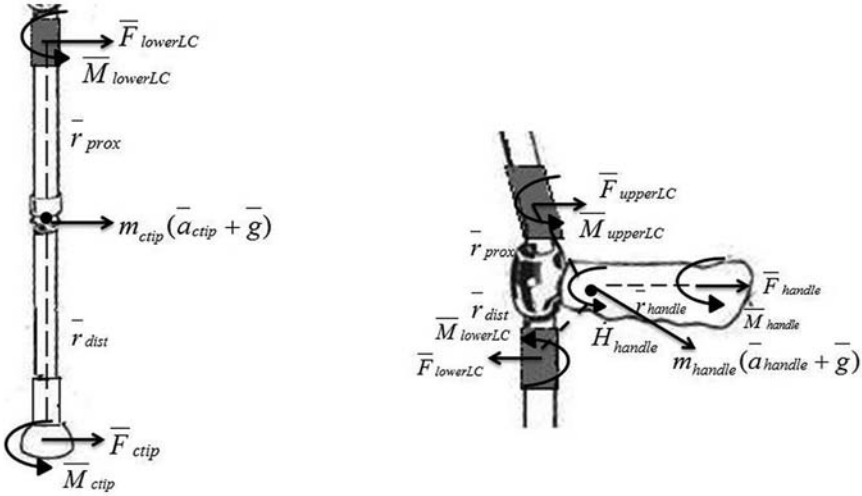

Figure 3. Kinetic model of the lower crutch and crutch handle segments. (Reprinted from Journal of Biomechanics, 44 (11), Brooke A. Slavens, Neha Bhagchandani, Mei Wang, Peter A. Smith, and Gerald F. Harris, An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait, Copyright 2011, with permission from Elsevier.[19])

Handle Segment

The handle segment consists of the crutch handle, and the lower and upper load cells. The force and moment from the lower and upper load cells were used to determine the force and moment contribution at the handle (Figure 3). These terms are

$$\overline{F}_{handle} = -m_{handle}(\bar{a}_{handle} + \bar{g}) + \overline{F}_{lowerLC} - \overline{F}_{upperLC} \tag{40}$$

$$\overline{M}_{handle} = \dot{H}_{handle} + \overline{M}_{lowerLC} - \overline{M}_{upperLC} + \bar{r}_{dist} \times \overline{F}_{lowerLC} - \bar{r}_{prox} \times \overline{F}_{upperLC} - \bar{r}_{handle} \times \overline{F}_{handle} \tag{41}$$

where $\overline{F}_{handle}$ and $\overline{M}_{handle}$ are the unknown force and moment occurring at the point of contact between the hand the crutch handle. m_{handle} and $\bar{a}_{handle}$ are the mass and the linear acceleration of the handle segment. $\overline{F}_{lowerLC}$ and $\overline{M}_{lowerLC}$ are the known force and moment at the lower load cell. $\overline{F}_{upperLC}$ and $\overline{M}_{upperLC}$ are the known force and moment at the upper load cell. $\dot{H}_{handle}$ is the rate of change of angular momentum of the handle segment. $\bar{r}_{dist}$ is the distance from the CoM of the lower load cell, $\bar{r}_{prox}$ is the distance from the CoM of the upper load cell and $\bar{r}_{handle}$ is the distance from the point of contact of the hand on the crutch handle to the CoM of the handle segment.[19]

Cuff Segment

The cuff segment consisted of the upper load cell and the cuff. The force and moment from the upper load cell were used to calculate the force and moment contribution at the cuff (Figure 4) as

$$\overline{F}_{cuff} = -m_{cuff}(\bar{a}_{cuff} + \bar{g}) + \overline{F}_{upperLC} \tag{42}$$

$$\overline{M}_{cuff} = \dot{H}_{cuff} - \overline{M}_{upperLC} + \bar{r}_{dist} \times \overline{F}_{upperLC} - \bar{r}_{prox} \times \overline{F}_{cuff} \tag{43}$$

where $\overline{F}_{cuff}$ and $\overline{M}_{cuff}$ are the unknown force and moment occurring at the point of contact of the cuff. m_{cuff} and $\bar{a}_{cuff}$ are the mass and the linear acceleration of the cuff segment. $\overline{F}_{upperLC}$ and $\overline{M}_{upperLC}$ are the known force and moment at the upper load cell. $\dot{H}_{cuff}$ is zero since the angular velocities and accelerations are zero for a rigid body. $\bar{r}_{dist}$ is the distance from the CoM of the upper load cell and $\bar{r}_{prox}$ is the distance from the point of contact at the cuff to the CoM of the cuff segment.[19]

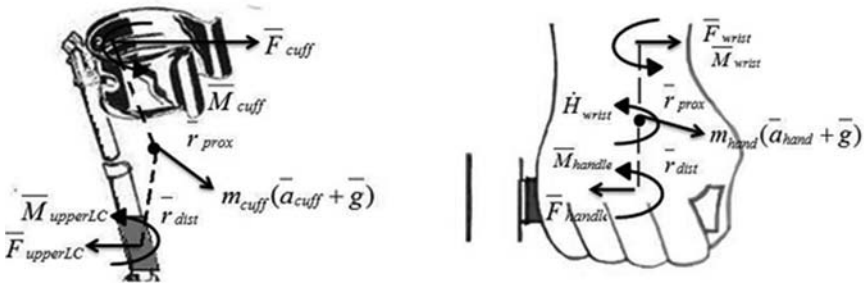

Figure 4. Kinetic model of the crutch cuff and hand segments. (Reprinted from Journal of Biomechanics, 44 (11), Brooke A. Slavens, Neha Bhagchandani, Mei Wang, Peter A. Smith, and Gerald F. Harris, An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait, Copyright 2011, with permission from Elsevier.[19])

Hand Segment

The force and moment from the lower load cell were used to evaluate the force and moment contribution at the wrist (Figure 4). These terms are

$$\overline{F}_{wrist} = -m_{hand}(\bar{a}_{hand} + \bar{g}) + \overline{F}_{handle} \tag{44}$$

$$\overline{M}_{wrist} = \dot{H}_{wrist} + \overline{M}_{handle} + \bar{r}_{dist} \times \overline{F}_{handle} - \bar{r}_{prox} \times \overline{F}_{wrist} \tag{45}$$

where $\overline{F}_{wrist}$ and $\overline{M}_{wrist}$ are the unknown force and moment occurring at the wrist joint. m_{wrist} and $\bar{a}_{wrist}$ are the mass and the linear acceleration of the wrist segment. $\overline{F}_{handle}$ and $\overline{M}_{handle}$ are the known force and moment at the point of contact between the hand and crutch handle. $\dot{H}_{wrist}$ is the rate of change of angular momentum of the wrist segment. $\bar{r}_{dist}$ is the distance from the point of contact between the hand and crutch handle and $\bar{r}_{prox}$ is the distance from the wrist joint center to the CoM of the wrist segment.[19]

Forearm Segment

The force and moment from the wrist joint and the point of contact at the cuff were used to compute the force and moment at the elbow (Figure 5) as

$$\overline{F}_{elbow} = -m_{forearm}(\bar{a}_{forearm} + \bar{g}) + \overline{F}_{wrist} + \overline{F}_{cuff} \tag{46}$$

$$\overline{M}_{elbow} = \dot{H}_{elbow} + \overline{M}_{wrist} + \overline{M}_{cuff} + r_{dist} \times \overline{F}_{wrist} + r_{cuff} \times \overline{F}_{cuff} - r_{prox} \times \overline{F}_{wrist} \tag{47}$$

where $\overline{F}_{elbow}$ and $\overline{M}_{elbow}$ are the unknown force and moment occurring at the elbow joint. m_{elbow} and $\bar{a}_{elbow}$ are the mass and the linear acceleration of the forearm segment. $\overline{F}_{wrist}$ and $\overline{M}_{wrist}$ are the known force and moment at the wrist joint. $\overline{F}_{cuff}$ and $\overline{M}_{cuff}$ are the known force and moment at the point of contact of the cuff. $\dot{H}_{elbow}$ is the rate of change of angular momentum of the elbow joint. $\bar{r}_{dist}$ is the distance from the wrist joint center, $\bar{r}_{prox}$ is the distance from the elbow joint center and $\bar{r}_{cuff}$ is the distance from the point of contact at the cuff to the CoM of the elbow segment.[19]

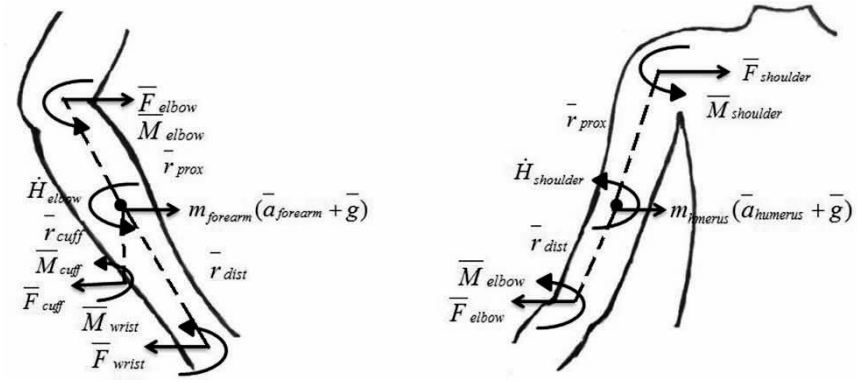

Figure 5. Kinetic model of the forearm and upper arm segments. (Reprinted from Journal of Biomechanics, 44 (11), Brooke A. Slavens, Neha Bhagchandani, Mei Wang, Peter A. Smith, and Gerald F. Harris, An upper extremity inverse dynamics model for pediatric Lofstrand crutch-assisted gait, Copyright 2011, with permission from Elsevier.[19])

Upper Arm Segment

The upper arm segment consisted of the humerus. The force and moment from the elbow joint were used to calculate the force and moment contribution at the shoulder (Figure 5), which are

$$\overline{F}_{shoulder} = -m_{humerus}\left(\bar{a}_{humerus} + \bar{g}\right) + \overline{F}_{elbow} \tag{48}$$

$$\overline{M}_{shoulder} = \dot{H}_{shoulder} + \overline{M}_{elbow} + \bar{r}_{dist} \times \overline{F}_{elbow} - \bar{r}_{prox} \times \overline{F}_{shoulder} \tag{49}$$

where $\overline{F}_{shoulder}$ and $\overline{M}_{shoulder}$ are the unknown force and moment occurring at the shoulder joint. $m_{humerus}$ and $\bar{a}_{humerus}$ are the mass and the linear

acceleration of the upper arm segment. $\overline{F}_{elbow}$ and $\overline{M}_{elbow}$ are the known force and moment at the elbow joint. $\dot{H}_{shoulder}$ is the rate of change of angular momentum of the shoulder joint. $\bar{r}_{dist}$ is the distance from the elbow joint center and $\bar{r}_{prox}$ is the distance from the shoulder joint center to the CoM of the upper arm segment.[19]

System Evaluation

Static evaluation was conducted by applying two pound loads along the three primary axes of the instrumented crutches at the shaft and the forearm cuff while the crutch was supported by an alignment device to independently evaluate each 6-axis load cell. Dynamic evaluation of the system was then performed by having a normal subject walk with the instrumented crutches over a calibrated force plate, which was similar to previous validation methods.[19,26,28] The resultant forces measured by both systems were calculated. Percentage root mean square (RMS) error and standard deviation (SD) from five trials was computed for static and dynamic evaluations to determine system accuracy and precision.[19]

Subject Demonstration

A female subject with type I OI (age: 16 yrs, height: 1.4 m, weight: 44 kg) participated in the study after acquiring written parental consent and subject assent in compliance with Shriners Hospitals for Children-Chicago's Institutional Review Board (IRB) requirements. Exclusion criteria included orthopaedic surgery in the last one-year or a fracture in the last six months. The instrumented Lofstrand crutches were adjusted to match the height and cuff size of the subject's current crutches. A 14-camera Vicon motion analysis system (Vicon, Oxford, England) recorded the subject ambulating with the kinetic Lofstrand crutches and the marker system on a six-meter walkway at a self-selected pace and gait pattern (two-point reciprocal gait pattern). The kinematic data were sampled at 120 Hz and filtered with a Woltring filter. The gait cycle was normalized from heel strike to heel strike and averaged over six trials. Matlab (MathWorks Inc., Natick, MA) was used for post-processing. Joint reaction forces and moments were computed and normalized to % body weight (% BW) and % body weight multiplied by height (% BW*H), respectively.

Data Collection and Analysis

Mean cadence, walking speed, stride length, and stance duration were determined from the lower extremity kinematics data. Motions of the crutch, thorax, shoulder, elbow, and wrist were evaluated three-dimensionally. The range of motion (ROM) was computed as the difference of the maximum and minimum motions. Mean external forces and moments at the crutch tip, handle, and cuff were computed. Mean joint reaction forces and joint reaction moments were calculated bilaterally for the wrist, elbow, and shoulder. Forces were normalized to percent body weight (% BW) and moments were normalized to percent body weight times height (% BW*H). Peak forces and moments were defined as the absolute maximum forces and moments during the gait cycle, respectively.

RESULTS

System Evaluation

The % RMS error and standard deviation (SD) in the sagittal plane during static validation were most notable (Table 1). The smallest error of 0.84% RMS was documented in the inferior force of the lower right load cell. The smallest SD of 0.001 N was documented in the fore tilt moment of the lower left load cell. The left crutch presented a smaller error and SD than the right crutch during dynamic validation against the force plate (Table 2).

Table 1. Static evaluation of the crutch sensor system measured by root mean square (RMS) error and standard deviation (SD).[19]

Forces and moments	Root mean square error (%)		Standard deviation (N)	
	Right	Left	Right	Left
Upper load cell: inferior force	4.06	1.11	0.11	0.04
Upper load cell: fore tilt moment	4.09	4.76	0.001	0.05
Lower load cell: inferior force	0.84	0.90	0.05	0.05
Lower load cell: fore tilt moment	3.74	5.20	0.03	0.001

Table 2. Dynamic evaluation of the right and left crutch load cells resultant force measured by root mean square (RMS) error and standard deviation (SD).[19]

Resultant force	Root mean square error (%)		Standard deviation (N)	
	Right	Left	Right	Left
	2.81	1.43	0.55	0.29

Kinematics

The subject presented with 103 steps/min cadence, 0.78 m/s walking speed, 0.91 m stride length, and a stance duration of 65%. Cadence, walking speed, and stride length were relatively high as compared with other crutch-user pathologies.[19] Kinematic curves are presented for the crutches and UEs for the primary weight bearing extremity (Figure 6).

Crutches

The subject demonstrated crutch fore tilt for 0-30% of the gait cycle, followed by aft tilt for the rest of the gait cycle (Figure 6). Throughout the gait cycle, the crutches were titled laterally and internally rotated. Crutch ROM in the sagittal plane was 31 degrees.

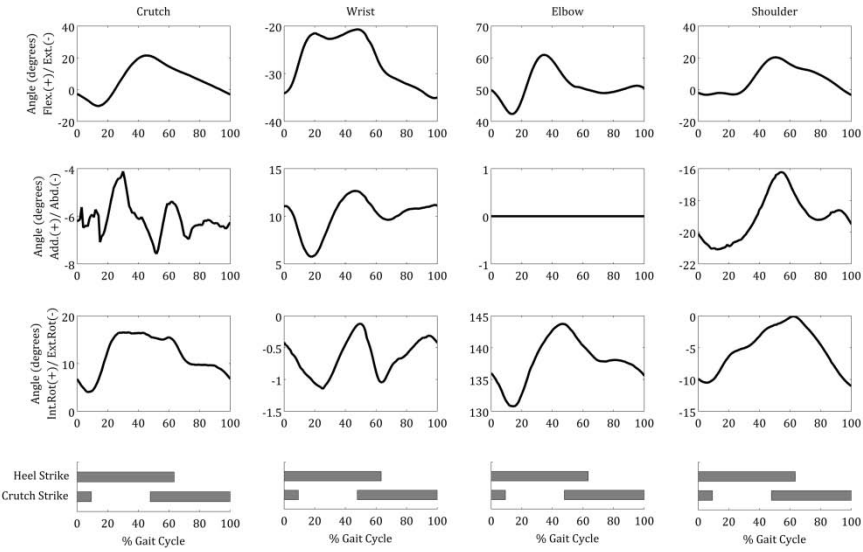

Figure 6. Crutch, wrist, elbow, and shoulder joint motions for the primary weight bearing extremity (right side) from 0-100% of the gait cycle .

Wrist

The wrist demonstrated the smallest ROM of the UE joints (Figure 6). Wrist kinematics displayed extension, adduction and external rotation for the entire gait cycle. Wrist ROM in the sagittal plane was 14 degrees.

Elbow

The elbow moved in flexion and internal rotation throughout the gait cycle (Figure 6). The elbow was constrained in the coronal plane. Elbow ROM in the sagittal plane was 18 degrees.

Shoulder

The shoulder demonstrated the largest ROM of the UE joints (Figure 6). Shoulder ROM in the sagittal plane was 24 degrees. Sagittal plane shoulder motion displayed extension from 0-30% of gait cycle, which was followed by flexion until the end of the gait cycle. Shoulder motion remained abducted and externally rotated during the gait cycle.

Thorax

The frontal plane showed the greatest ROM for the thorax in lateral bending (Figure 6). Sagittal plane motion presented as flexion throughout the gait cycle. The subject demonstrated clockwise rotation for 0-40% of the gait cycle, followed by counterclockwise rotation for rest of the gait cycle.

Kinetics

The subject presented a primary weight bearing extremity (right leg), which showed more significant, higher joint reaction forces and moments than the contralateral extremity. Kinetic forces and moments of the crutches, shoulder, elbow and wrist for the right side are depicted (Figures 7-10).

Crutch

Forces and moments were measured at the crutch tip, handle, and cuff for improved accuracy from previous models. Due to the calibration procedure, all forces were zero when the crutch was off the ground.

Crutch tip

Crutch tip forces were minimal in the anterior/posterior and medial/lateral directions (Figure 7). The largest crutch tip forces occurred in the inferior direction, with a peak of 21% BW. Crutch tip abduction moments were largest followed by extension moments (Figure 8). Internal and external rotation moments were minimal.

Crutch handle

The largest forces at the crutch handle were directed superiorly (Figure 7). Peak superior force was 16% BW. Lateral and posterior forces were also present. Cuff moments presented relatively similar magnitudes for extension, adduction, and internal rotation (Figure 8).

Crutch cuff

Anteriorly directed forces were the largest forces at the cuff (Figure 7). The peak anterior force was 4.3% BW. The cuff forces were also directed laterally, superiorly, and inferiorly. Cuff moments were minimal in all planes, showing extension, adduction, and external rotation (Figure 8).

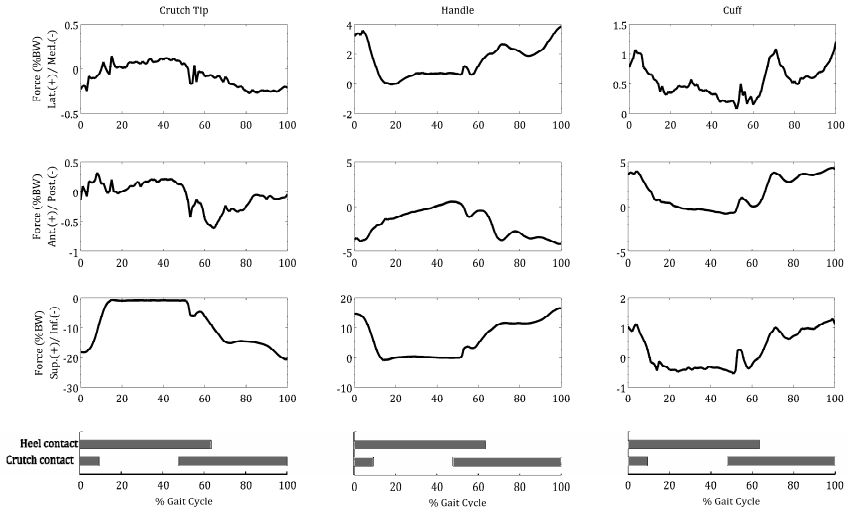

Figure 7. Crutch tip, handle, and cuff reaction forces for the primary weight bearing extremity (right side) from 0-100% of the gait cycle. Forces are normalized to percent body weight (% BW).

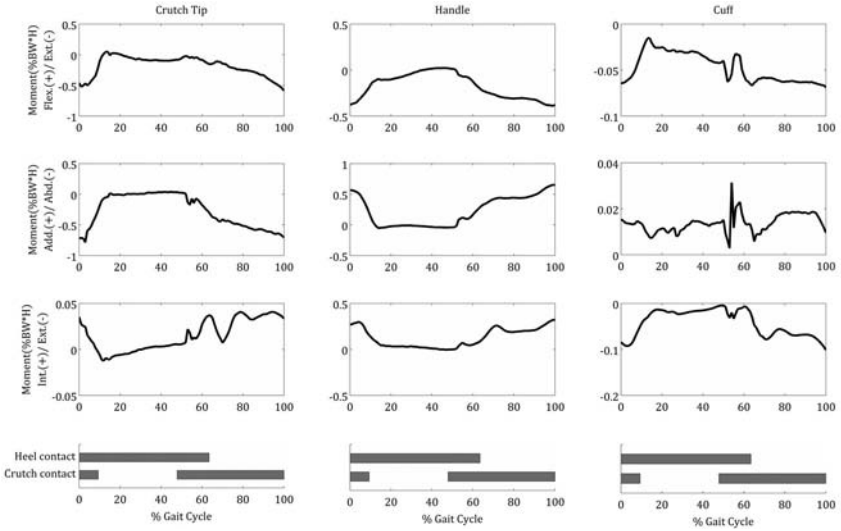

Figure 8. Crutch tip, handle, and cuff reaction moments for the primary weight bearing extremity (right side) from 0-100% of the gait cycle. Moments are normalized to percent body weight multiplied by height (% BW*H).

Wrist

Wrist joint reaction forces presented medially, posteriorly, and superiorly during the gait cycle (Figure 9). The largest peak forces were 15% BW and were directed posteriorly. The wrist joint reaction moments presented in the directions of flexion, adduction, and internal rotation (Figure 10). The peak wrist moment was 0.7 % BW*H.

Elbow

The elbow displayed the largest joint reaction forces of all UE joints (Figure 9). The elbow joint reaction forces were largest in the superior direction with a peak of 15% BW. Forces were also directed posteriorly during crutch contact, anteriorly during heel contact, and medially throughout the gait cycle. The largest moment at the elbow was the adduction moment (1.1% BW*H), followed by the extension moment, and then the internal rotation moment (Figure 10).

Shoulder

The shoulder joint showed forces in all directions (Figure 9). The largest shoulder joint forces were in the superior direction, with a peak of 9% BW.

The flexion moment was the largest shoulder joint reaction moment, followed by the abduction moment, and external rotation moment (Figure 10). The peak flexion shoulder moment was 1.9 % BW*H. The shoulder had the largest moments of all UE joints.

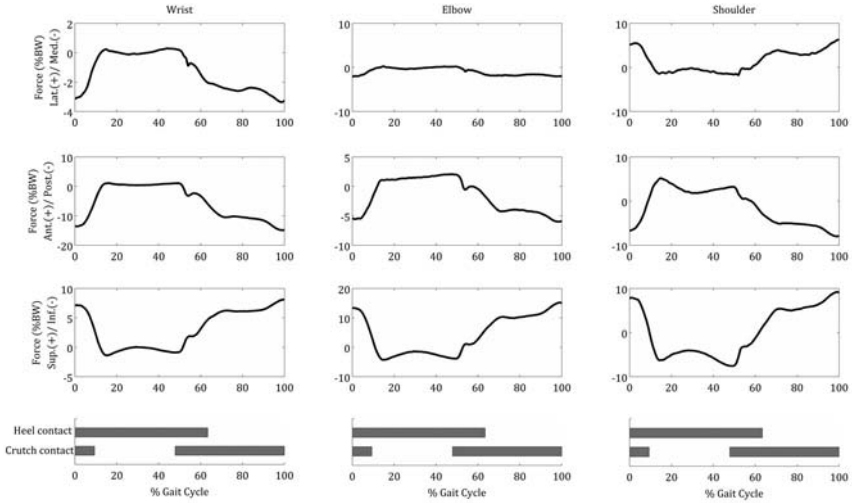

Figure 9. Wrist, elbow, and shoulder joint reaction forces for the primary weight bearing extremity (right side) from 0-100% of the gait cycle. Forces are normalized to percent body weight (% BW).

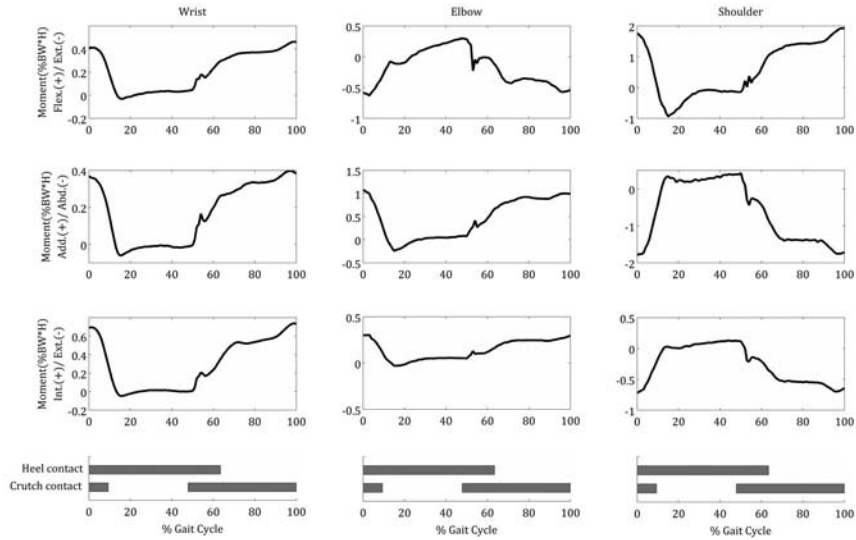

Figure 10. Wrist, elbow, and shoulder joint reaction moments for the primary weight bearing extremity (right side) from 0-100% of the gait cycle. Moments are normalized to percent body weight multiplied by height (% BW*H).

DISCUSSION

Upper extremity movement assessment in children with OI has been limited. Nonetheless, UE model development and application to assisted gait has been of great interest to our group. Slavens et al. designed the first generation Lofstrand crutch model for evaluation of UE dynamics in children with myelomeningocele.[22,28] This ISB compliant model used 26 markers and a kinetic Lofstrand crutch system to acquire 3-D shoulder, elbow, and wrist joint forces and moments. Hardware limitations only allowed single force transducers to be placed at the distal end of the Lofstrand crutches to capture 3-D reaction forces and moments. This model was applied to nine subjects with myelomeningocele for comparison of common Lofstrand crutch assisted gait patterns, including reciprocal gait and swing-through gait. Findings showed that swing-through gait placed the greatest forces on the shoulder and elbow joints, which were approximately 50% BW. Accurate quantitative assessment was shown to be essential for preventing injury in long-term crutch users. Results of this study led to a new Lofstrand crutch hardware design for further investigation of joint load demands on the UEs during assisted gait. New advances in hardware technology led us to our current research, incorporating dual sensors per crutch, for improved accuracy of joint kinetics. This system enabled the crutch cuff kinetics to be resolved. In addition, the newest design is lighter weight and has a reduced moment of inertia due to the location of the hardware components. The kinetic Lofstrand crutch system has been applied to children with orthopaedic disabilities for quantification of UE joint load demands.[19] Specifically, the application of this system to children with OI will help determine their risk for fracture, and may provide insight for ways to decrease joint loads during assisted gait.

This work supports the use of a technically validated inverse dynamics model to evaluate UE ambulation patterns of children with OI during Lofstrand crutch-assisted gait. The crutch system was utilized for characterizing 3-D joint kinematics and kinetics of the shoulder, elbow, and wrist. The superior joint forces at the shoulder and elbow, and the posterior wrist forces demonstrate the most significant findings concerning joint loading demands for this subject with OI. The flexion moment at the shoulder was the largest joint moment of the UEs. These joint forces and moments are of concern with long-term crutch usage in the OI population, since it has been shown that UE pain and pathology may develop.[10,13,15]

We hope to clinically utilize the UE dynamics results to identify potential kinetic risk factors for the OI population. Our goal is to minimize skeletal loads in an effort to reduce fracture risk in children with OI. Through the use of advanced inverse dynamics models, along with computational modeling such as finite element and musculoskeletal modeling, new prediction tools may be developed to predict or prevent bone fractures. Advanced modeling techniques may also lead to innovative assistive device design and development. Improved crutch designs may allow one to be alerted when reaching concerning load levels. Alternative crutch cuff and handle designs may also be implemented to further reduce loading on the UE joints.

CONCLUSION

We conclude that the 3-D kinetic Lofstrand crutch system is useful for quantifying UE joint motions, forces, and moments during assisted gait. Risk factors for UE joint pathology may be identified using this kinetic system. The inverse dynamics model may be used to better understand joint load optimization through activity modification, gait training, and crutch re-design. This research may ultimately improve crutch prescription, therapeutic gait planning, and offer insight to longer-term joint loading effects in children with OI.

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REFERENCES

1. Kaye HS, Kang T, LaPlante MP. Mobility device use in the United States. *Disability Statistics Report (14)*. Washington, D.C.: U.S. Department of Education, National Institute on Disability and Rehabilitation Research; 2000.
2. Slavens BA, Frantz J, Sturm PF, Harris GF. Upper extremity dynamics during Lofstrand crutch-assisted gait in children with myelomeningocele. *Journal of Spinal Cord Medicine* 2007; 30: 77-83.
3. Slavens BA, Harris GF. The biomechanics of upper extremity kinematic and kinetic modeling: Applications to rehabilitation engineering. *Critical Reviews in Biomedical Engineering* 2008; 36(2-3): 93-125.

4. Slavens BA, Bhagchandani N, Wang M, Smith PA, Harris GF. Motion analysis of the upper extremities during lofstrand crutch-assisted gait in children with orthopaedic disabilities. *Journal of Experimental & Clinical Medicine* 2011; 3(5): 218-227.
5. Harris GF, Smith PA. *Human motion analysis*. New York: IEEE Press; 1996.
6. Slavens BA, Harris GF. Biomechanics. In: Abu-Faraj ZO, ed. *Handbook of research on biomedical engineering education and advanced bioengineering learning: Interdisciplinary concepts*. Hershey, PA: IGI Global; 2012.
7. Gajko-Galicka A. Mutations in type I collagen genes resulting in osteogenesis imperfecta in humans. *Acta Biochimica Polonica* 2002; 49(2): 433-441.
8. Osteogenesis Imperfecta Foundation. Facts about osteogenesis imperfecta. 2007; http://www.oif.org/site/PageServer?pagename=AOI_Facts.
9. Byers PH, Steiner RD. Osteogenesis imperfecta. *Annual Review of Medicine* 1992; 43: 269-282.
10. Klimaitis A, Carroll G, Owen E. Rapidly progressive destructive arthropathy of the shoulder--a viewpoint on pathogenesis. *Journal of Rheumatology* 1988; *15(12):1859-62*.
11. Newsam CJ, Lee AD, Mulroy SJ, Perry J, Newsam CJ, Lee AD, et al. Shoulder emg during depression raise in men with spinal cord injury: The influence of lesion level. *Journal of Spinal Cord Medicine* 2003; 26(1): 59-64.
12. Sharkey NA, Marder RA. The rotator cuff opposes superior translation of the humeral head. *American Journal of Sports Medicine* 1995; 23(3): 270-275.
13. Lal S. Premature degenerative shoulder changes in spinal cord injury patients. *Spinal Cord* 1998; 36(3): 186-189.
14. Opila KA, Nicol AC, Paul JP. Upper limb loadings of gait with crutches. *Journal of Biomechanical Engineering* 1987; 109(4): 285-290.
15. Kellner WS, Felsenthal G, Anderson JM, Hilton EB, Mondell DL. Carpal tunnel syndrome in the nonparetic hands of hemiplegics. Stress-induced by ambulatory assistive devices. *Orthopaedic Review* 1986; 15(9): 608-611.
16. Sala DA, Leva LM, Kummer FJ, Grant AD. Crutch handle design: Effect on palmar loads during ambulation. *Archives of Physical Medicine and Rehabilitation* 1998; 79(11): 1473-1476.
17. Waring WP, Werner RA. Clinical management of carpal tunnel syndrome in patients with long-term sequelae of poliomyelitis. *Journal of Hand Surgery* 1989; 14(5): 865-869.
18. Wu G, van der Helm FC, Veeger HE, Makhsous M, Van Roy P, Anglin C, et al. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion--part ii: Shoulder, elbow, wrist and hand. *Journal of Biomechanics* 2005; 38(5): 981-992.
19. Slavens BA, Bhagchandani N, Wang M, Smith PA, Harris GF. An upper extremity inverse dynamics model for pediatric lofstrand crutch-assisted gait. *Journal of Biomechanics* 2011; 44(11): 2162-2167.
20. Bhagchandani N. *Upper extremity kinetics during lofstrand crutch-assisted gait in children*. Milwaukee, WI: Biomedical Engineering, Marquette University; 2010.
21. Nguyen TC, Baker R. Two methods of calculating thorax kinematics in children with myelomeningocele. *Clinical Biomechanics* 2004; 19(10): 1060-1065.
22. Slavens BA, Sturm PF, Bajorunaite R, Harris GF. Upper extremity dynamics during Lofstrand crutch-assisted gait in children with myelomeningocele. *Gait & Posture* 2009; 30: 511-517.
23. Rab G, Petuskey K, Bagley A. A method for determination of upper extremity kinematics. *Gait & Posture* 2002; 15(2): 113-119.

24. Schmidt R, Disselhorst-Klug C, Silny J, Rau G. A marker-based measurement procedure for unconstrained wrist and elbow motions. *Journal of Biomechanics* 1999; 32(6): 615-621.
25. Hingtgen BA, McGuire JR, Wang M, Harris GF. An upper extremity kinematic model for evaluation of hemiparetic stroke. *Journal of Biomechanics* 2006; 39(4): 681-688.
26. Requejo PS, Wahl DP, Bontrager EL, Newsam CJ, Gronley JK, Mulroy SJ, et al. Upper extremity kinetics during lofstrand crutch-assisted gait. *Medical Engineering & Physics* 2005; 27(1): 19-29.
27. Zatsiorsky VM. Joint torques and forces: The inverse problem of dynamics. In: Robertson LD, ed. *Kinetics of human motion.* Vol 2. Champaign, IL: Human Kinetics; 2002: 365-454.
28. Slavens BA, Sturm PF, Harris GF. Upper extremity inverse dynamics model for crutch-assisted gait assessment. *Journal of Biomechanics* 2010; 43(10): 2026-2031.

21 WHOLE-BODY VIBRATION: CONSIDERATIONS FOR STUDY DESIGN

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INTRODUCTION

Patients with severe forms of OI often not only suffer from their primary bone disorder but also from secondary problems that are due to immobilization, such as joint contractures and muscle weakness.[1] Preventing and treating disuse might be useful for improving both motor function and bone development in children with OI. Whole-Body Vibration (WBV) training of the musculoskeletal system is increasingly used in a variety of situations that require muscle and bone stimulation.[2-6] It is usually practiced on a vibrating platform on which the person is standing in a static position or moving in dynamic movements. A number of vibration devices are currently marketed for use in fitness or health care environments, but scientific data tend to be sparse on most of them. There are large differences between devices with regard to the kind of vibration that they generate.

Adding WBV to the therapeutic armamentarium of rehabilitation has several putative advantages. Vibration treatment could result in a faster gain of muscle function, as many more stimulation cycles are applied to the muscles than, for example, during walking. A 3-minute WBV session at a frequency of 20 Hz applies 3600 stimulatory impulses. This corresponds to the number of impulses received during one hour of walking, assuming a step frequency of one per second. WBV might also be safer than treatment modalities that involve walking. As the patient stands on the platform and does not actively move the limbs, there is less opportunity for slipping, tripping or awkward movements than when the patient is walking with walking aids. This should reduce the risk of accidents related to therapy. Finally WBV is accessible, especially if it can be performed at home. Various financial and societal barriers, such as those related to lack of equipment, availability of exercise instructors, and access to adapted transportation greatly limit the accessibility to physical activity in children with disabilities.[7]

Many WBV treatment studies aim at improving some aspect of neuromuscular performance or at increasing bone mass or density (for recent reviews see[8-14]). There is very little information on whether and how WBV can be used to treat patients with OI, but there is widespread interest in the topic.[15] In order to assess the utility of WBV in OI, clinical studies are required. This chapter provides some issues that need to be considered when setting up a WBV study.

PHYSICAL PRINCIPLES OF WBV

The physical principles of WBV have recently been summarized in detail by Rittweger.[10] Vibration is oscillatory motion about an equilibrium point. Several types of vibration can be distinguished but only sinusoidal vibrations are considered here, as this is the type of vibration that currently available WBV devices aim to provide (Figure 1).

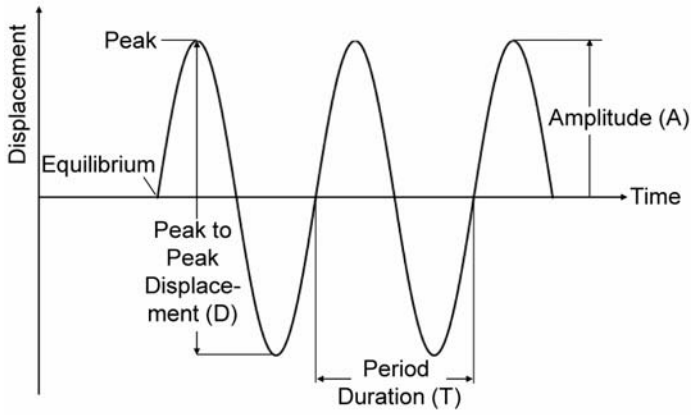

Figure 1. A plot of displacement against time in sinusoidal vibration. The definitions of the terms amplitude (A), peak-to-peak displacement (D) and period duration (T) are given in Table 1. The frequency (f) corresponding to the period duration is equal to: f=1/T (From: Rauch F, Sievanen H, Boonen S, Cardinale M, Degens H, Felsenberg D, Roth J, Schoenau E, Verschueren S, Rittweger J. Reporting whole-body vibration intervention studies: Recommendations of the International Society of Musculoskeletal and Neuronal Interactions. J Musculoskelet Neuronal Interact 2010;10:193-198).

WBV is applied through a vibrating surface that supports the study subject. WBV treatment studies are usually performed with the user standing on a motor-driven vibrating plate. The vibration transmitted to the body via the plate constitutes the vibration exposure to the user.

Terms that are commonly used to describe vibrations are defined and explained in Table 1. To describe a sinusoidal vibration, information is needed on both the frequency and the extent of the vibration. The extent of the vibration can be given as the displacement from the lowest to the highest point (= peak-to-peak displacement) or the maximum displacement from equilibrium (= amplitude).[16] In the WBV treatment literature, the term 'amplitude' has sometimes been confused with 'peak-to-peak amplitude'.[17] However, peak-to-peak amplitude is synonymous with peak-to-peak displacement and thus differs from the amplitude by a factor of 2 (Table 1). In order to avoid this confusion, it may be preferable to use the term 'peak-to-peak displacement' to indicate the extent of the vibration.

The commonly used descriptor of vibration, peak acceleration, can be mathematically derived from the frequency and the peak-to-peak displacement and therefore does not provide additional information once frequency and peak-to-peak displacement are known (Table 1). However, to facilitate comparisons between studies it is useful to provide acceleration levels associated with the vibration, preferably as the peak acceleration (a_{Peak}) in multiples of Earth's gravity (symbol: g; 1 g = 9.81 ms^{-2}). Alternatively, root-mean-squared acceleration (a_{RMS}) can also be reported. The root-mean-squared acceleration is the preferred descriptor if the WBV device produces vibrations that do not follow a pure sine wave pattern.[18] For a pure sinusoidal wave, a_{RMS} is obtained by dividing a_{Peak} by $\sqrt{2}$.

The actual oscillations generated by WBV devices may significantly deviate from a pure sine waveform. It is also possible that the frequency and amplitude generated by a device differ from the preset values, or from the values provided by the manufacturer, in particular when the participant is moving on the vibration plate.[19] The displacement and acceleration generated by a device also depend on the rigidity of the plate, which may differ between brands and between devices. These considerations highlight the need to evaluate the vibrations produced by a WBV device in a given study setting.

It is therefore useful to measure the actually generated vibration parameters (frequency, amplitude, acceleration) in a pilot test that is appropriate for the target group and WBV protocol of the planned intervention study. See section 'Ascertaining Vibration Parameters' for a description of how the accuracy of a vibration plate can be tested.

Table 1. Terms used to describe sinusoidal vibration.

	Unit	Definition	Symbol	Formula	Comments
Period duration	s	Duration of one oscillation cycle	T		
Frequency	Hz, s^{-1}	Repetition rate of the cycles of oscillation	f	$f = 1/T$	1 Hz = 1 s^{-1}
Peak-to-peak displacement	mm	Displacement from the lowest to the highest point of the total vibration excursion	D	$D=a_{Peak}/(2\pi^2f^2)$	Synonymous to 'peak-to-peak amplitude'
Amplitude	mm	Maximal displacement from equilibrium position	A	$A = D/2$	Synonymous to 'peak amplitude'
Peak acceleration	ms^{-2}	Maximal rate of change in velocity during an oscillation cycle	a_{Peak}	$a_{Peak} = 2\pi^2 f^2 D$ $a_{Peak} \approx 20f^2D$	Often expressed as multiples of Earth's gravity*
Root mean squared acceleration	ms^{-2}	Average rate of change in velocity during an oscillation cycle	a_{RMS}	$a_{RMS} = a_{peak}/\sqrt{2}$	

*Earth's gravity (commonly used symbol: g) is a constant (9.81 ms^{-2}) that denotes the nominal acceleration due to gravity at the Earth's surface at sea level. Example for calculating peak acceleration when vibration with a frequency of 20 Hz and a peak-to-peak displacement of 4 mm is used: Peak acceleration = 2 x π^2 x 400 s^{-2} x 0.004 m = 31.6 ms^{-2}. Expressed as a multiple of standard gravity, peak acceleration in this example is 31.6/9.81 g ≈ 3.2 g. The root-mean-squared acceleration is 31.6 $ms^{-2}/\sqrt{2}$ = 22.3 ms^{-2}. From Rauch et al.[23]

Depending on the vibration parameters, it is possible that the acceleration transmitted to the body does not follow the acceleration waveform of the plate but can be substantially distorted and attenuated.[20] The acceleration transmitted to the body can also be assessed, similar to the measurement of the acceleration produced by the WBV device. However, assessing vibration transmission in human subjects requires more experience and expertise than determining the vibration parameters of a vibration plate and therefore is useful only where such special expertise is available.

Vibration devices do not only differ with regard to the frequency and peak-to-peak displacement that they generate. Some models apply the vibration to the right and the left foot in a side-alternating way (Figure 2). On other vibration plates, the right and the left foot move up and down at the same time. These latter devices are said to operate in a synchronous way.[10] The difference between synchronous and side-alternating devices is a key consideration when planning WBV interventions.

For synchronous WBV, the peak-to-peak displacement and peak acceleration are identical for the entire surface of the plate, if the force transmission from the motor to the plate is rigid. However, springs attached to the vibrating plate (e.g., to the corners) may affect the local acceleration. For side-alternating WBV, the vibrating plate typically oscillates about a horizontal anteroposterior central axis. The peak-to-peak displacement and thus peak acceleration of a given point on the surface of such a vibration plate depends on the distance of this point from the central axis, while the rigidity of the plate accounts for the actual displacements and accelerations at the given point. At least some inter-device variation in the flexural rigidity of the plate can be expected, which underpins the importance of measuring the actual performance of the given vibration device, as indicated in the next section.

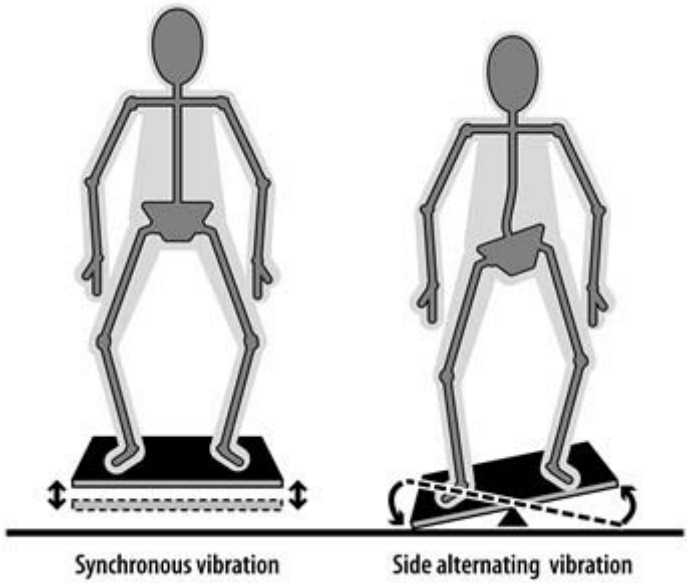

Figure 2. Direction of vibration movement in synchronous and in side-alternating vibration. (From: Rauch F, Sievanen H, Boonen S, Cardinale M, Degens H, Felsenberg D, Roth J, Schoenau E, Verschueren S, Rittweger J. Reporting whole-body vibration intervention studies: Recommendations of the International Society of Musculoskeletal and Neuronal Interactions. J Musculoskelet Neuronal Interact 2010;10:193-198).

ASCERTAINING VIBRATION PARAMETERS

The accuracy of vibration settings on a given device can be verified using an accelerometer. Many commercially available accelerometers measure acceleration in all three dimensions and are therefore called tri-axial

accelerometers, but a two-axial or even a one-axial accelerometer could still be used for verifying WBV parameters.

The accelerometer needs to be firmly affixed to the plate. This can be done with double-sided sticky tape from a local hardware store. It is important that the accelerometer is affixed exactly at the location on the plate for which vibration parameters are to be determined. This is particularly relevant for side-alternating systems.

The remainder of the testing setup depends on the type of accelerometer that is used. The simplest solution is probably to use an accelerometer that stores vibration data on an integrated storage chip without the need for additional equipment. Once the accelerometer is calibrated and solidly affixed to the vibration plate, the WBV system can be switched on and the accelerometer signal can be recorded. The WBV system will usually take a few seconds to get to speed, so the analysis should include only recordings that were obtained after acceleration readings have stabilized.

It first should be verified whether the vibration signal is sinusoidal. This could be done by simple visual inspection of the graphical read-out of the recording device. Alternatively, the recorded vibration measurements could be imported into a software that evaluates how much of the signal power is within the fundamental frequency of oscillation.

In synchronous systems, there should normally be no or only very little acceleration in directions other than the vertical. For side-alternating systems, a small acceleration in a lateral direction is expected. In either type of vibration plate, if there is considerable acceleration in planes other than the vertical, then the fixation of the accelerometer to the vibration plate probably needs to be improved. However, if the accelerometer fixation is solid and the vibration signal is still not sinusoidal, then it is likely that the WBV system does not produce sinusoidal vibration and registration of the two other orthogonal acceleration axes are useful.

Next, the frequency of the vibration should be evaluated on the basis of the accelerometer read-out. One way to do this is to count a given number of vibration cycles (e.g., from one peak to the next) and to divide that number by the time (in seconds) interval between the peaks. The resulting ratio is the frequency in Hz. Finally, one should assess peak acceleration. It should be

possible to obtain peak acceleration directly from the accelerometer readings.

CONSIDERATIONS REGARDING THE INTERVENTION PROTOCOL

Apart from details about the settings of the WBV device, the actual intervention protocol of how WBV is applied needs to be given careful consideration. A number of key decisions have to be made when setting up a WBV study.

It is essential to decide which type of vibration plate is to be used (synchronous, side-alternating, other), as well as its frequency, peak-to-peak displacement and measured peak acceleration in different vibration settings appropriate for the study. A study protocol should describe the vibration produced by the device with sufficient detail, so that readers can appreciate the applied vibration without consulting the user manual of the device. For side-alternating devices, it is critical to indicate the peak-to-peak displacement for the precise foot position that is used in a study. The recommended landmark for indicating peak-to-peak displacement is the second toe, which is at about mid-distance between the contact points of the forefoot.

The study protocol should further indicate whether the accuracy of these vibration parameters was tested and if so, how this was done. The vibration settings may change during the study interval (e.g., in order to provide progressive training). If so, these changes should be listed. If changes in vibration settings are dependent on some characteristic of the study participants then this should be clearly stated. Whatever vibration settings are selected, a rationale for their choices should be provided.

Apart from these device-oriented descriptors, the force and acceleration produced by the vibration in the body depend on how the device is used. It is essential to decide whether study participants are to stand freely on the device, hold on to some support or whether the vibration plate is to be combined with some other device, such as a tilt table. The type of footwear, if any, also has an obvious influence on the vibration transmitted to the study participant.[21] Another critical element is the description of the body position and posture of the study participant on the plate.[10] The relevant information in this respect includes knee and hip angle, whether the participant is

standing on one or two legs, leaning on toes or heels, and whether the trunk is upright or tilted forward.

Study participants may perform exercises while using the WBV device. If so, the exercise should be described in sufficient detail. For dynamic exercises the speed of the movement and the range of motion should be indicated.[22]

CONCLUSION

WBV is a new treatment modality for rehabilitation that may also be of interest for use in patients with OI. Setting up trials on WBV is not a trivial undertaking, as treatment protocols tend to be complex. The considerations here should be helpful in drawing up study protocols and implementing them.

ABBREVIATIONS

A	Amplitude
a_{Peak}	Peak acceleration
a_{RMS}	Root mean squared acceleration
D	Peak-to-peak displacement
f	Frequency
T	Period duration
WBV	Whole body vibration

REFERENCES

1. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet.* 2004;363(9418):1377-1385.
2. Lindberg J, Carlsson J. The effects of whole-body vibration training on gait and walking ability - A systematic review comparing two quality indexes. *Physiotherapy theory and practice.* Jan 3 2012.
3. Perraton L, Machotka Z, Kumar S. Whole-body vibration to treat low back pain: fact or fad? *Physiotherapy Canada. Physiotherapie Canada.* Winter 2011;63(1):88-93.
4. Pozo-Cruz BD, Adsuar JC, Parraca JA, Pozo-Cruz JD, Olivares PR, Gusi N. Using Whole-Body Vibration Training in Patients Affected with Common Neurological Diseases: A Systematic Literature Review. *Journal of alternative and complementary medicine (New York, N.Y.).* Jan 10 2012.
5. Sitja-Rabert M, Rigau D, Fort Vanmeerghaeghe A, Romero-Rodriguez D, Bonastre Subirana M, Bonfill X. Efficacy of whole body vibration exercise in older people: a systematic review. *Disabil Rehabil.* Jan 6 2012.
6. Slatkovska L, Alibhai SM, Beyene J, Cheung AM. Effect of whole-body vibration on BMD: a systematic review and meta-analysis. *Osteoporos Int.* Dec 2010;21(12):1969-1980.

7. Fowler EG, Kolobe TH, Damiano DL, et al. Promotion of physical fitness and prevention of secondary conditions for children with cerebral palsy: section on pediatrics research summit proceedings. *Phys Ther.* Nov 2007;87(11):1495-1510.
8. de Zepetnek JO, Giangregorio LM, Craven BC. Whole-body vibration as potential intervention for people with low bone mineral density and osteoporosis: a review. *J Rehabil Res Dev.* 2009;46(4):529-542.
9. Prisby RD, Lafage-Proust MH, Malaval L, Belli A, Vico L. Effects of whole body vibration on the skeleton and other organ systems in man and animal models: what we know and what we need to know. *Ageing Res Rev.* Dec 2008;7(4):319-329.
10. Rittweger J. Vibration as an exercise modality: how it may work, and what its potential might be. *Eur J Appl Physiol.* Mar 2010;108(5):877-904.
11. Marin PJ, Rhea MR. Effects of vibration training on muscle power: a meta-analysis. *J Strength Cond Res.* Mar 2010;24(3):871-878.
12. Marin PJ, Rhea MR. Effects of vibration training on muscle strength: a meta-analysis. *J Strength Cond Res.* Feb 2010;24(2):548-556.
13. Merriman H, Jackson K. The effects of whole-body vibration training in aging adults: a systematic review. *J Geriatr Phys Ther.* 2009;32(3):134-145.
14. Mikhael M, Orr R, Fiatarone Singh MA. The effect of whole body vibration exposure on muscle or bone morphology and function in older adults: A systematic review of the literature. *Maturitas.* Feb 18 2010.
15. Semler O, Fricke O, Vezyroglou K, Stark C, Stabrey A, Schoenau E. Results of a prospective pilot trial on mobility after whole body vibration in children and adolescents with osteogenesis imperfecta. *Clin Rehabil.* May 2008;22(5):387-394.
16. Griffin MJ. *Handbook of human vibration*. San Diego: Elsevier Academic Press; 1996.
17. Lorenzen C, Maschette W, Koh M, Wilson C. Inconsistent use of terminology in whole body vibration exercise research. *J Sci Med Sport.* Nov 2009;12(6):676-678.
18. Cartwright KV. Determining the effective or RMS voltage of various waveforms without calculus. *Technology Interface.* 2007;8:20.
19. Pel JJ, Bagheri J, van Dam LM, et al. Platform accelerations of three different whole-body vibration devices and the transmission of vertical vibrations to the lower limbs. *Med Eng Phys.* Oct 2009;31(8):937-944.
20. Kiiski J, Heinonen A, Jarvinen TL, Kannus P, Sievanen H. Transmission of vertical whole body vibration to the human body. *J Bone Miner Res.* Aug 2008;23(8):1318-1325.
21. Marin PJ, Bunker D, Rhea MR, Ayllon FN. Neuromuscular activity during whole-body vibration of different amplitudes and footwear conditions: implications for prescription of vibratory stimulation. *J Strength Cond Res.* Nov 2009;23(8):2311-2316.
22. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med.* Feb 19 2008;148(4):295-309.
23. Rauch F, Sievanen H, Boonen S, et al. Reporting whole-body vibration intervention studies: Recommendations of the International Society of Musculoskeletal and Neuronal Interactions. *J Musculoskelet Neuronal Interact.* Sep 2010;10(3):193-198.

SECTION 4

Clinical

22 PEDIATRIC CLINICAL OVERVIEW: A MEDICAL PERSPECTIVE

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INTRODUCTION

Patients with osteogenesis imperfect (OI) can have many different medical needs, which calls for a multidisciplinary team approach. The pediatrician's role in this team often involves diagnosing OI and providing drug therapy. This chapter will therefore focus on these two aspects.

MANIFESTATIONS OF OI THROUGHOUT THE LIFE CYCLE

OI is a congenital disorder but can present throughout the life cycle, from the time of intrauterine development to late in life. It is not uncommon for mildly affected adults to be only identified when their affected child presents with fractures. This wide range in the time of presentation reflects the similarly wide range in the severity of the disease. The typical findings are different during the various phases of life.

Fetal Life

Abnormal skeletal findings such as micromelia and lack of mineral in the skeleton ('undermineralization') can be detected on ultrasound as early as 13 to 14 weeks of gestation.[1,2] The differential diagnosis includes achondrogenesis, perinatal or infantile hypophosphatasia, thanatophoric dysplasia and OI type II. OI type III can be detected from 16–20 weeks gestation, and OI type IV can occasionally be detected at a scan performed at 20 weeks.

If there is a family history of OI with a known mutation, then this can be screened for in the fetus using chorionic villus sampling or amniocentesis. Both collagen protein screening and DNA analysis can be performed on

chorionic villus samples. Amniocytes, however, do not produce enough protein for this analysis to be performed and therefore only DNA testing is possible.[3]

Perinatal Period

Infants with severe OI have a higher incidence of breech presentation at birth.[4] This may be because of decreased mobility or because of their relatively large head and small, deformed long bones. Babies with neuromuscular or congenital abnormalities may also have a higher incidence of breech presentations and these conditions must be considered at birth. Questions often arise during antenatal counseling regarding the best mode of delivery of children with suspected OI. There has not been any evidence to date that caesarian section changes outcome in terms of either reducing fractures or mortality.[4] However if severe OI is suspected, delivery at a tertiary centre is recommended as these neonates can develop respiratory complications which may need assisted ventilation and careful pain management. At birth, babies with OI types II and III typically have dark sclera, triangular facies and bowing of their extremities. They may have multiple fractures on skeletal survey including long bones, rib and vertebral. There may be Wormian bones on skull radiographs.[5]

Infants

The diagnosis of OI can be difficult to distinguish from non-accidental injury in an infant presenting with unexplained fractures but none of the other classical signs of the disease. To compound matters, infants with OI can have bone mineral density within the normal range, which then does not increase at the expected rate of other children.[6] In addition, blue sclera can also be present in the general population, especially in Asian and younger children.[7] DNA analysis for OI can help in some circumstances but a negative result does not rule out the diagnosis. A detailed history, examination and long term follow up can at times be the only way to proceed.

Young Children

As children start mobilizing and become more active, they are more susceptible to long-bone fractures. Children with lower limb deformities may need corrective surgery when they start weight bearing. Deformities of the lower limbs can lead to an abnormal mechanical strain on the bones which makes them more vulnerable to fractures. Low trauma femur and tibia

fractures are extremely rare in healthy children and unless there is a clear explanation for such an event these children should be carefully assessed for underlying bone pathology.

School Children and Adolescents

Another period of vulnerability for children with OI is during phases of rapid growth such as puberty. It is important to especially monitor for vertebral compression fractures and any development of scoliosis. Recurrent fractures can lead to deformity and severely limit mobility. Other surgical complications that can manifest are coxa vara, basilar invagination and acetabular protrusion in the more severe types of OI.[8]

Adults

Patients with OI tend to fracture less in adulthood as the skeleton has matured and is not undergoing the instability of growth. However, patients can suffer chronic bone pain and mobility limitation as a result of deformations that have occurred from previous fractures. Adults can also experience other complications of OI such as hearing loss which is rare in the first two decades but can manifest in the third. Lung complications which may be in part due to the underlying collagen disorder as well as from severe scoliosis are the leading cause of mortality in OI type III [9].

MEDICAL MANAGEMENT OF OI

There is, at present, no cure for OI, so the goal is to 'manage' the disease rather than to heal it. The management of OI includes multidisciplinary input with experienced medical, orthopedic, physiotherapy and rehabilitation specialties. OI management ideally should take place in a specialized center.

Intravenous Bisphosphonate Treatment

Bisphosphonate therapy has been used widely for over 15 years in children with moderate to severe osteogenesis imperfecta and is now considered standard of care.[10] Bisphosphonates are potent anti-resorptive agents that inhibit osteoclast function (Table 1). The chemical structure of all bisphosphonate is based on a P-C-P backbone resembling pyrophosphate (P-O-P), a naturally occurring molecule that is involved in the mineralization process. The chemical structure explains the affinity of bisphosphonates for

mineralized surfaces. The various members of the bisphosphonate family differ in the two side chains that are attached to this backbone molecule.

Table 1. Commonly used bisphosphonate drugs.

	Trade Name	Application
Pamidronate	Aredia®	intravenous
Zoledronate	Reclast®	intravenous
Alendronate	Fosamax®	oral
Risedronate	Actonel®	oral
Ibandronate	Boniva®	oral

More than a dozen bisphosphonates have been used in humans. From a clinician's perspective, this class of drugs can be separated into 'oral bisphosphonates' and 'intravenous bisphosphonates'. This distinction does not indicate some fundamental differences in physico-chemical characteristics between these compounds, but rather reflects the marketing decisions of the pharmaceutical companies that produce bisphosphonates.
The hypothesis initially underlying the use of an anti-osteoclast medication in an osteoblast disorder such as OI was that a decrease in the activity of the bone resorbing system might compensate for the weakness of the bone forming cells. The use of these drugs in OI and other pediatric disorders became widespread after the 1998 publication of a series of children and adolescents with OI who had been treated with cyclical intravenous pamidronate. [11]

Although the quality of the new bone that is formed remains unchanged, the bones benefit from greater mechanical strength due to overall increased bone mass. Traditionally, intravenous pamidronate has been used in children. There is less information on intravenously administered bisphosphonates other than pamidronate. A controlled trial on prepubertal OI patients who received intravenous neridronate, a bisphosphonate similar to pamidronate, yielded results that were comparable to those observed with pamidronate.[12] Zoledronate is a newer intravenously applied bisphosphonate that been used in a few studies.[13-15]

Treatment Effects

Cyclical intravenous pamidronate is currently the most widely used medical therapy for children with moderate to severe OI. Pamidronate is often given in cycles of three days.[10] Cycles are repeated every 2 to 4 months depending

on the age of the child. In the most widely used protocol this will correspond to an annual dose of 9 mg per kg body weight.[10] The literature reports a rapid increase in well-being and decrease in chronic bone pain with therapy. When pamidronate is commenced early in life it can lead to significant improvement in ambulation. The two largest studies report improved mobility in more than half the patients.[16,17] Muscle force measured by maximal isometric grip force of the non-dominant hand showed significant increases with pamidronate therapy that was maintained over two years.[18] Patients with OI types I, II and IV showed a significant improvement in height Z scores after four years of pamidronate therapy.[19]

Bone mineral density in the lumbar vertebrae show a rapid increase with pamidronate therapy as does radial peripheral quantitative computed tomography.[20,21] Radiographically the cycles of pamidronate leave dense sclerotic bands at the metaphysis of long bones.[22] These may contribute to the increased strength of the bones.

Fracture rates in treated children can be difficult to assess, as with increased mobility there may be a transient increase in fractures. However, a decrease in overall fracture rate has been demonstrated after therapy when compared to historical controls.[11] Compressed vertebral bodies have been shown to recover when therapy is given during growth (Figure 1),[23] and cortical thickness increases as measured at the second metacarpal[11] and in trans-iliac bone biopsy specimens.[24]

The effects of bisphosphonates seem to be amplified by the growth process. However, there still remain concerns about the effects of long term treatment, especially when children are started on treatment at an early age. The greatest treatment effect is realized in the first two years with benefits in terms of density and possibly fracture reduction being maintained but not showing the same degree of improvement thereafter.[25]

Zoledronic acid is a bisphosphonate which has recently been subject of an international multi-center drug trial comparing its efficacy and safety to that of pamidronate. Although completed in older children, the results of this trial have not yet been published. However, because zoledronic acid is an infusion given over 45 minutes for one day, its advantage in terms of duration of treatment may soon result in zoledronic acid becoming the bisphosphonate of choice.

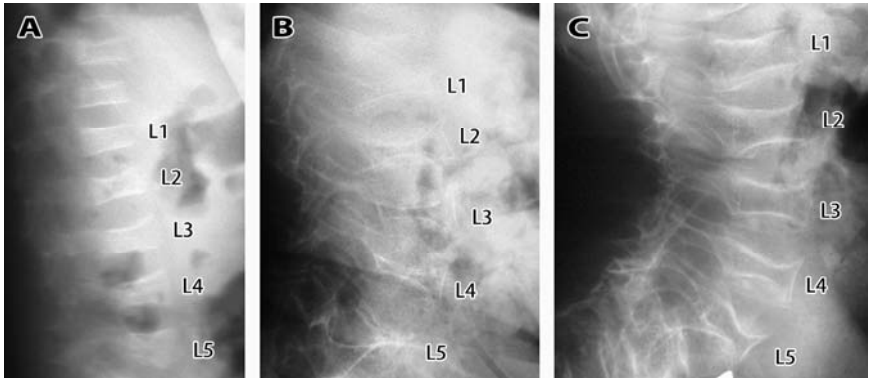

Figure 1. Lateral lumbar spine radiographs of a boy with OI type III at age 1.0 year (A), 9.8 years (B) and 13.0 years (C). Pamidronate treatment was started at the age of 10.1 years. Vertebral bodies were flattened before treatment was started (A and B). This was partially corrected after 3 years of pamidronate treatment (C). (From: Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH. Vertebral morphometry in children and adolescents with osteogenesis imperfecta: Effect of intravenous pamidronate treatment. Bone 2006; 39: 901-906).

Oral Bisphosphonates

Oral medication has obvious practical advantages over intravenous infusions, at least in patients who are able to swallow pills and who can take the precautions that are required with oral bisphosphonates (such as drinking a large glass of water with the pill, staying in an upright position for at least 30 minutes thereafter). However, oral therapy also has a number of drawbacks, such as uncertain compliance, low and variable bioavailability, as well as the possibility of gastrointestinal side effects. Oral treatment exposes the skeleton to frequent small doses of medication, whereas intravenous treatment acts with lower frequency but at higher doses. In growing children this difference leads to specific radiographic features: intravenous treatment leads to discrete metaphyseal lines that correspond to horizontal trabecula, whereas oral treatment may lead to a blurry zone of denser looking bone adjacent to the growth plate.

A double-blind placebo-controlled trial in 139 children and adolescents found that two years of oral alendronate significantly decreased bone turnover, increased spine bone mineral density, and was generally well tolerated.[26] However, no significant effect on the incidence of fractures, bone pain or functional status was evident. Sakkers et al. tested oral olpadronate at a daily dose of 10 mg per m^2 body surface area in a randomized placebo-controlled study that comprised 34 children and adolescents with OI.[27] After

a treatment period of two years, the group receiving active therapy had a higher lumbar spine areal bone mineral density and a lower incidence of long-bone fractures. No difference in functional outcome such as mobility and muscle force was detected. In a study on children and adolescents with mild OI who were treated with risedronate, we observed a difference in lumbar spine areal bone mineral density, but not in fracture rate.[28]

Complications of Medical Management

There is ample documentation of the acute phase reaction in children receiving the initial intravenous dose of bisphosphonate; this has been shown with pamidronate and zoledronic acid.[13] This can be controlled with simple analgesics and does not recur on subsequent infusions, however, it may be of more concern in small infants who have concurrent respiratory compromise.[29] Intravenous infusions can also cause a transient drop in serum calcium with compensatory rise in parathyroid hormone and 1, 25 vitamin D.[30] The potent anti-resorptive properties of bisphosphonates inhibit the normal remodeling activity that acts to renew and repair bone. Concerns linger about the potential buildup of microcracks and calcified cartilage which could potentially lead to poor bone healing and increased fragility. It is unknown if the alteration of modeling of the shape of bones (Figure 2) may also lead to some detrimental consequences.[31] Osteonecrosis of the jaw is a complication of poor soft tissue and bone healing which is associated with bisphosphonate therapy. This complication has mainly been reported in elderly patients with cancer who have been given very high doses of bisphosphonates.[32] Subsequent concerns have been raised about whether this complication could arise with the long term use of bisphosphonates in children. However, in 338 pediatric patients who were treated with pamidronate at the Montreal Shriners Hospital there was no evidence for delayed healing, exposed bone, or osteonecrosis of the jaw in any patient, even though 242 teeth were extracted from 65 patients.[33] Also, no osteonecrosis of the jaw was reported in any of the 102 patients treated with neridronate.[34]

Although there is no evidence of delay in fracture healing, there is significant delay in the healing of osteotomy sites after surgery for intramedullary rod insertion and correction of deformities.[35] Treatment is not recommended until 4–6 months after osteotomy and radiographs have shown adequate healing. When bisphosphonates have been discontinued in growing children, the new bone that is formed at the growth plate of the long bones has a lower density.[21,36] This interface between treated bone and treatment naive bone

causes a stress riser through which fractures can occur. Some form of maintenance therapy may thus be warranted until growth is completed. Current trials are exploring this avenue.

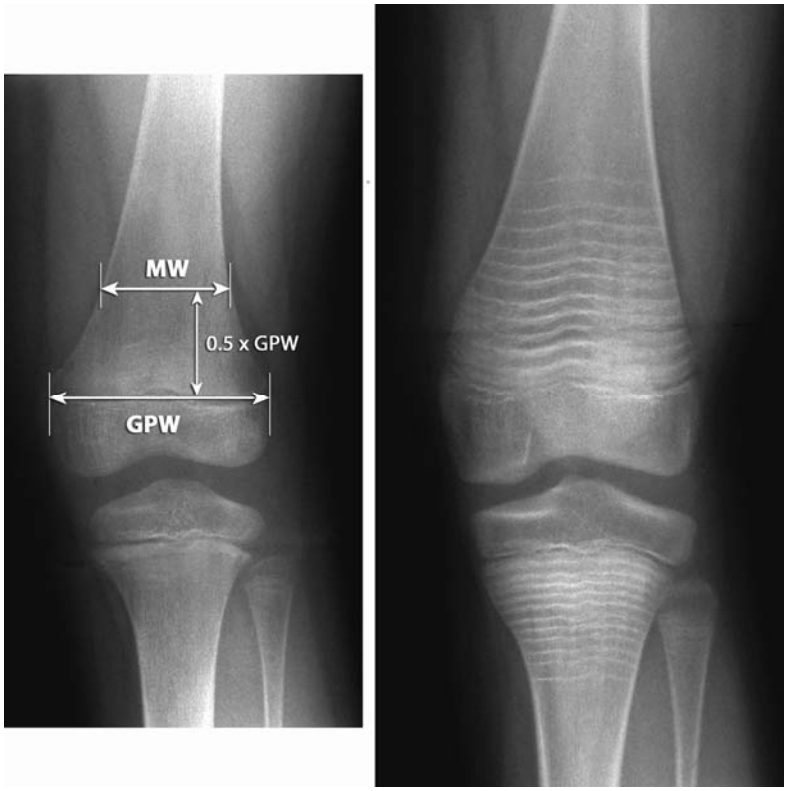

Figure 2. The metaphyseal index at the distal femur can be calculated as the ratio between metaphyseal width (MW) and growth plate width (GPW). Shown are radiographs of a boy with OI type I that were taken at the start of pamidronate treatment (left; age 7.3 years; metaphyseal index, 0.59) and 3.6 years later, when 11 pamidronate cycles had been given (right; metaphyseal index, 0.72). All expected 11 transverse lines are visible in the proximal tibial metaphysis as well as in the distal femur (From: Land C, Rauch F, Glorieux FH. Cyclical intravenous pamidronate treatment affects metaphyseal modeling in growing patients with osteogenesis imperfecta. J Bone Miner Res 2006; 21: 374-379).

Bisphosphonates are buried in the skeleton where they have a half-life of many years, so long term side effects may still surface. This is particularly of concern in cases where bisphosphonates have been given to young women who then go on to bear children and lactate. This is a time of greater bone turnover and may mean higher release of medication from the skeleton. At

present no such adverse effects have been seen, however, this cannot be discounted altogether.[37,38] Despite the obvious benefits of treatment, caution is still advised when starting treatment and the risk benefit ratio must always be carefully considered.

Other Medical Treatments

Growth hormone has long been proposed as a possible treatment for OI.[39] A few studies suggest that growth hormone treatment may accelerate short-term height velocity in some patients.[40-42] Calcium kinetic studies after one year of growth hormone therapy revealed that bone turnover had increased, but that calcium retention was unchanged compared to the pretreatment situation.[41] Increased bone turnover during growth hormone therapy was also found in histomorphometric studies of iliac bone samples.[42] As bone turnover is already abnormally high in untreated children with OI,[43] further stimulation does not appear to be a desirable goal. Possibly, growth hormone would be more useful in combination with bisphosphonate therapy, but this remains to be tested.

Parathyroid hormone is a potent bone anabolic agent and has been shown to reduce the fracture incidence in postmenopausal osteoporosis.[44] These results made parathyroid hormone look like an attractive candidate for treating children with OI. However, a substantial proportion of young rats receiving parathyroid hormone subsequently developed osteosarcoma.[45] It cannot be excluded that a similar effect could happen in humans. Thus, parathyroid hormone should probably not be used in children until these issues have been resolved.

Future Treatments

Potential future treatments include a novel antiresorptive approach using inhibitors of the receptor activator of nuclear factor κB-ligand, a key molecule in osteoclastogenesis.[46] Stimulators of bone formation are also being developed, in particular sclerostin inhibitors. Sclerostin is a protein that reduces bone formation and its inhibition has bone anabolic effects.[46] New drugs based on these approaches are currently undergoing clinical trials for the treatment of osteoporosis in adults and may be evaluated for the treatment of children with OI in the near future.[46]

OI murine models (oim, brtl IV, crtap-/-, Mov-13, OASIS-/-), are currently, used to investigate gene and cell therapies with the aim to either replacing

or silencing the mutant allele, thus transforming biochemically, a severe form of OI into a mild form.[47-50]

CONCLUSION

OI patients require a multi-disciplinary treatment approach. Bisphosphonates can be useful to support other treatment modalities and is indicated in moderate to severe OI. Intravenous bisphosphonates are more effective than oral bisphosphonates. Thus, intravenous bisphosphonates can be considered the current standard of care for treating moderate to severe OI forms. Other emergent newer drugs seem to be promising.

ABBREVIATIONS

C	Carbon
GPW	Growth plate width
MW	Metaphyseal width
OI	Osteogenesis imperfecta
P	Phosphorus

REFERENCES

1. Krakow D, Alanay Y, Rimoin LP, Lin V, Wilcox WR, Lachman RS, et al. Evaluation of prenatal-onset osteochondrodysplasias by ultrasonography: a retrospective and prospective analysis. *Am J Med Genet A* 2008; 146A:1917-1924.
2. Morgan JA, Marcus PS. Prenatal diagnosis and management of intrauterine fracture. *Obstet Gynecol Surv* 2010; 65: 249-259.
3. Byers PH, Krakow D, Nunes ME, Pepin M. Genetic evaluation of suspected osteogenesis imperfecta (OI). *Genet Med* 2006; 8: 383-388.
4. Cubert R, Cheng EY, Mack S, Pepin MG, Byers PH. Osteogenesis imperfecta: mode of delivery and neonatal outcome. *Obstet Gynecol* 2001; 97: 66-69.
5. Semler O, Cheung MS, Glorieux FH, Rauch F. Wormian bones in osteogenesis imperfecta: Correlation to clinical findings and genotype. *Am J Med Genet A* 2010; 152A: 1681-1687.
6. Munns CF, Rauch F, Travers R, Glorieux FH. Effects of intravenous pamidronate treatment in infants with osteogenesis imperfecta: clinical and histomorphometric outcome. *J Bone Miner Res* 2005; 20: 1235-1243.
7. Sillence D, Butler B, Latham M, Barlow K. Natural history of blue sclerae in osteogenesis imperfecta. *Am J Med Genet* 1993; 45: 183-186.
8. Violas P, Fassier F, Hamdy R, Duhaime M, Glorieux FH. Acetabular protrusion in osteogenesis imperfecta. *J Pediatr Orthop* 2002; 22: 622-625.
9. Paterson CR, Ogston SA, Henry RM. Life expectancy in osteogenesis imperfecta. *BMJ* 1996; 312: 351.
10. Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet* 2004; 363: 1377-1385.
11. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta.

N Engl J Med 1998; 339: 947-952.
12. Gatti D, Antoniazzi F, Prizzi R, Braga V, Rossini M, Tato L, et al.Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled study. *J Bone Miner Res* 2005; 20: 758-763.
13. Munns CF, Rajab MH, Hong J, Briody J, Hogler W, McQuade M, et al. Acute phase response and mineral status following low dose intravenous zoledronic acid in children. *Bone* 2007; 41: 366-370.
14. Vuorimies I, Toiviainen-Salo S, Hero M, Makitie O. Zoledronic acid treatment in children with osteogenesis imperfecta. *Horm Res Paediatr* 2011; 75: 346-353.
15. Brown JJ, Zacharin MR. Safety and efficacy of intravenous zoledronic acid in paediatric osteoporosis. *J Pediatr Endocrinol Metab* 2009; 22: 55-63.
16. Astrom E, Soderhall S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002; 86: 356-364.
17. Land C, Rauch F, Montpetit K, Ruck-Gibis J, Glorieux FH. Effect of intravenous pamidronate therapy on functional abilities and level of ambulation in children with osteogenesis imperfecta. *J Pediatr* 2006; 148: 456-460.
18. Montpetit K, Plotkin H, Rauch F, Bilodeau N, Cloutier S, Rabzel M, et al. Rapid increase in grip force after start of pamidronate therapy in children and adolescents with severe osteogenesis imperfecta. *Pediatrics* 2003; 111: E601-603.
19. Zeitlin L, Rauch F, Plotkin H, Glorieux FH. Height and weight development during four years of therapy with cyclical intravenous pamidronate in children and adolescents with osteogenesis imperfecta types I, III, and IV. *Pediatrics* 2003; 111: 1030-1036.
20. Rauch F, Plotkin H, Zeitlin L, Glorieux FH. Bone mass, size, and density in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate therapy. *J Bone Miner Res* 2003; 18: 610-614.
21. Rauch F, Cornibert S, Cheung M, Glorieux FH. Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. *Bone* 2007; 40: 821-827.
22. Rauch F, Travers R, Munns C, Glorieux FH. Sclerotic metaphyseal lines in a child treated with pamidronate: histomorphometric analysis. *J Bone Miner Res* 2004; 19: 1191-1193.
23. Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH. Vertebral morphometry in children and adolescents with osteogenesis imperfecta: Effect of intravenous pamidronate treatment. *Bone* 2006; 39: 901-906.
24. Rauch F, Travers R, Plotkin H, Glorieux FH. The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. *J Clin Invest* 2002; 110: 1293-1299.
25. Rauch F, Travers R, Glorieux FH. Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. *J Clin Endocrinol Metab* 2006; 91: 511-516.
26. Ward LM, Rauch F, Whyte MP, D'Astous J, Gates PE, Grogan D, et al. Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Clin Endocrinol Metab* 2011; 96: 355-364.
27. Sakkers R, Kok D, Engelbert R, van Dongen A, Jansen M, Pruijs H, et al. Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. *Lancet* 2004; 363: 1427-1431.
28. Rauch F, Munns CF, Land C, Cheung M, Glorieux FH. Risedronate in the treatment of mild pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Bone Miner Res* 2009; 24: 1282-1289.

29. Munns CF, Rauch F, Mier RJ, Glorieux FH. Respiratory distress with pamidronate treatment in infants with severe osteogenesis imperfecta. *Bone* 2004; 35: 231-234.
30. Rauch F, Plotkin H, Travers R, Zeitlin L, Glorieux FH. Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. *J Clin Endocrinol Metab* 2003 ;88: 986-992.
31. Land C, Rauch F, Glorieux FH. Cyclical intravenous pamidronate treatment affects metaphyseal modeling in growing patients with osteogenesis imperfecta. *J Bone Miner Res* 2006; 21: 374-379.
32. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007; 22: 1479-1491.
33. Chahine C, Cheung MS, Head TW, Schwartz S, Glorieux FH, Rauch F. Tooth extraction socket healing in pediatric patients treated with intravenous pamidronate. *J Pediatr* 2008; 153: 719-720.
34. Maines E, Monti E, Doro F, Morandi G, Cavarzere P, Antoniazzi F. Children and adolescents treated with neridronate for osteogenesis imperfecta show no evidence of any osteonecrosis of the jaw. *J Bone Miner Metab* 2011; DOI: 10.1007/s00774-011-0331-3
35. Munns CF, Rauch F, Zeitlin L, Fassier F, Glorieux FH. Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. *J Bone Miner Res* 2004; 19: 1779-1786.
36. Rauch F, Munns C, Land C, Glorieux FH. Pamidronate in children and adolescents with osteogenesis imperfecta: effect of treatment discontinuation. *J Clin Endocrinol Metab* 2006; 91: 1268-1274.
37. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? *J Obstet Gynaecol Can* 2008; 30: 1146-1148.
38. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone* 2009; 44: 428-430.
39. Kruse HP, Kuhlencordt F. On an attempt to treat primary and secondary osteoporosis with human growth hormone. *Horm Metab Res* 1975; 7: 488-491.
40. Antoniazzi F, Bertoldo F, Mottes M, Valli M, Sirpresi S, Zamboni G, et al. Growth hormone treatment in osteogenesis imperfecta with quantitative defect of type I collagen synthesis. *J Pediatr* 1996; 129: 432-439.
41. Vieira NE, Marini JC, Hopkins E, Abrams SA, Yergey AL. Effect of growth hormone treatment on calcium kinetics in patients with osteogenesis imperfecta type III and IV. *Bone* 1999; 25: 501-5.
42. Marini JC, Hopkins E, Glorieux FH, Chrousos GP, Reynolds JC, Gundberg CM, et al. Positive linear growth and bone responses to growth hormone treatment in children with types III and IV osteogenesis imperfecta: high predictive value of the carboxyterminal propeptide of type I procollagen. *J Bone Miner Res* 2003; 18: 237-243.
43. Rauch F, Travers R, Parfitt AM, Glorieux FH. Static and dynamic bone histomorphometry in children with osteogenesis imperfecta. *Bone* 2000; 26: 581-589.
44. Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet* 2002; 359: 2018-2026.
45. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicol*

Pathol 2002; 30: 312-321.
46. Quemerais-Durieu MA, Kerlan V, Chabre O. Therapeutic innovation in osteoporosis (antisclerostin antibody and denosumab). *Ann Endocrinol (Paris)* 2011; 72 Suppl 1: S15-22.
47. Marini JC, Gerber NL. Osteogenesis imperfecta. Rehabilitation and prospects for gene therapy. *JAMA* 1997 ;277: 746-750.
48. Millington-Ward S, McMahon HP, Farrar GJ. Emerging therapeutic approaches for osteogenesis imperfecta. *Trends Mol Med* 2005; 11:299-305.
49. Chamberlain JR, Deyle DR, Schwarze U, Wang P, Hirata RK, Li Y, et al. Gene targeting of mutant COL1A2 alleles in mesenchymal stem cells from individuals with osteogenesis imperfecta. *Mol Ther* 2008; 16: 187-193.
50. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. *Nat Rev Endocrinol* 2011; 7: 540-557.

23 ORTHOPEDIC MANAGEMENT OF OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable disease characterized by abnormal collagen synthesis, bone fragility, and frequent fracture. The primary treatment objectives in the care of patients with OI are to decrease the number of pathologic fractures, to minimize the incidence and extent of deformity, reduce pain, and improve function. With these goals in mind, orthopedic management of patients with OI is a multidisciplinary effort that involves medical management, physical therapy, immobilization of injuries with casting, bracing, splinting, and operative internal fixation. Due to the broad variability of expression of OI, each individual's functional ability as determined by disease severity must be considered in treatment decisions. Although there is no medical cure for OI, the use of bisphosphonates in patients with severe OI has dramatically improved bone mineral density, reduced the incidence of fracture, and improved quality of life.[1-4] Similarly the application of principles of rapid rehabilitation following fracture, with or without the use of internal fixation, has decreased disability and time away from work or school. Despite these improvements, fracture and progressive deformity remain significant challenges in patients with OI. In this chapter, we will discuss the role of the orthopaedic surgeon in making decisions as part of a multidisciplinary team, including the impact of bisphosphonates on the natural history of OI, the role of physical therapy in preventing deformity and promoting mobility, special considerations in casting and splinting the patient with OI, and the indications for and techniques of surgical intervention in patients with OI.

Bisphosphonate Treatment

Bisphosphonates are the most commonly prescribed pharmacologic treatment for OI. Bisphosphonate use has significantly changed the natural

history of severe OI to allow some individuals to be more mobile and pain free, and it may also alter the natural history of scoliosis progression. Since the early 1990s, intravenous bisphosphonates have been administered to patients with OI in an attempt to reduce fractures and prevent deformity. Bisphosphonates are synthetic analogs to pyrophosphate that act by inhibiting osteoclast-mediated bone resorption. Most published series have reviewed IV pamidronate and more lately zolendronate, although several well-designed prospective studies have also examined the use of oral bisphosphonates, alendronate and olpandronate. Glorieux and colleagues at the Shriners Hospital in Montreal were the first to popularize the bisphosphonates in OI, although they had been previously used in Europe. In evaluating bone mineral density after 1.3-5 years of IV pamidronate, these investigators demonstrated an average increase in bone mineral density from −5.3 ± 1.2 to −3.4 ± 1.5 in 30 patients with severe OI.[1] This increase in bone mineral density has translated into a significant decrease in fracture frequency. The same investigators reported a decrease in fracture incidence from 2.3 to 0.6 per year in the same population.[1] Similarly using a comparison with historical controls, Plotkin and colleagues demonstrated a dramatically lower rate of fracture in infants less than two years of age with severe OI treated with IV pamidronate (2.6 events per year compared to 6.3 in untreated controls).[3] This reduction in fracture frequency has resulted in a reduced healthcare burden. de Graaf and colleagues demonstrated that patients who were treated with bisphosphonates had fewer outpatient office visits (3.35 versus 2.14) and fewer operative fracture interventions (0.73 versus 0.38) compared with patients who were not treated with bisphosphonates.[4] Additionally, Anissipour and colleagues showed a reduction in the progression rate of scoliosis in type III OI in those treated with bisphosphonates before age 5.[5] Although there are no prospective randomized studies of the use of intravenous bisphosphonate use in severe OI, significant benefits in improved bone density have been associated with decreased fractures, improved mobility and decreased spinal deformity and have led to the adoption of bisphosphonate therapy in most clinics for individuals with severe OI. The orthopaedist treating OI can be familiar with the indications for treating OI with bisphosphonates, and make that recommendation. For our institution generally this is in individuals with severe OI (modified Sillence type III and IV), and in patients with milder types who have had major fractures including compression fractures of the spine, femur fractures, and in individuals with significant disuse osteopenia and disability.

Physical Therapy

Children with OI are often functionally limited as a result of an acute fracture, muscle weakness secondary to disuse, bowing of the long bones, external rotation and flexion deformities of the hips, equinus foot deformities, and spinal deformities. Physical therapy plays an important role in rehabilitating patients acutely after a fracture and promoting functional independence in the setting of chronic deformity. The main goals of physical therapy in the patient with OI are (1) to promote normal gross motor development, (2) to foster safe modes of movement, and (3) to optimize functional independence.

Patients with poor limb alignment, poor balance, gait abnormalities, or low endurance can improve with a rehabilitation program structured to their needs. Therapists may help to promote frequent change in position for infants and toddlers. Position changes help to strengthen a variety of muscle groups, prevent contractures and long bone deformities, maintain a straight spine, and prevent plagiocephaly (flattened head). As children become more functional, physical therapists may help children to achieve the next level of mobility. For severely affected individuals, helping a child learn to sit-scoot may make him more independent. The physical therapist can also provide invaluable support and advice about wheelchairs and other mobility devices (e.g. Star Car) that allow them to explore their environment. For more mildly affected individuals, providing braces or walking aids may make a child more stable and reduce fatigue, and allow them to walk at school or in the community. Water therapy can be particularly beneficial in patients with OI as water cushions bones, provides buoyancy for early walkers, and provides resistance along the length of long bones to strengthen bones and muscles. The pool also provides a protective environment for children to learn new skills and regain function after fracture, which permits step-wise progression in capabilities. Finally, for the well-functioning child with OI, therapists may provide a maintenance fitness program that emphasizes flexibility, endurance training, and gentle strengthening. Most of all, a physical therapist familiar with the abilities of patients with OI can motivate individual patients to achieve realistic goals, often above and beyond the expectations of those unfamiliar and afraid of the condition. The partnership of a knowledgeable therapist with an intelligent and motivated patient can produce remarkable results.

Immobilization

Fractures in patients with OI remain common. Closed methods of immobilization are the primary mode of fracture management in children with OI. Many fractures in OI occur from relatively low energy events, with correspondingly minimal soft tissue damage. The soft tissue envelope remains intact and allows relatively greater stability and subsequent rapid healing, especially in non-displaced fractures. Bony healing in patients with OI typically occurs at the same rate or more rapidly than a normal population; therefore, duration of cast treatment should be the same or less for patients with OI as those without the disease. Nonetheless, one of the principal challenges in treating fractures in the setting of OI is prevention of the "fracture cycle." That is prolonged immobilization leading to disuse osteopenia, ultimately leads to a further increase in fracture risk. With this in mind, physicians treating fractures in patients with OI should make every effort to minimize disuse osteopenia related to immobilization. Therefore, immobilization should be maintained only as long as is necessary and, if possible, early transition should be made to lightweight, removable orthoses once the fracture is deemed stable. Additionally, lightweight casts of limited size are preferred to heavy, plaster casts as they result in reduced stress shielding and resultant osteopenia. Moreover, heavy casts or splints can cause increased forces and fractures at the proximal end.

While spica casts work well for vigorous toddlers with an isolated femur fracture, for young children and small individuals with severe OI, even femur fractures can be treated with light "spica splints" that immobilize the thigh segment, without the need for a spica cast. Similarly upper extremity fractures in individuals with severe OI can often be managed with light splints. In terms of duration of protected weight bearing, it is not uncommon for children to begin moving and using a fractured extremity when healing has been established and pain stops. It is commonplace for children to return to their follow-up clinic visit without any trace of a cast or splint! Such behavior is encouraged in OI, because of the danger of prolonged immobilization leading to bone loss and more fragility fractures.

SURGICAL MANAGEMENT FOR THE UPPER AND LOWER EXTREMITIES

The indications for surgical treatment of fractures in OI are similar to those for typically developing children, with some special considerations. In

addition, elective surgical treatment in the extremities of patients with OI is useful for rehabilitating patients with repeated long bone fracture or severe deformity that is functionally limiting. Severity of disease should also be taken into account when considering surgical intervention, as the child's general health, bone quality, and size demand meticulous planning. The goals of surgery are to restore normal mechanical alignment, prevent further bowing, and prevent future fractures. Although the timing for lower extremity surgery often coincides with the child's attempts to pull up to stand, lower extremity alignment and protection are important but not sufficient in themselves for ambulation. Therefore, independent ambulation should not be presented as the primary goal of surgery. Most orthopaedic implants including plates and screws, external fixators, and multiple iterations of intramedullary rods and have been trialed in for the management of OI with varying levels of success, and it is useful to review the results, particularly failures, to demonstrate particular features of surgery for brittle bones.

Plates and Screws

Although plates and screws are popular in the management of long-bone fractures in adults, they should be used sparingly in patients with OI. Plates and screws are generally contraindicated in OI patients with long-bone fractures because of the high risk of fracture above and below the construct and the high rate of screw cut-out (Figure 1). Enright and Noonan retrospectively reviewed the results of 13 platings for fracture fixation or deformity correction in patients with type III OI.[6] They determined that compared to intramedullary fixation with the Baily-Dubow nail, plating was associated with a shorter duration to revision (27 months versus 5 years) and higher rate of complication (69% versus 63.5%). The most common complication was screw cut-out (5 cases). However, even with locked plates designed for osteopenic bone we have observed significant stress shielding leading to nonunion as well as junctional deformity and fracture at the end of the construct. While intramedullary devices are generally preferred, it should be noted that some fracture types necessitate a plate and screw construct due to anatomic considerations (e.g. acetabular fractures).[7]

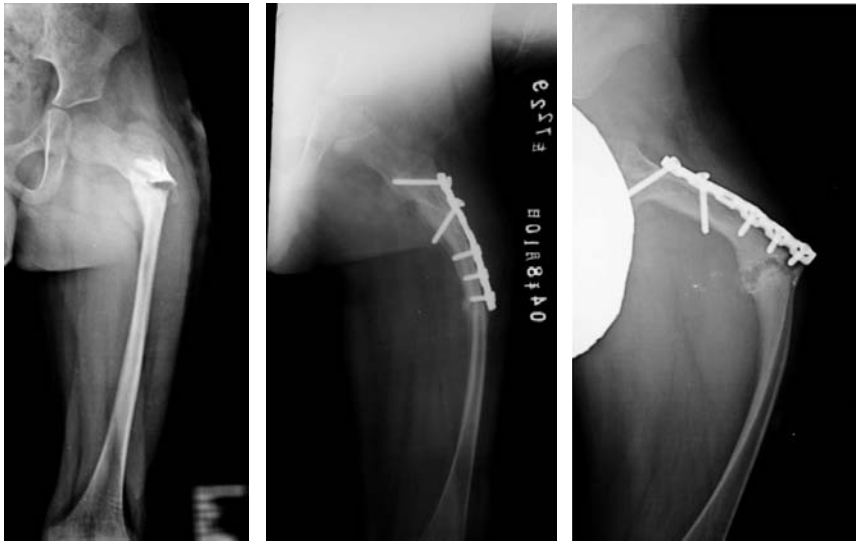


Figure 1. Left. Preoperative radiographs demonstrating subtrochanteric femur fracture. Center. Postoperative radiographs following open reduction internal fixation with plate and screws. Right. Follow-up radiographs revealing refracture below the plate and screw construct with associated screw cut-out.

Intramedullary Rodding

Intramedullary rodding of the long bones is particularly useful and has revolutionized the the management of OI since the introduction of the technique by Drs. Harold Sofield and Edward Millar at the Shriners Hospital for Children in Chicago in 1959. The principles and utility of treatment have endured, although dramatic changes in all aspects of modern surgery, including anaesthesia, imaging, electrocautery, and instrumentation have changed the techniques markedly from their illustrations of the "shish-k-bob procedure." Intramedullary rods serve as internal splints to promote fracture or osteotomy healing or prevent further deformity. [8,9] Meanwhile, they act as load-sharing devices, which help to prevent osteopenia secondary to stress shielding.

Intramedullary fixation for the treatment of OI was first proposed in 1959 when Sofield and Millar published their technique of multiple segmental osteotomies fixated using a solid intramedullary rod.[10] This technique involved subperiosteal exposure of the entire bone from proximal to distal metaphysis, multiple osteotomies to produce numerous segmental fragments, and fixation of the fragments around an appropriately size, solid intramedullary rod (Figure 2).

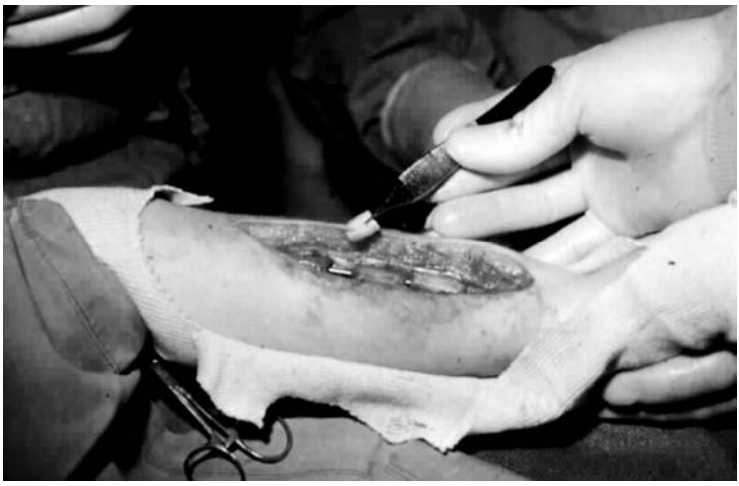


Figure 2. Historical photograph demonstrating the Soffield technique. Today, we discourage broad exposure of the involved bone due to the risk of complications relating to bony devascularization.

The Sofield technique was the first proposed solution to the treatment of severely bowed long bones as it improved mechanical characteristics of the bone and diminished fracture frequency. Although results were initially promising, with broader use complications including bone growth beyond the extent of the implant, devascularization of the involved bone, and rod migration have been recognized. In response, Bailey and Dubow were the first to ingeniously introduce telescopic rods in 1963, which were designed to elongate as children grew. They introduced a well thought out system for drilling the canal with a drill bit attached to the rod itself, which was then exchanged for an end cap. Telescoping rods more than doubled the interval between index and revision surgery (2.5 to 5 years); however, proximal migration and uncoupling of the proximal cap remained a common problem.[11] In the 1980s, the Sheffield group added a fixed "T-piece" to either end of a telescoping nail that could be rotated after nail insertion to improve epiphyseal fixation and reduce the likelihood of nail migration.[12] The latest major advance in intramedullary rodding for OI was developed by Dr. Francoise Fassier of the Shriners Hospital for Children in Montreal and Ariel Duval in 2003. The primary advantages of the Fassier-Duval nail include improved "screw-in" fixation in the epiphyses to prevent migration and a single proximal entry point, obviating the need for an arthrotomy (compared with proximal and distal entry points for the Bailey-Dubow and Sheffield nails).[13] Their instrumentation includes guide wires and long cannulated

drill bits useful for preparing the long bone canal without the need for a wide subperiosteal exposure, and often allowing application through a small incision.

Extensible intramedullary rodding has had favorable impact on the independence and mobility of patients with OI. Luhmann and colleagues reported results of 36 extensible-roddings in 12 patients with OI.[11] They demonstrated that all patients, including four who were unable to walk preoperatively, were able to ambulate at average 5-year follow-up. Likewise, Wilkinson and colleagues demonstrated that 16 of 24 patients were able to walk at a median 5.25 years after placement of Sheffield Telescopic IM rods, compared with 9 preoperatively.[12] el-Sobsky and colleagues demonstrated that the beneficial effect of intramedullary rodding is amplified by concomitant use of bisphosphonates. They compared clinical results of 40 patients (20 treated with bisphosphonates and 20 without bisphosphonates) who underwent intramedullary rodding for deformity correction. The authors reported that patients who were treated with bisphosphonates had improved subjective satisfaction, higher likelihood of independent ambulation, and lower rate of revision surgery. [14]. Intramedullary rodding is valuable in the treatment of young children with long bone deformity who are just beginning to pull to stand[15], and the rehabilitation of former walkers with milder OI who have had repeated setbacks and loss of function from disuse osteopenia and deformity.

The Fassier–Duval rod is applicable for use in the tibia. Distal fixation in the tibial epiphysis can be achieved with the threaded male rod or one that will accommodate a transfixing wire. Despite these adaptations, distal fixation is not always achieved and failure of rod expansion is occasionally witnessed. In addition, the diameter of the tibia to be rodded is often smaller than can accommodate a 3.2 mm rod, which is the smallest available FD rod. We have performed tibial rodding with the Peter Williams technique, which uses any diameter smooth Steinmann pin or Rush rod (with the hook removed). This technique has great utility in OI, as it can be used in patients of all sizes, requires very limited surgical exposure, and does not require an arthrotomy at the knee.

Surgical Techniques

Modified Peter Williams Tibial Rodding Technique for Deformity Correction

The patient is positioned supine on a radiolucent table and a padded tourniquet is applied to the thigh (Figure 3A). An incision 4-5cm in length is established over the apex of the deformity. The exposure should be limited to that necessary to remove a sufficient wedge of bone to correct the deformity. A limited exposure prevents devascularization of the tibia, which may predispose to nonunion or future fracture. The tibia is subperiosteally exposed proximal and distal to the deformity. A wedge of bone is resected to correct the deformity (Figure 3B). The intramedullary canal of the proximal and distal tibia is reamed using a 3.2 mm drill bit in a retrograde and antegrade fashion, respectively. In some cases, the deformity may have obliterated the intramedullary canal and the drill must be used to reestablish a canal. A Steinmann pin is inserted through the osteotomy site into the intramedullary canal of the distal tibia. A 2.4-3.0 mm Steinmann pin is advanced, in an antegrade fashion, through the distal tibia, across the ankle and subtalar joints, and exiting the heel through the plantar aspect of the calcaneus (Figure 3C). Once the proximal end of the Steinmann pin has passed the osteotomy site and is fully within the intramedullary canal of the distal tibia, the deformity is manually corrected and the Steinmann pin is directed retrograde into the proximal tibia. Under direct fluoroscopic visualization in both the coronal and sagittal planes, the appropriate rod length is determined. The rod is then cut to the desired length prior to definitively passing it into the proximal tibia. The distal tip of the Steinmann pin is then manually coupled with a threaded insertion rod (or alternatively a Frazier suction tip, which may serve as an insertion rod). The coupled rods are then driven retrograde into the region of the proximal tibial metaphysis just short of the proximal tibial physis (Figure 3D). The rod position is evaluated under fluoroscopy to confirm appropriate positioning (Figure 3E). The insertion rod is then uncoupled from the Steinmann pin, leaving the distal end of the Steinmann pin just proximal to the distal tibial physis. The wound is irrigated and closed, a sterile dressing is applied, and a lightweight splint is placed. Significant deformity correction can be achieved with the Modified Peter Williams Tibial Rodding Technique (Figure 3F).

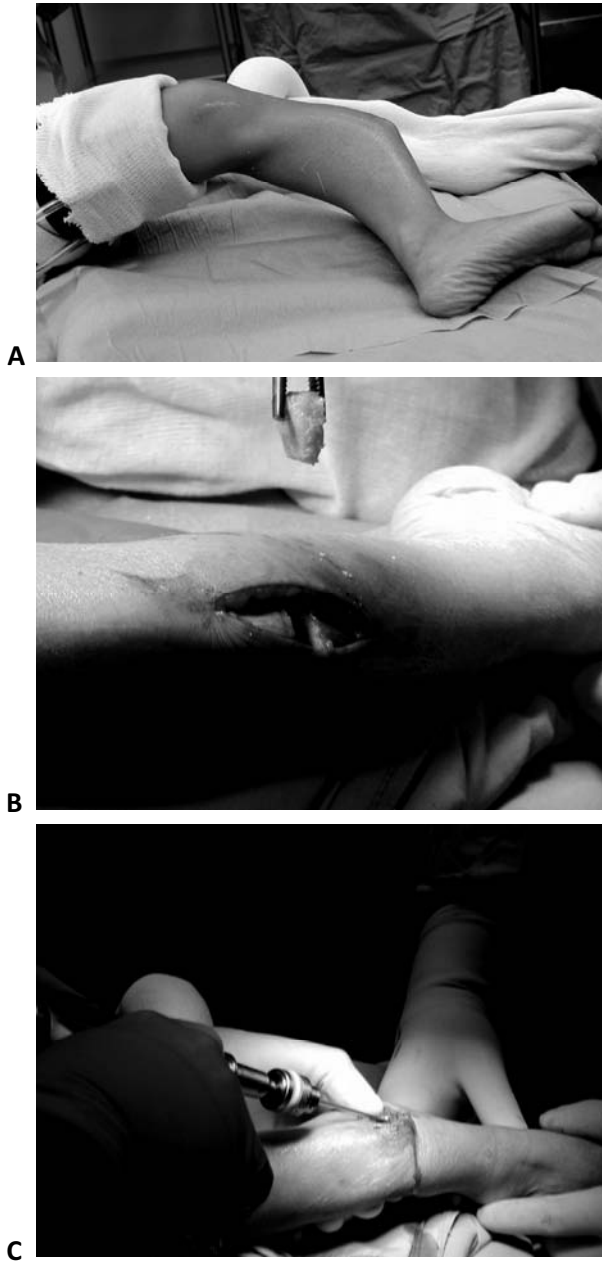
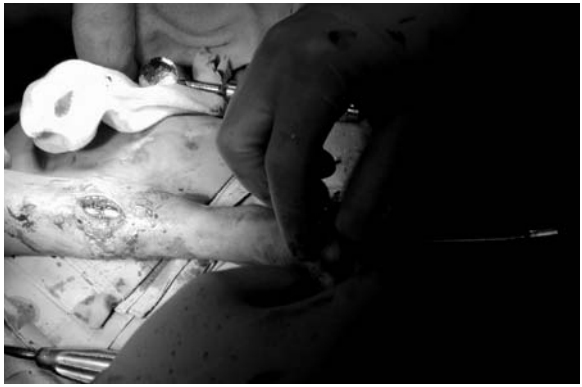


Figure 3. (A) Preoperative photograph demonstrating the preoperative setup and a significant flexion deformity involving the patient's right tibia. (B) A limited surgical exposure is established overlying the apex of the deformity and a wedge of bone is excised. (C) The Steinmann pin is first advanced antegrade through the distal tibia and out through the plantar heel.



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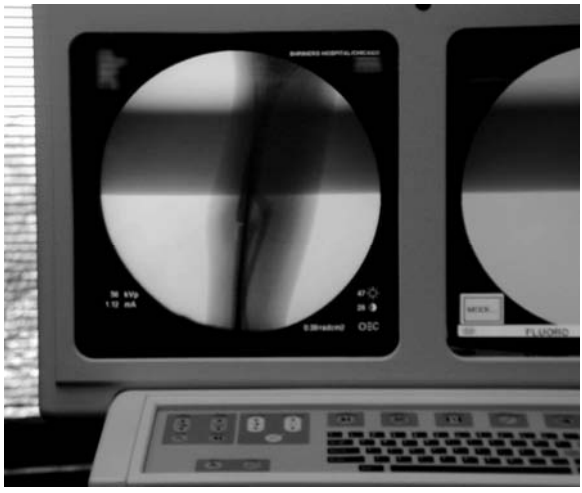

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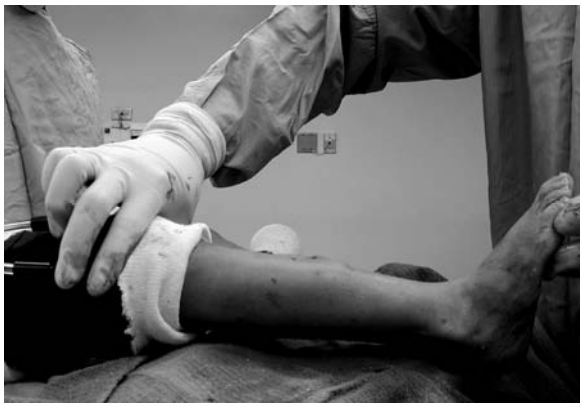
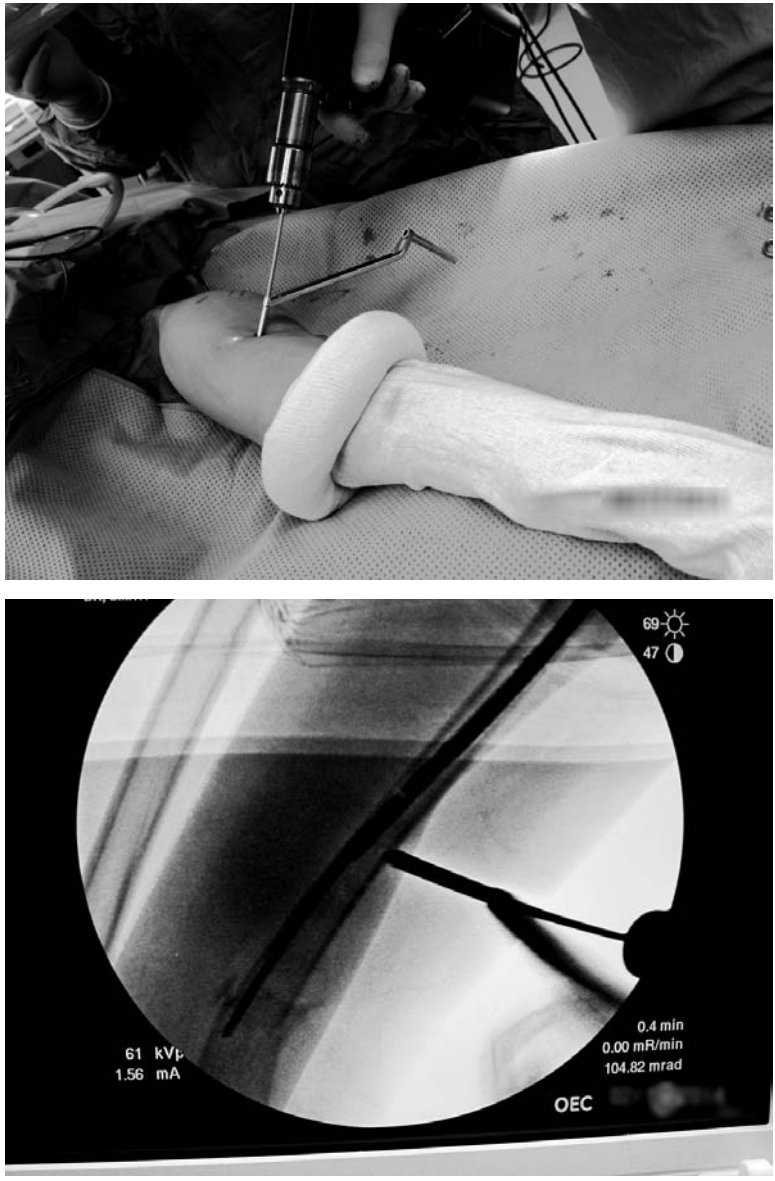


F

Figure 3 (continued). (D) After it has been cut to length, the Steinmann pin is driven retrograde back up the proximal tibia into appropriate position. (E) The appropriate final position of the rod is confirmed fluoroscopically prior to uncoupling the insertion rod. (F) Postoperative photograph demonstrates significant correction of the deformity.

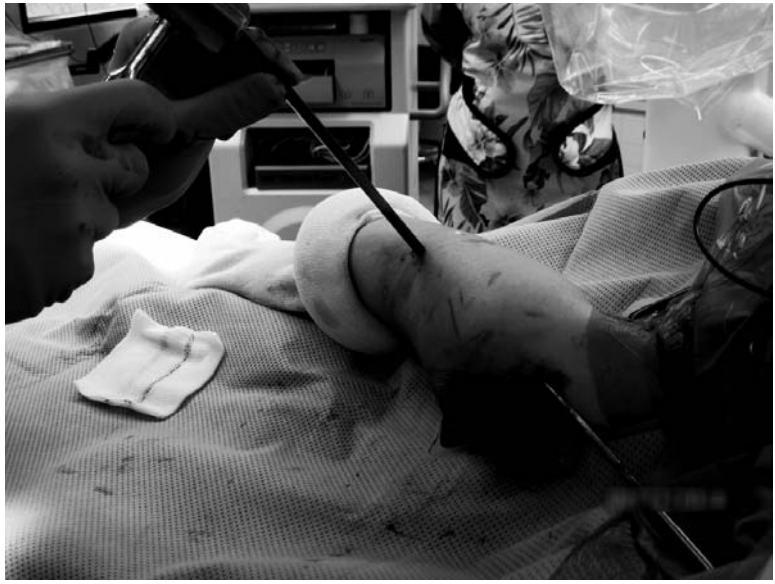
Fassier-Duval Intramedullary Femoral Rodding Technique with Percutaneous Osteotomy for Deformity

The patient is placed supine on a radiolucent table with a bump under the ipsilateral hip. A standard posterolateral approach is made beginning 2 cm proximal to the tip of the greater trochanter and extending 4 cm proximally. The tensor fascia is incised and the gluteus maximus is divided in line with its fibers. The greater trochanter is palpated and a small diameter guidewire is inserted through the tip of the greater trochanter. The wire is advanced under fluoroscopic guidance to the level of the distal femoral physis. The wire is then overreamed in a stepwise fashion with a 3.4 mm cannulated reamer and then, if the canal is large enough, with a 4.2 mm cannulated reamer. At this point, attention is turned to creation of the corrective osteotomy. A limited 2cm exposure is made overlying the apex of the deformity and, under fluoroscopy, the diaphysis of the femur is drilled bicortically with a 2.4 or 3.2 mm drill (Figure 4A-B). A ¼ inch straight osteotome is directed into the drill hole and used with a mallet to complete the osteotomy (Figure 4C-D). The proximal and distal femur are gently manipulated to correct the deformity. If deemed necessary, a second percutaneous osteotomy may be made in a similar fashion to obtain further correction. The wire is removed and the solid male nail is advanced by hand beyond the osteotomy site(s) and screwed into the distal femoral epiphysis (Figure 4E). Care is taken to ensure fluoroscopically that the entirety of the distal screw is beyond the physis to prevent growth disturbance. The desired length of the female nail is determined by taking the total length of the male nail and subtracting the length of residual male nail protruding beyond the greater trochanter (Figure 4F). The female nail is cut to length on the back table using a hacksaw. The hollow female nail is advanced by hand over the male nail and screwed into the greater trochanter to stabilize the implant. The residual male rod is cut flush with the proximal extent of the female nail using the rod cutter (Figure 4G). The wounds are irrigated and closed, a sterile dressing is applied, and a lightweight splint is placed (Figure 4H).



Figures 4. (A) Photograph and (B) fluoroscopic image demonstrating drilling of the femoral diaphysis to help create the corrective osteotomy.

C



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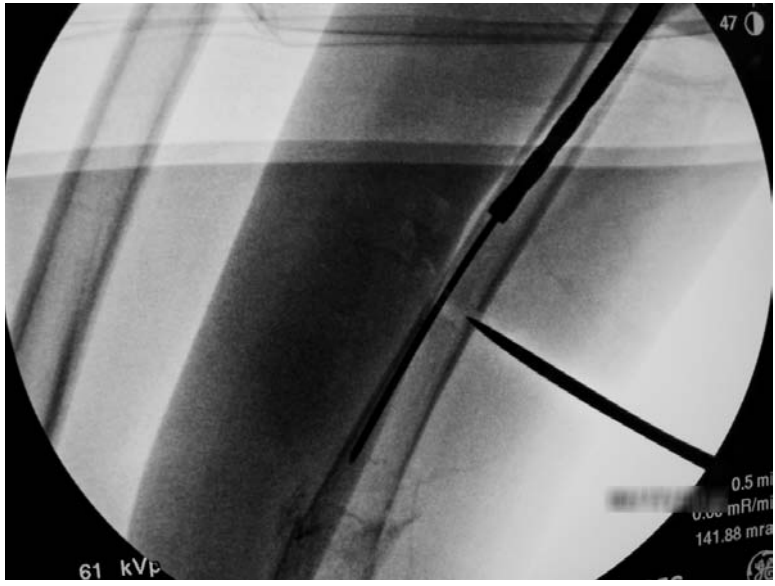


Figures 4 (continued). (C) Photograph and (D) fluoroscopic image demonstrating the creation of a percutaneous osteotomy using a ¼ inch osteotome.

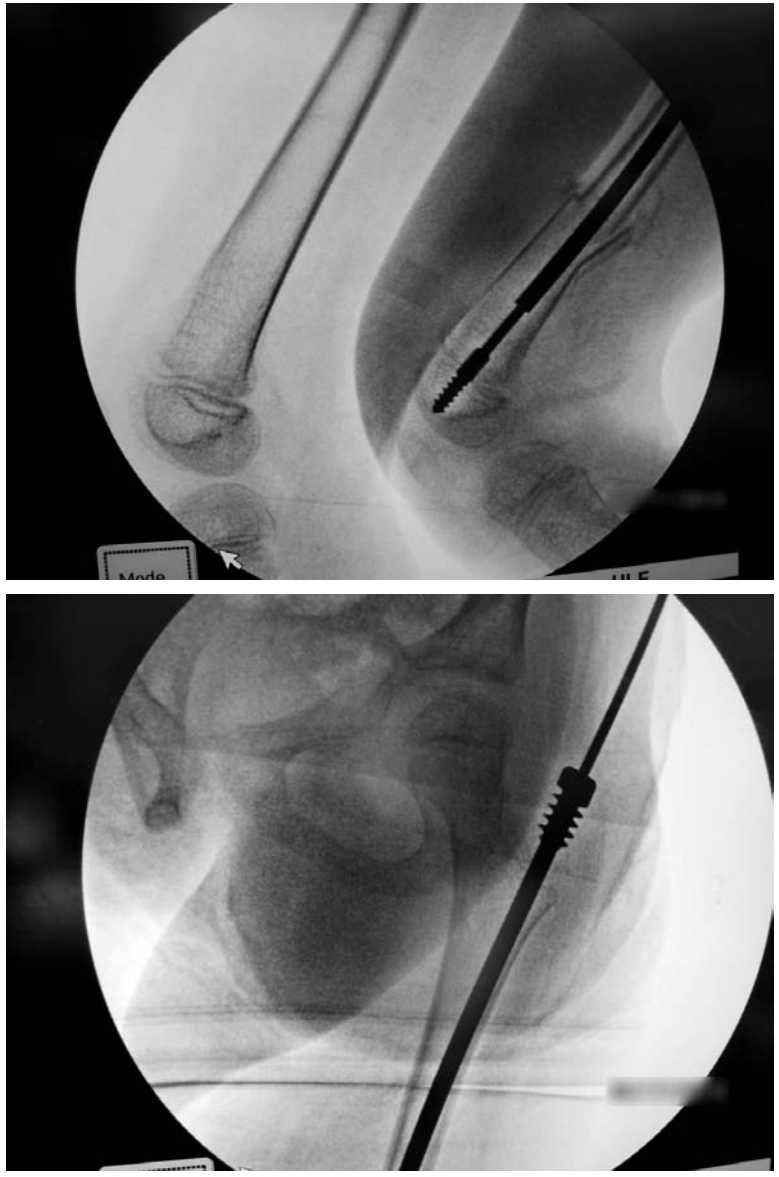
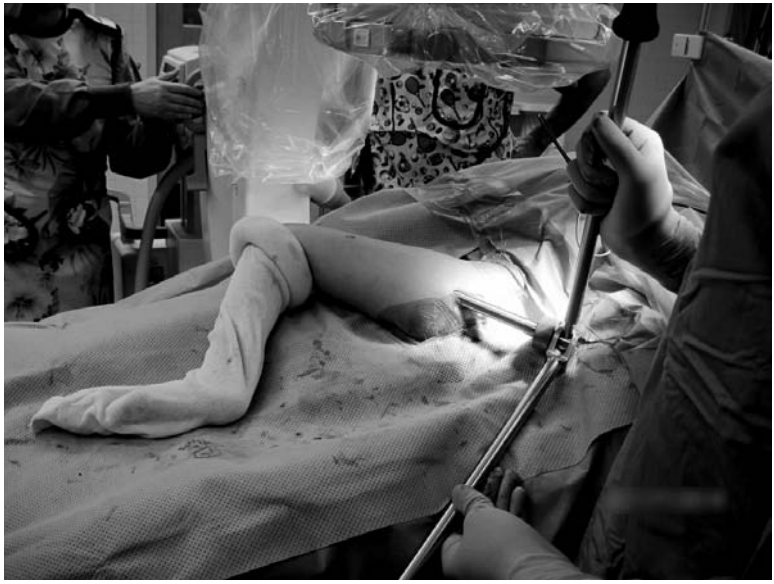


Figure 4 (continued). (E) Fluoroscopic image demonstrates appropriate positioning of the male nail with all screw threads beyond the distal femoral physis. (F) Fluoroscopic image with female nail screwed into place at the greater trocheric aphophysis with residual male nail protruding proximally.

G



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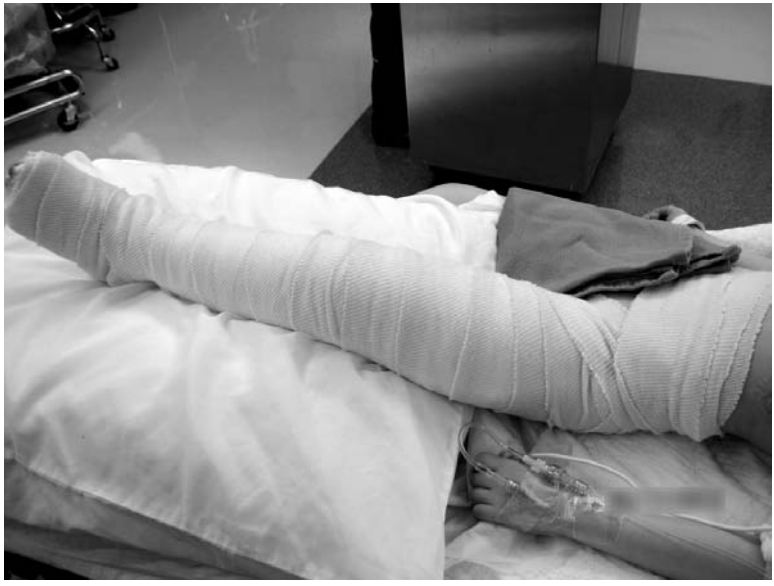

Figure 4 (continued). (G) A rod cutter is used to cut the residual male nail flush with proximal extent of the female nail. (H) A light postoperative long-leg splint is maintained for 4 weeks postoperatively to protect the osteotomy site.

Correction of Coxa vara in Children with OI

Coxa vara, defined as femoral neck-shaft angle <110°, occurs in 10.2% of patients with OI.[16] This deformity often leads to functional deficits relating to abductor weakness (including trendelenberg gait), leg length discrepancy, and restricted hip range of motion. Surgical correction of coxa vara is performed in a similar manner to that described by Fassier and colleagues.[17] After performing a standard lateral approach to the proximal femur, two 1.6mm K-wires are placed anteriorly and posteriorly along the inferior femoral neck into the femoral epiphysis. These K-wires must be far enough apart to accommodate a Fassier-Duval (FD) rod between them. Under fluorosocopy, a subtrochanteric valgus closing wedge osteotomy is performed to achieve a neck-shaft angle in accordance with the preoperative plan (typically about 150 degrees). After the osteotomy is created, the K-wires may be used as a "joy-stick" to control the proximal fragment and establish the desired femoral neck-shaft angle. At this point, the intramedullary canal is prepared and an FD rod is placed through a trochanteric starting point utilizing the technique described above. The K-wires are then bent in line with the femur and secured to the femoral diaphysis using cerclage wires (Figure 5).

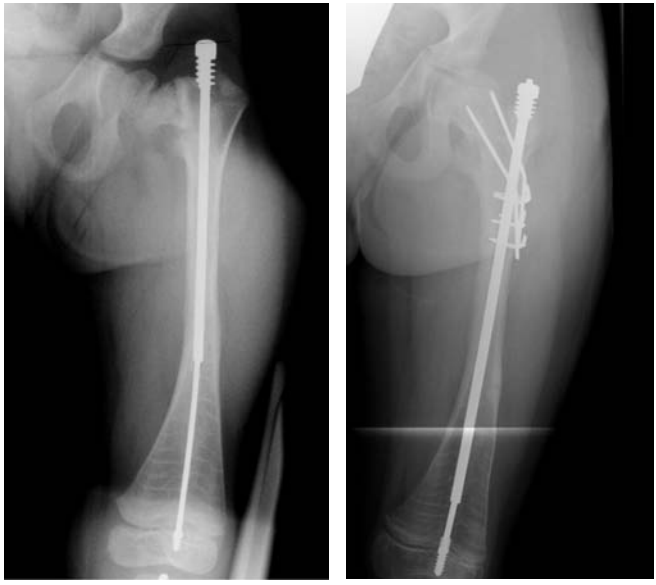

Figure 5. Left. Preoperative radiograph demonstrating coxa vara deformity with neck-shaft angle of 90 degrees. Right. Postoperative radiograph following osteotomy with improvement of neck-shaft angle to 150 degrees.

Treatment of Angular Deformity with Epiphysiodesis

While large, lower extremity deformities in the tibial or femoral diaphysis or proximal femur often require an osteotomy for correction, more subtle deformities about the knee in skeletally immature patients with OI can be managed safely and effectively with hemi-epiphysiodesis (Figure 6). Genu varum and valgum are commonly seen in patients with OI. Hemi-epiphysiodesis utilizing staples, tension-band plates, or transphyseal screws is a minimally invasive technique that affords the potential for significant deformity correction and a hastened recovery. Of note, there is little difference in effectiveness, speed of correction, and complication rate between staples, tension-band plates, or transphyseal screws.[18,19]

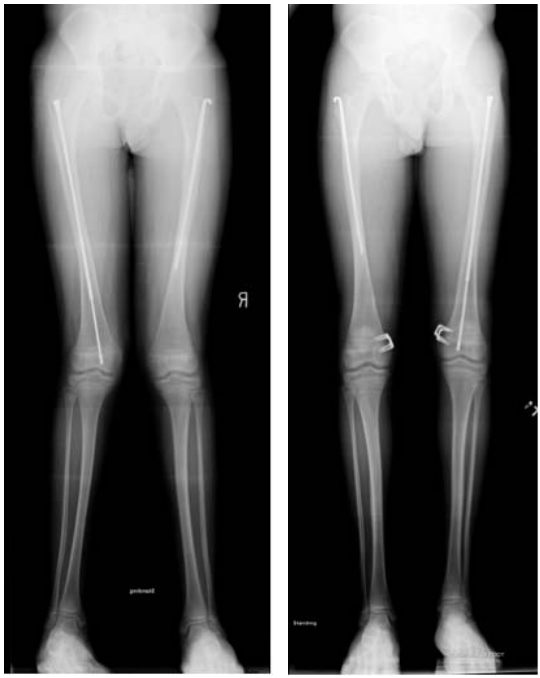

Figure 6. Left. Preoperative radiographs demonstrating bilateral genu valgum in a patient with OI. Right. Postoperative radiographs with improved mechanical alignment following placement of physeal staples around the bilateral medial distal femoral physes.

Treatment of Femoral Neck Fracture in Children with OI

Femoral neck fractures in children with OI are rare and the exact incidence is unknown. The literature on treatment of femoral neck fractures in children with OI is sparse and limited to case reports and small case

series.[20-22] The diagnosis of femoral neck fractures in OI can be challenging, as fractures may not be well visualized on plain radiographs (Figure 7). For patients complaining of persistent groin pain following a trivial injury, treating physicians should have a low threshold for obtaining advanced imaging (Figure 8). Additionally, these fractures can be quite challenging to treat in light of poor bone quality, the small size of the involved bones, and the presence of preexisting hardware (i.e. intramedullary rods). In one small series of five patients with femoral neck fractures, all fractures occurred at the proximal junction of preexisting plates or intramedullary nails.[22] Femoral neck fractures in children with OI are typically treated with cannulated screw fixation. Although the use of three screws is preferred, frequently there is only sufficient room for two screws. Similarly, 4.5mm cannulated screws should be utilized if possible; however, 3.5mm screws may be used in smaller patients and to avoid preexisting hardware. In light of small fragments and preexisting hardware, screws frequently cannot be placed parallel to one another. In some cases, pre-exiting hardware may need to be removed to achieve adequate fixation; however, we try to avoid hardware removal as residual bone defects and the distal extent of the cannulated screws will act as stress risers that may lead to fracture below the cannulated screw construct.

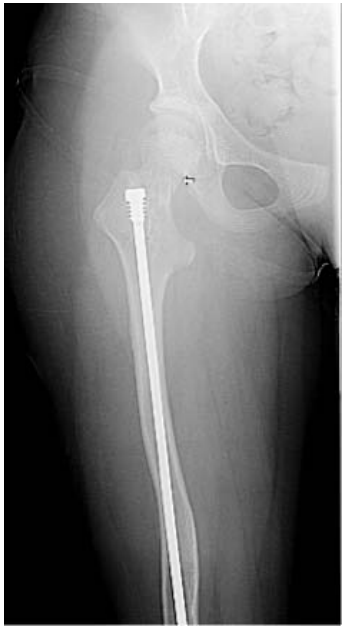

Figure 7. Plain radiograph of a patient with retained FD rod with groin pain following trauma demonstrating a subtle fracture involving the femoral neck.

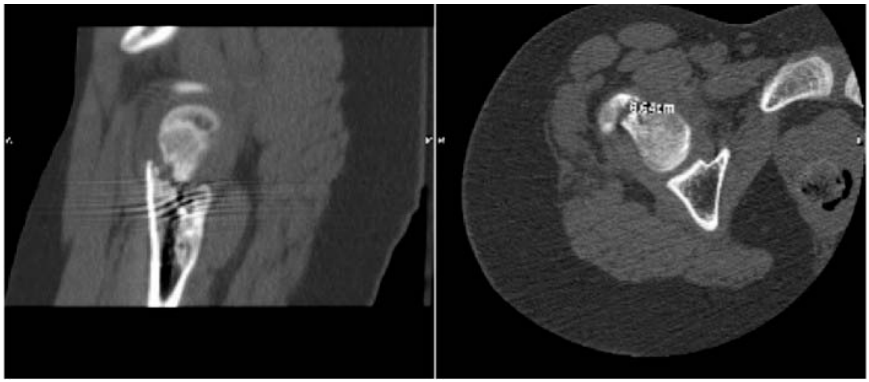

Figure 8. Computer Tomography (CT) slices demonstrating the same fracture as shown in Figure 7.

Surgical Complications

While modern intramedullary implants have rendered favorable clinical outcomes in the setting of OI, these devices are still plagued by high rates of surgical complication and revision surgery. The most commonly reported complications in the literature include rod migration (Figure 9), failure of telescoping (Figures 10), thread pullout, and rod fatigue fracture. Birke and colleagues reported a 40% complication rate and 13% reoperation rate in 15 intramedullary roddings (9 patients) performed with the Fassier-Duval telescoping rod with 1-2.4 year follow-up.[23] The complications they witnessed included rod migration and failure of telescoping (5 patients) and intraoperative joint intrusion (1 patient). Bintcliffe and Thomas also reported a high rate of complications using the third generation FD rod. They reported 3 cases of rod migration in 10 femoral roddings and 3 cases of thread pullout in the distal tibia in 6 tibial roddings at 14-20 months follow-up.[13] Ultimately, the Fassier-Duval rod is a step forward in the orthopaedic management of OI; however, given the nature of the disease, a moderate complication should be anticipated and repeated surgeries will likely be required.

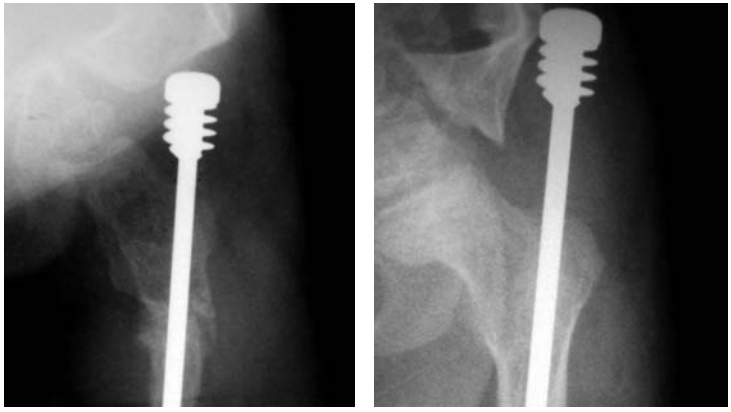

Figure 9. Left. Postoperative radiograph demonstrating the Fassier-Duval nail anchored in the greater trochanteric apophysis. Right. Postoperative radiograph two-years later demonstrating proximal migration of the Fassier-Duval nail following screw pull-out.

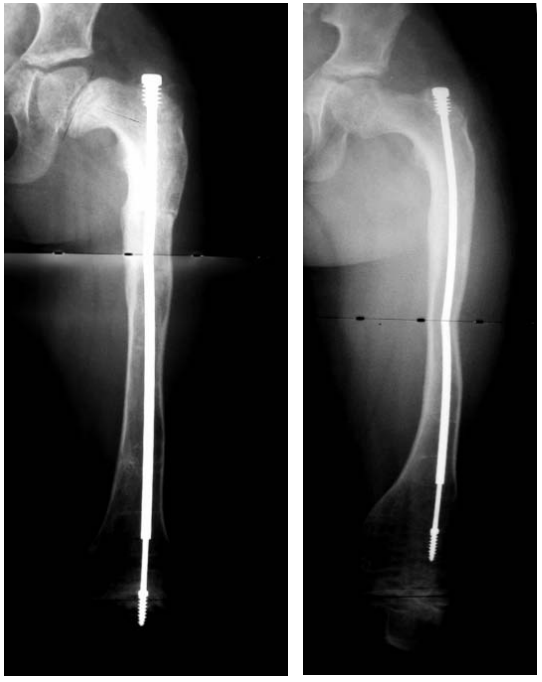

Figure 10. Left. Postoperative radiograph six months status post Fassier-Duval femoral rodding demonstrating instrumentation to be appropriately positioned. Right. Postoperative radiograph 2.5 years status post Fassiar-Duval femoral rodding demonstrating that threads have pulled out of the distal epiphysis creating a stress riser in the distal femur.

CONCLUSION

The treatment of the child with OI is a multidisciplinary team effort. At our institution, this effort involves routine patient monitoring in conjunction with physical therapists, nurse practitioners, and social work staff in our dedicated "OI Clinic." The primary objectives of OI clinic are to monitor bone density and to screen for the presence of deformity (namely scoliosis, coxa vara, or bowing of the long bones). In patients with severe OI (Sillence types III and IV), recurrent fracture, or progressive deformity we often recommend cyclic administration of IV bisphosphonates, as pamidronate and zolendronate have been shown to improve bone density, reduce fracture risk, and delay deformity progression. For patients with discrete fractures, we generally treat with a limited period of immobilization with lightweight splints or casts. However, for patients with recurrent long bone fractures or progressive deformity, we frequently recommend extensible intramedullary rodding. The recent introduction of bisphosphonates to patients with OI and improvements in surgical instrumentation for OI have reduced the incidence of fracture and increased the likelihood of independent mobility. Nevertheless, bisphosphonates are not curative and intramedullary rodding remains fraught with a relatively high rate of complications. In order to best treat children with OI, further research must be done to determine clear indications for bisphosphonate therapy and to develop implants that further reduce the rate of implant migration and periprosthetic fracture.

REFERENCES

1. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med*. 1998;339(14):947–952.
2. Glorieux FH. Experience With Bisphosphonates in Osteogenesis Imperfecta. *Pediatrics*. 2007;119(Supplement):S163–S165.
3. Plotkin H, Rauch F, Bishop NJ, et al. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *Journal of Clinical Endocrinology & Metabolism*. 2000;85(5):1846–1850.
4. de Graaff F, Verra W, Pruijs JEH, Sakkers RJB. Decrease in outpatient department visits and operative interventions due to bisphosphonates in children with osteogenesis imperfecta. *J Child Orthop*. 2011;5(2):121–125.
5. Anissipour AK, Hammerberg KW, Caudill A, et al. Behavior of Scoliosis During Growth in Children with Osteogenesis Imperfecta. *The Journal of Bone and Joint Surgery*. 2014;96(3):237–243.
6. Enright WJ, Noonan KJ. Bone plating in patients with type III osteogenesis imperfecta: results and complications. *Iowa Orthop J*.

2006;26:37–40.
7. Darmanis S, Bircher M. Fractures of the acetabulum in osteogenesis imperfecta. *Journal of Bone and Joint Surgery - British Volume*. 2006;88(5):670–672.
8. Stockley I, Bell MJ, Sharrard WJ. The role of expanding intramedullary rods in osteogenesis imperfecta. *Journal of Bone and Joint Surgery - British Volume*. 1989;71(3):422–427.
9. El-Adl G, Khalil MA, Enan A, Mostafa MF, El-Lakkany MR. Telescoping versus non-telescoping rods in the treatment of osteogenesis imperfecta. *Acta Orthop Belg*. 2009;75(2):200–208.
10. Sofield HA, Millar EA. *Fragmentation, Realignment, and Intramedullary Rod Fixation of Deformities of the Long Bones in Children*. 1959.
11. Luhmann SJ, Sheridan JJ, Capelli AM, Schoenecker PL. Management of lower-extremity deformities in osteogenesis imperfecta with extensible intramedullary rod technique: a 20-year experience. *J Pediatr Orthop*. 1998;18(1):88–94.
12. Wilkinson JM, Scott BW, Clarke AM, Bell MJ. Surgical stabilisation of the lower limb in osteogenesis imperfecta using the Sheffield Telescopic Intramedullary Rod System. *Journal of Bone and Joint Surgery - British Volume*. 1998;80(6):999–1004.
13. Bintcliffe FAC, Thomas S. Fassier Duval Rods for Osteognesis Imperfecta. *Orthopaedic Proceedings: A supplement to The Bone & Joint Journal*. 2013;95-B(SUPP_24):12.
14. el-Sobky MA, Hanna AAZ, Basha NE, Tarraf YN, Said MH. Surgery versus surgery plus pamidronate in the management of osteogenesis imperfecta patients: a comparative study. *J Pediatr Orthop B*. 2006;15(3):222–228.
15. Ruck J, Dahan-Oliel N, Montpetit K, Rauch F, Fassier F. Fassier-Duval femoral rodding in children with osteogenesis imperfecta receiving bisphosphonates: functional outcomes at one year. *J Child Orthop*. 2011;5(3):217–224.
16. Aarabi M, Rauch F, Hamdy RC, Fassier F. High prevalence of coxa vara in patients with severe osteogenesis imperfecta. *J Pediatr Orthop*. 2006;26(1):24–28.
17. Fassier F, Sardar Z, Aarabi M, Odent T, Haque T, Hamdy R. Results and complications of a surgical technique for correction of coxa vara in children with osteopenic bones. *J Pediatr Orthop*. 2008;28(8):799–805.
18. Wiemann JM, Tryon C, Szalay EA. Physeal stapling versus 8-plate hemiepiphysiodesis for guided correction of angular deformity about the knee. *J Pediatr Orthop*. 2009;29(5):481–485.
19. Shin SJ, Cho T-J, Park MS, et al. Angular deformity correction by asymmetrical physeal suppression in growing children: stapling versus percutaneous transphyseal screw. *J Pediatr Orthop*. 2010; 30(6):588–593. doi:10.1097/BPO.0b013e3181e04b5d.
20. Sillence D. Osteogenesis imperfecta: an expanding panorama of variants. *Clin Orthop Relat Res*. 1981;(159):11–25.

21. Tsang KS, Adedapo A. Cannulated screw fixation of fracture neck of femur in children with osteogenesis imperfecta. *J Pediatr Orthop B*. 2011;20(5):287–290.
22. Chow W, Negandhi R, Kuong E, To M. Management pitfalls of fractured neck of femur in osteogenesis imperfecta. *J Child Orthop*. 2013;7(3):195–203.
23. Birke O, Davies N, Latimer M, Little DG, Bellemore M. Experience with the Fassier-Duval telescopic rod: first 24 consecutive cases with a minimum of 1-year follow-up. *J Pediatr Orthop*. 2011;31(4):458–464.

24 ORTHOPAEDIC MANAGEMENT OF BRUCK SYNDROME

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INTRODUCTION

Bruck syndrome, a rare form of recessively inherited Osteogenesis Imperfecta presents an unusual challenge for the orthopedist to treat both contractures of the extremities and bone fragility. Bruck syndrome presents with contractures of the knees (pterygia) ankles and feet (clubfoot) similar to those seen in arthrogryposis with bone fragility. The sclerae are white, there is no dentinogenesis imperfecta, no hearing loss and normal intelligence. There is a progression to gradually deforming moderate to severe bowing of the long bones and spinal deformity. Bruck syndrome has a heterogeneous presentation and at least two different underlying causative genetic defects have recently been identified. Treatment of Bruck syndrome requires an individualized approach to treat the specific pathology. This chapter will discuss the presentation of Bruck syndrome, the genetics and current treatment for a few cases.

Timeline

In 1897, Alfred Bruck published in the *German Medical Weekly Journal* an article titled: About a rare form of disease of the bones and joints,[1] which described an adult who had OI and joint contractures.[2] In 2002, Steinmann stated that there were 21 reported cases of Bruck syndrome from India, Africa, Asia, Europe, Australia, and North America.[1,3] Since then the literature reports another 11 case reports for a total of 32 cases reported in the English written literature.[2,4-8] Since Bruck's article, there have been case reports from Ha-Vinh[2], Sharma and Anand,[9] Breslau-Siderius,[10] Leroy[7] and others that describe individual patient presentations and treatment. Since 1998, there have been a series of articles gradually defining Bruck syndrome and identifying underlying genetic causes. In 1998, Leroy published a case study

of contractures and OI where screening did not reveal mutations in COL1A1 or COL1A2, stating the pathogenesis of Bruck syndrome was largely unknown.[7] Bank discovered in 1999, defective collagen crosslinking that was unique to bone and did not affect cartilage or skin. They identified a genetic defect found to be the locus for the alteration in function of the enzyme they called telopeptide lysyl hydroxylase (TLH)[11], later confirmed by Ha-Vinh.[2] Van der Slot investigated TLH further to find PLOD2 as the putative TLH gene.[12] Alanay et al[13-15] was the first to describe FKBP10 mutations. This finding was confirmed by Kelley in 2011, who showed the collagen chaperone complex FKBP10 is mutated in recessive OI and Bruck syndrome.[16] Also in 2011, Shaheen showed that FKBP10 previously reported as a novel autosomal recessive OI gene also defines a novel Bruck syndrome locus (BKS3).[14] In 2012 Puig-Hervas detected changes in PLOD2 and FKBP10 in 6 Bruck syndrome families.[17] Table 1 is a summary of the discoveries, which have been described in Bruck syndrome. The locus and enzyme findings have subsequently been shown to correspond with the PLOD2 or FKBP10 genes.

Table 1. Summary of genetic findings related to Bruck Syndrome

Gene Alteration	Source
Unknown	Leroy 1998
TLH (enzyme)	Bank 1999
17p12 (locus)	Bank 1999
PLOD2	Van der Slot 2003, Ha-Vinh 2004, Puig-Hervas 2012
FKBP10	Alanay 2010, Kelley 2011, Shaheen 2011, Puig-Hervas 2012
BKS3 (locus)	Shaheen 2011

GENETICS

Mutations in Bruck syndrome can occur in at least two different genes related to the crosslinking of collagen by a lysyl hydroxylase, which acts at the telopeptide region of the collagen fibril. In connective tissue, collagen fibrils are stabilized by covalent bonds formed between amino acid residues, called pyridinolines. The amino acid residues involved in crosslinking are lysine (Lys) and hydroxylysine (Hyl).[18-22] Crosslinking is variable and tissue specific, and is initiated after specific Lys and Hyl residues of telopeptides are converted extracellularly by lysyl oxidase into aldehydes allysine and hydroxyallysine. These aldehydes then react with Lys, Hyl, or histidyl on another collagen strand to give di-, tri-, and tetrafunctional crosslinks.

Bruck syndrome occurs both sporadically and in an autosomal recessive manner.[1] Although two types of Bruck syndrome have been postulated by Bank, these have been distinguished by the underlying genetic abnormality and not clinical presentation, which has been described as variable between moderate and severe within each type. Type I involves mutations in a gene which affects terminal lysyl hydroxylase 1 (TLH1) located on chromosome 17. TLH1 is involved in the registration of type I collagen polypeptides prior to assembly of triple helices.[6] Subsequently, this locus has been identified as identical to the FKBP10 gene. This gene encodes a FKBP protein which acts as an important chaperone in the processing of collagen type I in bone. The exact mechanism for how FKBP protein interacts with the telomere LH and why sometimes FKBP 10 mutations result in contractures is not known. Moreover genetic mutation in FKBP10 can cause either type IV (moderate) OI or Bruck syndrome, that is, OI without or with contractures.

Type II Bruck syndrome is caused by a mutation in the gene PLOD2 on chromosome 3, encoding a collagen lysyl hydroxylase.[8,16] Van der Slot proved the substrate specificity of LH2 is a telopeptide lysyl hydroxylase (TLH).[12] PLOD2 is expressed preferentially in cells with osteoblastic activity.[2,23] The PLOD2 mutation is more specific for hydroxylation of telopeptides in bone. There is associated high bone turnover, which is associated with the characteristic osteopenic appearing bone and multiple fractures, as well as a reduction in the absolute number of crosslinks in bone collagen.[2]

In a case report by Kelley, families with OI type bone fragility with congenital joint contractures, consistent with the diagnosis of Bruck Syndrome, all had FKBP10 mutations. Kelly further explored how COL1A1/COL1A2 mutations were involved with OI and Bruck syndrome. Both COL1A1 and COL1A2 were normal: however FKBP10 was mutated.[16] Although patients with COL1A1 or COL1A2 mutations may have knee contractures associated with congenital dislocation of the patella, they do not have Bruck syndrome, without having other gene mutations, such as FKBP10 or PLOD2. Interestingly, FKBP10 mutations can cause a condition of congenital contractures without bone involvement in Kuskokwim syndrome, which is an arthrogryposis like condition seen in native Alaskans.[24, 25]

Presentation

Bruck syndrome is characterized by joint contractures at birth, fragile bones, and short stature due to progressive skeletal deformities.[10] Clubfoot is fairly common. In addition to the patient identified by Bruck in 1897, there have been reports of at least 32 patients with Bruck syndrome in the literature. Sharma and Anand reported a case study from India in 1964 that involved a 34-week-old infant born with multiple fractures. The infant was diagnosed with Arthrogryposis multiplex congenita and had fractures that involved bilateral humeral shafts, bilateral tibia and fibula, right femoral shaft, multiple old rib fractures, and wormian bones of the skull.[9] The infant had white sclerae. Although arthrogryposis itself may present with fractures, evidence of a primary bone abnormality, such as bowing leads to a suspicion of Bruck syndrome. In most cases, reported length is usually normal at birth; with normal sclerae, normal dentinogenesis, no hearing loss, normal vision, and normal intelligence.[2, 6, 10]

There is a broad range of severity in Bruck syndrome. Most cases reported in the literature state the affected child is unable to walk or walks with maximal assistance. However, after successful treatment of contractures, a few children can stand and walk, usually with an assistive device. Bruck syndrome can usually be distinguished from other types of OI due to the presence of clubfoot and joint limitations that are congenital.[2, 6] Fractures usually present postnatal. The contractures are usually around major joints and are a primary abnormality (appearing antenatal or postnatal), as opposed to a secondary manifestation. Contractures are not the complication of multiple fractures, which are usually found in severe types of OI and are asymmetric.[6, 26]

The combination of primary bone fragility and contractures is unique to Bruck syndrome. There are other conditions that cause contractures, such as arthrogryposis, Ehlers Danlos, or Ptyrigium syndrome. At times failure to thrive or extreme immobility can lead to fractures from a secondary bone abnormality. The nature of the contractures in Bruck Syndrome is different from the progressive contractures seen in mucopolysaccharidoses.

IMAGING

Bruck Syndrome stems from OI and has similar characteristics; therefore the radiographic features are similar to OI patients. Examination of the skull

reveals persistent wormian bones, typical in more severe types of OI.[8] Long bones show bowing, poor bone quality and occasional incomplete fractures.

Bruck Syndrome's radiographic findings are more similar to the severe types of OI, types III and IV. Fractures are very likely to occur and fracture susceptibility is higher than expected.

According to Ha-Vinh's case study, there were more rib and vertebral fractures in Bruck syndrome than other types of OI.[2] Features in radiographs include mild osteopenia to osteoporotic bone, parieto-occiptal wormian bone (accessory skull bones completely surrounded by a suture line), pre-, peri-, and postnatal rib fractures with prompt and adequate callus formation are common.[7]

NATURAL HISTORY OF DISEASE

Bruck syndrome is progressive and leads to severe limb deformities, short stature, progressive kyphoscoliosis and multiple fractures.[6] There is variability of expression. Affected individuals may have limited mobility and require a wheelchair for transportation, or they may be independent community ambulators with an assistive device. However, intelligence is normal and most patients achieve independence and good quality of life. In a case study by Leroy a 14-year-old male was retrospectively reviewed along with two other patients to find the natural course of Bruck Syndrome.[7] The 14-year-old patient was found to possess multiple contractures of bilateral elbows, bilateral hips, bilateral wrists, and extended metacarpophalangeal joints with ulnar deviation of all fingers. Clubfoot deformities were present bilaterally.[7] Treatment consisted of prompt physical therapy, surgical correction of bilateral clubfoot, hamstring elongation, popliteal capsulotomy, and elongation of the Achilles tendon isolated to the left leg. The flexion deformities of the elbows and knees and residual equinovarus feet yielded gradually but only partly to regular physical therapy.[7] Even with early treatment, the patient at 14 years of follow up had difficulty maintaining symmetric posture, mainly due to body asymmetry in the spine and pelvis. Gait was broad based and laborious. The limitation of full extension in the previously treated left lower extremity was gradually re-emerging.

ORTHOPEDIC TREATMENT

In most cases the presentation in infants is for treatment of multiple joint contractures, and fractures leading to the diagnosis of Bruck syndrome are

recognized during the course of casting (Figure 1). Despite bone fragility some individuals have had successful Ponseti serial cast management of clubfoot. We have seen one patient whose clubfoot treatment was complicated by a femur fracture, but subsequent resumption of Ponseti treatment after healing the fracture was successful. Knee contractures generally respond partially to casting and fractures may complicate treatment. Joint contractures have been are often resistant to conservative treatment,[10] and operative releases may be effective.

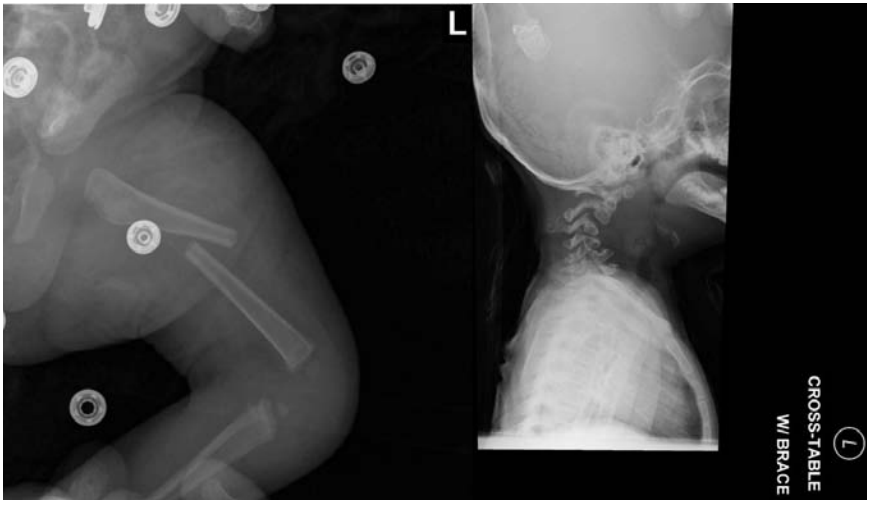

Figure 1. This three month old girl underwent casting for clubfoot. She sustained a femur fracture on the ipsilateral side (left) and family was investigated for child abuse. Subsequent evaluation revealed cervical kyphosis (right). She was diagnosed with Bruck syndrome. Genetic testing revealed FKBP10 defect.

Fracture Care

Treatment of the bone abnormalities is very similar to other types of Osteogenesis Imperfecta.[10] In infants fractures are treated with simple splints or wraps until spontaneous movement signals healing. Intramedullary rodding of long bones remains the standard of care for fracture as well as preventing more bowing of long bones (Figure 2). This treatment stabilizes the fracture and allows the patient to weight bear and increase activity sooner than with cast immobilization. The majority of children with Bruck syndrome at our institution have had eventual rodding of the lower extremities and some have had upper extremity rodding as well.

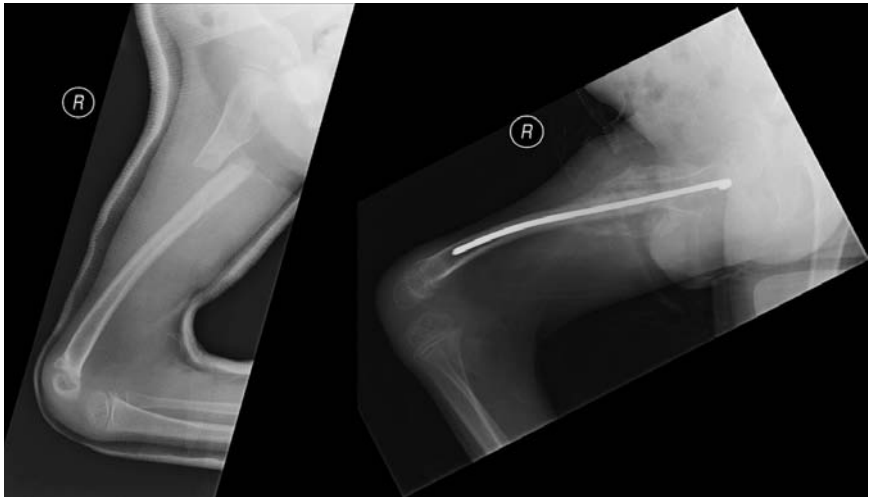

Figure 2. Subtrochanteric femur fracture in a child with Bruck syndrome. The patient has a primary joint contracture of the right knee with an associated fracture (left). The child was treated in the emergency department with a cast, and then converted to intramedullary fixation (right), which allowed faster rehabilitation and treatment of the flexion contracture subsequently operatively.

The presence of an intramedullary rod does not always protect against fracture, but usually allows more rapid rehabilitation. Abundant callus formation has been noted in some Bruck syndrome patients, which is occasionally painful and responds to non-steroidal medication.

Joint Contractures

The management of clubfoot, knee contractures and upper extremity contractures starts with gentle passive motion. Often manipulation is complicated by fracture, leading to the diagnosis. Fracture care may interrupt attempts at deformity correction, but may resume slowly after complete healing. Despite setbacks it has been possible in a few cases to correct clubfoot deformity with the Ponseti method, which involves serial placement of week-long leg casts, with a heel cord tenotomy before the final cast. More commonly, a comprehensive surgical release of the foot is performed after one year of age.

Knee contractures are generally resistant to casting or splinting alone, particularly if there is a pronounced pterygium with poor or absent quadriceps function (Figure 3). However, after a posterior surgical release of the knee flexors, including the hamstrings and gastrocnemius origin, as well

as the posterior knee capsule, there can be dramatic improvement with subsequent serial casting (Figure 3). Immediately after surgery the correction is underwhelming, and indeed this is necessary for preservation of vascular perfusion of the limb, but with each subsequent cast there is dramatic improvement. As a final stage when the knee is within 30 degrees of full correction a knee ankle foot orthosis (KAFO) is fabricated with a dial lock, and final correction to full extension can be achieved with supervised physical therapy.

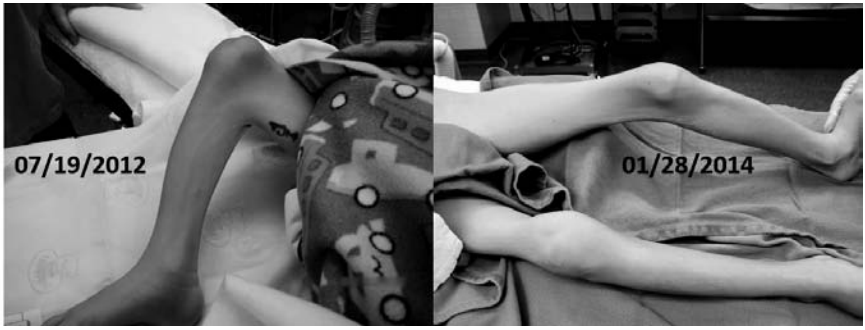

Figure 3. Treatment of pterygium in a 6-year-old male with Bruck Syndrome. Right knee flexion contracture measured 120 degrees (Left). Four months after posterior release and casting the knees come within 25 degrees of full extension. Twelve months after surgery the knee comes within 15 degrees of full extension (Right). The quadriceps are atrophic and he walks independently with a walker and KAFO braces.

Cast application can be performed in the operating room under general anesthesia (Figure 4). Casts are changed at 1-week intervals until the patient has a 10-15 degree residual flexion contracture. At this point a knee ankle foot orthosis (KAFO) should be fitted and advance weight bearing status to as tolerated (Figure 5). KAFOs should be used to improve weight bearing function and prevent recurrence, and a knee immobilizer can be substituted at night. Physical therapy is continued throughout the postoperative course to maintain extension and assist in flexion.

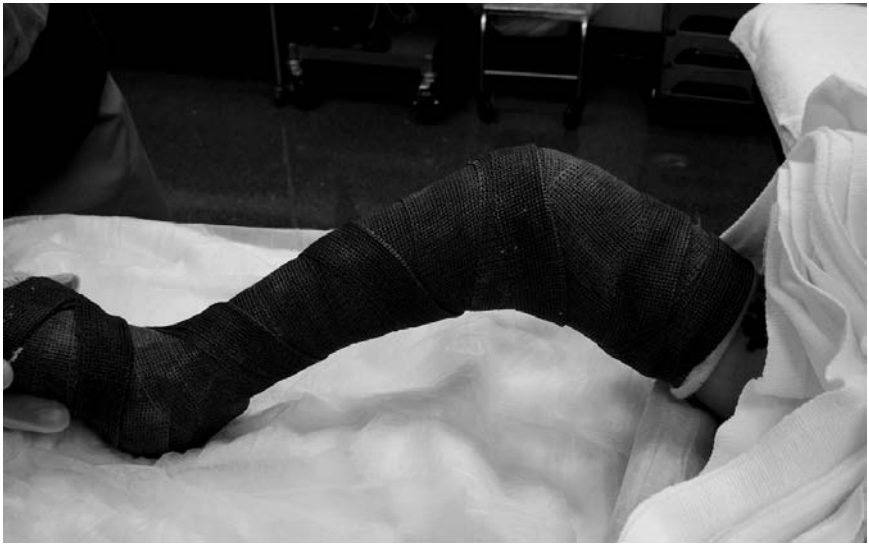

Figure 4. 6-year-old patient with Bruck syndrome (previously shown) immediately after surgical release of joint contracture. Note the contracture is not completely corrected immediately after surgery but improves with further cast changes.

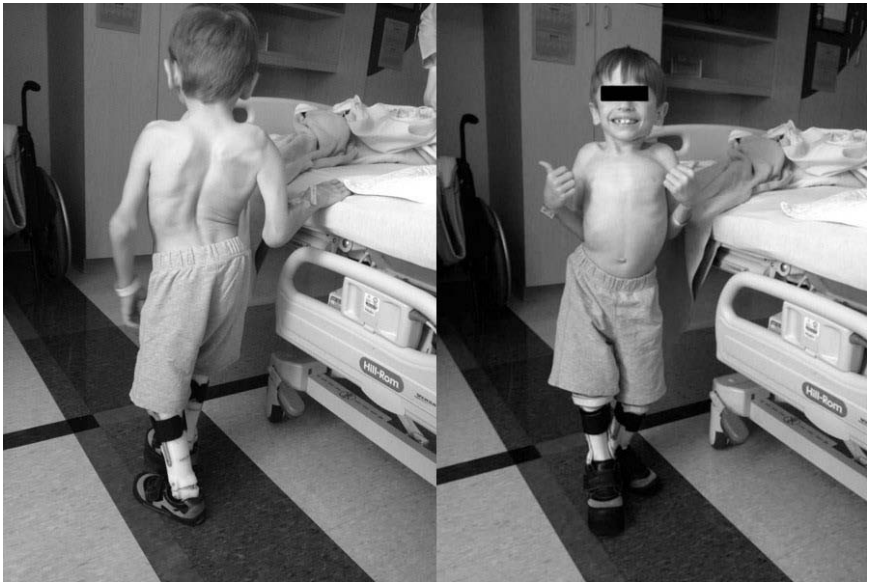

Figure 5. This child was able to be fitted in bilateral KAFOs and walk independently with residual 10 degree flexion contracture in the right knee and no flexion contracture in the left knee.

We have seen one instance where correction of a knee deformity was achieved with an external fixator. This was complicated by a fracture and subsequent stiffness in extension. The long term function of knees with absent or weak quadriceps is often complicated by recurrence, and long term use of a KAFO brace is required.

Bisphosphonates

Children with OI have been administered cyclic intravenous pamidronate with improved clinical outcomes, reduced bone resorption and increased bone density.[27] Andiran et al. published a case report, the first of its kind to treat a Bruck Syndrome child with IV pamidronate in 2007.[4] An increase in bone mineral density and decreased incidence of fractures was noted.[4]

Our experience has been limited but with similar good results. One patient in our clinic experienced over 200 fractures before age 13. After starting cyclic pamidronate infusions, at regular 6-month intervals, the patient recorded less than 10 fractures in the next 7 years. Recently patients with OI and Bruck Syndrome have been treated with intravenous zoledronic acid, rather than pamidronate. We have noted a rapid increase of axial bone mineral density, but persistence of fractures with increased activity (i.e. walking).

Response to therapy is usually monitored by densitometric studies.[6] We recommend performing a dual-energy X-ray absorptiometry (DEXA) scan annually to monitor the change in bone mineral density (Figure 6). The Z score is the number we follow for measurement and trends of bone mineral density, which is formulated by comparing the patient age matched controls. Clinical response to intravenous bisphosphonates can be significant. The patient described earlier with over 200 fractures in our institution was able to remain functional with minimal fractures over her course of treatment and attend a university and live independently.

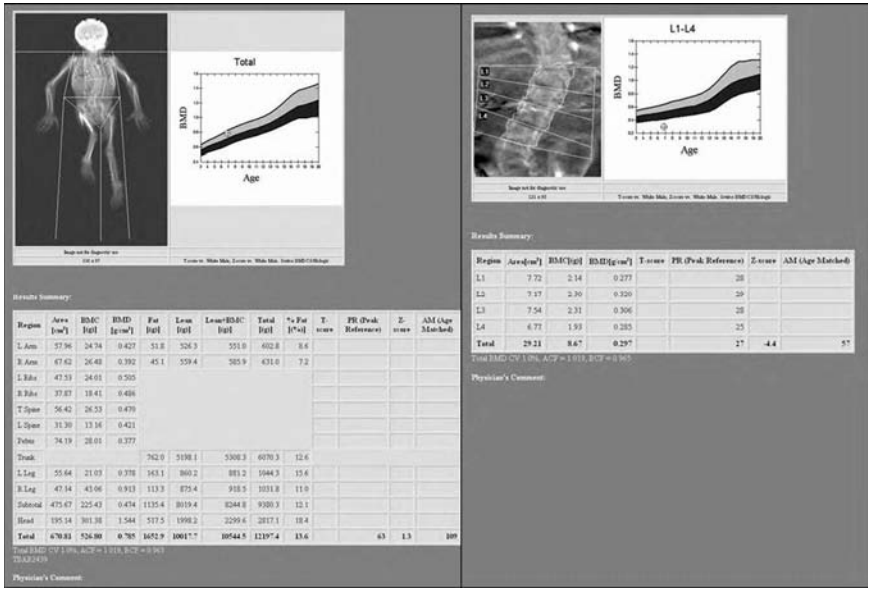

Figure 6. DEXA scan for appendicular (left) and axial (right) bone mineral density measures of a patient with Bruck syndrome. Z-scores are given. The patient started with a Z-score of -4.4 in the axial skeleton and after one year treatment of IV zoledronic acid the Z-score improved to -1.3 in the axial skeleton.

Scoliosis and Kyphosis

It is known that the prevalence of scoliosis in patients with OI, especially severe types, is high.[5] Patients with Bruck syndrome develop scoliosis early and it progresses rapidly. Bracing and bisphosphonate treatment may help slow progression. In a series of OI patients, bisphosphonate therapy initiated before the age of six can modulate curve progression.[5] Spinal fusion may be beneficial if the bone quality is sufficient for fixation. Kyphotic deformities of the spine are particularly common in Bruck syndrome. We have seen three children with severe cervical kyphosis. Two infants have no neurological symptoms as yet, and an adolescent has myelopathy (but intact sensation). There is no known effective treatment. Like cervical kyphosis in other conditions (Ehlers Danlos, Larsens Syndrome) attempts at cervical spinal deformity correction and fusion have been attempted but complications are frequent. A 10-month-old patient with diagnosed Bruck syndrome presented to our clinic with a 90-degree cervical kyphosis without neurological deficits. The patient was braced with soft cervical orthosis and administered intravenous zoledronic acid at 0.025mg/kg (half dose). We plan to continue bracing until more definitive correction can be achieved.

CONCLUSION

Bruck syndrome is a rare disorder of collagen crosslinking with an autosomal recessive inheritance, which causes brittle bones and contractures. There are only a few described cases. The presentation is severe but heterogeneous within the spectrum of OI individuals. There are at least two known genes associated with the syndrome. Future treatment of Bruck Syndrome can be improved with identification of a larger number of patients, a better understanding of the disease mechanism, and possibly anti-fibrotic medications.[12] Patients require a multidisciplinary approach with surgeons, internists, physical therapists, nurses and social workers. Fortunately, most individuals with Bruck syndrome possess excellent minds. Individuals with Bruck Syndrome can lead meaningful, independent lives with proper management.

REFERENCES

1. A., B., 1897, "Ueber eine seltene Form von Erkrankung der Knochen und Gelenke". Dtsch Med Wochenschr. 23: pp. 152-155.
2. Ha-Vinh, R., Y. Alanay, R.A. Bank, A.B. Campos-Xavier, A. Zankl, A. Superti-Furga, and L. Bonafe, 2004, "Phenotypic and molecular characterization of Bruck syndrome (osteogenesis imperfecta with contractures of the large joints) caused by a recessive mutation in PLOD2". Am J Med Genet A. 131(2): pp. 115-20.
3. Steinmann, B.a.R., Bruck Syndrome: Connective Tissues and its Heritable Disorders. 2002: Wiley-Liss, Inc.
4. Andiran, N., A. Alikasifoglu, Y. Alanay, and N. Yordam, 2008, "Cyclic pamidronate treatment in Bruck syndrome: proposal of a new modality of treatment". Pediatr Int. 50(6): pp. 836-8.
5. Anissipour, A.K., K.W. Hammerberg, A. Caudill, T. Kostiuk, S. Tarima, H.S. Zhao, J.J. Krzak, and P.A. Smith, 2014, "Behavior of scoliosis during growth in children with osteogenesis imperfecta". J Bone Joint Surg Am. 96(3): pp. 237-43.
6. Datta, V., A. Sinha, A. Saili, and S. Nangia, 2005, "Bruck syndrome". Indian J Pediatr. 72(5): pp. 441-2.
7. Leroy, J.G., L. Nuytinck, A. De Paepe, M. De Rammelaere, Y. Gillerot, A. Verloes, B. Loeys, and W. De Groote, 1998, "Bruck syndrome: neonatal presentation and natural course in three patients". Pediatr Radiol. 28(10): pp. 781-9.
8. Renaud, A., J. Aucourt, J. Weill, J. Bigot, A. Dieux, L. Devisme, A. Moraux, and N. Boutry, 2013, "Radiographic features of osteogenesis imperfecta". Insights Imaging. 4(4): pp. 417-29.

9. Sharma, N.L. and J.S. Anand, 1964, "Osteogenesis Imperfecta with Arthrogryposis Multiplex Congenita". J Indian Med Assoc. 43: pp. 124-6.
10. Breslau-Siderius, E.J., R.H. Engelbert, G. Pals, and J.A. van der Sluijs, 1998, "Bruck syndrome: a rare combination of bone fragility and multiple congenital joint contractures". J Pediatr Orthop B. 7(1): pp. 35-8.
11. Bank, R.A., S.P. Robins, C. Wijmenga, L.J. Breslau-Siderius, A.F. Bardoel, H.A. van der Sluijs, H.E. Pruijs, and J.M. TeKoppele, 1999, "Defective collagen crosslinking in bone, but not in ligament or cartilage, in Bruck syndrome: indications for a bone-specific telopeptide lysyl hydroxylase on chromosome 17". Proc Natl Acad Sci U S A. 96(3): pp. 1054-8.
12. van der Slot, A.J., A.M. Zuurmond, A.F. Bardoel, C. Wijmenga, H.E. Pruijs, D.O. Sillence, J. Brinckmann, D.J. Abraham, C.M. Black, N. Verzijl, J. DeGroot, R. Hanemaaijer, J.M. TeKoppele, T.W. Huizinga, and R.A. Bank, 2003, "Identification of PLOD2 as telopeptide lysyl hydroxylase, an important enzyme in fibrosis". J Biol Chem. 278(42): pp. 40967-72.
13. Alanay, Y., H. Avaygan, N. Camacho, G.E. Utine, K. Boduroglu, D. Aktas, M. Alikasifoglu, E. Tuncbilek, D. Orhan, F.T. Bakar, B. Zabel, A. Superti-Furga, L. Bruckner-Tuderman, C.J. Curry, S. Pyott, P.H. Byers, D.R. Eyre, D. Baldridge, B. Lee, A.E. Merrill, E.C. Davis, D.H. Cohn, N. Akarsu, and D. Krakow, 2010, "Mutations in the gene encoding the RER protein FKBP65 cause autosomal-recessive osteogenesis imperfecta". Am J Hum Genet. 86(4): pp. 551-9.
14. Shaheen, R., M. Al-Owain, E. Faqeih, N. Al-Hashmi, A. Awaji, Z. Al-Zayed, and F.S. Alkuraya, 2011, "Mutations in FKBP10 cause both Bruck syndrome and isolated osteogenesis imperfecta in humans". Am J Med Genet A. 155A(6): pp. 1448-52.
15. Shaheen, R., M. Al-Owain, N. Sakati, Z.S. Alzayed, and F.S. Alkuraya, 2010, "FKBP10 and Bruck syndrome: phenotypic heterogeneity or call for reclassification?". Am J Hum Genet. 87(2): pp. 306-7; author reply 308.
16. Kelley, B.P., F. Malfait, L. Bonafe, D. Baldridge, E. Homan, S. Symoens, A. Willaert, N. Elcioglu, L. Van Maldergem, C. Verellen-Dumoulin, Y. Gillerot, D. Napierala, D. Krakow, P. Beighton, A. Superti-Furga, A. De Paepe, and B. Lee, 2011, "Mutations in FKBP10 cause recessive osteogenesis imperfecta and Bruck syndrome". J Bone Miner Res. 26(3): pp. 666-72.
17. Puig-Hervas, M.T., S. Temtamy, M. Aglan, M. Valencia, V. Martinez-Glez, M.J. Ballesta-Martinez, V. Lopez-Gonzalez, A.M. Ashour, K. Amr, V. Pulido, E. Guillen-Navarro, P. Lapunzina, J.A. Caparros-Martin, and V.L. Ruiz-Perez, 2012, "Mutations in PLOD2 cause autosomal-recessive connective tissue disorders within the Bruck syndrome--osteogenesis imperfecta phenotypic spectrum". Hum Mutat. 33(10): pp. 1444-9.
18. Eyre, D.R., M.A. Paz, and P.M. Gallop, 1984, "Cross-linking in collagen and elastin". Annu Rev Biochem. 53: pp. 717-48.

19. Herbage, D., Le Lous, M., Cohen-Solal, L. & Bazin, S., Front. Matrix. Biol. Vol. 10. 1985. 59-91.
20. Reiser, K., R.J. McCormick, and R.B. Rucker, 1992, "Enzymatic and nonenzymatic cross-linking of collagen and elastin". FASEB J. 6(7): pp. 2439-49.
21. Robins, S.P., 1982, "Analysis of the crosslinking components in collagen and elastin". Methods Biochem Anal. 28: pp. 329-79.
22. Yamauchi, M.M., G. L., Collagen. Vol. 1: Biochemistry, ed. M.E. Nimni. 1988, Boca Raton, FL: CRC. 157-172.
23. Uzawa, K., W.J. Grzesik, T. Nishiura, S.A. Kuznetsov, P.G. Robey, D.A. Brenner, and M. Yamauchi, 1999, "Differential expression of human lysyl hydroxylase genes, lysine hydroxylation, and cross-linking of type I collagen during osteoblastic differentiation in vitro". J Bone Miner Res. 14(8): pp. 1272-80.
24. Barnes, A.M., G. Duncan, M. Weis, W. Paton, W.A. Cabral, E.L. Mertz, E. Makareeva, M.J. Gambello, F.L. Lacbawan, S. Leikin, A. Fertala, D.R. Eyre, S.J. Bale, and J.C. Marini, 2013, "Kuskokwim syndrome, a recessive congenital contracture disorder, extends the phenotype of FKBP10 mutations". Hum Mutat. 34(9): pp. 1279-88.
25. Petajan, J.H., G.L. Momberger, J. Aase, and D.G. Wright, 1969, "Arthrogryposis syndrome (Kuskokwim disease) in the Eskimo". JAMA. 209(10): pp. 1481-6.
26. Viljoen, D., G. Versfeld, and P. Beighton, 1989, "Osteogenesis imperfecta with congenital joint contractures (Bruck syndrome)". Clin Genet. 36(2): pp. 122-6.
27. Glorieux, F.H., N.J. Bishop, H. Plotkin, G. Chabot, G. Lanoue, and R. Travers, 1998, "Cyclic administration of pamidronate in children with severe osteogenesis imperfecta". N Engl J Med. 339(14): pp. 947-52.

25 SPINAL DEFORMITY IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Spinal deformities are frequently observed in patients with osteogenesis imperfecta (OI). The deformities that are typically seen include scoliosis and kyphosis in the thoracolumbar spine, spondylolisthesis in the lumbosacral spine, and basilar invagination at the craniocervical junction. The prevalence has been reported to be between 39% and 90%.[1-5] This wide range is a reflection of the heterogeneity of osteogenesis imperfecta and differences in various classification systems. Most authors agree that patients with more severe types of OI have a higher incidence of spinal deformity.

THORACOLUMBAR DEFORMITY

King and Bobechko[5] reported on 60 patients with OI classified according to Looser as congenital, tarda gravis or tarda levis.[6] The prevalence of scoliosis was 43% for the congenital type, 70% for tarda gravis, and 28% for tarda levis. They also reported 9 cases (15%) of kyphosis, but did not specify in which types of OI.[5,6] Falvo et al. reported a prevalence of scoliosis of 92% for the congenital type, 44% for tarda type I, and 11% for tarda type II in 90 patients.[2] Kyphosis was not mentioned.

In a large series of 103 children treated at the Shriners Hospitals for Children® - Chicago, Benson et al. reported an overall prevalence of scoliosis

of 62%.[1,7] They classified their patients into 2 groups, either mild or severe depending on their long bone deformities. They found that the risk of spinal deformity increased with the severity of the disease, non-ambulatory status, and the age of the patient. The percentage of children with scoliosis increased with age as well as with the severity of the deformity. Kyphosis was not specifically addressed (Figure 1).

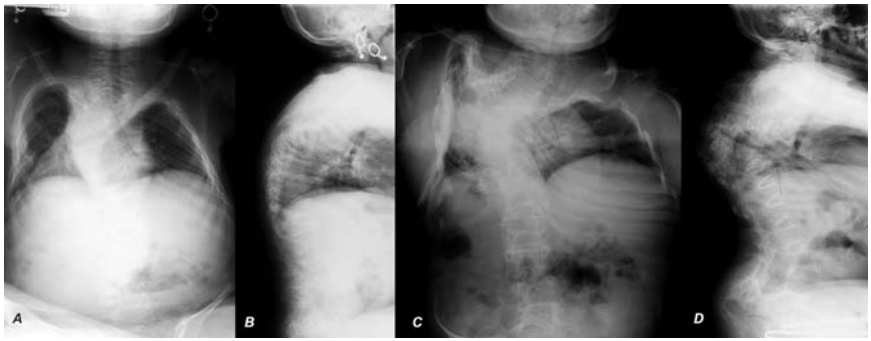

Figure 1. Radiographs of an 8 year-old female with OI type III demonstrating significant progression of a left thoracic scoliosis measuring 41° at the age of 8 (A) and 85° at age 18 (C). There is also progression of her thoracic kyphosis, measuring 55° at age 8 (B) and nearly 160° at age 18 (D). Note also the biconcave shape of the vertebral bodies demonstrating the fragile nature of the bone.

In contrast, Engelbert et al.,[8] in a study of 47 patients, did not find a significant relationship between age and the presence of scoliosis. In a second retrospective review, including 96 children with osteogenesis imperfecta, Engelbert et al.[9] classified the severity of the disease according to Sillence.[10] They reported a prevalence of 19% scoliosis for OI type I, 72% for OI type III, and 61% for OI type IV. They also reported increased kyphosis in 5% of OI type I, 11% of OI type III, and 19% of OI type IV. The age of developing an increased kyphosis was significantly older than the age of developing scoliosis.[9] Hanscom et al. reported that 24 of 40 patients with scoliosis had an increased kyphosis that was correlated with the severity of the disease.[11]

In the largest series to date, Anissipour et al.[12] examined 316 patients with OI, the overall prevalence of scoliosis was found to be 50%. Scoliosis prevalence (68%) and mean progression rate (6° per year) were largest in the modified Sillence type III children. A group with intermediate OI severity, modified Sillence type IV, demonstrated intermediate scoliosis values (54%, 4° per year). The patient group with the mildest form of OI, modified Sillence

type I, had the lowest scoliosis prevalence (39%) and rate of progression (1° per year). Figure 2 demonstrates the behavior over time among the three most common types of OI. This report also found that early treatment – before the patient reached the age of six years – of type III OI with bisphosphonate therapy decreased the curve progression rate by 3.8 degrees per year. Bisphosphonate treatment did not demonstrate a beneficial effect on curve behavior in patients with other types of OI or in patients of older age.

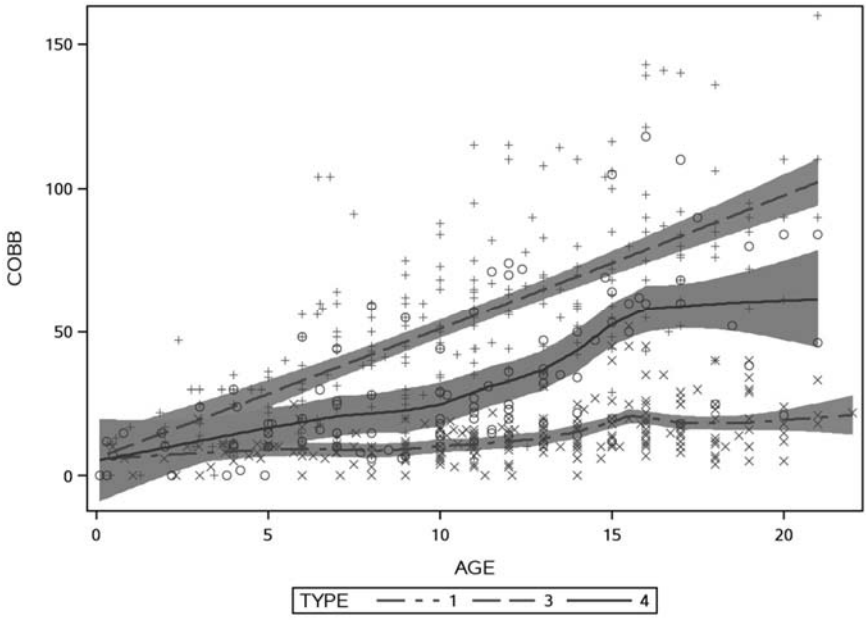

Figure 2. Graphic representation of patient age versus Cobb angle measurement for patients with osteogenesis imperfecta type I (x), type III (+), and type IV (o). Reprinted from Anissipour et al. Behavior of scoliosis during growth in children with osteogenesis imperfecta, Copyright 2014, with permission from Journal of Bone and Joint Surgery American (www.jbjs.org).[12]

The reports are in agreement that the prevalence and severity of scoliosis is related to the severity of OI, and that scoliosis is more common than kyphosis. Also, the spinal curvature tends to be progressive, sometimes quite rapidly with accelerated growth.[13] Unfortunately, there are only incidental reports in the literature regarding the natural history of this process in adulthood but continued progression has been observed.[14,15] We do know that thoracic curvatures greater than 60° have severe adverse effects on pulmonary function and physical health as assessed by the SF-36 in those

with osteogenesis imperfecta.[16] Adult patients with OI and scoliosis have an increased pulmonary morbidity secondary to spine and chest deformity.

Pathogenesis of Spinal Deformity

The pathogenesis of spinal deformity in OI has not been conclusively determined, but a primary cause is thought to be vertebral fractures and injury to the vertebral growths plates due to the brittle bone. This hypothesis fits well with the observations that the prevalence and severity of spinal deformities are greater in patients with the more severe forms of OI. Secondary factors include ligamentous laxity, leg length discrepancy, pelvic obliquity and delayed motor development.[1,13,14]

Ishikawa et al.[4] analyzed 44 patients with OI followed over an average of 12 years. They found the prevalence of scoliosis to be 68% and kyphosis to be 41%, again correlated with the severity of the disease. A predictor of severe progression was the presence of six biconcave vertebrae before puberty. Biconcave vertebrae are a common finding in OI and indicate the fragile nature of the bone.

The significance of vertebral fragility in the pathogenesis of scoliosis in OI is supported by Watanabe et al.[17] They studied 19 patients with OI and scoliosis, correlating the Cobb measurement with bone mineral density, body mass index, and leg length discrepancy. They found that the patients with lower bone mineral density had larger curvatures, which supports the role of vertebral fragility in the development of spinal deformity. They also demonstrated a significant positive correlation between the magnitude of the curvature and body mass index, as well as leg length discrepancy.

The role of vertebral fragility in the development of scoliosis was further demonstrated in a study by Engelbert et al.[9] Bone mineral density was measured in 53 children with OI, 28 of whom developed scoliosis and 25 of whom did not. The mean dual energy x-ray absorptiometry (DEXA) score for the 28 children with scoliosis was significantly lower than that of the 25 children without. Another interesting finding of this study was that the earlier achievement of the motor milestone “supported sitting” predicted a later development of pathologic spinal curvatures independent of the Sillence type of OI. The authors contend that delayed motor development may be a result of impaired proprioception and postural control contributing to the development of scoliosis.[9]

Treatment

Medical

There is no medical treatment for scoliosis, however, bisphosphonate therapy may prove to delay the onset and modulate the progression of scoliosis in osteogenesis imperfecta. Cyclical intravenous pamidronate has been shown to increase vertebral bone mineral density and improve vertebral height.[18-20] Vertebral fragility fractures play an important role in the development of scoliosis and it follows that improved bone density may alter the natural history of this process. In a small but prospective study, 11 infants with severe OI and average age of 3.6 months were started on pamidronate therapy.[21] During treatment of 3 to 6 years, vertebral bone density and height increased, and no child developed scoliosis, kyphosis or basilar invagination. The authors caution that whether early treatment can prevent the development of thoracolumbar deformity is not established, but these results are encouraging. The therapeutic effects of pamidronate therapy have been consistent regardless of age from infancy to adulthood.[22]

Orthoses

Bracing has been attempted in these patients to control the scoliotic deformity, but the results have been disappointing and usually have been abandoned.[15] Benson et al. found the Milwaukee brace ineffective in controlling progressive scoliosis, and contributed to chest wall deformity or compounded pre-existing chest wall deformity.[1,7] Other reports support the failure of orthotic management in the treatment of spinal deformity related to osteogenesis imperfecta.[11,16,24] In a survey review, Yong-Hing and MacEwen identified 83 patients treated with a spinal orthosis with a failure rate of 82%.[25] They concluded that it was highly likely that the curves in the remaining patients would progress with longer follow-up after the brace was discontinued at skeletal maturity.

Surgical

The surgical treatment of thoracolumbar deformity secondary to OI has followed the same evolution as the treatment for adolescent idiopathic scoliosis, but at a somewhat slower pace. A report by King and Bobechko mentions two patients treated with Harrington instrumentation and fusion for scoliosis secondary to OI, both having been performed in 1968.[5] They suggested delaying surgery until late adolescence when the bone becomes stronger. In contrast, Benson et al. suggested that surgery should be done

early because of the predictable progression of the curves and the limited correction that could be achieved because of the brittle bone.[1,7] Hanscom has recommended surgery at 45° curvature for patients with mild disease, and at 35° for those with more severe involvement regardless of age.[23] Generally, 50° is regarded as a surgical indication, but many authors caution that not all patients can be helped with surgery.

A variety of procedures were employed in attempts to surgically control the scoliosis including fusion in situ after halo gravity traction, halo hoop traction, anterior releases, and augmentation of distraction hooks with methylmethacrylate.[7,14,15,25] The incidence of instrumentation related complications and continued curve progression remained high.[23,24]

The value of segmental instrumentation to more evenly distribute the forces of curve correction and maintenance was recognized after the introduction of Luque instrumentation for the treatment of other forms of scoliosis.[11,26] Initially sub-laminar wires were used and later dual rods with multiple hooks. Janus et al.[27] reported on their results for 20 children treated with pre-operative traction averaging 90 days. The traction period was followed by *in situ* fixation in 18 of 20 patients with dual rods and multiple hook fixation. The halo was left on for several weeks following surgery to facilitate early mobilization, prior to the application of a cast. The overall improvement in scoliosis was 32% and in kyphosis 24%. A modest loss of correction over 4.8 years follow-up was noted. A postoperative loss of fixation and correction was noted in only 4 patients, and improved functional level in 7 patients.

Currently, segmental fixation is achieved with multiple pedicle screw instrumentation (Figure 3). Pre-operative pamidronate therapy seems to improve bone quality, providing better intra-operative fixation. A case report from Pan et al.[28] described the use of pre-operative bisphosphonate therapy, halo-gravity traction, followed by an all pedicle screw construct in a 14 year old girl. They achieved a 38% correction of the scoliosis and 63% correction of the kyphosis with no loss of correction in one and a half years.

The insertion of pedicle screws at every level may not be possible due to the thinness and elongation of the pedicles and posterior elements. Additionally, the vertebral bodies in the more severe types of OI are often wafer thin. The surgeon should be prepared to employ alternative methods of posterior fixation such as hooks , sublaminar wires or mersiline tapes. Techniques to reduce intra-operative corrective forces include pre-operative halo-gravity

traction with multiple pins and anterior releases.[24,25,27] Anterior releases should be approached with caution in the more severe types of OI with thin vertebral bodies because resection of the relatively large discs can destabilize the anterior column. Allograft bone is advised with demineralized bone matrix because autogenous iliac bone graft is usually inadequate secondary to the thin and deformed pelvis.

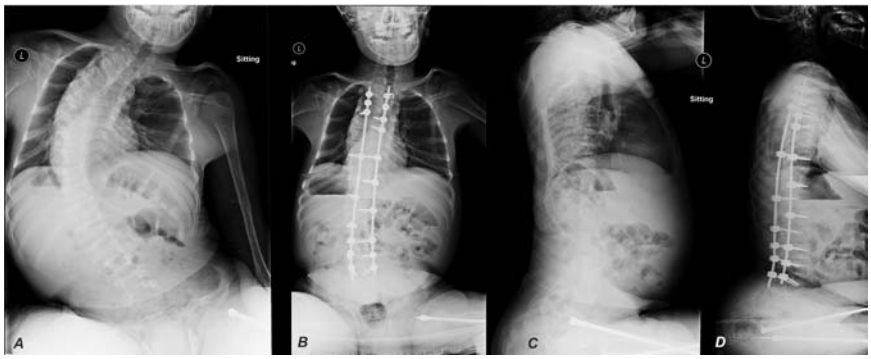

Figure 3. Radiographs of a patient with OI type IV who presented at 4 years of age with a 20° left thoracic scoliosis and progressed to 97° by 15 years of age (A,C), when he underwent T2-L4 instrumented posterior spinal fusion (B,D).

The outcomes of spinal fusion and instrumentation remain poorly defined. Janus and colleagues concluded that although some loss of correction was inevitable, stabilization of the deformity could be achieved.[27] In another study, children who were not treated with bisphosphonates demonstrated no improvement in functional ability or ambulatory capacity following spinal fusion.[30] Curve progression continued despite posterior fusion and instrumentation and junctional curve progression was noted as well. Complications with instrumentation and curve stabilization remain problematic. Hopefully, the use of bisphosphonates before and after surgery will prove valuable in the surgical treatment of thoracolumbar deformity in osteogenesis imperfecta.

LUMBOSACRAL DEFORMITY

The typical lumbosacral deformities observed in osteogenesis imperfecta are spondylolysis, spondylolisthesis, and sacral kyphosis. Spondylolysis is defined as a fracture or defect in the pars interarticularis. Spondylolisthesis is the ventral translation of a cephalad vertebra on a caudal vertebra. This slippage may be the result of a spondylolysis or the elongation of the lumbar

pedicles and posterior elements.[30,31] In the literature there have been sporadic reports of spondylolysis and spondylolisthesis occurring in OI.[30,32] King and Bobechko noted 4 cases of spondylolisthesis with elongated pedicles among a group of 60 patients.[5] Hanscom et al. reported 3 cases of spondylolisthesis among a group of 43 patients.[11]

Two recent retrospective radiographic reviews have specifically studied the prevalence of spondylolysis and spondylolisthesis in OI. Verra et al. reviewed the radiographs of 113 patients older than 6 years of age.[33] They found 6 instances of pars defects for a prevalence of 5.3%, which fits in the range of prevalence for the normal population.[34-36] There were 2 cases of spondylolisthesis both associated with a pars defect, but no cases of elongated pedicles. Interestingly, they found an inverse relationship between the severity of the OI type and the occurrence of pars defects. Many patients in their study group were treated with bisphosphonates.

A report by Hatz et al.[37] is somewhat contradictory to the paper by Verra et al. They reviewed the radiographs of 110 patients with OI with an average age of 6.1 years. They found the incidence of spondylolysis to be 8.2% and spondylolisthesis to be 10.9%, much higher than the general population. Among those with spondylolisthesis , 9 were due to spondylolysis and 3 due to elongated pedicles. Overall, they observed elongated pedicles in 40.0% of their patients. Unlike Verra et al., they found that the severity of the disease directly correlated with the higher prevalence of abnormalities in the posterior elements of the lumbar spine. All of the more severe types and many of the more mild types received pamidronate therapy. Obviously, more research is needed to clarify the role of disease severity, bisphosphonate therapy, and ambulatory capacity on the prevalence of spondylolysis and spondylolisthesis in osteogenesis imperfecta.

Pathophysiology

The normal morphology of the lumbosacral junction resists high shear and compressive forces. The loss of posterior restraint through incompetent posterior elements may result in the forward displacement of one vertebra and the cephalad levels of the spinal column on its subjacent vertebra.[38]

According to the Marchetti/Bartolozzi classification, the vast majority of spondylolysis reported in children with osteogenesis imperfecta are considered pathologic.[39] Patients with OI are prone to sustain pathologic fractures. Pathologic fractures due to micro-motion, posture, and repetitive

activities may weaken the pars interarticularis leading to spondylolysis and spondylolisthesis. More commonly, spondylolisthesis has been described in patients with OI to be associated with pedicle elongation.[5,11,30,31,37] Ivo et al.[31] presented three patients with OI showing a severe form of hyperlordosis caused by lumbar pedicle elongation and consecutive levels of spondylolisthesis without spondylolysis (Figure 4). This form of spondylolisthesis is considered pathologic.

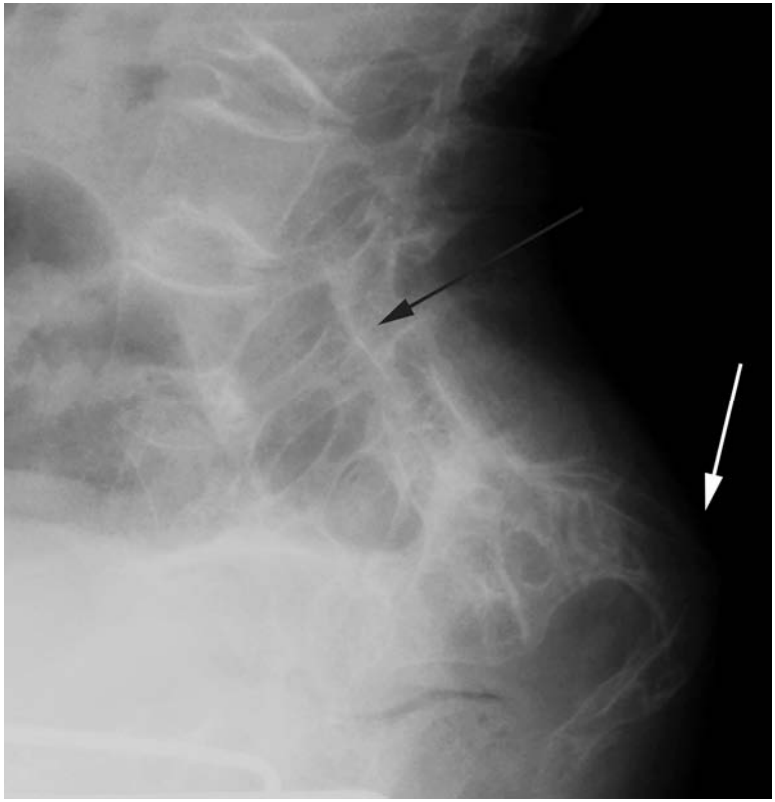

Figure 4. Lateral radiograph of an 18 year-old female with OI type III demonstrating an angular hyperlordosis and extreme elongation of lumbar pedicles (dark arrow) resulting in high grade spondylolisthesis and hyperkyphosis of the sacrum (white arrow).

Treatment

The main goals of treatment for spondylolisthesis are to relieve pain, stabilize the spine, and increase functional capacity. Achieving these goals enables the patient to return to more normal activity without restriction. Treatment for spondylolisthesis depends on several factors, including the

age and overall health of the patient, extent of the slip, and severity of the symptoms.

Initial conservative management in the form of activity modification and bracing may relieve symptoms in patients with spondylolysis. Stabilization exercises are the mainstay of treatment. The use of a total-contact, low-profile polyethylene orthosis (Boston brace) can be tried.

Although bisphosphonates have been used to treat patients with OI, their role in the treatment of spondylolysis is unclear. Astrom et al. reported that in 7 of 11 young children with OI who had been treated with intravenous disodium pamidronate developed spondylolysis of the 5th lumbar vertebra.[21] They postulate that spondylolysis may be underdiagnosed due to the low mineralization of untreated children with OI. Whether bisphosphonate therapy can be a risk factor for spondylolysis remains to be seen.

Unfortunately, little has been published about the surgical treatment of spondylolisthesis in patients with osteogenesis imperfecta. Basu et al. reported on a 14-year-old patient with OI with dysplastic and elongated pedicles of L4 and L5 causing spondylolisthesis, as well as hyperlordosis and thoracic scoliosis.[30] She underwent an in-situ, non-instrumented, anterior spinal fusion of L3 to the sacrum at age 11 with satisfactory results at three-year follow-up. Of note, the patient did have a delayed fusion of L5-S1 and was treated with a brace until she ultimately fused.

Ivo et al. reported on three cases of children with OI with pedicle elongation causing hyperlordosis, and spondylolisthesis without spondylolysis, one of whom underwent surgery.[31] This patient was a 17 year old who developed hyperlordosis and L2-L5 extreme pedicle elongation with consecutive spondylolisthesis (Meyerding grade 2 and 3). Therefore, a lumbar laminectomy and postero-lateral fusion with instrumentation was performed. Placement of screws was partially extrapedicular due to the dysplastic nature of the pedicles. After surgery, lumbar pain was slightly improved. As subsequent radiographs confirmed fusion and the patient complained about local pressure sores, instrumentation was removed until 23 years of age. An MRI of the lumbar spine at the age of 28 years demonstrated that the lumbar deformation showed no significant progression following the postero-lateral fusion.

In summary, as with healthy patients, treatment of spondylolisthesis in OI depends on clinical and radiological findings. Physical therapy and bracing are acceptable first line treatments. Bisphosphonates can be used to supplement treatment in patients with OI but its effects remain unclear. Treatment of patients who have spondylolisthesis caused by elongated lumbar pedicles in OI is preferably conservative.[31] Surgical intervention may be indicated for patients with persistent pain, progressive spondylolisthesis, or neurologic symptoms who fail conservative management.

The biomechanics of osteogenesis imperfecta are difficult to anticipate. Lumbar decompression without instrumentation is predisposed to instability of the decompressed segment. Furthermore, pedicle screw placement is technically difficult to perform due to elongated pedicles. One can consider the limited success of anterior interbody fusion without instrumentation to treat spondylolisthesis.[30] All risks must be considered and fully discussed with the patient and family before the decision is made to proceed with surgical intervention.

CRANIOCERVICAL DEFORMITY

Basilar impression (BI) is a common manifestation of osteogenesis imperfecta. It is a potentially devastating anatomic deformity characterized by the migration of the atlas and odontoid process through the foramen magnum. Sillence et al. have reported that 8-25% of patients with OI develop radiographic evidence of BI, but not all become clinically symptomatic.[41,42] Basilar impression can lead to brainstem and cerebellar compression, alteration of cerebrospinal (CSF) flow, and mechanical stretching of the cranial nerves.[41-44] These findings can be progressive and can lead to rapid neurological deterioration,[41,45] respiratory arrest,[41,46] and sudden death.[41,47] The highest incidence of BI occurs in patients with Sillence types IB and IVB in association with dentinogenesis imperfecta.[8,42,48] Osteogenesis imperfecta type II is uniformly fatal and BI in OI type III is less common likely due to a delay in upright sitting posture.[8,9] However, Menezes states that BI clearly contributed to death from respiratory compromise and progressive BI in OI type III compared to types I and IV.[47,49-51]

Pathophysiology

As a result of abnormal collagen synthesis in osteogenesis imperfecta and the resulting osteopenia, all bony structures including the skull are fragile and prone to progressive deformity. Basilar impression is the result of abnormal

development of the occipital bone with a progressive softening and repeated sequential trauma.[46,47,52] The floor of the posterior fossa becomes elevated by squamo-occipital infolding and the rim of the foramen magnum folding upward.[53] The basiocciput is shortened and elevated while the clivus is thinned, shortened, and takes on a more horizontal angle.[44,53] The petrous portion of the temporal bone is also deformed allowing the clivus-atlas-odontoid complex to elevate through the foramen magnum and further crowd the posterior fossa.[53] As a result the brainstem is pushed upward and splayed over the clivus-atlas-odontoid complex. Together the compression and traction secondary to basilar impression can lead to brainstem dysfunction, myelopathy, and stretching of the lower cranial nerves leading to multiple lower cranial nerve palsies resulting in difficulty with airway protection and swallowing. Cerebellar dysfunction can be a result of direct compression or hindbrain herniation. In addition to direct neurological dysfunction as a result of compression within the posterior fossa or at the foramen magnum, vascular insufficiency, and/or altered CSF flow can result leading to further clinical decline.[44,47,50,53]

In addition to the inherent collagen abnormality specific to OI, Frank et al. have postulated that the weight of the cranium overwhelms the pliable occipital bone and thus leads to continued deformation of the foramen magnum allowing some cranial settling.[46,53] Sasaki-Adams et al. point out in their review of the neurosurgical implications of OI, a study that revealed 13.1% of patients with OI have macrocephaly.[52,54,55] Overall, skull deformity commonly occurs in OI resulting in a helmet-like shape of the head by flattening the anterior-posterior diameter and the prominence of the frontal and occipital bones.[52] Repeated microfractures and subsequent abnormal healing throughout the skull and at the craniocervical junction likely also contribute to BI in osteogenesis imperfecta.[41,44,47,53]

The development of appropriate head control, in particular at the craniocervical junction, may contribute to more normal bone formation at the foramen magnum and the clivus-atlas-odontoid complex. In another study on 47 children with OI, Engelbert et al. revealed that BI was more commonly associated with kyphosis than scoliosis and that no children with BI had evidence of generalized hypermobility.[8]

Clinical Presentation

Symptomatic BI is a progressive disease process leading to significant neurological deterioration and even death. The largest published case series

by Menezes reviewed 52 children with symptomatic BI (28 of which had OI), and found that 80% presented with occipital and vertex headaches.[50] Involvement of cranial nerves VIII, IX, and X was found in 70% while additional common symptoms included dysphagia (66%), respiratory difficulty (60%), weakness (48%), and ataxia (32%).[50,53] An additional 25-35% of patients with BI will present with additional neural axis abnormalities including Chiari malformation, syringomyelia, syringobulbia, and hydrocephalus.[56] The most common age of presentation is during adolescence ranging between 11-15 years age.[50,53] However, Sawin and Menezes state that patients who experience more long bone fractures and earlier development of skeletal deformity thus demonstrating a more severe form of OI, tended to develop BI at an earlier age.[53]

Historically the diagnosis of BI was made on radiographs of the skull (Figure 5).[56-58] The development of computed tomography (CT) and magnetic resonance imaging (MRI) has lead to improved visualization of the craniovertebral junction and has allowed improved evaluation of bony, ligamentous, and vascular anatomy. Thus, the diagnosis of BI is now routinely made with a combination of imaging modalities in conjunction with a patient's clinical presentation (Figures 6-7).

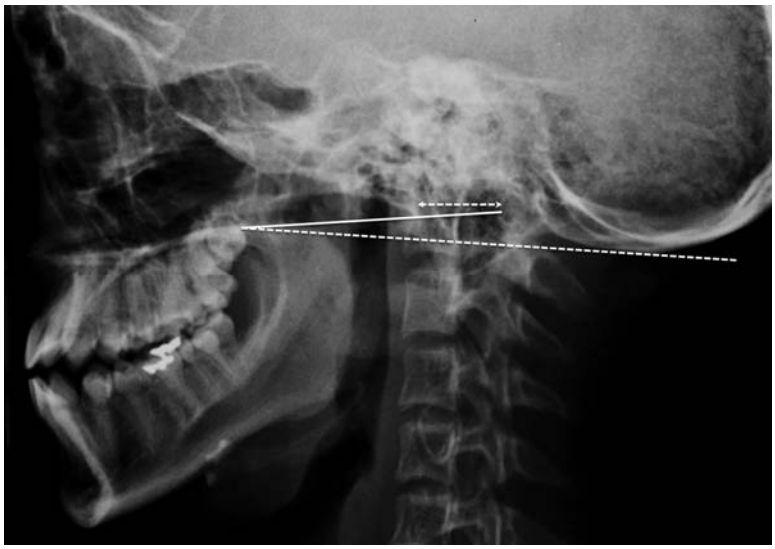

Figure 5. Lateral radiograph of a 15 year-old male with OI type IV and basilar impression. The odontoid process is 6 mm above McRae's line, (basion to opisthion) (*dashed white line with arrows)*, 7 mm above Chamberlain's line (hard palate to opisthion) (*solid white line)* and over 2 cm above McGregor's line, (hard palate to caudal occipital bone) (*dashed white line).*

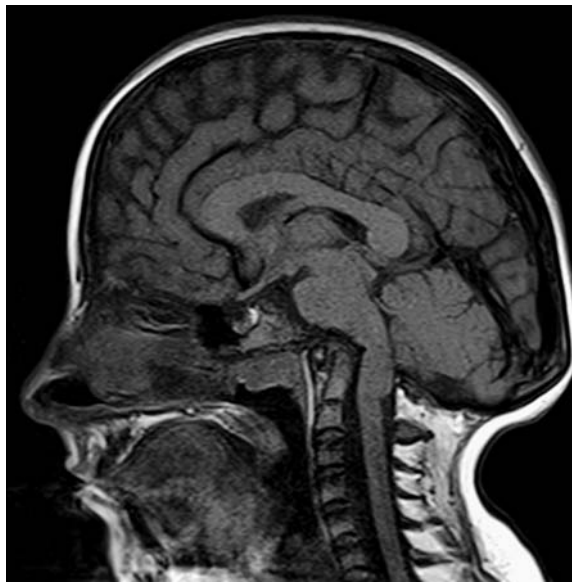

Figure 6. T1-weighted sagittal MRI of the brain of an 11 year-old female with OI type IV and basilar impression. Note the kinking of the brainstem over the odontoid and the overall helmet shape of the skull.

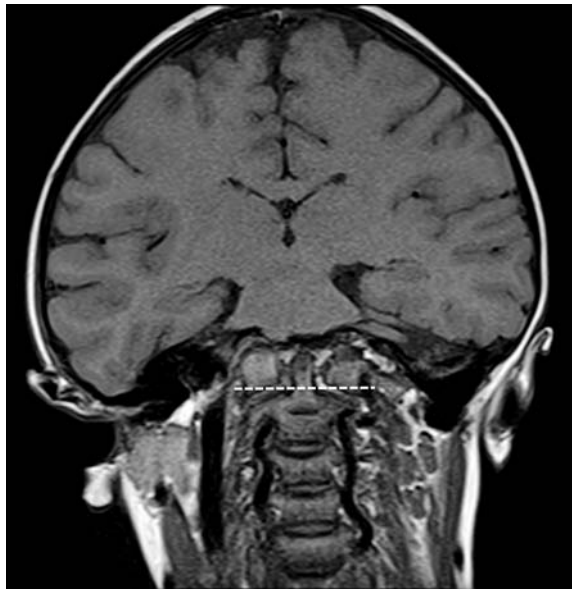

Figure 7. T1-weighted coronal MRI of the brain of an 11 year-old female with OI type IV and basilar impression. The atlas and odontoid are above the foramen magnum (dashed white line) within the posterior fossa compressing the brainstem above.

Management

Surgical

Surgical intervention for symptomatic BI is based on a few principles. First, BI in osteogenesis imperfecta is likely to progress if untreated and the consequences of progression can be devastating. There are some rare patients however who present with BI and are asymptomatic. They can often be followed clinically and radiographically in an orthosis,[56] but most patients will require surgical decompression. Basilar impression can also cause an obstructive, noncommunicating form of hydrocephalus as the clivus-atlas-odontoid complex crowds the posterior fossa leading to compression of the cerebral aqueduct of Sylvius.[52-54] The true incidence of hydrocephalus in BI and OI is unknown, but Sawin and Menezes[53] report a 44% rate of hydrocephalus in their series of patients with OI and related osteochondrodysplasias. Sasaki-Adams et al. report a 30% prevalence of hydrocephalus in their retrospective review of patients with osteochondrodysplasias.[52] In either case, patients with evidence of hydrocephalus first underwent placement of a ventriculoperitoneal shunt. Sawin and Menezes also report two patients who experienced complete resolution of symptoms with shunting alone.[53] They were subsequently managed in a modified Minerva brace and did not require further surgical intervention.

In the case series reported by Sawin and Menezes,[53] patients first underwent a trial of axial cervical halo-gravity traction in an effort to reduce ventral brainstem compression prior to surgical decompression, with a 40% successful reduction rate. These patients then underwent posterior fossa decompression and occipitocervical instrumented fusion. The 60% of patients who were unable to be reduced with axial halo-gravity traction required anterior (transoral-transpalatopharyngeal, transmaxillary) odontoidectomy and decompression followed by posterior decompression and fusion. Following ventral decompression all patients underwent posterior decompression and fusion similar to the patients who achieved successful reduction via halo-gravity traction. Posterior fossa decompression is achieved by performing a suboccipital craniectomy, C1 laminectomy, and duraplasty. Subsequent to decompression, occipital-cervical fusion must be performed. There are a variety of techniques available for achieving occipital-cervical fusion ranging from the use of wiring techniques with autogenous bone graft or contoured loop

instrumentation to rod and screw constructs using occipital plate fixation in conjunction with C1 lateral mass fixation, C2 pars, pedicle, or translaminar fixation, and subaxial lateral mass fixation.[56,59] Postoperatively the patients were maintained in halo vest immobilization or modified Minerva brace until solid bone fusion was observed radiographically. Despite achieving radiographic evidence of solid fusion, 80% of these patients went on to demonstrate radiographic evidence of progression of BI over time. Only 6 of the 25 patients developed symptoms such as headache, neck pain, dysphagia, or myelopathy. The rate of progression was greatest during the adolescent period and was similar in cases with and without ventral decompression. All of these patients were subsequently managed with prolonged use of a modified Minerva brace to be worn during the day and a rigid cervical collar to be worn at night.[53]

Medical

While the surgical management of BI in osteogenesis imperfecta targets the anatomical or structural manifestations at the craniocervical junction, systemic therapy must also be initiated in order to address the global problems associated with OI. The mainstays of pharmacological treatment for OI in children include antiresorptive bisphosphonates including intravenous pamidronate and neridronate, and oral alendronate, olpanronate and residronate.[60] While each of these interventions has different advantages and disadvantages, the surgical management of BI targets only a focal issue for a systemic problem. Thus, both medical and surgical interventions are required for management of BI in the setting of osteogenesis imperfecta.

ABBREVIATIONS

BI	Basilar impression
CSF	Cerebrospinal fluid
CT	Computed tomography
DEXA	Dual energy x-ray absorptiometry
MRI	Magnetic resonance imaging
OI	Osteogenesis imperfecta

REFERENCES

1. Benson DR, Donaldson DH, Millar EA. The spine in osteogenesis imperfecta. *J Bone Joint Surg Am.* Oct 1978;60(7):925-929.

2. Falvo KA, Root L, Bullough PG. Osteogenesis imperfecta: clinical evaluation and management. *J Bone Joint Surg Am.* Jun 1974;56(4):783-793.
3. Hoek KJ. Scoliosis in osteogenesis imperfecta. Proceedings of the Western Orthopaedics Association. *J Bone Joint Surg Am.* 1975;57A(1):136.
4. Ishikawa S, Kumar SJ, Takahashi HE, Homma M. Vertebral body shape as a predictor of spinal deformity in osteogenesis imperfecta. *J Bone Joint Surg Am.* Feb 1996;78(2):212-219.
5. King JD, Bobechko WP. Osteogenesis Imperfecta: An Orthopaedic Description and Surgical Review. *J Bone Joint Surg Am.* 1971;53 B(1):72-89.
6. Looser E. Zur Kenntnis der Osteogenesis imperfecta congenita und tarda (sogenannte idiopathische Osteopsathyrosis). *Mitteil Grenzgeb Med Chir.* 1906;15:161-207.
7. Benson DR, Newman DC. The spine and surgical treatment in osteogenesis imperfecta. *Clin Orthop Relat Res.* Sep 1981(159):147-153.
8. Engelbert RH, Gerver WJ, Breslau-Siderius LJ, et al. Spinal complications in osteogenesis imperfecta: 47 patients 1-16 years of age. *Acta orthopaedica Scandinavica.* Jun 1998;69(3):283-286.
9. Engelbert RH, Uiterwaal CS, van der Hulst A, Witjes B, Helders PJ, Pruijs HE. Scoliosis in children with osteogenesis imperfecta: influence of severity of disease and age of reaching motor milestones. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Apr 2003;12(2):130-134.
10. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *Journal of medical genetics.* Apr 1979;16(2):101-116.
11. Hanscom DA, Winter RB, Lutter L, Lonstein JE, Bloom BA, Bradford DS. Osteogenesis imperfecta. Radiographic classification, natural history, and treatment of spinal deformities. *J Bone Joint Surg Am.* Apr 1992;74(4):598-616.
12. Anissipour A, Hammerberg KW, Caudill A, Kostiuk T, Tarima S, Zhao H, Krzak J, Smith PA. Behavior of Scoliosis During Growth in Children With Osteogenesis Imperfecta: *J Bone Joint Surg Am. 2014*;96: 237-43
13. Norimatsu H, Mayuzumi T, Takahashi H. The development of the spinal deformities in osteogenesis imperfecta. *Clin Orthop Relat Res.* Jan-Feb 1982(162):20-25.
14. Cristofaro RL, Hoek KJ, Bonnett CA, Brown JC. Operative treatment of spine deformity in osteogenesis imperfecta. *Clin Orthop Relat Res.* Mar-Apr 1979(139):40-48.
15. Renshaw TS, Cook RS, Albright JA. Scoliosis in osteogenesis imperfecta. *Clin Orthop Relat Res.* Nov-Dec 1979(145):163-167.
16. Widmann RF, Bitan FD, Laplaza FJ, Burke SW, DiMaio MF, Schneider R. Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. *Spine (Phila Pa 1976).* Aug 15 1999;24(16):1673-1678.
17. Watanabe G, Kawaguchi S, Matsuyama T, Yamashita T. Correlation of scoliotic curvature with Z-score bone mineral density and body mass index in patients with osteogenesis imperfecta. *Spine (Phila Pa 1976).* Aug 1 2007;32(17):E488-494.
18. Land C, Rauch F, Munns CF, Sahebjam S, Glorieux FH. Vertebral morphometry in children and adolescents with osteogenesis imperfecta: effect of intravenous pamidronate treatment. *Bone.* Oct 2006;39(4):901-906.
19. Letocha AD, Cintas HL, Troendle JF, et al. Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains

but not short-term functional improvement. *J Bone Miner Res.* Jun 2005;20(6):977-986.
20. Rauch F, Glorieux FH. Osteogenesis imperfecta, current and future medical treatment. *American journal of medical genetics. Part C, Seminars in medical genetics.* Nov 15 2005;139C(1):31-37.
21. Astrom E, Jorulf H, Soderhall S. Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. *Archives of disease in childhood.* Apr 2007;92(4):332-338.
22. Morris CD, Einhorn TA. Bisphosphonates in orthopaedic surgery. *J Bone Joint Surg Am.* Jul 2005;87(7):1609-1618.
23. Hanscom DA, Bloom BA. The spine in osteogenesis imperfecta. *Orthop Clin North Am.* Apr 1988;19(2):449-458.
24. Yong-Hing K, MacEwen GD. Scoliosis associated with osteogenesis imperfecta. *J Bone Joint Surg Br.* 1982;64(1):36-43.
25. Gitelis S, Whiffen J, DeWald RL. The treatment of severe scoliosis in osteogenesis imperfecta. Case report. *Clin Orthop Relat Res.* May 1983(175):56-59.
26. Trotter D. Spinal fusion for scoliosis in osteogenesis imperfecta: The Chicago Shriners Hospital experience. *Orthop Trans.* 1986;10:28.
27. Janus GJ, Finidori G, Engelbert RH, Pouliquen M, Pruijs JE. Operative treatment of severe scoliosis in osteogenesis imperfecta: results of 20 patients after halo traction and posterior spondylodesis with instrumentation. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Dec 2000;9(6):486-491.
28. Pan CH, Ma SC, Wu CT, Chen PQ. All pedicle screw fixation technique in correcting severe kyphoscoliosis in an osteogenesis imperfecta patient: a case report. *J Spinal Disord Tech.* Jul 2006;19(5):368-372.
29. Tolboom N, Cats EA, Helders PJ, Pruijs JE, Engelbert RH. Osteogenesis imperfecta in childhood: effects of spondylodesis on functional ability, ambulation and perceived competence. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Mar 2004;13(2):108-113.
30. Basu PS, Hilali Noordeen MH, Elsebaie H. Spondylolisthesis in osteogenesis imperfecta due to pedicle elongation: report of two cases. *Spine (Phila Pa 1976).* Nov 1 2001;26(21):E506-509.
31. Ivo R, Fuerderer S, Eysel P. Spondylolisthesis caused by extreme pedicle elongation in osteogenesis imperfecta. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Oct 2007;16(10):1636-1640.
32. Rask MR. Spondylolisthesis resulting from osteogenesis imperfecta: report of a case. *Clin Orthop Relat Res.* Mar-Apr 1979(139):164-166.
33. Verra WC, Pruijs HJ, Beek EJ, Castelein RM. Prevalence of vertebral pars defects (spondylolysis) in a population with osteogenesis imperfecta. *Spine (Phila Pa 1976).* Jun 1 2009;34(13):1399-1401.
34. Fredrickson BE, Baker D, McHolick WJ, Yuan HA, Lubicky JP. The natural history of spondylolysis and spondylolisthesis. *J Bone Joint Surg Am.* Jun 1984;66(5):699-707.
35. Herman MJ, Pizzutillo PD. Spondylolysis and spondylolisthesis in the child and adolescent: a new classification. *Clin Orthop Relat Res.* May 2005(434):46-54.

36. Wiltse LL, Newman PH, Macnab I. Classification of spondylolisis and spondylolisthesis. *Clin Orthop Relat Res.* Jun 1976(117):23-29.
37. Hatz D, Esposito PW, Schroeder B, Burke B, Lutz R, Hasley BP. The incidence of spondylolysis and spondylolisthesis in children with osteogenesis imperfecta. *J Pediatr Orthop.* Sep 2011;31(6):655-660.
38. Hammerberg KW. New concepts on the pathogenesis and classification of spondylolisthesis. *Spine (Phila Pa 1976).* Mar 15 2005;30(6 Suppl):S4-11.
39. Rahman RK, Perra J, Weklenbaum M. *Wiltse and Marchetti/Bartolozzi Classifications of spondylolithesis Guidelines for treatment in The textbook of spinal surgery (Eds. Bridwell, Keith H., Dewald, Ronald L.) Chapter 58: 556-562*. 3rd ed. Philadelphia, PA: Lippincott-Raven; 2011.
40. Antoniades SB, Hammerberg KW, DeWald RL. Sagittal plane configuration of the sacrum in spondylolisthesis. *Spine (Phila Pa 1976).* May 1 2000;25(9):1085-1091.
41. Ibrahim AG, Crockard HA. Basilar impression and osteogenesis imperfecta: a 21-year retrospective review of outcomes in 20 patients. *J Neurosurg Spine.* Dec 2007;7(6):594-600.
42. Sillence DO. Craniocervical abnormalities in osteogenesis imperfecta: genetic and molecular correlation. *Pediatric radiology.* 1994;24(6):427-430.
43. Hayes M, Parker G, Ell J, Sillence D. Basilar impression complicating osteogenesis imperfecta type IV: the clinical and neuroradiological findings in four cases. *Journal of neurology, neurosurgery, and psychiatry.* Mar 1999;66(3):357-364.
44. Harkey HL, Crockard HA, Stevens JM, Smith R, Ransford AO. The operative management of basilar impression in osteogenesis imperfecta. *Neurosurgery.* Nov 1990;27(5):782-786; discussion 786.
45. Ziv I, Rang M, Hoffman HJ. Paraplegia in osteogenesis imperfecta. A case report. *J Bone Joint Surg Br.* Mar 1983;65(2):184-185.
46. Frank E, Berger T, Tew JM, Jr. Basilar impression and platybasia in osteogenesis imperfecta tarda. *Surg Neurol.* Feb 1982;17(2):116-119.
47. Pozo JL, Crockard HA, Ransford AO. Basilar impression in osteogenesis imperfecta. A report of three cases in one family. *J Bone Joint Surg Br.* Mar 1984;66(2):233-238.
48. Janus GJ, Engelbert RH, Beek E, Gooskens RH, Pruijs JE. Osteogenesis imperfecta in childhood: MR imaging of basilar impression. *Eur J Radiol.* Jul 2003;47(1):19-24.
49. McAllion SJ, Paterson CR. Causes of death in osteogenesis imperfecta. *Journal of clinical pathology.* Aug 1996;49(8):627-630.
50. Menezes AH. Specific entities affecting the craniocervical region: osteogenesis imperfecta and related osteochondrodysplasias: medical and surgical management of basilar impression. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* Oct 2008;24(10):1169-1172.
51. Pauli RM, Gilbert EF. Upper cervical cord compression as cause of death in osteogenesis imperfecta type II. *The Journal of pediatrics.* Apr 1986;108(4):579-581.
52. Sasaki-Adams D, Kulkarni A, Rutka J, Dirks P, Taylor M, Drake JM. Neurosurgical implications of osteogenesis imperfecta in children. Report of 4 cases. *Journal of neurosurgery. Pediatrics.* Mar 2008;1(3):229-236.
53. Sawin PD, Menezes AH. Basilar invagination in osteogenesis imperfecta and related osteochondrodysplasias: medical and surgical management. *J Neurosurg.* Jun 1997;86(6):950-960.

54. Charnas LR, Marini JC. Communicating hydrocephalus, basilar invagination, and other neurologic features in osteogenesis imperfecta. *Neurology.* Dec 1993;43(12):2603-2608.
55. Charnas LR, Marini JC. Neurologic profile in osteogenesis imperfecta. *Connective tissue research.* 1995;31(4):S23-26.
56. Smith JS, Shaffrey CI, Abel MF, Menezes AH. Basilar invagination. *Neurosurgery.* Mar 2010;66(3 Suppl):39-47.
57. Smoker WR. Craniovertebral junction: normal anatomy, craniometry, and congenital anomalies. *Radiographics : a review publication of the Radiological Society of North America, Inc.* Mar 1994;14(2):255-277.
58. Smoker WR, Khanna G. Imaging the craniocervical junction. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* Oct 2008;24(10):1123-1145.
59. Ahmed R, Traynelis VC, Menezes AH. Fusions at the craniovertebral junction. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery.* Oct 2008;24(10):1209-1224.
60. Shapiro JR, Sponsellor PD. Osteogenesis imperfecta: questions and answers. *Current opinion in pediatrics.* Dec 2009;21(6):709-716.

26 CRANIOFACIAL CONSIDERATIONS IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Osteogenesis imperfecta (OI) is a rare heritable system disorder of the connective tissue characterized by bone fragility and reduced bone mass.[1, 2] Caused by mutations in collagen type I,[3-5] it frequently affects tissues including tendons, ligaments, skin, sclera, teeth, and the middle and inner ear. Osteogenesis imperfecta is frequently associated with craniofacial deformity and dentinogenesis imperfecta (DI) as part of the phenotypic presentation.[6]

Craniofacial Deformity

The abnormal synthesis of collagen type I in patients with OI leads to abnormal growth of the craniofacial bones.[4] Characteristically, patients with OI display triangular faces, protrusive bi-temporal bones, prominent frontal bones,[7, 8] and thus comparatively larger heads.[9] Variations of the craniofacial deformity in patients with OI are shown in Figure 1.

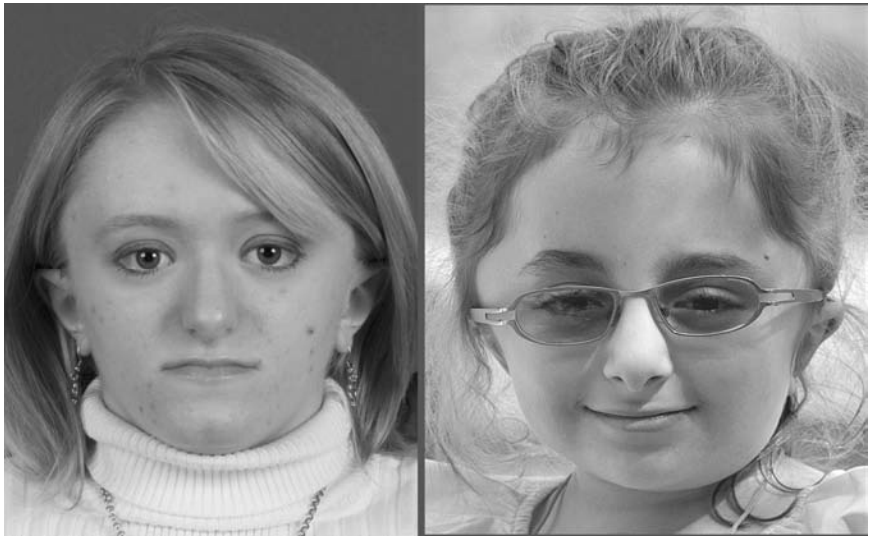

Figure 1. Characteristic craniofacial features in patients with OI: triangular face, maxillary deficiency.

The continuum of clinical features exhibited in patients with OI ranges from perinatal lethality to individuals with gross skeletal deformity to virtually asymptomatic individuals who experience limited osseous fragility and achieve normal stature and normal facial appearance.[6] The different facial characteristics of the various types of OI are related to their severity [10, 11] and development over age, as summarized in Table 1.

Insufficient growth of the jaws is marked by maxillary deficiency and 'relative' mandibular excess. The net effect is a prognathic jaw misaligned relative to the cranial base and with each other resulting in occlusal violations, as shown in Figures 1 and 3. Studies have demonstrated that 66-80% of OI patients develop Angle's Class III malocclusion[†1] with a high incidence of anterior or posterior cross bites and open bites.[12, 13]

[†]Angle's classification of malocclusion, which is based upon the first molar relationship: Class I: Neutrocclsion, where the mesiobuccal cusp of the maxillary first molar is aligned with the buccal groove of the mandibular first molar; Class II: Distocclusion, a malocclusion where the buccal groove of the mandibular first molar distally/posteriorly positioned when in occlusion with the mesiobuccal cusp of the maxillary first molar; and Class III: Mesiocclusion, a malocclusion where the buccal groove of the mandibular first molar mesially/anteriorly positioned to the mesiobuccal cusp of the maxillary first molar when in occlusion.

Table 1. Craniofacial characteristics of osteogenesis imperfecta.

Type	I	II	III	IV
Severity	Mild	Severe (prenatally lethal)	Severe	Mild to Severe
Bone deformity	None	Severe	Severe limb and spinal deformities	Mild
Statue	Normal height	Reduced	Reduced	Reduced
Dental manifestations	10-50% DI	-	81% DI	Variable
Craniofacial anomalies	Tendency to maxillary hypoplasia	Severe	Severe	Tendency to maxillary hypoplasia
Craniofacial morphology	Normal	-	Triangular	Variable
Cranial base		-	Flattened	Maybe flattened
Size of skull	Slightly reduced	-	Large, asymmetric	Moderately reduced
Class III malocclusion	Rare	-	80%	70%, acceleration in 23%
Orthognathic surgery	Rarely	-	Likely	Likely

Note: DI: dentogenesis imperfecta

Cranial base abnormalities presenting as platybasia, basilar impression, and basilar invagination are often coexpressed, but each is also present as an isolated abnormality.[14,15] These three abnormalities and wormian bones are predominantly found in OI types III and IV as well as in patients exhibiting dentinal abnormality.[16] The occurrence of the cranial base abnormalities is estimated to be at least 22% of patients with OI and the patient height is a

significant indicator: shorter height indicated greater possibility of abnormalities.[16]

Severe disruptions to the facial skeleton not only distorts facial portions but also compromises oral function.[13] These functional limitations include difficulty with mastication and eating hard and /or chewy food, prolonged chewing, and lower efficiency in separating the food, which may cause digestive problems. The function of the temporomandibular joint (TMJ) may be affected resulting in typical TMJ signs and symptoms that include pain, discomfort, clicking and locking. In addition, such children may present with articulation disorders in speech depending on the extent of the discrepancy between the maxilla and mandible. Upper airway that involves the nasal and retro-nasopharyngeal passages is also compromised by the lack of development of the midface structures.

Dentinogenesis Imperfecta

Abnormal production of collagen type I affect the structural integrity of teeth, which lead to dentinogenesis imperfecta (DI) type I.[17,18] This condition can also result in tooth discoloration. Common presentations include blue-gray or yellow-brown coloration, translucency or an opalescent hue.[4] The enamel is usually lost quite early (Figure 2).[19, 20] Teeth are also weaker than normal, making them prone to dental decay, rapid wear, and breakage. The vertical dimension of the patient's jaw may also diminish.[21] Dental arch deformity, impaction and agenesis of teeth can also be observed in patients with this disorder.[19, 22]

Radiographically, the crowns are bulbous as a result of significant cervical constriction, roots are short, and the dentin is defective although normal enamel in thickness and density exists.[23] All of the three types of DI demonstrate similar changes in dentin structure microscopically.[23] Normal mantle dentin, irregular circumpulpal dentin with abnormal dentinal tubules, and some atubular areas are evident in the histological study.[23]

The phenotypic presentation of DI is usually expressed in both the primary and permanent teeth in varying degrees. [22, 24] Individuals with OI and DI may have some teeth that appear more affected than others. Primary and/or secondary dentition may be affected differently in the same patient.[25] The incidence of DI in patients with OI has been estimated between 28% and 80%, depending on age, primary versus permanent dentition, and the mix of

OI types being studied.[12,22,26] However, the overall affected percentage of DI for most OI samples is approximately 50%.[26]

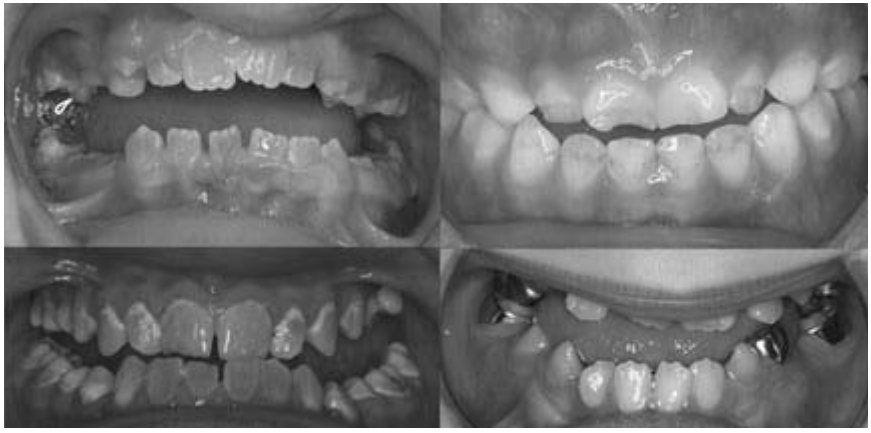

Figure 2. Variations of dentinogenesis imperfecta (DI) in patients with OI: blue-gray or yellow-brown color, translucency or an opalescent hue, dental decay, and breakage.

MANAGEMENT OF DENTOFACIAL DEFORMITY

Philosophy

In order to fully understand the magnitude of OI-DI it is important to understand its origins and its many manifestations. The knowledge of how to manage this rare, largely unknown disease needs to be accumulated and analyzed systematically. Treatments need to be explored with the adaptation of the emerging technology and innovations. The ultimate goal is to improve the patient's condition and quality of life. Therefore, the risk and benefit of each specific treatment individualized for the patient should be carefully evaluated.

The management and treatment of OI-DI requires a multidisciplinary team to minimize loss of tooth structure and to correct the jaw structure so as to restore function and esthetics, as evidenced in some cases.[11, 27] This team may include a pediatric dentist, orthodontist, prosthodontist, plastic and maxillofacial surgeon, pediatricians and supportive professionals.

Dental Care

Due to the weakened condition of the teeth, many common cosmetic procedures such as braces and bridges are likely to adversely affect the dentition. Thus, special care is required.

In reviewing literature, it appears that early preventive dental visits with a dentist, early detection, patient/parent education, and proper preventive treatment can increase the patient's retention of teeth.[22,24,27] It is of utmost importance to screen patients with OI for DI as soon as possible since early diagnosis results in a better outcome.

For some adult patients, dental implants and denture prosthetics can be applied to restore the dentition and compensate for the lost teeth.[27,28] Bone graft may be performed if needed at least 6 month prior to the implantation.[27]

Orthodontic Treatment

Although the dental skeletal deformity is common in patients with OI, orthodontic treatment without orthognathic surgery is generally limited to mild to moderate Class III malocclusion. Patients with severe maxillary/mandibular discrepancies may not benefit from orthodontic treatment alone while patients with minor deformity may not require orthodontic treatment at all. The risk and benefit need to be evaluated on an individual basis.

Earlier experiences suggest that aside from the issue of enamel and dentin integrity, there are no serious contraindications to orthodontic treatment in patients with DI. The clinical course of treatment is essentially normal.[29]

Orthodontic treatment includes performing orthodontic leveling, alignment, and even decompensation of the incisors (for orthognathic surgery) by use of a full orthodontic banded and bonded preadjustable appliance.[30] So far no practical guidelines have been established for orthodontic treatment of patients with OI-DI.[25] Some experiences reported in the literature are summarized as follows:

- A non-extraction approach is preferred considering the tendency of tooth loss in patients with OI-DI.[30]
- Significant upper arch expansion may be required for correlation of arch form. The expansion can be carried out orthodontically as most

of the discrepancy related to a constriction in arch form is in the premolar region.[31]

- The greatest concern is the stability of the enamel of each tooth to withstand the stress of the bonded bracket, and during the eventual debonding procedure when treatment is complete. Alternatively, bands may be placed around those teeth where there is concern about the integrity of the enamel and dentin.[29]
- Teeth with substantial wear or structural compromise are best managed with a stainless steel crown with a bracket attached. Additional points to consider are to be careful with clasps in undercuts of bulbous crowns and to avoid excessive mechanical forces.[29]
- Restorations in the primary or permanent dentition may be necessary not only to improve esthetics, but also to regain or maintain the vertical dimension of occlusion.[29]

The orthodontic treatment duration may be longer considering that relatively less mechanical force can be used. Presurgical orthodontic treatment with leveling and alignment may last for approximately 2 years.[30,31] Postsurgical orthodontics is likely to take an extended 6-12 months.[30]

Orthognathic Surgery

Skeletal deformities and occlusal dysfunctions that cannot be treated with orthodontics alone require surgical intervention. Orthognathic surgery is commonly selected to correct the maxillary deficiency, concave facial profile and Angle's Class III malocclusion.[6,32,33] In most cases, maxillary advancement alone suffices to achieve such goal. The surgical procedure involves a variation of Le Fort I type osteotomy, sagittal and vertical repositioning of the maxillary segment with titanium plate and screw fixation.[34] Patients with OI, however, present a unique set of challenges to surgery. Inherent bone weakness, atypical fracture patterns, and propensity to bleed are of particular concerns.[35-37]

In terms of the bone quality and healing, the knowledge largely relies upon those accumulated from the long bones so far. Patients with OI are at risk of fractures of the long bones as a result of developmental failure in collagen maturation, which results in osteoid formation deficiency and, consequently, a thin cortical bone structure with fine trabeculae susceptible to pathologic fractures.[7,26] Healing is, however, normal with occasional exuberant callus formation.[10,13]

The Le Fort I osteotomy in patients with OI is technically challenging given the bone fragility and atypical fracture patterns. Therefore, appropriate measures are taken to minimize complications and to achieve satisfactory results. In order to maximize the precision of the osteotomy and reduce bony tissue trauma, Lopez-Arcas et al. performed osteotomies with a saw and restricted the use of chisels to avoid errant fractures.[38] Tashima et al. recommended simplifying orthognathic surgeries from two-jaw to one-jaw procedures to limit disease-related complications and optimize plate-segment fixation.[39]

Given the potential risk of Le Fort I osteotomy that may lead to an unexpected atypical fracture in the fragile bone, conventional orthognathic surgery may even be contraindicated in some cases of atrophic maxillae. As an alternative to the conventional Le Fort I osteotomy, osteodistraction of the maxilla can be performed omitting the precarious down-fracture procedure.[27] This appears to be a feasible technique to treat patients with severe maxillary deficiency and Class III malocclusion. The bleeding tendency, however, can be a major concern since the distractor would remain in the patient for at least six weeks.

Considering the quality of the bone, in particular the maxilla, securing either positioning plates or distraction devices requires fixation to thicker bones. It is critical to select an ideal anchor site such as the zygomatic buttress/piriform aperture to minimize relapse and maintain long-term stability.[34]

In cases of severe Class III malocclusion and/or asymmetrical facial appearance, however, the bimaxillary surgery, that is, both maxillary advancement and mandibular rotation and setback is necessary.[40] In the past, mandibular surgery has been avoided because of a possible risk of poor bone formation and subsequent fracture of the thin mandible.[10, 30, 43] Recent articles advocate that bimaxillary orthognathic procedures in patients with OI are feasible, including mandibular body osteotomy, and result in good healing.[41-43] Encouraging results producing occlusal correction with long-term skeletal (dentofacial) stability have been achieved.[41,42] Lopez-Arcas et al. reported a case in which a one-piece Le Fort I osteotomy with advancement and impaction of the maxilla was performed via rigid skeletal fixation. Bilateral intraoral vertical ramus osteotomies were performed with a setback to correct mandibular prognathism, sagittal maxillomandibular skeletal and dental relations, and excessive lower facial height.[38] Aizenbud et

al. reported a case with similar bimaxillary procedures except for the mandibular setback and rotation to correct the mandibular excess and asymmetry by use of intermaxillary wire fixation for 8 weeks.[30] Bimaxillary surgery may be performed as either a one-stage surgery or two-stage surgery. Kindelan et al. reported a bimaxillary surgery case that was carried out as two discrete surgical episodes: first, the mandibular setback and 7 months later, the maxillary advancement.[31]

Although it is still debatable which approach is better, orthognathic surgery treatment is feasible to correct the severe maxillary hypoplasia in patients with OI. It is, however, important that the individual conditions of each patient at the time of the surgery should be the primary concern since every case is different in this population.

Perioperative Considerations

In addition to the surgical challenges, several medical and anesthetic problems may be encountered in patients with OI.[44] Firstly, bleeding is a concern for this population. Inadequate vasoconstriction by small blood vessels, tissue fragility and platelet dysfunction may complicate (inhibit) hemostatic control.[35,36] Functional platelet disorder is particularly relevant, and indeed, severe hemorrhage can occur in patients with OI.[32] Bleeding may vary, depending on the type of OI or the severity of the disease.[4] These situations are difficult to either predict or anticipate as bleeding may occur in the presence of normal coagulation studies and bleeding times.[45, 46]

Additionally, numerous reports of intraoperative hyperpyrexia continue to drive concerns regarding to the correlation between OI and hyperthermia.[44,47-50] These episodes are likely attributed to an elevated metabolic rate[51] and unrelated to concurrent instances of malignant hyperthermia.[50] However rare, hyperthermia in patients with OI is well recognized and should be managed with standard cooling measures during surgery.[52]

Intubation may be difficult due to bone fragility, short neck, large tongues and thoracic deformity.[48] Increased occipital projection and/or short neck length inhibit extension of the neck while mandibular protrusion may limit opening of the mouth. In severe cases care must be taken to avoid fracture of the mandible or cervical vertebrae resulting from general congenital osteoporosis and bone fragility.[10, 48, 52]

Application of the Virtual Surgical Planning (VSP) Technology

Conventional two-dimensional (2D) panoramic and cephalometric X-rays have been used for orthodontic treatment, orthognathic surgery planning and outcome evaluation. This conventional technology is adequate to symmetric cases, but inadequate to most patients with OI in whom more complicated asymmetric facial skeletal deformities are involved since it cannot provide anatomical details in three-dimension (3D) with clarity to the surgeon.

Recent developments in the medical imaging technology provide better tools to acquire patient information in 3D. Computer tomography (CT) and cone beam computer tomography (CBCT) scans acquire the volumetric images with sufficient resolution to detect the details of the bony structure and allow the surgeon and clinicians to have a better understanding of the anatomy specific to the patient. Three-dimensional surface images such as 3D photos provide 3D images with color and texture without the risk of X-ray exposure to patients.

Newly developed medical image analysis software is capable of extracting complicated geometrical information of a skull from CT scans to build a 3D digital model virtually. This 3D digital model can then be manipulated by segmentation and the elements are repositioned to simulate the surgical procedure to create a virtual surgical plan. Integrating these technologies forms the virtual surgical planning (VSP) technology that can be used to assist in planning and execution of maxillofacial surgery,[53,54] offering improved intraoperative precision and efficiency.[55-57] These emerging computer aided tools are of particular benefit when utilized in complicated cases such as patients with OI.

Orthognathic surgery in patients with OI is confounded by the fragile bone structure and risk of atypical fractures. Nevertheless, these operations are feasible when appropriate measures are taken to minimize such occurrences. The goal is to maintain precision while minimizing trauma.

In the case shown in Figure 3, the osteotomy pattern was optimized based on CBCT derived bony architecture, and maxillary advancement was simulated using the virtual composite model which combines skeletal structure from

CBCT with teeth from laser scans to achieve ideal occlusion, as shown in Figure 4.

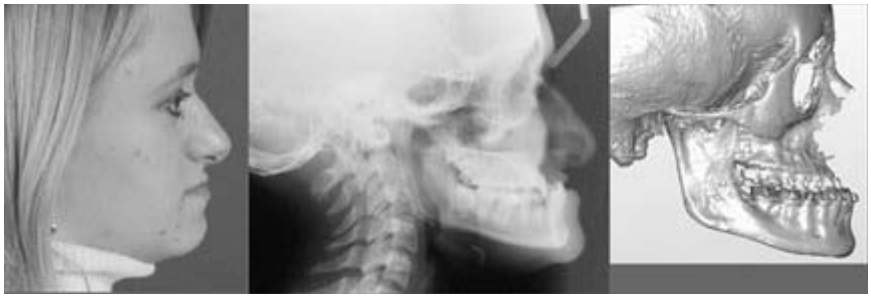

Figure 3. A typical OI patient with maxillary deficiency, concave profile and Class III malocclusion as shown in photo (left), lateral cephalometric X-ray (middle), and 3D reconstruction of the skull from CBCT scans (right).

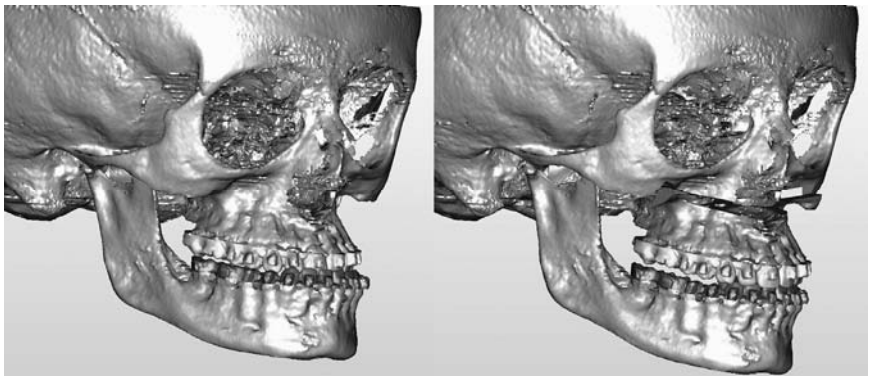

Figure 4. Virtual surgical planning (VSP) of the orthognathic surgery for the patient with OI-DI in Figure 3: Le Fort I osteotomy (left) and maxillary advancement (right).

The virtual surgical plan was executed and reproduced intra-operatively, as it was for the majority of patients who undergoes orthognathic surgery (Le Fort/BSSO/osseous genioplasty) in our hospital, and satisfactory treatment outcomes have been achieved, as demonstrated via 3D anthropometric analysis in Table 2 and photos in Figure 5.

Table 2. Three-dimensional (3D) anthropometric analysis: an example.

Measurement	Pre-OP 3D	Pre-OP 2D	1Y 3D	1Y 2D	2D Normal
Convexity (degree)	0	0	2.4	2.4	2 ± 1
Facial plane (degree)	84.9	84.8	89.8	89.8	80 ± 2
Maxillary plane (degree)	84.1	85.6	89.0	88.4	90 ± 3
SNA[1] (degree)	75.8	75.9	83.4	83.4	82 ± 4
SNB[2] (degree)	85.6	85.7	84.1	84.1	78 ± 3
ANB[3] (degree)	10.0	9.8	0.8	0.6	2± 1
Overjet, (mm)	-3.6	-3.6	2.4	2.4	2 ± 1
Overbite, (mm)	-2.6	-2.6	2.4	2.4	2 ± 1
UFH/LFH[4] ratio	1.3	1.3	1.1	1.1	1.0 ± 0.2
SN[5] (mm)	64.6	64.6	64.0	64.0	

Note: Pre-OP 3D is for pre-operative 3D anthropometric measurements; Pre-OP 2D for pre-operative 2D cephalometric measurements; 1Y 3D for one year post-operative 3D anthropometric measurements; 1Y 2D for one year post-operative 2D cephalometric measurements; and 2D Normal for 2D cephalometric measurements from normal population.
In addition, abbreviations are the following measurements:
[1] SNA is the Sella-Nasion-A Point angle;
[2] SNB is the Sella-Nasion-B Point angle;
[3] ANB is the A Point-Nasion-B Point angle;
[4] UFH is upper facial height; LFH is the lower facial height; and
[5] SN is the distance between Sella and Nasion.

SUMMARY

Patients with OI-DI present with a complex pattern of craniofacial deformity with fragility of the facial skeleton and the dentition. Such patients require a multidisciplinary evaluation and treatment planning that requires coordination of the various specialties. Earlier dental evaluation and dental care is preferred. Orthodontic treatment can be performed with caution. Although facial skeletal reconstruction is difficult and can be fraught with complications, satisfactory aesthetic and functional outcomes are achievable.

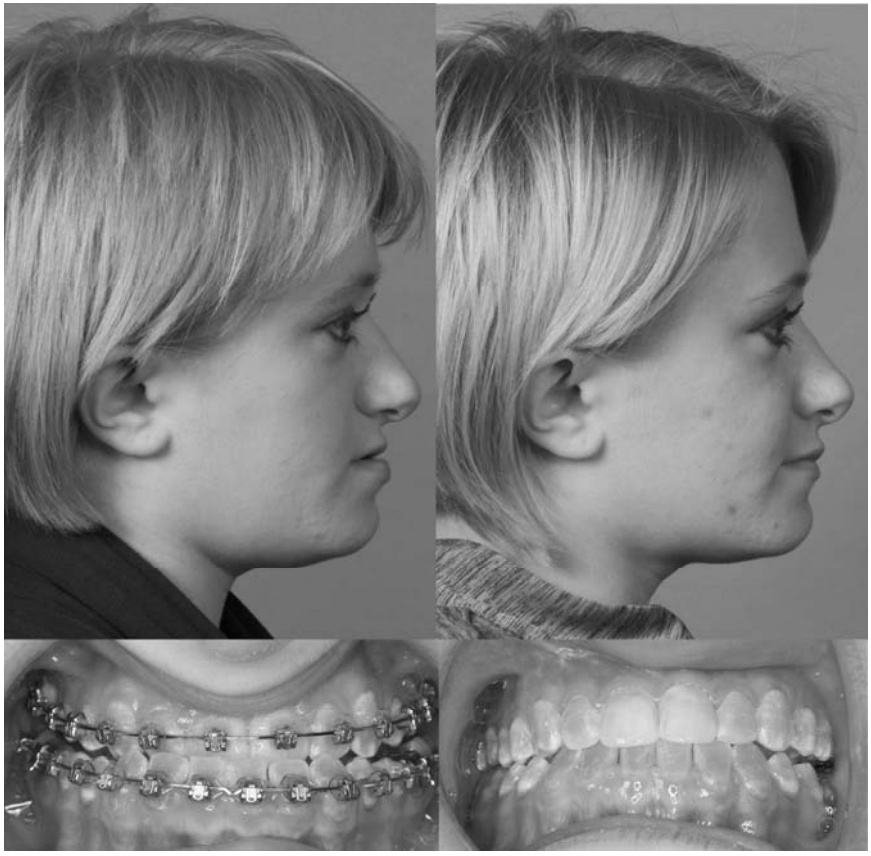

Figure 5. Outcome of the orthognathic surgery for the patient with OI-DI in Figure 3: from concave profile before the surgery (top left) to normal profile one year after the surgery (top right), and from Angle's Class III malocclusion before the surgery (bottom left) to Angle's Class I occlusion one year after the surgery (bottom right).

ABBREVIATIONS

2D	Two-dimension, two-dimensional
3D	Three-dimension, three-dimensional
CBCT	Cone beam computer tomography
CT	Computer tomography
DI	Dentinogenesis imperfecta
OI	Osteogenesis imperfecta
OI-DI	Osteogenesis imperfecta and dentinogenesis imperfecta
TMJ	Temporomandibular joint
VSP	Virtual surgical planning

REFERENCES

1. Byers PH, and Cole WG. Osteogenesis imperfecta. In: Royce PM and Steinmann B, eds. *Connective Tissue and Its Hereditable Disorders: Molecular, Genetic, and Medical Aspects*. New York: Wiley-Liss, 2002: 385–430.
2. Martin E, Shapiro JR. Osteogenesis imperfecta: epidemiology and pathophysiology. *Curr Osteoporos Rep*. 2007; 5(3): 91-97.
3. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet*. 1979; 16(2): 101-116.
4. Witecka J, Augusciak-Duma AM, Kruczek, Szydlo A, Lesiak M, Krzak M, Pietrzyk JJ, Mannikko M, Sieron AL. The novel COL1A1 mutations in patients with osteogenesis imperfecta (OI) affect the stability of the collagen type I triple-helix. *J Appl Genet*. 2008; 49(3): 283-295.
5. Marini JC, Forlino A, Cabral WA, Barnes AM, San Antonio JD, Milgrom S, Hyland JC, Körkkö J, Prockop DJ, De Paepe A, Coucke P, Symoens S, Glorieux FH, Roughley PJ, Lund AM, Kuurila-Svahn K, Hartikka H, Cohn DH, Krakow D, Mottes M, Schwarze U, Chen D, Yang K, Kuslich C, Troendle J, Dalgleish R, Byers PH. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. *Hum. Mutat*. 2007; 28: 209-221.
6. Jensen BL, Lund AM. Osteogeneisis imperfecta: clinical, cephalometric, and biochemical investigations of OI types I, III, and IV. J *Craniofac Genet Dev Biol*. 1997; 17(3): 121-132.
7. Freedus MS, Schaaf NG, Ziter WD. Orthognathic surgery in osteogenesis imperfecta. *Journal of Oral Surgery*. 1976; 34: 830 – 834. .
8. Libman RH. Anesthetic considerations for the patient with osteogenesis imperfecta. *Clinical Orthopaedics and Related Research*. 1981; 159: 123 – 125
9. Lund AM, Muller J, Skovby F. Anthropometry of patients with osteogenesis imperfecta. *Arch Dis Child*. 1999; 80(6): 524-8.
10. Ormiston IW, Tideman H. Orthognathic surgery in osteogeneisis imperfecta: a case report with management considerations. *J Craniomaxillofac Surg*. 1995; 23(4): 261-265.
11. Waltimo-Sirén J, Kolkka M, Pynnönen S, Kuurila K, Kaitila I, Kovero O. Craniofacial features in osteogenesis imperfecta: a cephalometric study. *Am J Med Genet A* 2005; 133: 142-150.
12. Schwartz S. Tsipouras P. Oral findings in osteogenesis imperfect. *Oral Surg Oral Med Oral Pathol*. 1984; 57(2): 161-167.
13. Chang PC, Lin SY, Hsu KH. The craniofacial characteristics of osteogenesis imperfecta patients. *Eur J Orthod*. 2007; 29:232,
14. Janus GJ, Engelbert RH, Beek E, Gooskens RH, Pruijs JE. Osteogenesis imperfecta in childhood: MR imaging of basilar impression. *Eur J Radiol*. 2003; 47(1): 19-24.
15. Kovero O, Pynnönen S, Kuurila-Svahn K, Kaitila I, Waltimo-Sirén J. Skull base abnormalities in osteogenesis imperfecta: a cephalometric evaluation of 54 patients and 108 control volunteers. *J Neurosurg*. 2006; 105(3): 361-70.
16. Cheung MS, Arponen H, Roughley P, Azouz ME, Glorieux FH, Waltimo-Sirén J, Rauch F. Cranial base abnormalities in osteogenesis imperfecta: phenotypic and genotypic determinants. *J Bone Miner Res*. 2011; 26(2): 405-13.
17. Witkop CJ Jr. Manifestations of genetic diseases in the human pulp. *Oral Surg Oral Med Oral Pathol*. 1971; 32: 278- 316.

18. Shields ED, Bixler D, el-Kafrawy AM. A proposed classification for heritable human dentine defects with a description of a new entity. *Arch Oral Biol*. 1973; 18: 543-553.
19. Isshiki Y. Morphological studies on osteogenesis imperfecta, especially in teeth, dental arch, and facial cranium. *Bull Tokyo Dent Coll*. 1966; 7(1): 31-49.
20. Levin LS: The dentition in the osteogenesis imperfect syndromes. *Clin Orthop*. 1981; 159: 64-74.
21. Stenvik A, Larheim TA, Storhaug K. Incisor and jaw relationship in 27 persons with osteogenesis imperfecta. *Scand J Dent Res.* 1985; 93(1): 56-60. 22. Malmgren B, Norgren S. Dental aberrations in children and adolescents with osteogenesis imperfecta. *Acta Odontol Scand*. 2002: 60: 65–71.
23. Majorana A, Bardellini E, Brunelli PC, Lacaita M, Cazzolla AP, Favia G. Dentinogenesis imperfect in children with osteogenesis imperfecta: A clinical and ultrastructural study. Int J Paediatr Dent. 2010; 20:112–8.
24. Muhney K, Campbell PR. Pediatric dental management of a patient with osteogenesis imperfecta and dentinogenesis imperfecta. *Spec Care Dentist*. 2007; 27(6): 240-245.
25. Hartsfield JK Jr, Hohlt WF, and Roberts E. Orthodontic treatment and orthognathic surgery for patients with osteogenesis imperfecta. *Semin Orthod*. 2006; 12: 254-271.
26. O'Connell AC, Marini JC. Evaluation of oral problems in an osteogeneisis imperfecta population. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999; 87(2): 189-196.
27. Binger T, Rucker M, Spitzer WJ. Dentofacial rehabilitation by osteodistraction, augmentation, and implantation despite oeteogenesis imperfecta. *Int J Oral Maxillofac Surg*. 2006; 35: 559-562.
28. Zola MB. Staged sinus augmentation and implant placement in a patient with osteogenesis imperfecta. *J Oral Maxillofac Surg*. 2000: 58: 443–447.
29. Gibbard PD: The management of children and adolescents suffering from amelogenesis imperfecta and dentinogenesis imperfecta. *Int J Orthod.* 1974: 12: 15-25.
30. Aizenbud D, Peled M, Figueroa AA. A combined orthodontic and surgical approach in osteogenesis imperfecta and severe class III malocclusion: case report. *J Oral Maxillofac Surg*. 2008; 66(5): 1045-1053.
31. Kindelan J, Tobin M, Roberts-Harry D, Loukota RA. Orthodontic and orthognathic management of a patient with osteogenesis imperfecta and dentinogenesis imperfecta: a case report. *J Orthod*. 2003; 30(4): 291-296.
32. Cole NL, Goldberg MH, Loftus M et al. Surgical management of patients with osteogenesis imperfecta. *J Oral Maxillofac Surg*. 1982; 40(9): 578-584.
33. Bell RB, White RP Jr. Osteogenesis imperfecta and orthognathic surgery: case report with long-term follow-up. *Int J Adult Orothodon Orthognath Surg*. 2000; 15(3): 171-178.
34. Posnick JC. Craniofacial and Maxillofacial Surgery in Children and Young Adults, 2nd Ed. St. Louis: Mosby. 2000: 1081-1100.
35. Hathaway WE, Solomons CC, Ott JE. Platelet function and pyrophosphates in osteogenesis imperfecta. *Blood*. 1972; 39(4): 500-509.
36. Morton ME. Excessive bleeding after surgery in osteogenesis imperfecta. *Br J Oral Maxillofac Surg*. 1987; 25(6): 507-511.
37. Lewis MK, Stoker NG. Surgical management of the patient with osteogenesis imperfecta. *J Oral Maxillofac Surg*. 1987; 45(5): 430-437.

38. Lopez-Arcas J, Chamorro M, Del Castillo J, Cebrian J, Palacios E, Burgueno M. Osteogenesis imperfecta and orthognathic surgery: case report and literature review. J Oral Maxillofac Surg. 2009; 67: 1128-1132.
39. Tashima H, Wattanawong K, Ho CT, Wen-Ching-Ko E, Nguyen A, Lo LJ.. Orthognathic surgery considerations for patients with undiagnosed type I osteogenesis imperfecta. *J Oral Maxillofac Surg*. 2011; 69(8): 2233-2241.
40. Rosaen A, Modig M, Larson O. Orthognathic bimaxillary surgery in two patients with osteogenesis imperfecta and a review of the literature. Int J Oral Maxillofac Surg. 2011; 40(8): 866-873.
41. Whitestone BW, Chapnick P: Correction of mandibular prognathism in osteogenesis imperfecta tarda: a case report. *J Can Dent Assoc*. 1986: 52: 853-856.
42. Jakobsone G, Stenvik A, Sandvik L, Espeland L.. Three-year follow-up of bimaxillary surgery to correct skeletal class III malocclusion: stability and risk factors for prolapse. *Am J Orthod Dentofacial Orthop*. 2011; 139(1): 80-89.
43. Ehrenfeld M, Schwenzer N. Fracture of the mandible in osteogenesis imperfecta. Case report and literature review. *Dtsch Z Mund Kiefer Gesichtschir*. 1989; 13: 49–53.
44. Stynowick GA, Tobias JD. Perioperative care of the patient with osteogenesis imperfecta. *Orthopedics*. 2007; 30(12):1043-1049.
45. Wong RS, Follis FM, Shively BK et al. Osteogenesis imperfecta and cardiovascular diseases. *Ann Thorac Surg*. 1995; 60(5): 1439-1443.
46. Keegan MT, Whatcott BD, Harrison BA. Osteogenesis imperfecta, perioperative bleeding, and desmopressin. *Anesthesiology*. 2002; 97(4): 1011-1013.
47. Brownell AKW. Malignant hyperthermia: relationship to other diseases. *Br J Anaesth.* 1988; 60:303-308.
48. Rodrigo C. Anesthesia for maxillary and mandibular osteotomies in osteogenesis imperfecta. *Anesth Prog*. 1995; 42(1): 17-20.
49. Ryan CA, Ali-Ghamdi AS, Gayle M, Finner NN. Osteogenesis imperfecta and hyperthermia. *Anesth Analg*. 1989; 68(6): 811-814.
50. Porsborg P, Astrup G, Bendixen D, Lund AM, Ording H.. Osteogenesis imperfecta and malignant hyperthermia. Is there a relationship? *Anaesthesia*. 1996; 51(9): 863-865.
51. Cropp GJ, Myers DN. Physiological evidence of hypermetabolism in osteogenesis imperfecta. *Pediatrics*. 1972; 49(3): 375-391.
52. Bojanić K, Kivela JE, Gurrieri C, Deutsch E, Flick R, Sprung J, Weingarten TN.. Perioperative course and intraoperative temperatures in patient with osteogenesis imperfecta. *Eur J Anesthesiol.* 2011; 28(5): 370-375.
53. Alves PV, Bolognese AM, Zhao L. Three-dimensional computerized orthognathic surgical treatment planning. *Clin Plast Surg*. 2007; 34(3): 427-436.
54. Patel PK, Zhao L, Morris DE, Alves PV. Our experience with virtual craniomaxillofacial surgery: planning, transference and validation. *Stud Health Technol Inform*. 2008; 132: 363-365.
55. Pham AM, Rafii AA, Metzger MC, Jamali A, Strong EB.. Computer modeling and intraoperative navigation in maxillofacial surgery. *J Orolaryngol Head Neck Surg*. 2007; 137(4): 624-631.
56. Mavili ME, Canter HI, Saglam-Aydinatay B, Kamaci S, Kocadereli I.. Use of three-dimensional medical modeling methodes for percise planning of orthognathic surgery. *J Craniofac Surg*. 2007; 18(4): 740-747.

57. Kang SH, Kim MK, Park SY, Lee JY, Park W, Lee SH.. Early orthognathic surgery with three-dimensional image simulation during presurgical orthodontics in adults. J Craniofac Surg. 2011; 22(2): 473-481.

27 DENTINOGENESIS IMPERFECTA: FUNDAMENTALS OF CARE FROM THE PERSPECTIVE OF A PRACTICING DENTIST AND UTILIZATION OF THE CHILD ORAL HEALTH IMPACT PROFILE TO ASSESS QUALITY OF LIFE

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INTRODUCTION

The fundamental issue that most practicing dentists encounter when treating patients that have dentinogenesis imperfecta (DI) is being able to define a treatment plan that solves all of the issues that a patient with this diagnosis has. Dentinogenesis imperfecta is one of the most complicated diagnoses to treat due to the severity in which all of the patient's teeth are affected. Current literature does clearly define the manifestations of this disease however, treatment modalities are merely explored in case studies and anecdotal evidence. These case studies help to define potential treatment proposals, but they lack the authority that a clearly defined, controlled study would have in the dental community. With these obstacles in mind, this chapter looks into the treatment plans that were explored in these case studies, and attempts to clearly define steps to take when treatment planning for patients that have DI.

One of the major focuses of this chapter is the importance of the transitional period between deciduous and adult teeth. By reviewing several successful case studies, practicing dentists will have a clearer idea of how and when to treat the patient's dentition in order to establish a healthier oral system. This chapter also looks into unique risks that DI patients run into due to their diagnosis and presents ideas for future study and helps raise concern for this debilitating disease. Additionally, we will discuss the results of a small study

looking at quality of life in osteogenesis imperfecta (OI) and DI utilizing the Child Oral Health Impact Profile (COHIP).

DEFINITION

Dentinogenesis imperfecta is an autosomal dominant hereditary tooth disorder that affects dentin of both dentitions, deciduous teeth and permanent teeth, with inconsistent clinical appearances.[1] Three subtypes of DI have been used to categorize this disorder: type I which occurs concurrently with OI, type II which does not occur with skeletal defects, and type III or Brandywine type which is rare and occurs as a racially isolated disease in the state of Maryland.[1] "About 50% of patients with Osteogenesis Imperfecta show some form of the dental abnormality usually called Dentinogenesis Imperfecta."[2] Dental treatment for dentinogenesis imperfecta can be complicated and is a major concern for most dentists because both sets of dentition are affected in varying ways. All authors would agree, however, that early diagnosis and treatment is one of the most effective ways of creating a treatment plan for these patients, in order to achieve the best prognosis and success.

"Osteogenesis Imperfecta is a heterogenous group of heritable disorders of connective tissue characterized by bone fragility."[3] One of the main concerns regarding treatment modalities for patients with osteogenesis imperfecta is bone deformity and frequent fractures. The disease can also be associated with hearing loss, short stature and malformation of teeth (DI).[4]

Clinical presentations of this disease (DI) are due to the weakness and malformation of the dentin. As the dentin is the underlying and supportive structure of the teeth, its weakness makes treatment very difficult. Some of the clinical manifestations include teeth that chip away very easily and soon become worn to the level of the gingiva and teeth that appear translucent or opalescent.[5] As the enamel of the tooth surface fractures away from the tooth, a very rough surface is left behind. These surfaces promote the retention of plaque and bacteria and may lead to an increased risk in caries formation. Therefore, early diagnosis, treatment and an emphasis must be placed upon good home care and oral hygiene in order to prevent severe decay problems, and periodontal disease.

On a molecular level, DI that is associated with OI is a genetic disease. This disease affects the production of type I collagen, which is a molecule responsible for the proper construction of bones as well as dentin found in

the underlying surface of teeth.[6] The affect that this genetic mutation can have upon dentin is threefold. First, the fusion between the enamel and dentin layers is abnormal and can lead to large areas of enamel separation. Second, the tubules found within the dentinal matrix are abnormal and in some cases completely absent and also have an incomplete calcification of the substrate. And third, the dentinal matrix contains a higher percentage of water and a lesser percentage of the inorganic content.[7] This malformation of the dentin can lead to some difficult clinical situations as the malformed architecture of these teeth becomes progressive over time.

Historically, dentists waited until a patient with DI reached adolescence, and then they proceeded to extract all of the patient's teeth, and fabricated complete upper and lower dentures.[7] Currently, patients, as well as their families, demand a more comprehensive treatment plan that takes into consideration treating deciduous teeth, esthetic demands, as well as a more stable and fixed solution for permanent teeth. Therefore, current research has been looking at different solutions for these patients and treatment modalities that may slow the progression of the disease and improve the prognosis for these patients. However, a proper diagnosis of this disease must first occur in order to begin planning treatment.

An early and complete diagnosis becomes important as the preservation of the deciduous dentition, which in turn maintains the vertical dimension and health of the permanent dentition. If not recognized early, the teeth may become so worn, and the vertical dimension so collapsed, that the teeth may not be restorable creating a situation where extractions and dentures becomes the only treatment option. Another problem seen in DI is the obliteration in the pulpal chamber and canals, which can lead to spontaneous abscesses. Without patent canals, root canal therapy is oftentimes impossible, leading to extraction as the only remaining viable option.[8] It is in this example that the importance of early diagnosis of the disease as well as a reasonable treatment begins as soon as possible in order to avoid infection and extractions.

DIAGNOSIS

In order to correctly diagnose DI, a few clinical and imaging recommendations must be made. First, radiographs are an invaluable tool when attempting to determine the restorability of teeth, their eruption patterns, and which teeth are affected. Because DI is a hereditary disease, every tooth that the patient has with this disease will be affected, both

deciduous and permanent, although possibly to varying degrees. A panoramic x-ray is the best option for gaining insight into the overall stage of the disease and treatment options for the patient. When looking at the panoramic x-ray, several things must be determined including whether or not additional radiographs are necessary. The current status of the patient's teeth must be established. In other words, an overall assessment must be performed to determine which teeth have obliterated pulp chambers, severe occlusal wear, periapical lesions, shortened roots, and are missing from the oral cavity. With this in mind, and using a treatment plan model that attempts to preserve space for permanent teeth, bone for future restorations, and esthetics for the patient, many different treatment modalities surface. Because of the eruption pattern of the deciduous teeth, it has been recommended that patients with DI begin to see their dentist at age 1 and continue to return every six months to check the progression of the disease and status of their teeth.[5] The diagnosis of dentinogenesis imperfecta includes teeth that may be opalescent, have short roots, obliterated pulpal chambers, moderate to severe attrition, abscesses, missing teeth or loss of facial vertical dimension. If a patient presents with type I DI, that patient may also be of short stature, have blue sclera and a history of bone fractures.

TREATMENT

Once an accurate DI diagnosis has been made for the patient, the next step would be identifying a comprehensive treatment plan. The first step should be alleviating any ongoing symptoms that the patient has been experiencing. In patients that have DI, this may range from dentinal sensitivity stemming from lost enamel, to periapical radiolucencies from infected and nonrestorable teeth. If a tooth is determined to be nonrestorable and has an apical infection, an extraction may be necessary. Prior to the extraction, a clear medical history including concurrent OI diagnosis and bisphosphonate use must be considered. The 2008 Montreal Children's Hospital research must also be taken into account. This study found that the risk with IV bisphosphonate therapy and primary dentition extractions in patients that were diagnosed with OI revealed no appearance of osteonecrosis. And even though a dental extraction on a patient that presents with OI and has a history of BP therapy may not be risk free, the risk may be very low.[9] Dentinal sensitivity may be alleviated by using resin bonding techniques with a glass ionomer material. This will not only decrease sensitivity for the patient, but will also improve esthetics. Most pedodontists suggest that the resin bonding can begin as soon as the disease has been diagnosed.[10]

Yet another issue that these patients may develop over time is a loss of vertical dimension of occlusion due to the extreme occlusal wear that can be created by the loss of enamel. As the deciduous molars develop and the disease progresses, patients begin to lose enamel surface and the mouth begins to slowly close together over time. Therefore, the best recommendation for these teeth are stainless steel crowns or indirect cast onlays which can be built vertically to a higher degree in order to "open" the vertical dimension and, at the same degree, maintain the vertical dimension that the patient already has. As the patient continues to develop and the 6 year molars erupt, the same treatment modality can be used in order to maintain the patient's vertical height of occlusion. Once these crowns or onlays are placed however, the treatment does create a decrease in vertical overlap of the incisors. Due to the age of these patients, within a few weeks, full occlusion is usually reestablished with great success and is well tolerated by the patients.[10] If a child presents to the office with such severe attrition and occlusal wear of all posterior molars, the best treatment for that patient, in order to increase the vertical dimension of occlusion, may be to create overdentures. These appliances are created to rest on top of some of the patient's remaining teeth and are very similar to complete dentures. Repeated visits in order to check the fit of these over-dentures and to check the eruption of the other permanent teeth is necessary, due to the rapid growth that occurs in small children. With an ability to maintain space for the eruption of the patient's permanent teeth, as well as establishing improved esthetics, the real challenge presents itself as the patient completely develops permanent teeth.

Another way in which the treatment prognosis can be improved is through oral hygiene instruction. It is therefore imperative that a system be established with the patient and the parents with regards to creating an oral environment that is extremely hygienic. Pristine oral hygiene is important if the patient has stainless steel crowns and other restorative work in order to guard against recurrent decay under these restorations. One of the ways in which this can be done, is by demonstrating the ideal way to remove dental plaque by using a toothbrush and flossing effectively. Because some patients with severe DI also have severe attrition, there may be areas in the oral cavity that attract plaque more than others. By instructing the patients and parents on the best ways to clean these areas, the risk of developing caries decreases and the dental prognosis improves. Another way in which the dental environment can be protected from future caries risk is by using fluoride. Fluoride works by remineralizing early areas of dental decay in teeth.[2] Good

oral hygiene as well as preventative methods may improve the prognosis of the dental structures for these patients.

The transition into a permanent dentition, as seen before, can be eased by using stainless steel crowns on deciduous and six year permanent molars and with good oral hygiene. However, during the transition, several unique complications related to treating the permanent dentition will arise. For instance, deciduous teeth need only be maintained for a short period of time when compared to permanent teeth. Therefore, any definitive and comprehensive treatment plan created for the permanent dentition, must take into consideration several complications that DI creates. For example, as the disease progresses, there will be a slow obliteration of the pulpal chamber and a continual loss of enamel from the tooth structure. Second, because of the side effects of weakened dentin, and an increase in the amount of time the patient will retain these permanent teeth, some authors have stated that the only treatment modality that will be feasible are complete dentures.[1] As a result, when looking at the effects that this disease can have on teeth, it's easy to understand why this is a common conclusion. The mere diagnosis of DI creates many difficulties for treatment from a dental standpoint. Obliterated pulp chambers create nearly impossible situations for root canal therapy to even be considered. Shortened and thin roots lead to a questionable prognosis for crown and bridge work. The consistent loss and discoloration of enamel from all of the teeth, causes many patients to be treated with anterior crowns and veneers. The progression of the disease also leads to a loss of vertical dimension of occlusion, which must be treated with full mouth reconstruction. Additionally, due to the loss of the vertical amount of space from each individual tooth, there is a loss of support for crowns on these teeth and crown lengthening procedures is oftentimes common and necessary before final restorative work is completed.[10] If tooth loss does occur, options may be limited for restoring missing teeth due to the loss of support that may have occurred for possible bridge abutment teeth. Moreover, with poor oral hygiene, the loss of abutment strength, and progressive periodontal disease, removable partial appliance therapy may also be contraindicated. However, even though the disease in itself reduces many viable treatment options, implant therapy for DI patients has yet to be explored and may lead to a more successful treatment modality for these patients. With these problems in mind, once a definitive treatment plan has been set into motion, updating the patient's records with radiographs as well as maintaining pristine oral hygiene is imperative for any long-term success for DI patients. Current literature and research is very helpful in defining

some treatments that have the ability to work around most of these clinical manifestations of DI. The following review of case studies will demonstrate potential treatment modalities that have been successful in the past.

CASE STUDY: FULL MOUTH RECONSTRUCTION

In order to demonstrate the complexities that may arise from cases of patients with DI, a recent research review was conducted. During the review, a case study describing complete treatment using fixed prosthesis for a 6 year old girl from France was discovered. This case had several complexities including severe attrition involving all of the deciduous teeth, the appearance of a cyst during treatment, as well as the fact that the treatment time extended over several years. However, with all of these complexities, the treatment outcome and prognosis for this patient was excellent. The importance of this case stemmed from the fact that the treating dentists were attempting to halt the severe attrition affecting the deciduous teeth, and created a vertical dimension of occlusion for the eruption of her permanent teeth. They were also able to create fixed prostheses for the patient's permanent teeth as they erupted into place and used temporary crowns until she reached gingival maturity in order to halt attrition, preserve tooth structure, and create a good esthetic result.

During this patient's treatment, the dentists decided to tackle the situation as a two-stage process that will be described. The first and most important stage of the treatment involved diagnosis of the problem and assessing which deciduous teeth needed to be maintained for the best prognosis. Due to the severe attrition and loss of vertical dimension, full coverage stainless steel crowns were placed on all six year molars as well as the second deciduous molars. As the patient returned for regular maintenance appointments and checkups, a follicular cyst was discovered surrounding her second mandibular right permanent molar. This illustrates the fact that regular 3 month interval appointments are necessary for these patients as cysts and other pathologies have a tendency to appear spontaneously due to pulpal obliteration and other issues stemming from the disease. As the cyst was surgically removed by marsupialization, it disappeared and allowed the tooth to successfully erupt. Later, as the patient's permanent incisors erupted, they were temporarily crowned using polycarbonate resin restorations, as were her premolars and canines.

The patient's second stage of treatment began as soon as it was determined that her maxillary and mandibular bones had stopped growing. All

provisional restorations were removed, the underlying teeth were prepared for full coverage crowns, and an occlusal registration was taken. This registration was used in order to fabricate permanent crowns that would; maintain vertical dimension of occlusion, and be cemented into place to provide an ideal occlusion and stabilize her temporomandibular joints in the future. Regular maintenance appointments were established every 3 months.[11] The authors of this article placed great importance upon having the restoring dentist be able to identify and diagnose DI as soon as possible. Treatment of DI immediately after diagnosis can preserve tooth structure, improve esthetics and the prognosis of permanent treatment. The authors also suggested that regular maintenance appointments are a necessity in order to find any new problems either pathologies or those affecting the teeth.

CASE STUDY: FULL MOUTH REHABILITATION

The next case study presented is of a young teenager where orthodontic treatment, albeit slowly, was successfully performed. However, due to the decrease in esthetics resulting from discoloration and enamel/dentin fractures, the patient was not satisfied with the final result. As a resolution to this problem, the treating dentist decided to perform full mouth rehabilitation for the patient. It is interesting to note that this patient was seen and treated after the transition between deciduous and permanent teeth had been surpassed, and that the previous dentist had conservatively treated the patient's teeth with composite resin until a more permanent treatment plan could be agreed upon.

After the orthodontic treatment was completed, the dentist captured full upper and lower impressions and made study models of the patient's teeth. These models were then mounted on an articulator and a full mouth wax-up was fabricated. The dentist then decided upon all-ceramic crowns due to the increased esthetic results that these crowns portray. A three month time period of observation during which the patient wore provisional crowns, was used by the dentist in order to monitor symptoms after a change in vertical dimension was created. After cementation of the all-ceramic crowns, the patient was seen at regular follow-up checks, and a centric relation splint was created to prevent nocturnal bruxism and help protect the crowns from fracturing. The authors continued to state that the use of full coverage crowns could be an extremely important tool to use for patients that have dentinogenesis imperfecta. This stems from the idea that these crowns can prevent further deterioration of the dentinal system and provide excellent

functional and esthetic results. The all-ceramic crowns also have an advantage over metal-ceramic crowns in that they can be adhesively bonded to the tooth structure when cemented into place.[12] This technique increases the bond strength and helps the treating dentist when the teeth are not ideally shaped or have inherent malformation of the dentin. Overall, the treatment of using all-ceramic crowns to help restore and create full mouth rehabilitation with predictable success will help the treating dentist when creating a treatment plan for patients that have dentinogenesis imperfecta.

Crown and Bridge Failures

Within the successes demonstrated by these full mouth reconstruction cases, it's also important to understand their failures. For instance, one study demonstrated that out of diseases that were considered to be birth defects that affect the teeth, DI along with amelogenesis imperfecta (a hereditary condition in which a thin layer of abnormally developed enamel in which yellow underlying dentin is visible), had the most frequent number of failed prostheses for teeth.[13,14] The most common reason for failure of these single unit crowns was esthetic. The authors demonstrated that the majority of the crowns to be replaced over time were due to the margins of many of the anterior crowns becoming visible. For many patients this was esthetically unacceptable and many of the crowns were removed and later replaced by the practicing dentist. In these failures, we can also learn to avoid potential pitfalls when creating treatment plans for our own patients. A possible solution to this obstacle may be in the use of anterior resins veneers before the patient reaches an age of "gingival maturity," which is around 18 years of age. Some of these veneers have the added benefit of being in a group of glass ionomers that have added fluoride placed within the matrix of the material. These resins give the patient the added benefit of reducing caries activity overtime as well as maintaining an acceptable esthetic result until permanent porcelain crowns can be placed.

Treatment of Occlusions

The other side effect of DI that occurs with many of these patients is a class III occlusion. In other words, an occlusion that is defined as the mandible being more protruded than normal. A class I occlusion, as described by Angle, defines that the mesiobuccal cusp of the maxillary first molar be aligned over the buccal groove of the mandibular first molar.[15] Further complicating the occlusal situation is the occurrence of attrition, enamel loss and shortened roots that may further complicate orthodontic treatment. However, if the

teeth do not occlude in a class I situation, occlusal wear occurs more frequently as the guidance of the anterior teeth may be less than normal or entirely missing from the picture. Because DI patients already suffer from enamel loss and severe attrition, creation of a class I occlusion for these patients would be part of any ideal treatment plan. Once the malocclusion has been identified, treatment must be defined. If the malocclusion is severe, orthognathic surgery (surgically moving the tooth-bearing segments of the maxilla and mandible) may be the only treatment that can correct the occlusion.[16] If a mild malocclusion exists, orthodontic treatment to move the teeth should begin. If orthodontic treatment is agreed upon, it is important to recognize some of its limitations. For instance, many orthodontists would prefer to band all of the patient's teeth instead of bracketing them in order to conserve as much enamel as possible. Treatment must also progress as slowly as possible so that the already shortened roots do not continue to resorb from orthodontic tooth movement. According to Hartsfield et al, "the treatment plan should be designed to minimize heavy stress on the teeth due to uncontrolled functional and parafunctional loading.[17] However, if orthognathic surgery is the only option at a dentist's disposal for treatment, it's also important to understand the limitation and risks associated with that treatment modality. Several case studies have been published regarding this mode of care for DI patients and are described below.

CASE STUDY: OSTEODISTRACTION

In another case study involving a patient with DI, a boney pathology was found leading the authors to have to perform a surgical intervention using a distraction osteogenesis procedure. The importance of this article originates from the fact that distraction osteogenesis had never been reported in the literature for treating a DI patient's mandible. In the past, this technique has been used with great success in patients with OI for limb lengthening procedures as well as angulation deformity corrections.[18,19] The success of this study may aid future research in creating and defining a safe and predictable treatment plan for patients with DI who have a class III malocclusion.

The young Japanese patient presented with an ossifying fibroma in the mandible. This pathology required the surgeons to resect the mandible and reconstruct it using a distraction osteogenesis procedure. The patient in the case refused to have bone grafting done after the lesion had been removed from his mandible, leading the surgeon to perform a segment bone transport procedure. The distraction device was engaged after a seven-day latency

period at a rate of 0.25mm twice daily. This rate was continued for ten days followed by an advancement of 0.50mm twice daily for 35 more days. Due to the complication of the patient's brittle teeth, the distraction device was actually removed from his mandible prior to confirmation of bone consolidation via x-rays. The newly reconstructed mandible was then fixed with a fracture plate. The authors also took a bone biopsy from the site of new bone and determined that the newly formed bone was similar in trabecular structure to the original bone surrounding the surgical site.

A removable partial denture was then fabricated for the patient, as some of the posterior teeth were involved in the pathology and removal of the lesion. After the procedure had ended, the patient had gained about 40mm of new bone in the mandible. It has also been suggested in the literature, that alveolar ridge augmentation, distraction osteogenesis as well as dentinoalveolar implant placement has been successful in patients that have OI.[20] However, the authors did report some concerns regarding distraction osteogenesis in cases of patients with OI. These concerns included; the dysplastic bone may not have the ability to withstand a long-term presence of a distraction device, and that the new bone that is created will have the same structure with abnormal collagen as original bone in that area. However, as these authors later demonstrated with this case study, successful bone regeneration using a distraction osteogenesis device is possible. The authors did use a little more caution due to the medical history of the patient, in that they advanced the regenerating bone at a very slow rate, and also used ultrasound during the healing periods. The surgeons also left the inferior alveolar nerve and vessel bundles untouched, as well as the lingual periosteum of the transported segment.[21]

This case study demonstrates a potential treatment modality and the risks associated with that treatment for patients that have a non-ideal occlusion due to a DI and OI diagnosis. There are many patients that have this disease and also have a prognathic mandible, meaning that the horizontal length of the mandible exceeds the horizontal length of the maxilla causing severe occlusal discrepancies and severe dental attrition to occur. The fact that there are case studies that have been reported as having success with distraction osteogenesis procedures may also be helpful in treating any patient with DI that may develop a class II occlusion or one in which the mandible is deficient in horizontal length as compared to the maxilla. The results of this article may also be used as a good sign for the majority of patients with DI that have a class III mandible needing orthognathic surgical

intervention. If new and healthy mandibular bone can be created using distraction osteogenesis, then it may be safe to say that removing mandibular bone to correct a class III occlusion together with maxillary distraction osteogenesis may be successful. However, more research is needed in order to make any conclusions regarding this treatment.

CASE STUDY: ORTHOGNATHIC SURGERY/ PRECAUTIONS TO TAKE

In another case study, a woman with a type III malocclusion underwent orthognathic surgery at the University of Hong Kong. Her chief complaint was difficulty in chewing. This patient had a typical occlusion found in patients who have OI; prognathic mandible or angle class III molar occlusion. Historically, it has been found that with patients that have OI, 67% of them also have a prognathic mandible.[22] The authors of this case study described the idea that there are several medical, anaesthetic, surgical, and maxillofacial precautions to take before surgical intervention is started. However, they also deemed both maxillary and mandibular facial reconstructions safe as long as these previously listed precautions are taken. Descriptions of these precautions are listed below.

The first area in which extra precautions should be taken with patients undergoing maxillofacial surgery, who also have OI, is strictly medical and includes increased body temperature, increased heart rate, increased respiratory rate, increased risk of primary hyperthyroidism, a functional platelet disorder, and mitral valve involvement including prolapsed cusp and ruptured chordae. Due to these findings, surgeons must take extra caution as patients may bruise more easily and also have areas of hemorrhage. These risks can be avoided by not making any extraoral incisions. Scar formation is also a complication that may occur after surgery in OI patients. Bleeding disorders are also very common. The risk of malignant hyperthermia (a muscle disorder associated with a complication of general anesthesia) is real with OI patients and warrants investigation prior to surgical intervention (halothane/caffeine contraction test may be necessary). The authors did note that the association between OI and hyperpyrexia may be coincidental, but drugs that increase the patient's risk of hyperpyrexia (fever > 40°C) such as succinylcholine, isoflurane, halothane and enflurane should be avoided.[14, 23]

Caution with anaesthesia must also be taken with OI patients as they may suffer from several complications. These complications may include hyperthermia, kyphoscoliosis, difficult lung function interpretation, and difficulty with intubation. The problem with hyperthermia was previously discussed; however, the inherent problem with many severe cases of OI is the malformation of many bony structures. Many severe cases present with kyphoscoliosis, meaning an abnormal curvature of the spinal column in an anterior posterior and lateral direction. This abnormal spinal curvature can create issues when attempting to intubate the patient and care must also be taken not to fracture the mandible or cervical vertebrae. In cases where OI also presents with DI, care must be taken not to fracture the already fragile and brittle teeth. Interpretation of lung function is made more difficult as skeletal deformities lead to shorter stature, and this must be taken into consideration during anesthesia. However, the authors describe the fact that even in the most severe cases, normal ventilation and perfusion in the lungs does occur with OI patients.[23]

The third area where problems may be increased due to a diagnosis of OI are surgical considerations. Due to decreased platelet aggregation, poor skin healing, large callus formations, and increased bone fragility, some precautions must be taken. An increased risk of hemorrhage and bruising is a possibility for these patients, and care must be taken to manage the problem prior to surgery. Designing surgical intervention to have intraoral incisions may be a better idea as the skin can be very fragile and poorly formed. Extraoral incisions have been found to form hypertrophic scars and broad scars according to the authors. Because these patients innately have fragile bones, healing after orthognathic or other surgical interventions, may be compromised. The authors have demonstrated that healing occurs with an increased risk of forming osteoporosis. The authors also found that the healing process is thought to be normal with an increased risk of large callus formation.

Finally some of the inherent maxillofacial precautions should be considered. As already discussed, 67% of patients with OI also demonstrate a prognathic mandible. This can lead to poor facial aesthetics as well as functional problems and restorative problems for the general dentist. This problem has been demonstrated to be able to be fixed with proper surgical interventions with few postoperative complications. Some authors have described the occlusal discrepancy to be a hypoplastic maxilla with a normal mandibular length leading to a prognathic facial profile. Proper classification and

diagnosis with cephalometric measurements are required prior to surgical intervention. The mandible in these patients can also be very thin and extreme care during surgery is absolutely warranted. Some of the patients also present with DI leading to pulpal obliteration, short roots, discolored teeth, and easily fractured teeth. The authors also describe the fact that in some patients with DI, first and second mandibular molars may be impacted. Obviously, the position and condition of the patient's teeth may make the final occlusion postoperative, very difficult and non-ideal. And in most cases, additional restorative and dental work is necessary.

Even though there are many different difficulties to consider when treating patients with OI surgically, the final result and benefits outweigh the risks of surgery many times. And in fact, this may make the work of the restorative dentist easier and lead to less attrition, better esthetics, and a better functioning occlusion. All of these benefits may lead to a better standard of life for many of the patients with OI associated with DI. As the authors concluded with the case study, there may be additional risks to consider prior to surgery, but these should not by any means, discourage the surgeon from performing interventions that lead to a better esthetic and functional final result.[23]

IMPLANT CASES

Due to the fact that OI patients innately have weaker and more fragile bones, continued research into orthognathic surgery as a viable treatment option for these patients is absolutely necessary. This research has become a necessity due to the fact that an inordinately large percentage of these patients suffer from a class III malocclusion. In most situations, orthognathic surgery may be the only treatment option that these patients have in order to protect their teeth from further damage caused by progressive attrition. However, in some cases that present to the dental office, tooth loss may have already occurred. If crown and bridge treatment cannot be accomplished due to short root abutments, or the fact that multiple teeth are missing, dental implant treatment should be considered.

In a recent research article, it was demonstrated that osteodistraction of the maxilla, along with bone augmentation and dental implantation could be successful even in patients with osteogenesis imperfecta. The authors decided to use an osteodistraction procedure for the maxilla and a Le Fort I Osteotomy procedure in order to reduce the risk of an unpredictable fracture of the maxilla. The transition that a lot of OI patients face between their

deciduous and permanent dentitions is tooth loss. Along with the early loss of teeth, the alveolar bone also reduces in height and width. It is because of this bone loss, that boney ridge augmentation may also become a necessity for our patients as well as tooth replacements using dental implants.

The authors described a particular case study where ridge augmentation, dental implantation, and osteodistraction of the maxilla were completed. The woman in this case had suffered from early tooth loss, severe class III malocclusion, deficient maxilla, and atrophy of the anterior alveolar maxillary ridge. The surgeons performed a Le Fort procedure followed by osteodistraction of the maxilla. They also raised the maxillary sinuses bilaterally and augmented the alveolar crest with autogenous graft material harvested from the iliac crest. It is interesting to note that during the surgical procedures performed, no oral fractures were noted. However, a fracture did occur on the iliac spine. After postoperative healing occurred, five endosseous dental implants were placed. A normal healing pattern was then seen around the dental implants. The six month healing time for osseointegration of the implants was allowed, followed by the placement of a prosthetic overdenture. The authors stated that this case was successful after four years of follow-up. The authors also described the fact that the current research had indicated that even after a fracture occurs postoperatively, the healing patterns demonstrated adequate bone healing.[20] This is an extremely important idea to consider when treatment planning for these patients. For instance, if several teeth are lost due to the DI diagnosis or a patient presents with several missing teeth, these authors described the fact that dental implants were a viable and more importantly, successful treatment option for these patients.[20] This case study demonstrates that dental implants can be successfully used in OI/DI patients, which creates a greater number of possible treatment plans for these patients. And in another recent study, OI patients treated with dental implants (without concurrent treatment of bisphosphonates) were studied. The study demonstrated that the dental implant failure rate in OI and non-OI patients were the same.[24] In other words, if the permanent dentition begins to fail, options besides full mouth edentulation along with the creation of complete dentures, is not the only option. With this information, more treatment options become available including overdentures, fixed implant-retained prostheses, and dental implantation. As a result, when treating a patient with dentinogenesis imperfecta, the treating dentist must consider surgical intervention as well as dental implantation, as a viable treatment option for these patients.

CASE STUDY: OVERDENTURE

In the past, the use of overdentures was used frequently for severe congenital dental malformations. Due to the current dental philosophy of preservation of tooth structure, their use has gained popularity once again. It is important to note, however, that this treatment may, in the future, become one of the most significant treatments during the transition between deciduous and permanent teeth. The reason for this is that the overdentures have the ability to preserve or regain vertical dimension, maintain remaining teeth, and at the same time create an esthetically pleasing result. It is also important to note, however, that prior to the fabrication of overdentures, all carious teeth must be restored and the patient must understand the importance of pristine oral hygiene and homecare. Another important feature to consider with overdentures is their innate ability to solve many of the dental problems that many patients with DI may be facing, while at the same time, allowing the treating dentist more time to create a final prosthetic treatment plan when the permanent teeth erupt. As previously described, the transitional period between deciduous and permanent teeth can often lead to early tooth loss with patients that present with DI. As soon as teeth are lost, the alveolar process also begins to decrease in width and height. It is because of this very reason, that some treating dentists have started turning to overdentures as a viable treatment option for patients with DI so that alveolar bone is maintained at its current level. Essentially, when an overdenture is created for patients, it is a complete denture that is fabricated to sit on top of the gingival tissue and remaining teeth.

For instance, in a recent case study, a young patient presented with severe and extreme attrition of his primary dentition.[25] The treating dentist decided to use an overdenture in order to correct severe esthetic, and functional issues. The four year old did not demonstrate very good tolerance for the dental chair, and the dentist decided that an overdenture was the most suitable restoration possible. Impressions and jaw records were then taken for the fabrication of heat cured acrylic overdentures. It should be noted, however, that the intaglio (interior) surfaces of these dentures must be extremely smooth in order to provide the most comfort to the patient while wearing these prostheses.

The overdenture treatment is useful for pediatrics and adults. In pediatrics if the dentist deems no other restorations possible until more permanent teeth erupt, an overdenture is an excellent interim treatment. For adults an

overdenture is an efficient treatment in relation to finances and time, if crown and bridge and implants are not possible. An overdenture also preserves the bone and helps to increase esthetics and function better than a complete denture. These appliances may be very useful in treating patients that have DI for the very reason that masticatory forces are evenly distributed over the gingival tissue, remaining teeth, and the base of the overdentures. Because of the fact that the remaining teeth are subject to extremely severe attrition, the fabrication of a prosthesis, which spreads out the forces of mastication throughout the rest of the intraoral environment, may be able to preserve the remaining tooth structure and therefore alveolar process, for a longer period of time. Because preservation of tooth and alveolar structures are important for the remaining development of the permanent dentition, the preservation of these structures is very important for the treating dentist and patient.

The authors of this case study also examined the effects that the overdenture had on the gingival tissues, and tooth mobility. They found that no significant differences were noted with either tooth mobility or sore gingival tissues. They related these normal findings to be closely related to the fact that the occlusal forces were spread out evenly over the overdentures. The authors, however, also related the fact that in this case study, the patient had several remaining primary teeth and future research is necessary to study the effect that an overdenture may have in a patients mouth that has fewer teeth remaining. Therefore, a treatment plan that includes the fabrication of an overdenture gives the dentist another opportunity to treat younger patients that may have a loss of vertical dimension, loss in function, and loss in esthetics. The overdentures may also be used as custom fluoride trays which when used consistently, lowers the patient's risk of caries. The authors also stated, however, that the case study was only followed for a six month time period.[25]

BISPHOSPHONATE THERAPY

Another treatment that has recently surfaced in regards to treating patients with OI has been the administration of bisphosphonates (BP). It has been suggested that a continuous and frequent administration of bisphosphonates may decrease boney fractures and bone pain experienced by patients that have osteogenesis imperfecta. Interestingly enough, this new therapy has a couple of dental implications as well.

The first important implication of bisphosphonate use in any patient seen in the dental office is the increased risk of osteonecrosis that can be created post-extraction.[26, 27] The risk that is associated with osteonecrosis increases when IV bisphosphonate therapy is used instead of oral bisphosphonate use. In a recent systemic review, it was reported that in patients that contracted osteonecrosis of the jaw (ONJ), 94% had received bisphosphonate medication through an IV source. And that 60% of the osteonecrosis cases occurred after dentalalveolar surgery or extraction.[28] It is also important to consider the fact that the risk of osteonecrosis of the jaw increases depending upon the type of bisphosphonate therapy used, as well as the total dose that the patient receives.[28] It is extremely important for the patients and treating dentist to know whether the DI that these patients present with is also associated with OI. If the DI diagnosis is associated with OI, the patient may be receiving bisphosphonates which would increase their risk of osteonecrosis with any dental extractions.

The risk of osteonecrosis can be a severe consequence of using bisphosphonate therapy. This risk stems from the mechanism of action of this medication. First, the chemical formula of bisphosphonates makes them highly attracted to the physical makeup of boney tissue. Logically, if there is an area where more bone is exposed, the attraction of bisphosphonates to that area would be greater. During bone resorption, lacunae form due to the osteoclastic process. This opens up more surface area of the boney tissue, leading to a highly targeted area for bisphosphonates. It may therefore be stated that bisphosphonates are somewhat more selectively targeted to boney lacunae where osteoclasts are located. Second, it has also been demonstrated that bisphosphonates change the morphology of osteoclasts by eliminating their ruffled border and inhibiting an actin ring, which are both needed for bone resorption.[29] Fractures of the bone heal in three stages, the last of which uses osteoclasts to remodel trabecular with compact bone.[1] Without osteoclastic resorption, exposed bone in a dental socket cannot heal correctly, and osteonecrosis may occur. “BP-related ONJ is defined as exposed necrotic bone in patients receiving BPs that persists for at least eight weeks.”[27] This highlights the importance of trying to create a treatment plan for the patients with dentinogenesis imperfecta that incorporates as much tooth preservation and retention as possible. The historical solution of full mouth edentulation in order to fabricate complete dentures may be obsolete, especially when the patient is being treated with bisphosphonates, due to the risk of osteonecrosis after dental extractions.

Another area that treating dentists must be aware of when forming a treatment plan for these patients is the risk of osteonecrosis that appears with bisphosphonate use and dental implant placement. Dental implant placement may become the treatment plan of choice for patients that have lost teeth overtime due to periodontal disease and caries, and may become a key component of the treatment plans of patients with dentinogenesis imperfecta. However, due to the increase of bisphosphonate therapy use in patients that conjunctively present with DI and OI, caution must be taken prior to placing dental implants. In a recent study, researchers demonstrated that patients being treated with IV bisphosphonates had an increased risk of developing osteonecrosis of the bone surrounding their new dental implants.[30] They found that 59% of the patients that contracted osteonecrosis were taking IV bisphosphonates and 41% were taking oral bisphosphonates.[30] This is an extremely important risk to consider, due to the fact that the treatment for osteonecrosis of the jaw is mainly palliative. In purulent cases of osteonecrosis, patients were treated with oral doxycycline antibiotics for several months to over a year. When antibiotic treatment failed, dental implants were removed and antibiotic treatment was continued. This article reported that out of their patients that acquired osteonecrosis, the rate of healing for patients that had previously been treated with IV bisphosphonates was worse when compared to oral bisphosphonate use. They found that only 31% of IV bisphosphonate users fully recovered from the osteonecrosis when compared to 63% of oral bisphosphonate users.[30] However, the patients that had a complete recovery from osteonecrosis, even when treated concurrently with IV bisphosphonates, had been treated with doxycycline for the osteonecrosis.[30] The dosage of doxycycline that was used was 100-200mg a day for several months to a year and the dental implants were only removed when the antibiotic treatment failed to alleviate the osteonecrosis. The authors then related the conclusion that developing osteonecrosis associated with bisphosphonate therapy after dental implants were placed, was a late complication and therefore these patients should be monitored for a long period of time post oral surgery.[30]

UTILIZATION OF THE CHILD ORAL HEALTH IMPACT PROFILE TO ASSESS QUALITY OF LIFE IN OSTEOGENESIS IMPERFECTA AND DENTINOGENESIS IMPERFECTA

The physical consequences of dentinogenesis imperfecta, such as missing or discolored teeth and altered facial structures, clearly affect a child's oral and medical health. However, the poor facial aesthesis associated with these complications can also influence children's perception of well-being in many other domains, including their school adjustment, emotional functioning, and self-image. In an effort to examine overall health and well-being of children with dentinogenesis imperfecta an assessment of several domains of functioning was completed using the Child Oral Health Impact Profile (COHIP). The COHIP measures children's perception of oral health, functional well-being, social-emotional well-being, school environment, and self-image as well as providing an overall measure of oral health-related quality of life, with higher COHIP scores reflecting greater positive oral health-related quality of life.[31]

A subset of 40 male and female patients with osteogenesis imperfecta (OI) were administered the COHIP. Approximately 11 (27.5%) of the children also had dentinogenesis imperfecta (DI). All of the participants were included in the analyses, and several group differences emerged (see Table 1 for group differences and results). As expected, children with dentinogenesis imperfecta reported significantly worse oral health than their peers without DI. Additionally, children with DI reported significantly lower functional well-being, which measures their ability to perform everyday tasks. Overall oral-related quality of life was also significantly greater for children without DI. Although not significant, children with DI tended to report lower social-emotional well-being, which assesses comfort with peer interactions and general mood states. Children with and without DI were comparable on their perception of school environment quality of life and self-image.

The finding that children with both OI and DI report significantly lower scores than children solely with OI in the area of oral health is unsurprising; however, it is noteworthy that children with OI and DI also report lower functional well-being, social-emotional well-being, and overall quality of life in addition to concerns about oral health. This finding highlights the importance of attending to the psychosocial well-being of children with

dentinogenesis imperfecta in addition to their more overt physical symptoms and dental problems.

Given that all the children in this analysis have OI, it is possible that the severity of OI compounded with the added diagnosis of dentinogenesis imperfecta (DI), may in turn affect perception of oral quality of life. That is, children with DI and more severe forms of OI may have lower quality of life than children with DI but relatively mild forms of OI. In order to examine differences by OI types, descriptive statistics were computed and can be seen in Table 2. Unfortunately the small sample makes it difficult to test for statistical significance, but some general trends can still be observed by calculating simple means and standard deviations. As would be expected, the children with Type I OI, the mildest form of OI, and no diagnosis of dentinogenesis imperfecta, tended to have the highest level of oral health-related life satisfaction. Contrary to what would be expected, Type V, and not Type III (the most severe OI group) tended to have the lowest reported quality of life. In fact, the Type III OI group children in both the DI and non-DI group look similar on all factors except oral health.

While the diagnosis of dentinogenesis imperfecta can be associated with debilitating oral and physical consequences, it is also important to give careful consideration to the psychosocial consequences that may be associated with the disease. A complete treatment plan for a patient with DI should focus not only on correcting the oral health issues that occur with the diagnosis, but also on strategies to improve and address psychosocial issues that may co-occur.

Table 1. COHIP scores for DI and non-DI patients.

	NonDI (OI only) M(SD)	DI (DI and OI) M(SD)	Total M(SD)	Significance
Oral Health	29.93 (6.15)	23.06 (6.93)	28.04 (7.01)	$F(1,39)=9.29$, $p<.01$
Functional Well-being	22.00 (2.70)	19.27 (5.66)	21.25 (3.87)	$F(1,39)=4.30$, $p=.05$
Social-Emotional	29.00 (4.69)	26.45 (5.52)	28.30 (4.99)	$F(1,39)=2.13$, $p=.15$
School	15.31 (1.17)	15.36 (1.12)	15.33 (1.14)	$F(1,39)=0.02$, $p=.90$
Self-Image	20.09 (5.87)	19.82 (5.04)	20.01 (5.59)	$F(1,39)=0.02$, $p=.89$
Overall (0-136)	116.33 (15.11)	103.97 (15.62)	112.93 (16.06)	$F(1,39)=5.24$, $p=.03$

Table 2. Type of OI related to COHIP scores.

	OI TYPE I (N=24)		OI TYPE III (N=8)		OI TYPE IV (N=6)		OI TYPE V(N=2)*
	nonDI (N=20)	DI (N=4)	nonDI (N=5)	DI (N=3)	nonDI (N=4)	DI (N=2)	DI (N=2)
Oral Health	30.15 (7.13)	21.17 (10.47)	30.40 (4.04)	23.00 (2.00)	28.25 (2.36)	27.50 (2.12)	22.50 (9.19)
Functional well-being	22.45 (2.01)	21.75 (1.71)	21.00 (4.58)	20.67 (3.06)	21.00 (3.16)	17.50 (0.71)	14.00 (14.14)
Social-Emotional	29.60 (3.35)	26.25 (6.45)	25.80 (8.56)	25.67 (1.53)	30.00 (4.00)	31.00 (1.41)	23.50 (10.61)
School	15.55 (0.69)	15.50 (1.00)	15.00 (1.41)	16.00 (0.00)	14.50 (2.38)	16.00 (0.00)	13.50 (0.71)
Self-Image	20.47 (5.92)	20.50 (7.14)	20.04 (4.52)	20.67 (5.51)	18.25 (8.18)	19.50 (0.71)	17.50 (4.95)
Overall	118.22 (15.25)	105.17 (10.99)	112.24 (15.75)	106.00 (3.00)	112.00 (15.90)	111.50 (4.95)	91.00 (39.60)

* Since all children participating in the study with Type V OI also had a diagnosis of DI, means and SD could not be calculated for Type V, non DI.

General Information Regarding Treating DI Patients in the Dental Chair

When deciding upon treatment for a patient that has been diagnosed with dentinogenesis imperfecta, it is important to investigate whether that patient also has osteogenesis imperfecta. As reported earlier, there are clinical manifestations of OI that need to be considered when these patients undergo surgery. However, it's also important to realize that if a patient has been diagnosed with OI that is associated with DI, there are principles that should be followed in the dental chair. For instance, extra care must be taken due to the bone fragility. Both the ambulatory and non-ambulatory patient with OI may need extra support for their fragile skeletal structure. Some of these patients may be non-ambulatory with short stature and have difficulty getting into the larger dental chair. For nonambulatory patients, they will need assistance transferring to the dental chair using extreme care due to their increased risk of bony fractures. However, in some cases the patient will need to be treated carefully while still seated in their wheelchair. Extra support for the patient's head and neck are a necessity for safe and comfortable treatment of these patients.[2]

As previously stated, another area of concern when treating OI/DI patients is their increased risk of osteonecrosis caused by IV bisphosphonate therapy. These patients therefore, must be evaluated prior to dental extractions, especially to investigate for a history of bisphosphonate therapy treatment. OI patients also frequently suffer from mitral valve prolapse, floppy valves, aortic valve regurgitation, and other valvular defects.[32] Therefore, extra care must be taken when treating patients in a general dental office, due to the comorbidities that may be associated with osteogenesis imperfecta. Patients must be screened for these preexisting heart conditions. Premedication guidelines, as set forth by the American Heart Association should be followed when providing patients with treatments that could increase their risk of bacterial endocarditis. Some of these treatments range from tooth cleanings to root canals and extractions. This makes the diagnosis and general evaluation of the patient much more important when considering treatment options and an overall plan for the patient. By placing extreme importance upon preventative care and proper oral hygiene, these patients will have the ability to experience a greater quality of life and better oral health. Proper preventative care in the initial treatment will lead to reduced amounts of restorative work that needs to be done later in the treatment plan.

CONCLUSION

When treating patients that have dentinogenesis imperfecta, an early diagnosis of the disease is imperative for the best possible treatment outcome. And even though several different treatment plans may be clinically acceptable, full mouth reconstruction with crown and bridge placement may be the most successful. Furthermore, orthodontics and orthognathic surgery may be necessary, but they also present with inherent risks for DI patients. When the risks for these treatments outweigh the benefits, dental implants and or overdentures may be necessary. Finally, psychosocial issues are imperative when considering the patient's quality of life and the best treatment option for him or her.

REFERENCES

1. Sapp JP, Eversole LR, Wysocki GP. *Contemporary Oral and Maxillofacial Pathology.* 2nd ed. St. Louis, Mo.: Mosby; 2004.
2. Feigal R, King KJ. Dental Care for Patients with Osteogenesis Imperfecta. In: Wacaster P, ed. *Managing Osteogenesis Imperfecta : A Medical Manual*. Gaithersburg, MD: Osteogenesis Imperfecta Foundation, Inc; 1996:109-117.
3. Gorlin RJ, Cohen MM, Hennekam RCM. *Syndromes of the Head and Neck.* 4th ed. Oxford ; New York: Oxford University Press; 2001.
4. Landesberg R, Eisig S, Fennoy I, Siris E Alternative Indications for Bisphosphonate Therapy. *J Oral Maxillofac Surg*. 2009;67:27-34.
5. Schwartz S. Dental Care for Children with Osteogenesis Imperfecta. In: Chiasson R, Munns, C, Zeitlin, L, ed. *Interdisciplinary Treatment Approach for Children with Osteogenesis Imperfecta*. Montreal, QC: Shriners Hospitals for Children Canada; 2004:137-150.
3. Waltimo J, Ojanotko-Harri A, Lukinmaa PL. Mild forms of dentinogenesis imperfecta in association with osteogenesis imperfecta as characterized by light and transmission electron microscopy. *Journal of Oral Pathology & Medicine.* May 1996;25(5):256-264.
7. Piette EtGM. *La dent normale et pathologique.* Bruxelles: De Boeck Université; 2001.
8. Millett D, Welbury R. *Clinical Problem Solving in Orthodontics and Paediatric Dentistry*. Elsivier Inc. 2005 p. 138, 213-214.
9. Shapiro J, Byers P, Glorieux F, Sponseller P. *Osteogenesis Imperfecta A Translational Approach to Brittle Bone Disease*. Amsterdam: Elsevier; 2014. p. 316-317.
10. Welbury RR. *Paediatric Dentistry.* Oxford: Oxford University Press; 2001.
11. Bouvier D, Leheis B, Duprez JP, Bittar E, Coudert JL. Dentinogenesis imperfecta: long-term rehabilitation in a child. *Journal of Dentistry for Children.* May-Aug 2008;75(2):192-196.
12. Moundouri-Andritsakis H, Kourtis SG, Andritsakis DP. All-ceramic restorations for complete-mouth rehabilitation in dentinogenesis imperfecta: a case report. *Quintessence International.* Oct 2002;33(9):656-660.

13. Krieger O, Matuliene G, Husler J, Salvi GE, Pjetursson B, Bragger U. Failures and complications in patients with birth defects restored with fixed dental prostheses and single crowns on teeth and/or implants. *Clinical Oral Implants Research.* Aug 2009;20(8):809-816.
14. Kliegman RNWE. Nelson Textbook of Pediatrics. 2011; http://site.ebrary.com/lib/uqat/Doc?id=10567389.
15. Okeson JP. *Management of Temporomandibular Disorders and Occlusion.* St. Louis, Mo.: Mosby; 2003.
16. Figueroa AANPCMBFFFPJW. Plastic Surgery: 6-Volume Set. https://www.lib.umn.edu/slog.phtml?url=http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20111045095.
17. Hartsfield JK, Hohlt WF, Roberts WE. Orthodontic Treatment and Orthognathic Surgery for Patients with Osteogenesis Imperfecta. *Seminars in Orthodontics*. Dec 2006;12(4):254-271.
18. Green SA. Postoperative management during limb lengthening. *The Orthopedic Clinics of North America.* Oct 1991;22(4):723-734.
19. Ring D, Jupiter JB, Labropoulos PK, Guggenheim JJ, Stanitsky DF, Spencer DM. Treatment of deformity of the lower limb in adults who have osteogenesis imperfecta. *J. Bone Joint Surg. Am.* Feb 1996;78(2):220-225.
20. Binger T, Rucker M, Spitzer WJ. Dentofacial rehabilitation by osteodistraction, augmentation and implantation despite osteogenesis imperfecta. *Int. J. Oral Maxillofac. Surg.* Jun 2006;35(6):559-562.
21. Muraki Y, Tominaga K, Yoshioka I, et al. Mandibular reconstruction with bone transport in a patient with osteogenesis imperfecta. *Int. J. Oral Maxillofac. Surg.* Sep 2008;37(9):870-873.
22. Schwartz S TP. Oral findings in osteogenesis imperfecta. *Oral Surgery, Oral Medicine, and Oral Pathology.* 1984;57(2):161-167.
23. Ormiston IW, Tideman H. Orthognathic surgery in osteogenesis imperfecta: a case report with management considerations. *Journal of Cranio-Maxillo-Facial Surgery.* Aug 1995;23(4):261-265.
24. Shapiro J, Byers P, Glorieux F, Sponseller P. *Osteogenesis Imperfecta A Translational Approach to Brittle Bone Disease*. Amsterdam: Elsevier; 2014. p. 318.
25. Cehreli ZC, Altay N. Dentinogenesis imperfecta: influence of an overdenture on gingival tissues and tooth mobility. *J. Clin. Pediatr. Dent.* Summer 1996;20(4):277-280.
26. Saia G, Blandamura S, Bettini G, et al. Occurrence of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. *Journal of Cranio-Maxillo-Facial Surgery..* Apr 2010;68(4):797-804.
27. Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. *Journal of the American Dental Association.* Jan 2008;139(1):23-30.
28. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Annals of Internal Medicine.* May 16 2006;144(10):753-761.
29. Rogers MJ, Gordon S, Benford HL, et al. Cellular and molecular mechanisms of action of bisphosphonates. *Cancer.* Jun 15 2000;88(12 Suppl):2961-2978.
30. Lazarovici TS, Yahalom R, Taicher S, Schwartz-Arad D, Peleg O, Yarom N. Bisphosphonate-related osteonecrosis of the jaw associated with dental implants. *Journal of Cranio-Maxillo-Facial Surgery.* Apr 2010;68(4):790-796.

31. Broder HL, Wilson-Genderson M. Reliability and convergent and discriminant validity of the Child Oral Health Impact Profile (COHIP Child's version). *Community Dentistry and Oral Epidemiology.* Aug 2007;35 Suppl 1:20-31.
32. Abdelmalek NF, Gerber TL, Menter A. Cardiocutaneous syndromes and associations. *Journal of the American Academy of Dermatology.* Feb 2002;46(2):161-183.

28 UPPER EXTREMITY MANAGEMENT IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Individuals with all the varied types of Osteogenesis Imperfecta require specialized care to manage the upper extremity to maximize function. For some with Type I OI, the first recognition that there is an underlying bone problem comes after a fracture of the olecranon but they may also have upper extremity in adulthood[1]. Type V OI exhibits characteristic ossification of the interosseous membrane of the forearm and often dislocation of the radial head, and individuals with more severe types of OI (III and IV) exhibit forearm bowing associated with frequent fractures, angular deformities and periods of loss of use of their upper extremity. This chapter discusses priniciples in management of the upper extremity in OI.

Most Individuals with moderate and severe OI will develop bowing deformities of the upper extremities.[2] While mild to moderate bowing is well tolerated in the upper extremity, more severe bowing can have a profound effect on activities of daily living and mobility, because many individuals use a wheelchair or assistive devices. Upper extremity deformities can affect grip strength mobility, and the ability to function independently (Figure 1).[2,3] Bowed bones are more likely to fracture under stresses, thus perpetuating the fracture-refracture cycle.

Treatment of fractures in OI should preserve maximum function and minimize bowing deformities of long bones. Bone fragility requires special consideration in immobilization, operative techniques and rehabilitation. Light fiberglass splints are useful for most fractures, with emphasis on early return to function. Operative techniques to manage upper extremity fractures use intradullary rods or pins. Techniques in mild OI frequently follow the standard of care for patients with normal bone quality. For

example, avulsion fractures of the olecranon can be treated with tension band wiring and early motion[4,5] and angulated long bone fractures are treated with intramedullary nailing.

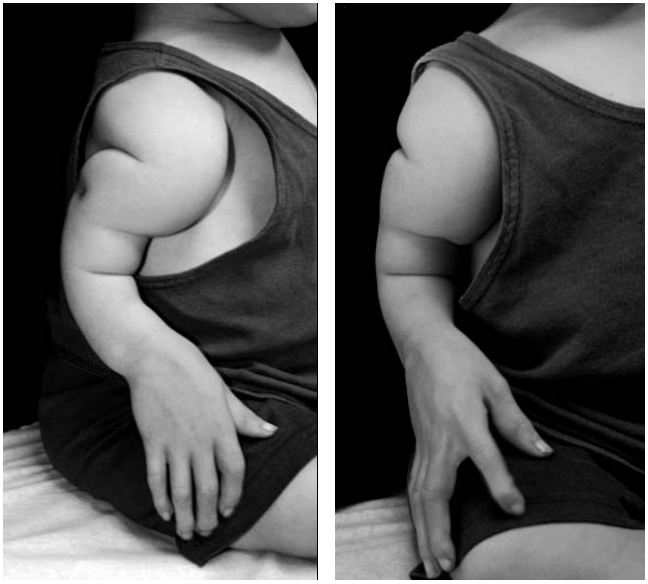

Figure 1. Patient with OI type III and severe humeral deformity.

A special considerations in brittle bone disease is the preference of rods over plates for fixation. Open reduction internal fixation of fractures with plates and screws is generally contraindicated in patients with OI because there is increased stress distal and proximal to the construct, increasing the risk of fracture or deformity of the unprotected bone areas after initial healing.[6] Rodding stabilizes the fracture to allow healing, minimizing the period of time that is spent non-weight bearing, thus minimizing the fracture-refracture cycle caused by the osteopenia associated with prolonged immobilization. Furthermore, rodding provides an internal support structure in long bones that helps minimize fracture recurrence, maximize distribution of forces, and minimize angular deformities. The principles of rodding are similar in the upper and lower extremities, but there have been advances in medication and mobility that allow more children to be candidates for surgery of the upper extremity**.**

The indications for upper extremity rodding are changing with increasing mobility and function in individuals with severe OI. Lower extremity surgical decisions are based on weight bearing and mobility considerations, but it is

more difficult to accurately evaluate the disability associated with upper extremity deformity. Often a decision for upper extremity surgery is deferred until there is a prolonged period of time in a splint or cast, or there has been a change in upper extremity side dominance. A good occupational therapy evaluation performed regularly at each clinic visit can bring upper extremity needs to earlier attention.

Even with advancements in the surgical technique, correction of upper limb deformities remains technically difficult and has poorer results than correction of lower limb deformities.[8,11,12] Despite advances in improving bone quality with medication, significant technical challenges remain, which may preclude a good technical result. In the setting of severe bowing there are significant anatomical distortions resulting in a medullary canal that is elliptical or flattened in shape, increasing the risk of splitting of the bone fragments and increasing the risk of neurovascular injury.[7] Although the bone to be rodded may appear of sufficient diameter on radiographs, often the bones are thin and flat, without a definable medullary canal. Currently, the principles applied to upper extremity rodding are the same as those for lower extremity rodding: reduce and prevent deformity, minimize fracture risk, and improve functional. Despite those goals, to date, intramedullary rodding of the upper extremities is less commonly performed; with only 11% of OI patients with upper limb deformities undergoing surgical correction versus 90% of OI patients with lower limb deformities.[8-10] Historically surgery required a wide-open exposure, which is more complicated in the upper extremity and involved multiple osteotomies with significant stripping of the soft tissue and periosteum. With current improved imaging in the operating room, less invasive procedures can often be used to aid placement of the intramedullary rods.[8]

HUMERUS

Humeral deformities are common, occurring in up to 25% of all OI patients and with an average angular deformity of 44 degrees. The most common is varus deformities in the distal humerus.[2] When there is an indication for surgery to improve alignment and function, it is typically performed with intramedullary rodding (Figure 2). Instrumentation varies based on the size of the patient. In young patients smooth Steinman pins are the most common option, though in larger bones elongating rods or rush nails may be used. Humeral rodding can be performed by inserting the rod through the lateral[10] or medial epicondyle[13] and advancing it proximally (Figure 3). It may also be introduced through an open osteotomy or fracture site and advanced

proximally through the humeral head and then distally after closing down the osteotomy site[8] or in an antegrade fashion. A modified approach to the proximal humeral can be performed to place solid or expanding rods, with open or percutaneous osteotomies of the humerus under radiographic guidance.

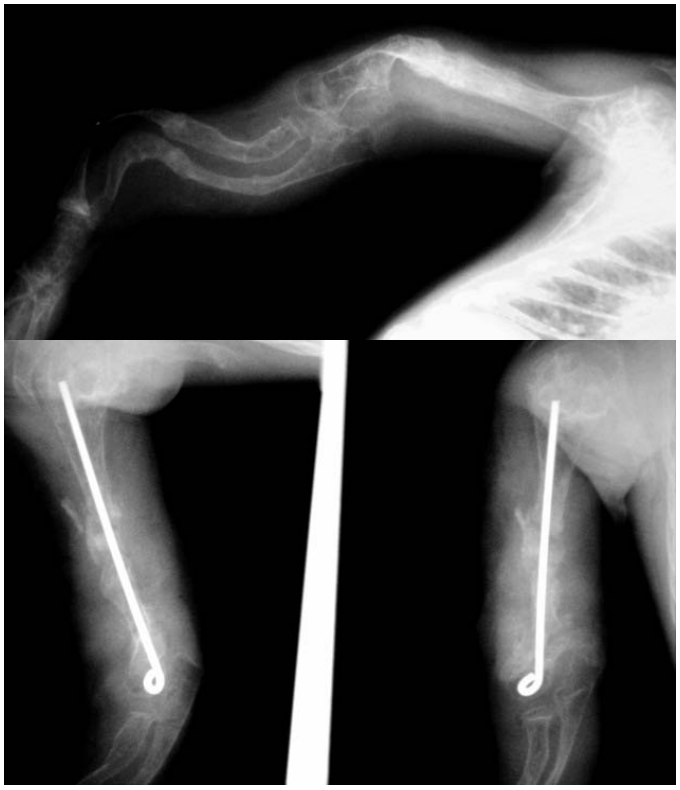

Figure 2. Patient with severe OI and humeral deformity who underwent distal humeral osteotomy and intramedullary nailing. A suture was placed through the loop in the rod near the elbow to prevent rod migration.

Complication rates can be high in humeral rodding. Gargain et al. reported a greater than 50% complication rate, However, the vast majority of reported complications from rod migration.[13] Multiple authors emphasize the importance of minimizing soft tissue interposition at the rod tip to minimize loosening of the pin and subsequent pin migration. Despite the high complication rate, up to 86% of patients have been satisfied with the outcome of surgery and demonstrated increased functionality when working with an occupational therapist.[13] Mulpuri et al. also found significant

improvement in the activities of daily living of all patients who underwent humeral rodding.[14]

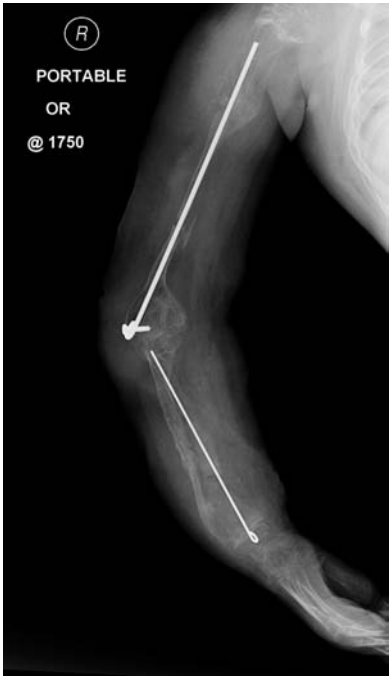

Figure 3. The rod (Steinman pin) can be modified and interlocked with a small screw at the distal insertion site to prevent otherwise predictable migration.

In cases of significant bowing of the humerus, there is often significant deformity of the forearm, which needs to be assessed prior to straightening just the humerus. For example, straightening a significant anterior bow of the humerus with a bowed forearm may limit overall extension of the upper extremity by revealing a significant flexion deformity. The forearm deformity may be addressed at the same time or at a different surgery.

OLECRANON

Olecranon apophyseal fractures occur commonly in Type I OI and indeed are so characteristic that they sometimes lead to the diagnosis. There is a high rate of bilaterality, and often the fractures occur within six months of each other. The reported range of bilateral olecranon apophyseal fractures is 33-100%[5,15,16]. While casting in extension has shown some success for nondisplaced fractures, there is a high rate of displacement and refracture. Most patients with OI and olecranon fractures can be treated successfully surgically. The tension band technique has demonstrated best utility (Figures 4-6). Plate and screw systems have a high failure rate. The goal should be to retain the hardware throughout growing years, as the fracture can promptly recur after removal. The pins should be set into the volar cortex, and the proximal rod ends and wire should be buried in the soft tissue as well as possible to avoid the most common bothersome complications of rod protrusion and prominent wires.

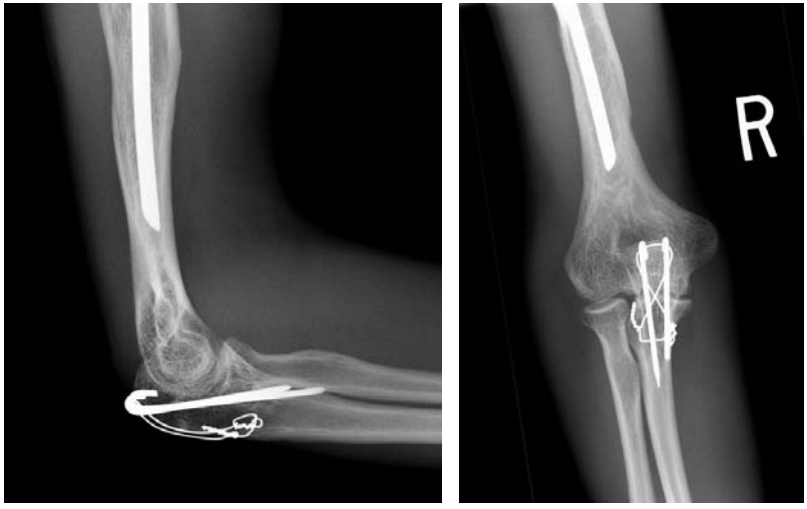

Figure 4. This patient with OI type I was successfully treated with tension band wiring.

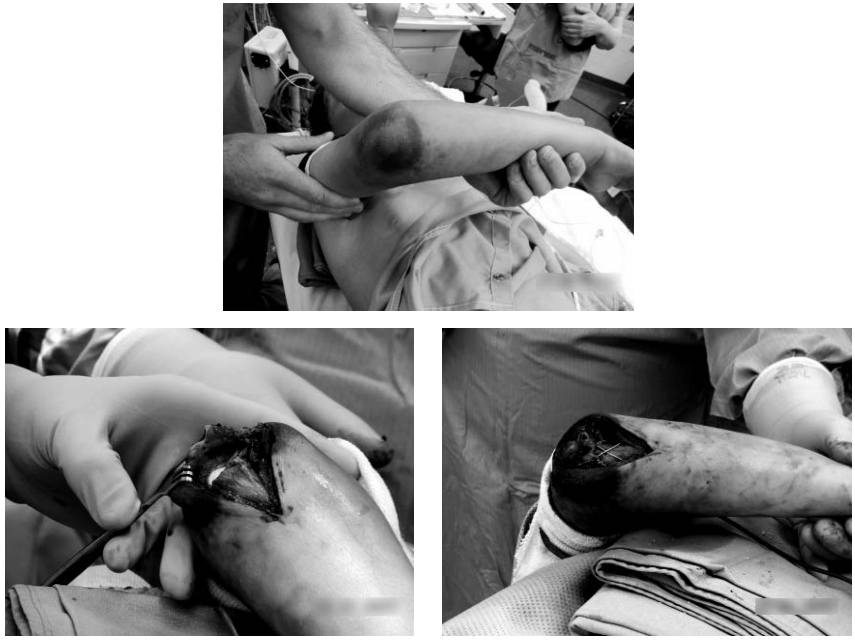

Figure 5. Clinical photo of an olecranon fracture at the surgical exposure for open reduction internal fixation. Note the articular nature of the injury.

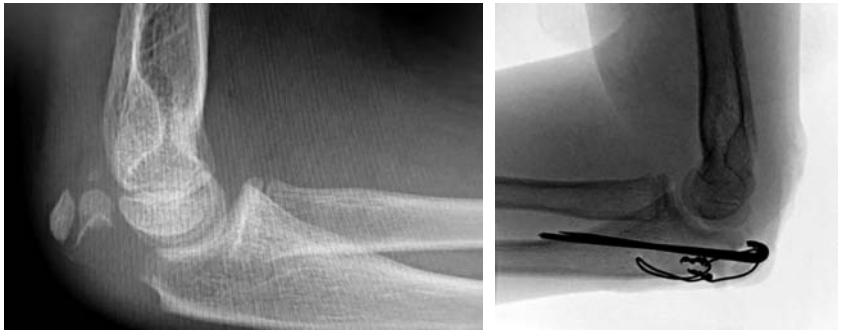

Figure 6. Radiographs of the fracture and reduction and fixation for the clinical case in Figure 5.

FOREARM

Forearm fractures are the second most common type of upper extremity fracture in children with osteogenesis imperfecta, occurring in up to 69% of patients in OI;[1] with a large percentage of individuals with moderate and severe types. developing bowing deformities of the radius and ulna, respectively.[2] Most forearm deformities involve both bones and primarily

occur proximally or in the mid-shaft.[2] Fractures and angular abnormalities of the upper extremity are particularly important in the OI population as their upper extremities may frequently become partially or fully weight bearing from dependence on crutches and wheelchairs. Furthermore they may have a profound impact on activities of daily living, including their ability to perform self-care and hygiene. Amako et al. determined that while mild and moderate deformities showed no diminution of self-care scores, those scores were reduced in severe deformities and mobility was markedly reduced in the moderate and severe deformity groups. Consequently, independence was significantly reduced in the moderate and severe upper extremity deformity groups.[2]

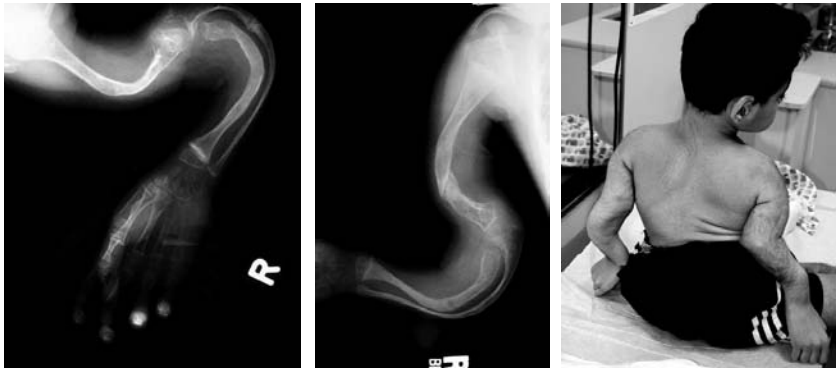

Figure 7. Patient with OI type VIII demonstrates significant upper extremity deformity.

An early study documented some success but also cataloged the difficulty of rodding procedures secondary to the severity of the deformities, and the lack of trabecular bone and a definable intramedullary canal for bony purchase.[8] The forearm bones can be osteotomized and rodded typically by inserting a Steinman pin through the olecranon for the ulna and through the radial styloid for the radius.[10] In our own series of patients treated at the Shriners Hospital for Children, Chicago over a thirty year period the goal of achieving forearm stability was met but there was a 50% incidence of rod revision or removal during long term follow-up, most commonly as a result of rod migration (Figures 8, 9).

While the majority of cases of upper extremity rodding were performed in older children who had already sustained multiple fractures with severe bowing, Khoshhal and Ellis had a 10-year follow-up on patients treated with intramedullary rodding of the humerus, radius or ulna and found that they

had significant functional improvements. All patients in that study were able to feed themselves and most were able to dress themselves or assist in transfers postoperatively.[17]

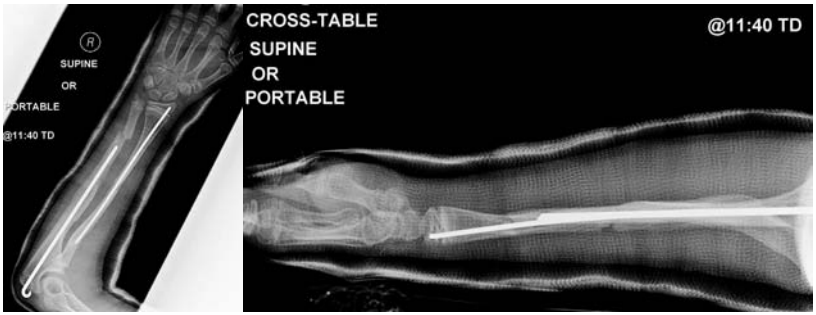

Figure 8. Patient with OI type IV who had previously undergone intramedullary nailing of the ulna, and who sustained a fracture of the radius and underwent revision nailing.

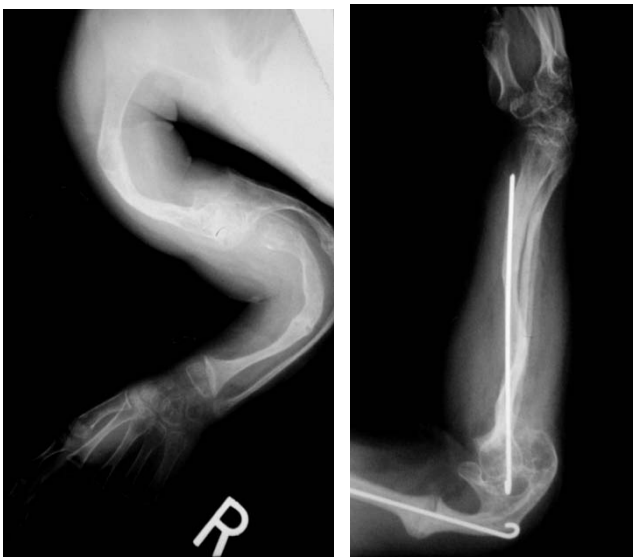

Figure 9. Patient with OI type VIII osteotomies and intramedullary nailing of the humerus and ulna.

TYPE V

OI type V is a distinct subtype of OI with characteristic involvement of the upper extremity. Generally, individuals are independent ambulators but have higher rates of scoliosis and forearm deformity, an autosomal dominant

disorder associated with mesh-like lamellae and hyperplastic callus in up to 65% of patients. Its etiology has recently been identified as a mutation in the BRIL gene.[18] Hyperplastic callus can be associated with loss of function.[19] Treatment is with non-steroidal medication, preferably indomethacin.[20-23]

Type V OI is associated with forearm deformities in up to 95% of cases which demonstrate calcification of the interosseous membrane, dysplastic capitellum and dislocation of subluxation of the radial head (Figure 10). Capitellar abnormalities are a negative prognostic factor and are highly associated with limb mal-alignment and radial head dislocation or subluxation.[3] These deformities result in decreased forearm pronation and supination and have been found in all patients with calcified interosseous membranes of one or both forearms.[24]

Forearm bowing in all types of OI may result in radial head dislocation in up to 27% of patients.[25] As the degree of curvature of ulnar bowing increases, so does the stress on the annular ligament, and this increased stress can ultimately result in dislocation of the radial head proximally. In a study by Fassier et al. of 254 patients with osteogenesis imperfecta, radial head dislocation or subluxation was found in 17% of patients, with a significantly higher rate of 86% in patients with OI type V. They found that in types I-IV the frequency of radial head dislocation was correlated to the severity of disease. Ninety percent of dislocations and subluxations were anterior, lateral or anterolateral in type V, whereas in all other forms dislocations were more commonly posterior or posterolateral (70%). Furthermore, the authors found that when they occurred, radial head dislocations resulted in significantly decreased grip strength and forearm range of motion.[3]

Several different techniques have been employed to address the radial head dislocation. Excision can sometimes be successful in removing a bothersome bump but this approach generally does not restore range of motion and can be associated with poor outcomes.[25] We have observed hyperplastic callus formation after radial head excision. Currently, there remains little literature on the treatment of radial head dislocation.

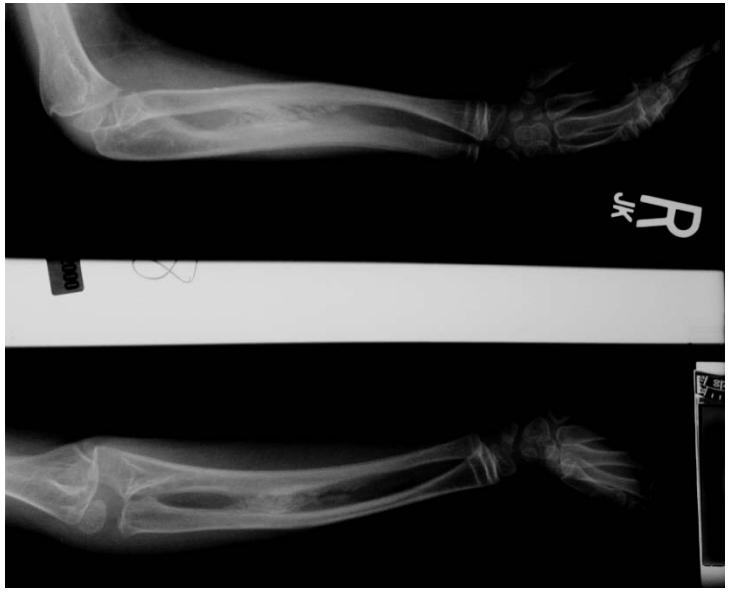

Figure 10. Patient with type V OI and ossification of the interosseous ligament.

NONUNION

Given the significant number of fractures that patients with OI will experience during their lifetime, the rate of nonunion is surprisingly low. This is largely due to the fact that the process of bony healing is not affected by OI. That said, there is still an approximately 18-20% lifetime risk of developing a long bone nonunion in patients with OI[26,27] and a significantly higher rate of nonunions in upper extremity fractures versus lower extremity fractures in OI patients. Most of the nonunions in the upper extremity occur after fractures. Nonunions after osteotomy stabilized by intramedullary nailing are rare, with only 2% going on to nonunion (Figure 11).[26] Agarwal and Joseph found that two-thirds of all nonunions were in the humerus and those predominantly occurred in the middle and lower third junctions and primarily occurred after fracture. The middle to distal third of the humerus is subjected to significant translational and rotational forces that are difficult to control in a cast or with an intramedullary nail. Furthermore, all of the nonunions after fracture occurred in patients that had little to no immobilization. All patients with humeral nonunions had significant limitations in their activities of daily living. The authors' recommendations were that care should be taken to minimize the number of osteotomies and to maximize the preservation of blood supply to the bone so as to prevent nonunions.[26]

Regarding nonunions after fractures, Agarwal and Joseph found that 66% of their nonunions were in the humerus, whereas humeral nonunions only represented 33% of the series reported by Gamble Et al.[26,27] Treatment of humeral nonunions can be difficult. Agarwal et al found that that, when performed, treatment with fixation often failed.[26] In Agarwal's study, all three patients with humeral nonunions due to fractures, the nonunions persisted despite revising their intramedullary fixation, iliac crest bone grafting, shoulder spica and in one case external fixation. Gamble et al. performed exchange nailing and grafting.[27] Those three patients had hypertrophic nonunions that underwent treatment and went on to unite. One patient with bilateral nonpainful nonunions elected to continue with bracing. A report by Hsiao et al. presented the case of a patient with an atrophic nonunion that subsequently went on to unite after excision of the nonunion site, Fassier Duval nailing, medial and lateral locked plating, and BMP augmentation.[28] Gamble found that with surgical treatment all cases subsequently went on to union once they had adequate fixation; except one patient with a lower extremity nonunion who went on to have an amputation, which significantly relieved her chronic pain.[27] All cases that united had improvement in their pain and activities of daily living. All authors emphasized excising the non-united portion of the bone as well as prolonged immobilization or protection for at least 6-8 months after healing.[26,27,28] Both Gamble and Agarwal used bone grafting when treating their nonunions and both felt that the nonunions they saw were likely attributable to lack of immobilization at the time of the initial fracture. Nonunions of the upper extremity in patients with OI, particularly the distal humerus, are commonly associated with elbow contracture and poor elbow motion, and are thus the site for some functional elbow motion. Any attempt at nonunion and deformity repair should be preceded by a careful assessment of other deformities in the arm that may result in loss of motion or difficulty positioning the arm after surgery.

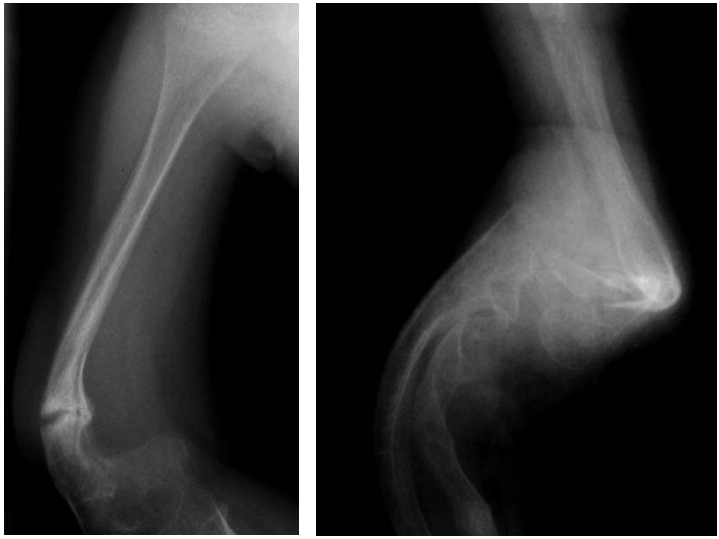

Figure 11. Patient with nonunion goes on to develop severe deformity. The elbow is commonly stiff and motion occurs at the nonunion.

HAND

There is little published information in the literature on the hand deformities associated with OI. In OI the hand is the third most common fracture site after the lower leg and forearm; with a reported 66.6% lifetime fracture risk in the fingers, 32.4% in the hand, and 58.6% in the wrist.[1] We found one case report of reducible z deformities and swan neck deformities of the digits without associated arthritis in an adult patient with blue sclera, multiple fractures and with suspected OI.[29] While hand fractures are a common feature of OI, treatment can follow general guidelines for treatment, with rare indications for operative treatment. The same preference for pins over plates applies.

LIGAMENTS

Tendons are composed primarily of parallel arrays of type I collagen fibers, and thus are also affected by the mutations associated with osteogenesis imperfecta. Tendon tissues are primarily noted to be lax, particularly in OI types IV and V, rather than weak.[25] Match and Corrylos theorized that despite the collagen mutation in muscles, tendons and ligaments, they were likely stronger than the bones onto which they were attached.[30]

Currently, there are few reports of upper extremity tendon ruptures in OI in the literature and those present are primarily case reports.[31] Tendon ruptures are frequently associated with apophyseal fractures rather than true tendon avulsions or ruptures.[30] In a retrospective study of adult patients with mild OI, however, respondents self reported a 66% rate of joint hypermobility, 56% rate of joint dislocation and 39% rate of previous tendon rupture; though there was no detail of the location of these injuries.[1] Joint hypermobility and joint range of motion decrease over time in adults, which may lead to an increased incidence of tendon injury and rupture. [31,32] It is therefore likely that true tendon injuries are relatively common in OI and underreported in the literature.

BISPHOSPHONATE TREATMENT

The use of IV bisphosphonates has increased in recent years and has been demonstrated to be safe even in young infants, though long-term studies are lacking. [34,35] Currently, there is a lack of evidence as to whether they should be stopped in the perioperative period, but concern about bisphosphonates impairing osteotomy healing generally results in a recommendation to withhold bisphosphonate treatment until union is evident. The literature in this area is inconclusive; some articles indicate that it does not interfere with fracture healing,[36] while others indicate that it may affect osteotomy healing.[37] Additionally there is a real concern that bone formed while off the bisphosphonates may be more fragile, thus creating stress risers.

In the OI population bisphosphonates have been proven to increase both bone size and volumetric density and do not appear to inhibit bone growth, but rather to facilitate it. [35,38,39] A study by Glorieux et al. on the cyclic use of pamidronate demonstrated increased cortical width of the metacarpals by 27.0 +/- 20.2% per year in patients with OI as compared with the 8-9% increase found in healthy children.[38] Additionally, after one year of treatment patients were found to have significantly lower fracture rates in their upper extremities.[40]

Any increase in bone density may not only be protective against fracture but may also be an important indicator of functionality. Huang's study found that bone mineral density of the wrist in patients with OI was a predictor of global functioning, upper extremity functioning and sports functioning.[41] There have additionally been found to be a rapid increase in grip strength within 4 months of a single pamidronate infusion cycle,[42] and a rapid decrease in bone pain in patients with severe OI that is maintained at 2 years.[38] Despite the

study's results, decreases in bone pain and increases in functionality due to bisphosphonates have not been measurable in studies of bisphosphonates in mild to moderate OI.[40] All studies demonstrate that there are significant differences in patients' responses to treatment and thus some types of OI are more responsive than others.

REHAB

Rehabilitation is of particular importance in patients with OI. Associated with structural abnormalities there exists a motor impairment which is related to the severity of OI type, with type III being significantly more impaired than other types, and all forms being impaired compared to healthy controls.[43] Excellent therapy advice and treatment can improve function and independence. Rehabilitation is also important in rapidly regaining function after fractures. Rehabilitation can begin while the patient is non-weight bearing in order to minimize contractures. Frequently, decreased muscle strength is present around the shoulder in patients with OI.[43]

CONCLUSION

The ramifications of the collagen mutations in OI are systemic, yet, most orthopaedic interventions are directed at the lower extremities and spine. This is primarily because the upper extremities have great potential for both tolerating and remodeling bowing deformities, especially in the very young. Nonetheless, we cannot neglect the upper extremities as the forearm is the second most common site of fractures and the cumulative effects of repeated fractures cause the humerus to be the most common site of deformity.[2] Modern surgical techniques combined with medical treatment to improve bone quality enable more individuals with OI to benefit from upper extremity surgery.

Despite the potential advantages, surgical treatment remains technically difficult even in the most experienced hands. For this reason, current goals in upper extremity OI management continue to be: minimizing of deformity, and maximizing function through diminished immobilization.

Bisphosphonates have greatly improved the quality of life in patients with osteogenesis imperfecta. They have done this not only by minimizing the number of fractures and reducing the period of time that they are non-weight bearing, but also by improving motor development and grip strength. Finally,

bisphosphonates can also reduce the risk of developing bowing deformities and their sequellae.

REFERENCES

1. McKiernan FE. Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. *Osteoporos Int*. Dec 2005;16(12):1698-1702.
2. Amako M, Fassier F, Hamdy RC, Aarabi M, Montpetit K, Glorieux FH. Functional analysis of upper limb deformities in osteogenesis imperfecta. *J Pediatr Orthop*. Nov-Dec 2004;24(6):689-694.
3. Fassier AM, Rauch F, Aarabi M, Janelle C, Fassier F. Radial head dislocation and subluxation in osteogenesis imperfecta. *J Bone Joint Surg Am*. Dec 2007;89(12):2694-2704.
4. Alman BA, Howard AW. Metabolic and endocrine abnormalities. In: Lovell WW, Winter RB, Morrissy RT, Weinstein SL, eds. *Lovell and Winter's pediatric orthopaedics*. 6th ed. Philsdelphia: Lippincott Williams and Wilkins; 2006: 180-187.
5. Zionts LE, Moon, CN. Olecranon apophysis fractures in children with osteogenesis imperfecta revisited. *J Pediatr Orthop*. Nov-Dec 2002;22(6):745-750.
6. Enright WJ, Noonan KJ. Bone plating in patients with type III osteogenesis imperfecta: results and complications. *Iowa Orthop J*. 2006;26:37-40.
7. Chotigavanichaya C, Jadhav A, Bernstein RM, Watts HG. Rod diameter prediction in patients with osteogenesis imperfecta Undergoing Primary Osteotomy. *J Pediatr Orthop*. Jul-Aug 2001;21(4):515-518.
8. Root L. Upper limb surgery in osteogenesis imperfecta. *Clin Orthop Relat Res*. Sep 1981;(159):141-146.
9. Sofield HA, Millar EA. Fragmentation, realignment, and intramedullary rod fixation of deformities of the long bones in children: a ten year appraisal. *J Bone Joint Surg Am*. Dec 1959;41(8):1371-1391.
10. Ryöppy S, Alberty A, Kaitila I. Early semiclosed intramedullary stabilization in osteogenesis imperfecta. *J Pediatr Orthop*. Mar-Apr 1987;7(2):139-144.
11. Lammens J, Mukherjee A, Van Eygen P, Fabry G. Forearm realignment with elbow reconstruction using the Ilizarov fixator. *J Bone Joint Surg Br*. May 1991;73(3):412-414.
12. Mirbaha M. Multiple osteotomies and intramedullary fixation of the radius and the ulna to correct severe deformity and improve function in osteogenesis imperfecta. *J Bone Joint Surg Am*. Apr 1966;48(3):523-527.
13. Gargan MF, Wisbeach A, Fixsen JA. Humeral rodding in osteogenesis imperfecta. *J Pediatr Orthop*. Nov-Dec 1996;16(6):719-722.
14. Mulpuri K, Joseph B. Intramedullary rodding in osteogenesis imperfecta. *J Pediatr Orthop*. Mar-Apr 2000;20(2):267-273.
15. Gwynne-Jones DP. Displaced olecranon apophyseal fractures in children with osteogenesis imperfecta. *J Pediatr Orthop*. Mar-Apr 2005;25(2):154-157.
16. Evans MC, Graham HK. Olecranon fractures in children. *J Pediatr Orthop*. Sep-Oct 1999;19(5):559-569.
17. Khoshhal KI, Ellis RD. Functional outcome of Sofield procedure in the upper limb in osteogenesis imperfecta. *J Pediatr Orthop*. Mar-Apr 2001;21(2):236-237.
18. Balasubramanian M, Parker MJ, Dalton A, Giunta C, Lindert U, Peres LC, Wagner BE, Arundel P, Offiah A, Bishop NJ. Genotype-phenotype study in type V osteogenesis imperfecta. *Clin Dysmorphol*. Jul 2013;22(3):93-101.

19. Cheung MS, Glorieux FH, Rauch F. Natural history of hyperplastic callus formation in osteogenesis imperfecta type V. *J Bone Miner Res*. Aug 2007;22(8):1181-1186.
20. Ramirez N, Vilella FE, Colón M, Flynn JM. Osteogenesis imperfecta and hyperplastic callus formation in a family: a report of three cases and a review of the literature. *J Pediatr Orthop B*. Mar 2003;12(2):88-96.
21. Strach EH. Hyperplastic callus formation in osteogenesis imperfecta; report of a case and review of the literature. *J Bone Joint Surg Br*. Aug 1953;35-B(3):417-422.
22. Apley AG. Hyperplastic callus in osteogenesis imperfecta: report of a case. *J Bone Joint Surg Br*. Nov 1951;33-B(4):591-593.
23. Banta JV, Schreiber RR, Kulik WJ. Hyperplastic callus formation in osteogenesis imperfecta simulating osteosarcoma. *J Bone Joint Surg Am*. Jan 1971;51(1):115-122.
24. Glorieux FH, Rauch F, Plotkin H, Ward L, Travers R, Roughley P, Lalic L, Glorieux DF, Fassier F, Bishop NJ. Type V osteogenesis imperfecta: a new form of brittle bone disease. *J Bone Miner Res*. Sep 2000;15(9):1650-1658.
25. King JD, Bobechko WP. Osteogenesis imperfecta: an orthopaedic description and surgical review. *J Bone Joint Surg Br*. Feb 1971;53-B(1):72-89.
26. Agarwal V, Joseph B. Nonunion in osteogenesis imperfecta. *J Pediatr Orthop B*. Nov 2005;14(6):451-455.
27. Gamble JG, Rinsky LA, Strudwick J, Bleck EE. Nonunion of fractures in children who have osteogenesis imperfecta. *J Bone Joint Surg Am*. Mar 1988;70(3):439-443.
28. Hsiao CM, Mormino MA, Esposito PW, Burke BA. Distal humerus atrophic nonunion in a child with osteogenesis imperfecta. *J Pediatr Orthop*. Oct-Nov 2013;33(7):725-729
29. Oz B, Olmez N, Memis A. Osteogenesis imperfecta: a case with hand deformities. *Clin Rheumatol*. Sep 2005;24(5):565-568.
30. Match RM, Corrylos EV. Bilateral avulsion fracture of the triceps tendon insertion from skiing with osteogenesis imperfecta tarda. A case report. *Am J Sports Med*. Mar-Apr 1983;11(2):99-102.
31. Ogilvie-Harris DJ, Khazim R. Tendon and ligament injuries in adults with osteogenesis imperfecta. *J Bone Joint Surg Br*. Jan 1995;77(1):155-156.
32. Bulbena A, Duró JC, Porta M, Faus S, Vallescar R, Martin-Santos R. Clinical assessment of hypermobility of the joints: assembling criteria. *J Rheumatol*. Jan 1992;19(1):115-122.
33. Engelbert RH, Uiterwaal CS, Gerver WJ, van der Net JJ, Pruijs HS, Helders PJ. Osteogenesis imperfecta in childhood: impairment and disability. A prospective study with 4-year follow-up. *Arch Phys Med Rehabil*. May 2004;85(5):772-778.
34. Aström E, Jorulf H, Söderhäll S. Intravenous pamidronate treatment of infants with severe osteogenesis imperfecta. *Arch Dis Child*. Apr 2007;92(4):332-338.
35. Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, Glorieux FH. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab*. May 2000;85(5):1846-1850.
36. Pizones J, Plotkin H, Parra-Garcia JI, Alvarez P, Gutierrez P, Bueno A, Fernandez-Arroyo A. Bone healing in children with osteogenesis imperfecta treated with bisphosphonates. *J Pediatr Orthop*. May-Jun 2005;25(3):332-335.
37. Munns CF, Rauch F, Zeitlin L, Fassier F, Glorieux FH. Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. *J Bone Miner Res*. Nov 2004;19(11):1779-1786.

38. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med*. Oct 1998;339(14):947-952.
39. Zeitlin L, Rauch F, Plotkin H, Glorieux FH. Height and weight development during four years of therapy with cyclical intravenous pamidronate in children and adolescents with osteogenesis imperfecta types I, III and IV. *Pediatrics*. May 2003;111(5 Pt 1):1030-1036.
40. Letocha AD, Cintas HL, Troendle JF, Reynolds JC, Cann CE, Chernoff EJ, Hill SC, Gerber LH, Marini JC. Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. *J Bone Miner Res*. Jun 2005;20(6):977-986.
41. Huang RP, Ambrose CG, Sullivan E, Haynes RJ. Functional Significance of bone Density measurements in children with osteogenesis imperfecta. *J Bone Joint Surg Am*. Jun 2006;88(6):1324-1330.
42. Montpetit K, Plotkin H, Rauch F, Bilodeau N, Cloutier S, Rabzel M, Glorieux FH. Rapid increase in grip force after start of pamidronate therapy in children and adolescents with severe osteogenesis imperfecta. *Pediatrics*. May 2003;111(5 Pt 1):e601-e603.
43. Engelbert RH, Uiterwaal CS, Gulmans VA, Pruijis HE, Helders PJ. Osteogenesis imperfecta: profiles of motor development as assessed by a postal questionnaire. *Eur J Pediatr*. Aug 2000;159(8):615-620.

29 REHABILITATION IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

The congenital weakness of bones, ligaments and muscles in osteogenesis imperfecta (OI) leads to delayed development during infancy and childhood, and depending on the severity of the disorder, can later result in varying degrees of skeletal deformities and functional limitations.[1] As in other congenital disorders, the attainment of independence in children with OI is more an issue of habilitation during development rather than rehabilitation, and the treatment strategies for these children in the early stages of life focus on achieving developmental skills required for active mobility. In the past, the emphasis of management was on protecting the child from potential trauma, usually involving isolation and immobilization. Such measures, however, result in further weakness of the bones, increased risk of fractures, and equally importantly, limited social interaction with peers and lack of training for independence in self-care and daily activities. These are unfortunate consequences given the fact that most individuals with OI have normal intelligence, and with training and education are capable of independent living and active social participation.[2,3] Recent consensus on rehabilitative management for individuals with OI is to allow as much active movement as possible to enhance musculoskeletal strength and cardiovascular fitness,[4,5] in addition to measures to maintain alignment of the extremities and spine.[6] Rehabilitative strategies vary depending on the degree of motor development of the child, clinical severity of OI, and functional ability, and thus must be highly specified for each individual.[7,8] Problems associated with OI include osteopenia/osteoporosis and fractures; skeletal deformities resulting from recurrent fractures, abnormal bowing of long bones, and joint contractures; ligament hyperlaxity and joint instability; limited gait and mobility; cardiovascular and pulmonary insufficiencies; and neurologic problems such as hearing loss and basilar impression.[1,9] The goals

of rehabilitation are to address these problems, to increase strength, and to maximize function in order to attain independence in life situations, including self-care, locomotion, social participation, education and work. A multidisciplinary approach of care for the individual with OI involves pediatricians, orthopedic surgeons, physiatrists, physical, occupational and recreational therapists, orthotists, psychologists, and social workers, and all of whom play an important role in the ongoing rehabilitation. This chapter presents general guidelines of rehabilitation for the child with OI, with special attention to positioning and handling, weight-bearing and mobility, exercise, and orthotics and assistive devices. A brief review of rehabilitation for the adult with OI is also presented.

POSITIONING AND HANDLING

Although bones are most fragile in early childhood, bone strength progressively increases during maturation such that youth with OI who maintain good skeletal alignment throughout childhood are able to achieve better overall functioning.[2] Thus, use of proper positioning and handling techniques to prevent fractures and deformities and to maintain normal alignment is one of the most important goals in children with OI, especially during infancy and early childhood when the risk of fracture is greatest. Due to muscle weakness and developmental delay, infants and young children with OI tend to move less and are prone to positional deformities. The resting position in supine places the hips in abduction and external rotation, while sitting places the hips in flexion as well as abduction. Maintaining such postures without frequent position changes can lead to joint contractures, which can further impede normal development and functioning. Prolonged position in supine can also lead to flattened occiput, postural torticollis, spinal deformity, decreased cardiac function, and minimal visual stimulation, all of which can be prevented with careful position changes on protective surfaces. For the child who cannot roll over independently, position changes every 20-30 minutes is recommended while the child is awake to encourage active movement.[4] Surfaces that the child is placed on should be stable and softly padded, with cushions or towel rolls placed to hold the extremities and joints in alignment. In supine, care should be taken to prevent flattening of the skull and torticollis by using a gel pad and frequent changes in head position, and the arms are placed near the trunk to allow for mid-line activities. Towel rolls can be placed next to the greater trochanter and knees to prevent excessive hip abduction and external rotation, while maintaining knee alignment. Side-lying with support under the head and between the legs can help to maintain the alignment of the spine and lower extremities.[6] If the

child's pulmonary function permits and active head-lifting is possible, assuming the prone position on top of a parent's chest or with a wedge cushion under the child's chest can promote strengthening of neck and spine extensor muscles. The partial weight-bearing on arms in the prone position can also be beneficial for strengthening the bones of the upper extremity (Figure 1).[6] Additional benefits of prone-lying include prevention of hip flexion contractures and spinal deformities. Inclined sitting with head and trunk support is a transitional step towards unsupported sitting, and its semi-upright position is useful for cardiovascular conditioning as well as for providing visual stimulation for the child to increase visual perception and awareness of his or her surroundings. The ability to maintain the head upright requires adequate strength of the neck extensors, which can be enhanced in the sitting position. It is important to encourage any active movement by the child and to educate their caregivers on frequent position changes, as these not only prevent disabling joint contractures, but also promote strengthening of different muscle groups and enhance systemic functions which are essential for endurance and independent living.

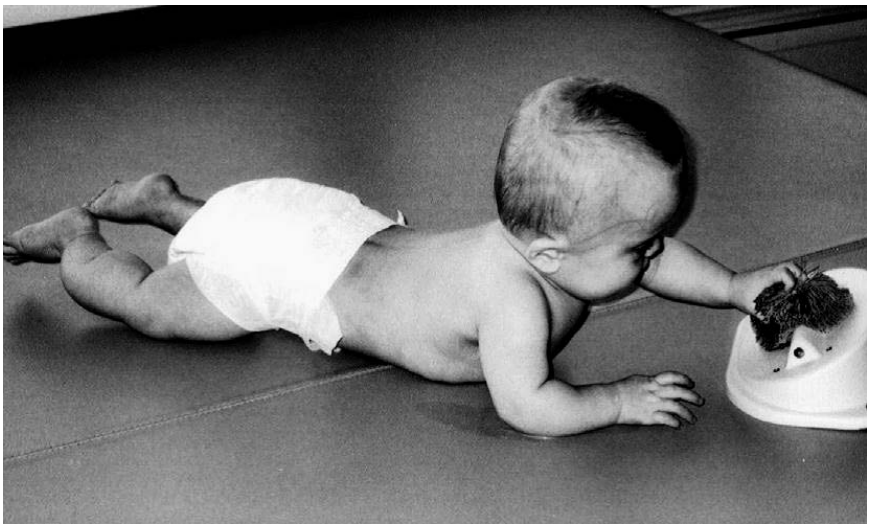

Figure 1. Prone lying promotes strengthening of neck and back muscles and weight-bearing on the upper extremities.

Handling an infant or child with OI should be initially discussed with the parents, taking into consideration their usual methods, as parents are most familiar with their child's condition. In general, handling the child should be gentle, always taking precaution not to pull, push or twist a limb, including avoidance of passive movement of the joints, trunk or neck. When handling

the child, hands should be positioned on or under the widest base on the body, taking caution to properly support the head and neck. Lifting a child is done with one open hand under the buttocks and legs, with the other hand under the shoulders, neck and head (Figure 2). The child must never be lifted from under the armpits, as this can stress the weak rib bones and unstable shoulder joints, leading to unwanted injuries. For diaper changes, one hand supports the buttocks with the legs resting on the forearm while the other hand places the diaper; pulling up the ankles in order to lift the buttocks is avoided.[10] Caution must also be taken to assure that the limbs are not placed in awkward or atypical positions that can predispose to skeletal injury.

Figure 2. Handling positions for protective holding with a wide base of support under the infant's buttocks. (A) Supporting the head and neck while the infant faces the holder. (B) Supporting the trunk while the infant faces away from the holder.

WEIGHT-BEARING AND MOBILITY

Weight-bearing in individuals with OI is important for promoting increases in bone density. The congenital bone fragility combined with delays in attaining developmental milestones, however, renders normal weight-bearing activities difficult to accomplish in infants and young children with OI. Once the child is able to maintain active sitting (either long-leg sitting on the floor, or chair sitting), weight-shifting techniques can be introduced by presenting toys in various places in space and having the child reach for it.[4]

Such weight-shifting activities promote strengthening of the truncal musculature as well as enhance balance and coordination. Increased weight-bearing can be introduced as the child learns to transition from sit to stand, then ultimately progress to active standing. The progression should be gradual in accordance to the child's overall increases in strength and confidence. To address the need for early weight-bearing in the long bones of the legs, Bleck and colleagues recommended application of custom-molded plastic orthoses which conform to the contour of the lower extremity and exerts mechanical stress to the bone by compressing the surrounding muscle mass.[11] When the child is able to, standing with plastic containment hip-knee-ankle-foot orthosis (HKAFO) with manual support or in a standing frame can be achieved for further weight-bearing. In addition to providing compressive forces to the bone and support for standing, the plastic containment lower extremity orthoses also function to maintain lower extremity alignment, which is essential for functioning. Tilt tables or supine standers with appropriate padding for protection and positioning are also useful for the younger child who has not yet developed adequate head and trunk control (Figure 3).[12] The inclination of the tilt table or stander can be gradually increased according to the child's progression in standing tolerance. The upright position in standing is beneficial for increasing bone density and for cardiovascular conditioning, and is also the starting point for walking.

Prognosis for walking was suggested to be favorable if the infant achieves developmental milestones of rolling-over before 8 months and independent sitting by 9-10 months.[13,14] However, the most important indicator of ambulation was reported to be the type of OI.[13] The majority of individuals with OI type I are community ambulators, and remain ambulatory throughout their lifetime, while those with OI types III and IV have the potential to ambulate but may have variable outcomes in adulthood.[7,15] The benefits of maintaining an upright position and weight-bearing on cardiovascular function and bone density, in addition to being an active whole-body movement, make walking the best form of exercise in the child with OI. Thus, attaining the ability to walk independently or with assistive devices is an important goal for the developing child,[7] and gait training can be integrated into the rehabilitation program even for those with more severe types of OI. Once again, it is emphasized that gait training strategies should be tailored individually for each child according to his/her functional abilities. In general, gait training begins when the child is able to sit independently and can scoot around on the buttocks, with progression to sit-

to-stand, and standing with or without support.[4] Once standing tolerance of at least 30 minutes has been achieved, walking can be initiated between parallel bars, and if needed, with HKAFOs and locked knee joint. With increasing strength and duration, training can be gradually progressed to walking with a rolling walker or forearm crutches and braces with a free knee joint. In children under the age of 2 years or those with more severe types of OI, gait training can be initiated in the pool with the water at the chest level and the use of floatation devices to maintain an upright posture. With increasing strength and function, walking can be continued in shallower depths of water, ultimately progressing to training on land.[10]

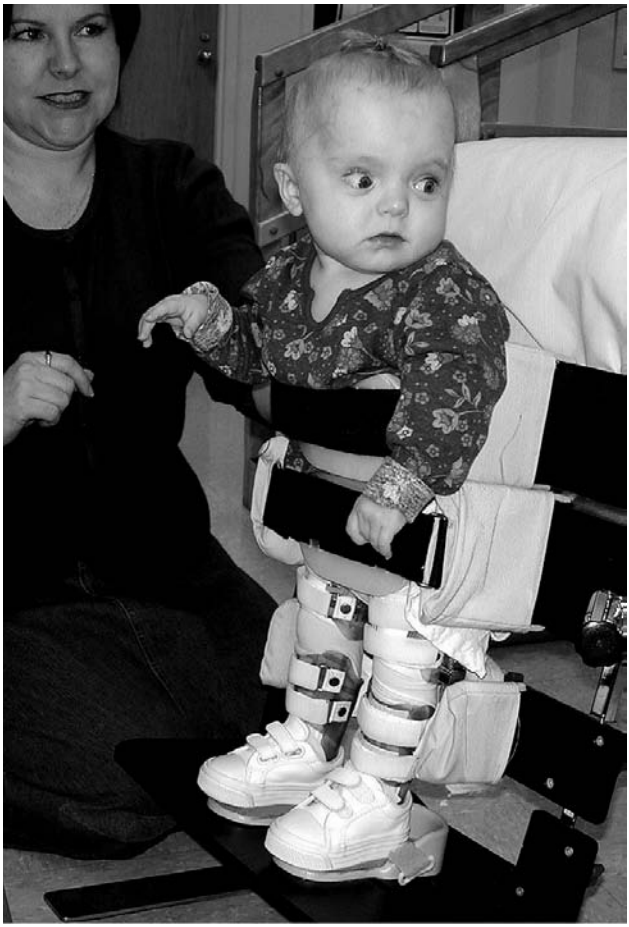

Figure 3. Standing in a supine stander with clamshell design long-leg braces.

Methods to attain mobility also include use of caster carts, modified scooter boards or tricycles with back support and protected seating for the younger

child or for those who may not be candidates for walking.[11] These devices provide independence in mobility and functional use of the legs that may otherwise not be possible. For children with adequate trunk stability and upper extremity strength, the manual wheelchair is a good modality because its use can enhance upper-body strength in addition to providing independent mobility. Manual wheelchairs with removable or low arm rests are preferred for children with OI so as to allow wheel propulsion with the upper extremity in straight alignment, rather than the bowed position that results from pushing the wheels over the arm rests.[10] Non-ambulatory children with upper extremity weakness, deformities or frequent fractures can attain mobility in power wheelchairs, with modifications such as seat elevators or power tilt to provide ease of transfers.

EXERCISE

Physical activity is important for individuals with OI as it promotes increases in bone density and cardiovascular fitness as well as the physical and psychological well-being that support independence in daily activities and social participation. While bone fragility limits activities involving physical contact or high-impact body-weight loading (e.g., football, jogging), exercises to enhance joint range of motion and muscle strength can be performed safely depending on age, functional status, and severity of OI. Recreational and play activities enhance the child's participation in their therapy, and should be always be incorporated into the therapeutic program.

Range of Motion Exercise

Bowing of the long limbs, joint malalignment, and muscle contractures contribute to reduced joint range of motion (ROM), which in turn leads to limitations in functional activities such as reaching, feeding, or donning and doffing clothes. It is important to maintain normal ROM during infancy and early childhood by allowing active movement of all extremities while taking precautions to prevent physical trauma to the body in a protected setting. Having a young child actively reach for objects in space while positioned in supine, prone, side lying and sitting can promote active motion in all ranges of the shoulder and elbow joints.[6] It is important, however, to avoid placing an object where it requires twisting of the spine to reach it. Active ROM of both upper and lower extremities can be accomplished successfully in the aquatic therapy setting with activities such as kicking and splashing in younger children, and swimming or sculling in older children.[6,16] Passive

ROM maneuvers are avoided as they may increase the risk of fractures and dislocations.

Strengthening Exercise

Muscle strengthening is beneficial as the contractile force transmitted from the muscle to the bone can provide the mechanical loading necessary to maintain bone density. In those with severe OI, however, excessive muscle forces or muscle imbalance can lead to bony deformities or fractures, and thus a delicate balance must be established between increasing muscle strength and maintaining skeletal integrity. In general, strengthening can be initiated when the child begins to reach, as this function can be used to strengthen the muscles of the upper extremities. Light-weight toys are introduced to the child in various supported positions (side-lying, supine, sitting, prone), and progressively heavier toys are given as strength increases.[6] The different positions promote strengthening of different muscle groups in the upper extremities, as well as the muscles of the neck, spine and trunk. Aquatic therapy is an excellent method of safe and effective strengthening,[16] as water provides gentle resistance along the entire length of bones, while protecting the body from traumatic joint forces and falls. As strength increases, light long-sleeved clothing can be worn in the water to add more resistance to the exercise. The strengthening program can be continued in progressively shallow depths of water, and progress to out of water exercises when all joints can move actively against gravity.

Formal exercise programs can be introduced around age two,[6] beginning with active-assisted exercises then progressing to resistive exercises for all major muscle groups of the shoulder and pelvic girdles, the abdominals, hip abductors and extensors, and knee extensors. Abdominal muscles can be strengthened with partial sit-ups with the knees bent, while hip extensors and abductors can be strengthened in prone position in bed with the leg over the edge to encourage active extension.[16] Resistance can be provided by adding small weights in 1-oz increments, but should be placed close to the joints to prevent injuries resulting from a long lever arm.[6,18] Isometric strengthening using the weight of one's own limb can be also trained for the shoulder girdle muscles and hip and knee extensors, which can be beneficial in stabilizing joints that are at risk of subluxation or dislocation due to ligamentous laxities.[5] A supervised 12-week muscle strengthening program using proper weight-training techniques and light weights up to 1kg was found to be effective in increasing muscle strength in adolescents with OI type I, but the effects wore off after the intervention period.[19] The results of

this study reflect that continuous training is warranted to maintain strength and function in youth with OI. The clinical severity and functional status in children with OI must be considered and exercises should be adjusted to the child's individual needs and goals prior to initiation of training.

Endurance Exercise

A study on cardiopulmonary fitness in adolescents with OI type I found no cardiac or pulmonary abnormalities at rest, but the VO_{2peak} and FEV_1, $MEF_{75\%}$, and FVC values were significantly reduced compared to normally developing age-matched peers.[20] From these results it can be postulated that cardiopulmonary function would be further reduced in children with OI types III and IV. The reduced cardiopulmonary fitness in OI has been attributed to muscle atrophy and the deconditioning that accompanies inactivity.[20] Decreased physical fitness is associated with fatigue, which in turn leads to exercise intolerance and limitations in daily activities. Thus, strategies to enhance aerobic fitness and exercise tolerance are an essential part of rehabilitation for children with OI. If possible, walking is encouraged as it has the multiple benefits of aerobic conditioning and weight-bearing to increase bone density. In nonambulatory children with sufficient joint motion and stability, stationary cycling or arm ergometry can enhance both aerobic capacity and muscle conditioning. Swimming and aquatic therapy are the most safe and effective methods to attain cardiopulmonary fitness as they require continuous whole body movements as well as induce the deep breathing techniques which enhance chest expansion.[6,16] Aerobic exercise programs should be continued regularly in order to maintain its effects and to further promote improved physical fitness in children with OI throughout their development.

Pulmonary Rehabilitation

The spinal manifestations of OI range from flattening of vertebral bodies which lead to short stature and kyphosis in children with OI type I to severe kyphoscoliosis in OI types III and IV.[21] The spinal deformities are usually progressive, and can lead to reduced ventilatory function as well as recurrent pulmonary infections. Thus, pulmonary rehabilitation should be an integral part of care in OI in order to enhance lung function for daily activities as well as to prevent potentially harmful respiratory complications. The structural deformities of the spine and ribs limit thoracic movement and contribute to a restrictive type of ventilatory dysfunction with reduced vital capacity.[9,22] Although restrictive dysfunction mainly affects inspiratory function,

rehabilitative measures should include modalities to address both inspiratory and expiratory function, as expiratory actions such as coughing are required for removal of secretions during respiratory infections. Inspiratory techniques such as diaphragmatic or deep breathing can be educated and performed safely to increase vital capacity, while activities such as blowing bubbles or pinwheels are effective methods of expiratory training.[23] If possible, strengthening the extra-thoracic respiratory muscles such as the upper trapezius and sternocleidomastoid muscles for inspiration, and the abdominal muscles for expiration, should also be part of pulmonary rehabilitation to enhance lung function.[23,24]

ORTHOTICS AND ASSISTIVE DEVICES

Orthoses

The goals of orthotics in OI are to prevent deformities and maintain alignment, to protect unstable joints, and to enhance function. The materials used for orthoses used in children with OI should be light-weight to prevent fatigue and allow heat dissipation in order to accommodate for the heat intolerance in those with the more severe types of OI. For the toddler who is able to pull-to-stand, clamshell-type long-leg braces with pelvic band (hip-knee-ankle foot orthosis, HKAFO) and drop-ring locks in the hip and knee joints provide the stability required for standing and ambulation with or without a walker or forearm crutches (Figure 4).[11,17] As children attain increased strength in the proximal muscles, orthoses can be transitioned to lower levels such as the knee-ankle-foot orthosis (KAFO) or ankle-foot orthosis (AFO).[12] The plastic clamshell-type or bivalve design of the long leg braces (Figure 5) are also favored over prolonged immobilization with plaster casts postoperatively, and are utilized to promote early weight-bearing and mobilization in postoperative rehabilitation.[9,11] Many children with OI have ligamentous laxities in the foot leading to planovalgus deformities,[7] which can ultimately result in pain and abnormal bone stress during ambulation and reduced overall functioning. In-shoe inserts that support the midfoot arches and add depth to the heel cup, such as the supramalleolar orthosis (SMO) or the University of California Biomechanics Laboratory (UCBL) orthosis, are useful to assist gait and prevent further planovalgus deformity.[12] Custom made orthopedic shoes are usually not required in OI unless there is significant leg length discrepancy, in which case sole thickness can be modified to correct the asymmetry and provide stability during gait. Light-weight plastic orthoses that conform to the shape of the extremity can be used in the arms and forearms to prevent further

deformity as well as to encourage functional activities. Cock-up wrist braces or functional wrist orthoses can be used to hold up the wrist in dorsiflexion and assist in hand activities for those with lax ligaments in the wrist and fingers.[12] Contoured seating inserts for wheelchairs or other mobility devices can be applied to maintain spinal and hip joint alignment and provide stability in sitting.[6]

Figure 4. Orthotics for OI: walking in hip-knee-ankle-foot-orthosis (HKAFO) with a push toy.

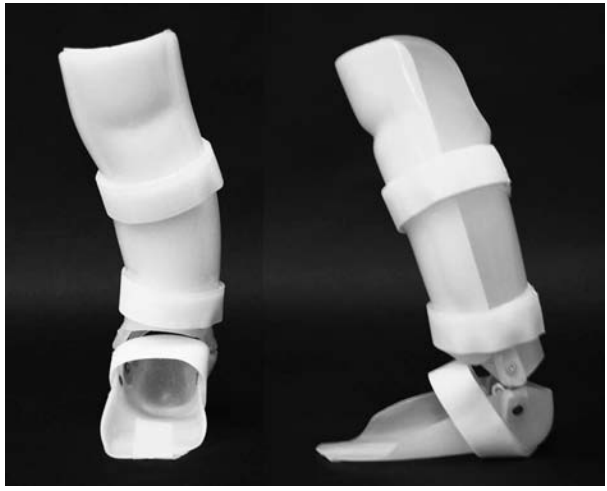

Figure 5. Orthotics for OI: plastic bivalve (clamshell) ankle foot orthosis (AFO).

Assistive Devices for Mobility

Hand-held mobility devices such as walkers, canes and crutches provide stability and assistance during gait. Most children start ambulation using anterior or forward rolling walkers, which have wheels on the front legs and rubber tips on the back so as to allow forward progression but limit backward movement. Forward walkers are placed in front of the child and provide anterior stability during forward progression, but may lead to unwanted flexion of the trunk. Reverse walkers used with the child standing within the frame of the walker have the advantage of maintaining the child in the upright position, but has less forward stability. Reverse walkers can have the option of adding a seat for the child to rest during prolonged periods of walking. Four-wheeled rolling walkers are options for the older child or those who require ease in maneuverability.[12]

With increases in strength and endurance of ambulation, children may transition to crutches or canes as these provide postural and dynamic stability without the bulk of the walker. Axillary crutches, however, should be avoided as its use can lead to unwanted stress in the axilla and malalignment of the shoulders and back. Lofstrand forearm crutches may be a better alternative. Quadripod canes can be used unilaterally or bilaterally, depending on the child's functional status. Quad canes provide a wider base of support and in some children, may be preferable to the forearm crutches as children are less likely to lean forward on the canes as they are with crutches.[12] The handles of crutches and canes should be appropriately placed

to allow functional grip and good alignment of the arms, and the rubber tips of all crutches and canes should be examined and replaced regularly to prevent slippage and ensure stability of the devices.

Assistive Devices of Daily Activities

The short stature and deformed extremities in children with OI lead to functional limitations in performing daily self-care activities and functions such as transfers to bed, chair, toilet, and other apparatus. Reaching for objects, getting in and out of vehicles or furniture, and toileting are examples of daily activities that can potentially result in falls or excessive twisting of the limbs. Steps or inclined wedges with handrails and transfer benches can be placed near the apparatus or furniture to allow independent access, and adaptive toilet seats, bath chairs, and grab bars can be placed for stability in toileting and bathing activities.[10] Various reach-aids, dressing hooks and long-handled devices can be readily made or are available for purchase to allow safe reaching, toileting, grooming, and dressing activities.[10] Consultation with an occupational therapist can help determine the type of assistive device to address the child's needs as well as train both the child and parent in the appropriate usage of the devices to attain independence in daily activities.

REHABILITATION FOR ADULTS WITH OI

The frequency of fractures in individuals with OI is reported to decrease upon reaching puberty as the strength of bone increases with skeletal maturation.[2,7] However, the innate fragility of the bone matrix renders the skeleton of adults with even milder types of OI to be at increased risk of fractures compared to the normal population.[25] Age-related musculoskeletal conditions or overuse injuries such as arthritis or joint instability may develop, leading to pain and stiffness that can limit functional activity.[26] Thus, the same precautions taken in the pediatric OI population should be applied and appropriate rehabilitative measures should be adapted for the adult with OI so as to enable independence in self-care, education, employment and social participation. Maintenance of physical fitness through individually tailored aerobic and strengthening exercise programs such as cycling or swimming should be a mainstay of rehabilitation. Those with progressive spine and rib cage deformities are encouraged to continue their pulmonary rehabilitation program and consult regularly with an experienced pulmonologist. Assistive devices for mobility and activities of daily living should be used as needed, and in the postoperative setting early

mobilization and rehabilitation is recommended as soon as it is determined safe.

Pain management in the adult with OI is an important issue to address in light of the potential for increased frequency of musculoskeletal conditions, including vertebral fractures, ligament and tendon ruptures, and arthritis.[26] Orthoses for joint protection, physical modalities, and soft tissue mobilization techniques[18] can be used for pain control, whereas some non-steroidal anti-inflammatory agents or COX-inhibitors should be used with caution or avoided as these agents have been associated with impaired bone healing.[26-28]

CONCLUSION

Individuals with OI have the potential to achieve independence in all aspects of life,[2,3] and accordingly, this is the main goal of rehabilitation for OI. Rehabilitative care for the child with OI begins with protective positioning and early intervention to promote the motor development needed for active functioning and mobility. Therapeutic strategies are specified for each child according to his/her developmental progress and severity of OI, and should be implemented with recreational and play activities for consistent and active participation. As the therapeutic effects have been reported to wear off after discontinuation of therapy,[19] exercises to maintain physical fitness such as swimming should be continued throughout life. In addition to enhancing function, rehabilitation during the transition period from adolescence to adulthood should focus on ensuring that individuals with OI have a clear understanding of their own physical condition. This will enable them to give appropriate instructions to their caregivers and to seek out appropriate healthcare providers.[29] Maintaining an active lifestyle from childhood throughout adulthood is encouraged in order to enhance the physical and psychological well-being, and continued rehabilitative measures should focus on overall functioning and social participation of the individual.

ABBREVIATIONS

AFO	Ankle-foot orthosis
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HKAFO	Hip-knee-ankle-foot orthosis
$MEF_{75\%}$	Maximum expiratory flow rate at 75% of vital capacity
VO_{2peak}	Maximum oxygen consumption

REFERENCES

1. Sillence D. Osteogenesis imperfecta: an expanding panorama of variants. *Clin Orthop Relat Res* 1981; 159: 11-25.
2. Albright JA. Management overview of osteogenesis imperfecta. *Clin Orthop Relat Res* 1981; 159: 80-87.
3. Wekre LL, Frøslie KF, Haugen L, Falch JA. A population-based study of demographical variables and ability to perform activities of daily living in adults with osteogenesis imperfecta. *Disabil Rehabil* 2010; 32: 579-587.
4. Cintas HL. Strategies for infants and young children: early intervention to enhance performance and minimize impairment. In Cintas HL and Gerber LH (eds): *Children with osteogenesis imperfecta: strategies to enhance performance.* Gaithesburg, Osteogenesis Imperfecta Foundation, Inc, 2005, pp 9-48.
5. Cintas HL. Strategies for children: improving strength and endurance while promoting optimal alignment and joint mobility. In Cintas HL and Gerber LH (eds): *Children with osteogenesis imperfecta: strategies to enhance performance*. Gaithesburg, Osteogenesis Imperfecta Foundation, Inc, 2005, pp 49-82 .
6. Binder H, Hawks L, Graybill G, Gerber NL, Weintrob JC. Osteogenesis imperfecta: rehabilitation approach with infants and young children. *Arch Phys Med Rehabil* 1984; 65: 537-541.
7. Sillence DO, Morley K, Ault JE. Clinical management of osteogenesis imperfecta. *Connect Tissue Res* 1995; 31: S15-21.
8. Engelbert RHH, Pruijs HEH, Beemer FA, Helders PJM. Osteogenesis imperfecta in childhood: treatment strategies. *Arch Phys Med Rehabil* 1998; 79: 1590-1594.
9. Kocher MS, Shapiro F. Osteogenesis impefecta. *J Am Acad Orthop Surg* 1998; 6: 225-236
10. King MM. Personal care for lifelong independence. In Dollar EP (ed): *Growing up with OI: a guide for families and caregivers*. Gaithersburg, Osteogenesis Imperfecta Foundation Inc, 2001, pp 87-130.
11. Bleck EE. Nonoperative treatment of osteogenesis imperfecta: orthotic and mobility management. *Clin Orthop Relat Res* 1981; 159: 111-122.
12. Ruck-Gibis J, Monpetit KM. Devices and equipment: their role in facilitating performance while enhancing safety and engaging children. In Cintas HL and Gerber LH (eds): *Children with osteogenesis imperfecta: strategies to enhance performance*. Gaithesburg, Osteogenesis Imperfecta Foundation, Inc, 2005, pp 161-194.
13. Engelbert RHH, Uiterwaal CSPM, Gulmans VAM, Pruijs H, Helders PJM. Osteogenesis imperfecta in childhood: prognosis for walking. *J Pediatr* 2000; 137: 397-402.
14. Daly K, Wisbeach A, Sanpera I Jr, Fixsen JA. The prognosis for walking in osteogenesis imperfecta. *J Bone Joint Surg Br* 1996; 78: 477-480.
15. Gerber LH, Binder H, Berry R, Siegel KL, Kim H, Weintrob J et al. Effects of withdrawal of bracing in matched pairs of children with osteogenesis imperfercta. *Arch Phys Med Rehabil* 1998; 79: 46-51.
16. Cintas HL. Aquatics. In Cintas HL and Gerber LH (eds): *Children with osteogenesis imperfecta: strategies to enhance performance.* Gaithesburg, Osteogenesis Imperfecta Foundation, Inc, 2005, pp 101-121.
17. Gerber LH, Binder H, Weintrob J, Grange DK, Shapiro J, Fromherz W et al. Rehabilitation of children and infants with osteogenesis imperfecta: a program for ambulation. *Clin Orthop Relat Res* 1990; 251: 254-262.

18. Binder H, Conway A, Gerber LH. Rehabilitation approaches to children with osteogenesis imperfecta: a ten-year experience. *Arch Phys Med Rehabil* 1993; 74: 386-390.
19. Van Brussel M, Takken T, Uiterwaal CSPM, Pruijs HJ, Van der Net J, Helders PJM et al. Physical training in children with osteogenesis imperfecta. *J Pediatr* 2008; 152: 111-116.
20. Takken T, Terlingen HC, Helders PJM, Pruijs H, Van der Ent CK, Engelbert RHH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. *J Pediatr* 2004; 145: 813-818.
21. Engelbert RH, Uiterwaal CS, van der Hulst A, Witjes B, Helders PJ, Pruijs HE. Scoliosis in children with osteogenesis imperfecta: influence of severity of disease and age of reaching motor milestones. *Eur Spine J* 2003; 12: 130-134.
22. Widmann RF, Bitan FD, Laplaza FJ, Burke SW, DiMaio MF, Schneider R. Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. *Spine* 1999; 24: 1673-1678.
23. Bach JR: Rehabilitation of the patient with respiratory dysfunction. In: DeLisa JA ed. Physical Medicine and Rehabilitation, 4th ed, Philadelphia: Lippincott Williams & Wilkins, 2005, 1843-1866.
24. Donner CF, Ambrosino N, Goldstein RS: Pulmonary Rehabilitation, 1st ed, London: Hodder Arnold, 2005.
25. Wekre LL, Eriksen EF, Falch JA. Bone mass, bone markers, and prevalence of fractures in adults with osteogenesis imperfecta. *Arch Osteoporos* 2011; 6: 31-38.
26. McKiernan FE. Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. *Osteoporos Int* 2005; 16: 1698-1702.
27. Gerstenfeld LC, Einhorn TA. COX inhibitors and their effects on bone healing. *Expert Opin Drug Saf* 2004; 3: 131-136.
28. Dimmen S. Effects of Cox inhibitors on bone and tendon healing. *Acta Orthop* Suppl. 2011; 82: 1-22.
29. Shapiro JR, Germain-Lee EL. Osteogenesis imperfecta: effecting the transition from adolescent to adult medical care. *J Musculoskelet Neuronal Interact* 2012; 12: 24-27.

30 POSITIONING AND MOBILITY IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Children with osteogenesis imperfecta (OI) have all of the same needs and interests as other children, yet their participation in daily activities may be limited or constrained by the fragility of their bones. According to Engelberts et al., osteogenesis imperfecta is a heterogeneous group of conditions due to one of several genetic defects, which produces either a reduced quantity or an abnormality of type-I collagen and affects much more than just bone.[1] The most obvious result is an increased tendency to sustain fractures, which appears to be related to the severity of the disease as judged by the degree of growth inhibition, other deformities such as scoliosis and the number of fractures. Beyond that, there may be obstacles to normal growth and development that also face these children and their families. Depending on the severity of the disease, motor development, joint range of motion, muscle strength, and functional ability may also be limited. Apart from improving joint range of motion and muscle strength, treatment strategies should focus on the improvement of functional ability, the adoption of compensatory strategies and improved independence.[1]

The Guide to Physical Therapist Practice suggests that goals of therapy should focus on the treatment of impairments (e.g. strength, endurance, or range of motion) but anticipated outcomes of intervention should include minimization of functional and activity limitations, with optimization of health status, prevention of disability in daily life and consumer satisfaction.[2] Treatment is often directed toward preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and

muscle strength. Care of fractures, extensive surgical intervention and dental procedures, and ongoing therapies are often a regular part of these children's lives. Yet deficits in positioning and mobility associated with OI may result in reductions of activity levels, participation of activities of daily living and functional independence.[3]

Because physical impairment can range from mild flat feet in children with type I OI to severe multiple fractures in infants with type IV OI, challenges in mobility can be perceived as miniscule in some cases to monumental in others. According to Graf et al, deficits in mobility can range from mild gait deficits in children with type I OI to complete dependency requiring custom seating components integrated into a power mobility device.[4] While the healthcare and medical equipment community may offer a number of potential solutions to these challenges, there are often large gaps in the provision of care and delivery of adaptive equipment. Having a keen eye and a creative mind can have an enormous positive impact on solving many of the problems that face these children and their families. Many of these great ideas have been created by the intuitive minds of parents and caregivers; the Internet is also a good resource of innovative ideas. A collaborative effort between therapists and assistive technology professionals with pediatric experience is essential to bring these ideas into fruition. The following chapter will identify impairments unique to patients with OI that impact positioning and mobility. Examples of high tech and low tech adaptive equipment intended to maximize the functional independence of children and young adults with OI will be presented. Additionally, ideas and equipment solutions that have been developed, recommended, trialed and utilized at Shriners Hospitals for Children - Chicago over the past 20 years will also be discussed.

POSITIONING

The first gross motor skill infants usually acquire is to lift their heads and shoulders before they can sit up, which, in turn, precedes standing and walking.[5] Lifting the head is usually followed by head control. Although infants are born with virtually no head or neck control, most can lift their head to a 45-degree angle by the age of four to six weeks. They can lift both their head and chest from a prone position at an average age of eight weeks. Most infants can turn their heads to both sides while lying on their tummy within 16 to 20 weeks and lift their heads while lying on their backs within 24 to 28 weeks. By about 9 to 10 months, most infants can sit up unassisted for substantial periods of time with both hands free for playing. One of the

major tasks in gross motor development is locomotion, the ability to move from one place to another. Infants progress gradually from rolling (8 to 10 weeks) to creeping on their stomachs and dragging their legs behind them (6 to 9 months) to actual crawling (7 to 12 months). This process may all be delayed or limited by the severity of the OI.

While infants are learning these temporary means of locomotion, they are gradually becoming able to support increasing amounts of weight on their lower extremities while in a standing position. In the second half-year of life, babies begin pulling themselves up on furniture and other stationary objects. By the ages of 28 to 54 weeks, on average, they begin navigating a room in an upright position by holding on to the furniture to keep their balance. Eventually, babies are able to walk while holding on to an adult with both hands and then progress to holding only one hand. They usually take their first uncertain steps alone between the ages of 9 and 15 months and are competent walkers by the age of 12 to 18 months.[5] For children with OI, this timetable is often delayed by pain, a tendency to fracture, bony deformities or contractures and in some cases, some of these milestones may be modified or skipped altogether.

Physical and occupational therapists can help children with OI to maximize their strength and overcome functional limitations by teaching them and their families about protective handling to avoid injuries. This includes providing protective positioning for activities, introducing movement to strengthen muscles and develop motor skills, and perhaps implementing appropriate mobility devices to increase independence and access to their environment. When working with an individual who has OI, it is most important to focus on his or her particular abilities, strengths, and weaknesses, rather than on the particular type of OI he or she has.[6] The long-term goal for people with OI is independence in all life functions (e.g., self-care, locomotion, recreation, social interaction, education, and work). This may include adaptive devices as needed to achieve this goal. In the case of an individual with severe OI, the ability to direct their own care is of utmost importance.

According to the Osteogenesis Imperfecta Foundation, a key method for helping a person with OI maximize their strength and function is to encourage them to adopt various positions throughout the day, or in the case of an infant or young child encourage parents and other caregivers to place the child into a number of different positions.[6] Positional changes not only

strengthen different muscle groups, but also help prevent contractures and deformities that can limit mobility and increase pain. It is important to keep the hips and spine as straight as possible; prevent flattening of the back of the head from prolonged lying in a supine position; and promote head turning in both directions during waking hours. In many cases, everyday objects can be used to make positioning easier and safer. For example, towel rolls, blankets and padding can be used to encourage upright posture and position the hips to avoid "frog-leg" positioning in a stroller, car seat or wheelchair. An infant or child can be introduced to the prone position by lying on the parent's chest, a partially inflated beach ball, pillow or a foam wedge.[6] To that end, the following text will discuss, in greater detail, salient points about positioning and mobility specifically: lying, crawling, sitting, standing, walking, manual and power mobility. Also, several positioning ideas will be discussed for the families and practitioners caring for these individuals. An introduction to positioning including some guidelines and goals for clinicians surrounding optimizing alignment, accommodating/supporting bony deformity or weight bearing restrictions, pressure distribution, and developmental appropriateness of the position will also be provided. Discussions of each position will be guided by the following questions: Why is the position important for a child's development, function, activity and participation? Is there an optimal age where attaining the position is integral for development? How do the impairments associated with OI create a barrier when assuming and maintaining the position? What adaptations can be implemented to accommodate for the impairments associated with OI?

Lying

The lying position is important for a child's development, function, activity and participation.[7,8] Lying serves as the foundation of a child developing floor mobility and establishing spatial awareness. Typically, developing babies independently assume a number of positions beginning supine on their backs and move to side lying and prone on their tummies as they grow. In the case of a child with OI with a history of fragility, fractures and bony deformities, these positions may not be easily achievable or assumable. By determining the unique needs of a particular child, one can begin the process of providing a number of positions to the infant to encourage alternatives to lying supine on his/her back in one position for a prolonged period of time. It is not certain if there is an optimal age where attaining these various positions is integral for development. All babies start off in the supine lying position; it is the first step in the developmental sequence. The process of

providing a number of positions to encourage alternatives to lying in one position for a prolonged period of time can prevent joint deformities and contractures, encourage active range of motion and assist with visual exploration of the infant's environment. Prone positioning in the normally developing infant provides head & neck extension accompanied by upper trunk extension as the three month old lifts and turns his/her head.[9] In children with OI, this process may once again be limited. Impairments associated with OI can create a barrier in getting into and maintaining the prone position. Babies with OI may have a difficult time getting comfortable in the supine position due to deformity or fragility, as well as an inability to move into and out of the position independently due to weakness or pain. Limited mobility can lead to flattening of the back of the head and limit range of motion of the upper and lower extremities. A variety of adaptations can be implemented to accommodate for the impairments associated with OI. Typically developing children require a variety of tactile stimulation, physical touch, handling and positioning in order to access and explore their environment, develop strength, balance, coordination and curiosity. Children with OI require these same experiences, yet the risk of fracture can often be an intimidating obstacle to many parents and caregivers. There are a number of simple products and devices that can help with safe handling and positioning. Starting with an infant car seat, one can easily position the newborn in most cases. If there are any bony deformities or contractures present, some simple modifications can be accomplished utilizing items such as towel rolls, pillow cases, swim noodles, pipe insulation, dishwashing sponges, sheets, and even Playdough or sand in a Ziploc bag. Often times adding some simple additional support can make a world of difference for promoting and improving a child's positional needs, support and access to their environment. In many cases, positioning a child in side lying can be as easy as using a towel roll for side lying or can be as complex as using a supine stander.

For positioning on the floor, having a soft blanket or an exercise/yoga mat may provide more than enough padding. There are also a number of baby play mats available on the market that provide a padded play/positioning surface available from Fisher Price (Mattel, Inc., El Segundo, CA), Baby Einstein (Kids II ® Inc., Atlanta, GA) and Infantino (Infantino LLC, San Diego, CA) to name a few. These products may include visual, auditory and tactile stimulation in addition to a padded play surface. Boppy (The Boppy Company, LLC, Golden, CO), Bummzie (Leachco, Inc., Ada, Oklahoma), Bright Starts (Kids II ® Inc., Atlanta, GA) and Sassy (Sassy, Inc., Kentwood, MI) offer

prone and side lying products that can provide an additional number of alternative positioning opportunities other than supine. Moving up to a more medical or therapeutic type of product, one can find the Leckey Squiggles Early Activity Seat (Lecky, Lisburn, Northern Ireland) (Figure 1) and the Leckey Early Sitting System (Figure 2). Each of these systems has small pads, straps and bolsters that will provide unlimited possibilities for safe, supported floor positioning and activity.

Figure 1. Leckey Squiggles Early Activity.

Figure 2. Leckey Early Sitting System.

The Tumble Forms Grasshopper (Patterson Medical Holdings, Inc., Warrenville, IL) is a larger modular positioning system that can also be used for positioning of the larger infant and toddler all the way up through childhood. The Grasshopper has seventeen different positioning modules, which allow positioning of the child in an infinite number of ways. There is a

padded base with locking casters makes the positioning system easy to move with the child in it while maintaining an adaptive, supportive position. Attaching a Tumble Forms 2 (Patterson Medical Holdings, Inc., Warrenville, IL) log to the Grasshopper base will transform it into an active therapeutic system for vestibular stimulation activities. Tumble Forms also makes a number of wedges, bolsters and a floor sitter that can also be used for floor positioning. In all cases, one must take care to have knowledge of the child's medical and fracture history as well as remain extra cautious when handling and positioning a child with OI for the first time around. Working with a trained physical or occupational therapist to provide the most optimal positions for a child's capabilities and restrictions is beneficial for any family.

Sleep positioning can often be a challenge for some children due to bony deformities, contractures or healing fractures that make simple positioning difficult. If a simple towel roll, pillow, and wedge are not working, one may consider a mattress overlay made of foam rubber or a sponge egg crate type. One must be cautious that the sleep surface is not too soft for the infant child and may reserve these softer surfaces for toddlers. For more advanced sleep needs, one may consider the Leckey Sleepform System (Lecky, Lisburn, Northern Ireland) as one product specifically designed for children with special sleep needs. According to the manufacturer, this sleep system was created based on clinical research into the requirements of individuals during their sleep along with the needs of their families and caregivers.[10] This system consists of a soft mattress under pad, called the Sleepform Mattress. This mattress is able to provide positive support to the individual in order to maintain a comfortable and desirable lying posture, either in supine, side lying or prone lying. The Sleepform Mattress is moldable and can easily be molded to the shape of the child's body providing contoured support, accommodating any deformity, and promoting symmetrical, uniform pressure distribution for the body and extremities. The mattress will retain its shape once it is individually "molded" to the child. Caregivers may choose to mold the bag each evening while others prefer to set it and leave it unchanged.

Based on an evaluation of current sudden infant death syndrome (SIDS) data, the American Academy of Pediatrics recommends that healthy infants, when being put down to sleep, be placed on their backs. Despite common beliefs, there is no evidence that choking is more frequent among infants lying on their backs (the supine position) when compared to other positions, nor is there evidence that sleeping on the back is harmful to healthy babies. In some

circumstances, there may be good reasons for placing certain infants on their stomachs for sleep but you should always discuss your individual circumstances with your pediatrician. Prone positioning may be reserved for waking hours. Since 1992, when the American Academy of Pediatrics began recommending the supine sleep position the annual SIDS rate has declined more than 50 percent.[11]

Crawling

The crawling position is important for development, function, activity and participation in one's environment. Crawling is often, but not always, part of a child's typical developmental milestones. It helps the child develop their ability to bear weight, develop joint articulations, introduce vestibular input, develop a sense of balance and coordination as well as development of muscular strength in the head, neck and trunk. Most babies learn to crawl between the ages of 6 and 10 months. Yet the range of crawling may extend into adolescence in some children while other children never crawl at all.

Crawling may be part of a child's physical repertoire but not in all cases. Many children skip this step in the process of development. Research has not identified absolute benefits on either side of this developmental step. For a child with severe fragility and contractures, this step may not be safely possible or even "try-able". Children with OI who are fragile or have a longstanding history of fractures may be unable to assume a prone or four-point position. Generalized weakness or joint contractures may prevent the child from actually moving once they are in a four-point position. Once in the position, they may get stuck and unable to move. There are a number of devices available which can support the child in a 4-point crawling position. Something as simple as a towel roll, a parent leg or thigh, or a swim noodle can be a valuable support for a child in the prone position to unweight the trunk and free up movement of the extremities. More advanced items may include a pillow or foam wedge. We have had some success with creating a homemade scooter board or padding a sibling's skateboard. This will allow for additional prone support, unloading the trunk and allowing for ease of mobility of the child's extremities. The Creepster Crawler (RedBarn Enterprises, Inc, Phoenix, AZ) (Figure 3) is an off the shelf product which can also provide crawling assistance for children. The Creepster Crawler has a seven-point harness to provide additional support for the head, arms and trunk and can free up the caregiver or therapists' hands to assist with the crawling process. Depending on the needs of the child, one may choose to use some but not all of the support harnesses. A number of other "crawler"

devices may also be able to assist children with OI to crawl. One of these products is the traditional Turtle T-Stool (Patterson Medical Holdings, Inc., Warrenville, IL). The T-stool has an adjustable/detachable height leg which, when detached, allows the T-Stool to function as a crawler. The T-Stool is latex free, height adjustable and also doubles as a scooter. The Kaye Scoot About (Kaye Products, Inc., Hillsborough, NC) (Figure 4) is a seat that is adjustable in height; the child can be positioned with the appropriate amount of hip and knee flexion for movement. In addition, this scooter makes a comfortable, stable therapy stool when a parent or therapist is assisting ambulation. Lastly, the Adjustable Supportive Crawler (Patterson Medical Holdings, Inc., Warrenville, IL) aids a child in exploring their surrounding environment and helps to develop basic crawling skills. The supporting surface is made of a soft waterproof vinyl sling, which tilts and supports the trunk to accommodate body movement.

Figure 3. Creepster Crawler.

Figure 4. Kaye Scoot About. *Photo courtesy of Kaye Products, Inc..*

Sitting

Sitting provides a horizontal view of the world while working on static and dynamic postural stability. It helps children develop upright balance, vestibular responses, along with development of normal spinal curves. Children typically begin sitting independently between 7 to 9 months. Once again, certain types of OI, which have significant fragility with a history of fractures, deformities or generalized weakness can either delay or place this milestone out of reach. If a child is able to get into a seated position, do they require additional support to maintain it? If they fall will they fracture if they are not properly supported? Do they have a tendency toward compression fractures that will predispose them to development of kyphosis or scoliosis of their spines? Something as simple as a towel roll or two for a little added support may be enough to facilitate an upright sitting position. A Boppy pillow or beanbag chair may also provide additional firm support necessary to assume and maintain a safe seated position.

There are countless sitting supports on the market ranging from those off the shelf seating systems available at large retail stores to custom molded seating and orthotic systems provided by therapists and orthotists. Many off-the-shelf seating systems will meet the needs of most users. For those needing a little additional support and padding, taking a trip to your local home improvement and construction retailer can be helpful. The trip will often provide you with enough supplemental padding and support that you may

not have in your home linen closet. Remember that a car seat can also provide supported sitting as well. Simple beanbag chairs sell for less than 25 dollars. Tumbleforms, Leckey, Rifton, Special Tomato, Jenx, Snug Seat and Theradapt all have a number of seating and positioning systems available that range from simple to very complex depending on your needs. For children with more complex sitting needs, one can create a custom molded seating system. One simple product that provides a more customized contoured sitting surface is the Versa Form Pillow (Patterson Medical Holdings, Inc., Warrenville, IL). The Versa Form pillow is a beanbag type device that will allow you to custom mold the pillow around the child and then remove the air to retain its unique shape. These are available through Patterson Medical, Adapted Mall and many other online sites. More advanced custom contoured seating is available via referrals to a rehabilitation facility, through an orthotics company or local DME vendor. This referral usually requires a physician referral and insurance precertification. These seating systems are custom formed to fit the specific, unique shape of the child. Once fit, they typically cannot be modified, grown or majorly adjusted and are often a bit expensive. They do however provide intimate, custom contact with the child and their unique shape. Included in the list of custom contoured seating devices, but not limited to, are: Invacare Contour U (Invacare Corp., Elyria, OH), Prairie Custom Seating (Prairie Seating Corporation, Skokie, IL) (Figure 5), Ottobock Shape System (Ottobock, Duderstadt, Germany) (Figure 6-7), Freedom Foam in Place & Ride Design (Freedom Designs, Inc., Simi Valley, CA).

Figure 5. Prairie Custom Seating.

Figure 6. OBSS Tru-Shape © by Ottobock.

Figure 7. OBSS Ortho-Shape © by Ottobock.

Standing

Standing promotes bone formation and strength, improves respiration, digestion and circulatory function, not to mention allowing one to view the world and one's peers eye to eye.[12] Typically developing children begin standing and weight bearing at about one year of age. Children with OI who have had multiple fractures and surgeries may have notable developmental delays with their standing. Very fragile children may not stand or bear weight at all. Pain associated with fragile long bones, fractures, as well as post-operative pain can severely limit the ability to initiate or sustain weight-bearing positions in the young child with OI. Pain, fragility and deformity are often the limiting factors. Some of this can be overcome with splinting, bracing or casting in the short term; however, not all children with OI will stand as the risks may outweigh the benefits. Standing can begin independently in some children. In others, standing may need to be "facilitated", braced and/or supported. This can include knee immobilizers or custom made orthoses such as ankle foot orthosis, knee ankle foot orthosis, hip knee ankle foot orthosis or a modified hip spica type brace. The range of necessary additional support can be as simple as supported standing from behind on the part of the parents to a very expensive, extensive standing device.

Benefits of standing include: providing weight bearing for promotion of increased bone density; stretching leg muscles to prevent them from becoming tight over time; improving functional transfers and mobility; improving function of internal organs and systems by enabling them to function more naturally for example: bowel and bladder function respiratory system; improved digestion and circulation; improving posture; preventing lower limb contractures by improving range of motion and joint flexibility; and preventing muscle atrophy.[13-15] Additional benefits include increasing self-confidence, self-esteem, self-image and overall quality of life.[16]

It has been demonstrated that immobilization of muscles and lack of weight bearing on bones causes bone demineralization and true osteoporosis. In the case of someone with OI, this can be devastating. Providing the opportunity for a developing child with special needs to stand can be a significant challenge for parents, caregivers and therapists alike. With a history of multiple lower extremity fractures, standing can be a long and winding road of bracing, standers, walkers, pool therapy and splints. For children needing just a little additional support, a good pair of shoes with an arch support may

be all that is necessary. For a child with delayed balance, bony fragility or deformity, the approach may change dramatically. The need for additional support, either externally with a device or with a splint or brace, adds some complexity to the equation. In more severe cases, surgical intervention for rodding procedures may be considered and instituted to strengthen the bones internally, which can occur at an early age. For smaller children to begin weight bearing with bracing or without, one can start with a laundry basket or a garbage can (new & clean) filled with blankets and/or pillows to provide total body support. This is a simple, inexpensive way to begin the weight bearing process. Generally, the children are placed near a coffee table or couch to provide a play surface for toys, books, or puzzles. For a more formal standing system, a number of devices are on the market. Names include Rifton, Giraffe (Snug Seat Inc., Matthews, NC) (Figure 8), EasyStand, Theradapt, and Buffalo.[17] These devices provide a number of options with regard to padding, support, strapping and hydraulics to facilitate the safe supported standing position.

Figure 8. Giraffe V2 by Snug Seat.

Walking

Walking generally begins around one year of age in children. According to Campbell, the development of a motor pattern such as walking depends on a combination of mechanical, structural, neurologic, cognitive and perceptual patterns.[8] When other factors are controlled, chronologic age is less significant than previously thought.[18] Adequate range of motion, strength, appropriate bone structure and composition, and body composition also

affect the emergence of locomotion and its refinement. These variables have significant ramifications as mechanical factors in the development of walking. Constraints in any of these mechanical variables change patterns along with the movement and muscle activity involved in motor control.[19] There are a host of gait devices available on the market, from the simplest shopping cart push toys at Toys R Us to the complex LiteGait suspension system (Mobility Research, Tempe, Arizona) (Figure 9) with a treadmill. The KidWalk Walker (Prime Engineering, Fresno. CA) may be a simpler alternative to the LiteGait suspension system. It allows for hands-free postural support, which may afford children the opportunity to explore their environment with their hands while in an upright walking position.

Bracing, as described in the standing section, may also be necessary to assure proper support while standing, walking or taking supported steps. Once again this may range from something as simple as a pair of arch supports to a more elaborate, custom made hip, knee, ankle foot orthosis. Assistive devices, including walkers, come in a variety of shapes, sizes and characteristics. Pick up walkers, rolling walkers, forward, reverse, seating, brakes and baskets are all examples and readily available. The key with any piece of equipment is to try it before you buy it if at all possible. This is not always an option in the case of durable medical equipment (DME), which is why befriending a local therapist or DME provider may be helpful. There are also a host of charities and organizations that have "loaner closets" available to local communities.

Walking may develop on an average timeline without any limitations; however, with the presence of pain, bone fragility, weakness or deformity, walking may be delayed, limited or unlikely depending on severity. According to O'Shea in Campbell, the role of adapted equipment is to promote the development and acquisition of skills that an individual lacks as a result of disease or injury.[20] With the advent of new gait devices such as the LiteGait, Rifton Pacer Gait Trainer (Rifton Equipment, Rifton, NY) (Figure 10), KidWalk suspension walker and the Airwalk treadmill, walking may become a viable option for previously non-ambulatory individuals. There is a new innovative device developed by Firefly called the UpSee (Leckey, Lisburn, UK) (Figure 11) that has been developed to promote standing and walking for children with special needs.

Figure 9. LiteGait® gait training system.

Figure 10. Rifton Pacer. Photo copyright © Rifton. Used with permission.

Figure 11. Firefly Upsee.

MOBILITY

Previous research has shown that independent mobility allows for developmental and psychosocial benefits in young children who are ambulatory or only have motor disability.[21] Some of these benefits include a positive perception of self, participation in activities and in group settings, adept spatial cognition, emotional control and capacity to face environmental stressors.[21] Children typically begin standing and walking to explore their environment around one year of age. With a diagnosis of OI, this timeline may be interrupted. The delayed ability of the child to stand and ambulate may impact their ability to interact with their environment and their cognitive and social development. Many factors come into play when assessing the development of a child including the child's cognitive status, the accessibility of their home and community environments, physical limitations and family support. Unfortunately, this lack of opportunity to move (provision) and the ensuing dependence on others for mobility may cause the child to miss periods of substantial cognitive and psychosocial growth.[22] In turn, this may lead to decreased quality of life and learned helplessness in which the child is unwilling to investigate his or her

environment privately and ultimately become unable to gain control over his or her environment independently.[23]

Manual vs. Power

If ambulation is not the primary means of mobility, it is imperative that the child be presented with other mobility alternatives. There is often debate among parents and clinicians over the optimal piece of mobility equipment to recommend or provide for a child with special needs. Unique to mobility, one must consider the child's potential ability to self-propel a manual wheelchair or wheeled mobility device. If a child has severe deformity, pain or bony fragility, self-propulsion manual mobility may not be a feasible possibility. The other option for independent mobility in children with severe OI is powered mobility. Several studies have shown that children around two years of age can learn to safely operate a powered wheelchair.[23,24] When it comes to powered mobility, there is limited evidence concerning the number of visits required for non-ambulatory young children to safely, independently operate a power wheelchair.

Funding and coverage for manual and powered mobility devices is a major consideration in today's economy. A number of insurance providers will provide for a mobility device every 5 years or so. Some insurance and funding providers have a lifetime cap on durable medical equipment. It is therefore imperative that the clinician or family prescribes the most suitable mobility device for the child, to prevent the child from having to use or not use an incorrect device until they are eligible for new funding. In the case of any type of mobility equipment, trying it out prior to buying it is often the key to success or at least one step towards providing the correct mobility device.

There are a multitude of manual and power mobility devices, but this discussion will focus on manual and power wheelchairs. An important consideration in choosing between manual and power mobility is determining the child's ability to self-propel a mobility device or the availability of a caregiver to push the wheelchair, if the child is dependent for propulsion. Once a decision is made regarding whether or not a child will need a manual or power wheelchair, several items may need to be considered. Supportive seating, growth potential, access to the wheels, weight and size of the chair, and the ability to transport the chair also need to be considered. In the case of a manual wheelchair, one must consider the weight of the chair, as a lighter chair is better for self-propulsion and accessibility to the wheels. Size and adjustability of the frame are important

considerations to fold and fit the wheelchair into a vehicle for transport. Panthera AB (Panthera AB, Spanga, Sweden) has created carbon fiber wheelchairs, such as the Panthera U2 light wheelchair, which is a lightweight alternative to heavier manual wheelchairs. Another consideration includes crash testing and durability of the chair. Lastly, one must consider the ease of getting parts and repairing the chair when the chair breaks down. So, having a maintenance record and a DME vendor to make repairs or provide a loaner in case the wheelchair breaks down are important considerations. Such considerations are much more difficult to determine when purchasing online. In addition, most insurance providers do not reimburse for purchases made on the Internet and sales are usually final. Frequently considered manufacturers of manual wheelchairs are: TiLite, Sunrise, Colours, Ki Mobility, and Invacare.

In the case of power mobility, one must consider some of the same criteria. Fit of the chair is most important. Next is the ability to safely control and drive the chair independently with the most appropriate input device, whether that is a joystick, button switch, head rim, proximity switch, head array or some other input device. Once again, durability of the chair and a good maintenance and warranty system are important, as are size and transportability. Several frequently considered power wheelchair manufacturers are: Permobil, Invacare, Sunrise & Quantum. One other consideration for powered mobility is rim assisted technology, which provides the user with the ability to self-propel with an assist from motors placed within the rims. Rim assisted technology can be swapped for regular manual hand rims and can often be the difference between independent and dependent mobility for someone with upper extremity weakness or range of motion limitations.

Mobility is important for independence and exploring the environment. Many individuals require powered mobility to provide movement in order to safely maneuver and negotiate in the community. Certain movement speeds are necessary to safely cross traffic intersections in an adequate time. Buildings that have vast space, such as grocery stores and shopping malls often are too large for persons with impaired mobility to maneuver without added fatigue. Powered wheelchairs and other vehicles aid persons with impaired mobility in these types of settings.

Safety Features in Power Wheelchairs

Powered wheelchairs are designed to adequately allow people with disabilities to maneuver throughout the community; however, there are many issues for both the family and the practitioner to consider when prescribing a powered wheelchair for children with OI. Axelson and Zollars stated that there are necessary safety features that should be observed when designing mobility devices, such as power wheelchairs, for children with OI.[25] Certain safety provisions necessary in power wheelchair design are related to protection from collisions with others, anti-tip over protection, with careful attention to stability in order to prevent unwanted movement of the child in the device. Seated and lying supports have been discussed throughout this chapter, custom molded seating could provide for a decrease in the amount of transfers needed, which could result in a decreased risk of fractures or injuries.

Uneven surfaces such as gravel and unpaved roads may cause bumps during wheelchair navigation in the form of vibrations. One important feature incorporated in power wheelchairs are suspension controls that aid in reducing shocks and vibration produced by the interaction of the ground with the wheelchair. Suspension controls work by dampening or attenuating shocks and vibration from the drive wheels that would otherwise be transferred to the frame of the wheelchair.[26] Passive suspensions are a certain type of suspensions that are not changed much once they are installed. They utilize springs and hydraulic shock absorbers in order to reduce vibration exposure.[27]

Surfaces such as wet grass, slippery sidewalks and uneven gravel provide challenges to the wheelchair user. Traction control systems are added to power wheelchairs in order to prevent slipping on slick surfaces. It improves driver safety by maximizing the friction between the ground surface and the wheelchair tires preventing the wheels from over spinning when accelerating from a dead stop.[27]

To provide more independence and exploration, certain powered wheelchairs have been developed for travel on more difficult outdoor terrain, such as grass, sand and mud. Manufacturers have created 4 x 4 powered wheelchairs in order to provide traction on unfavorable terrain. Magic Mobility (Noble Park, VIC 3174, Australia) has developed a power wheelchair to drive on sand, grass, wet ground, or slippery surfaces called the Extreme X8 4x4 power wheelchair (Figure 12-14). Magic Mobility is an

Australian company, however, Innovation in Motion (Angola, IN) is the American distributor of Magic Mobility's all terrain power wheelchairs. Action Manufacturing (Action Manufacturing, Inc., Marshall, MN) also, makes accessible all-terrain wheelchairs for sports and recreation.

Figure 12. Extreme X8 4x4 power wheelchair.

Figure 13. Extreme X8 4x4 power wheelchair.

Figure 14. Extreme X8 4x4 power wheelchair.

Stability control systems are an important safety feature added to powered wheelchairs to prevent the wheelchair from tipping over during maneuvering. Certain power wheelchairs have been developed with elaborate balance systems. Independence Technology (Johnson & Johnson Services, Inc., New Brunswick, NJ) developed the IBOT, which was recently discontinued, that allowed its users to "stand up" in the wheelchair. Many members of the power wheelchair community are actively trying to get Independence Technology to manufacture this product again.

There are innovative features in today's powered wheelchairs that provide children more versatility and independence in exploration of their environment. The Permobil K450MX (Permobil AB, Bolton, UK) (Figure 15-16) is a power wheelchair that features a powered seat to floor function using its powered high to low height setting ranging from roughly 3 inches to 5 feet 6 inches off the ground. This allows children to interact with the floor and also adjust to higher objects such as tables and furniture. The K450MX also features a powered tilt seating function and a Permolock C3 (Permobil AB, Bolton, UK) function, which locks the wheelchair to the floor of the vehicle allowing teenagers the ability to operate an automobile independently while sitting in their wheelchair.

Figure 15. Permobil K450MX.

Figure 16. Permobil K450MX.

Power Tricycles

Researchers at the University of Wyoming have been in the process of developing a power-assisted tricycle for children with OI, particularly those with type III. They have attempted to optimize safety systems in this trike by enhancing the brake system, enhancing the tip over sensors in the accelerometers when the tricycle turns corners and aid in preventing the trike from flipping backwards when maneuvering on an incline. Developers designed emergency power shutdown abilities in the trike and panic buttons in the steering wheel in order to shut down the trike in the event that unwanted buttons get stuck.[28,29]

Electric Bicycles

There are also adaptive products for safer and more efficient bicycle riding. Studies have shown that children with OI may demonstrate fatigue and reduced exercise capacity. Electric bicycles are made with battery operated DC motors attached to the wheel and offer an opportunity to aid in exercise capacitance with the help of a pedal assist system (PAS drive). A PAS drive system is designed to cause the motor to adjust to the pedal cadence of the rider. The rider can increase the speed setting on the bicycle for more power output from the motor. There are also electronic bicycles with a Twist and Go feature in which the rider can twist the throttle on the bike and it will travel pedal free using electronic power only. Top bicycle manufacturers such as Schwinn (Dorel Industries, Inc., Westmount, Quebec Canada) have designed electronic bicycles (Schwinn Tailwind). Also, electronic bike kits may be added to bicycles. Many electric bike kits can allow for an increase of up to 15 mph and 10 mph for tricycles. The Electric Bike Factory (Electric Vehicle Outfitters LLC, Fort Myers, FL) has developed a Universal Power Bike Motor Kit (Figure 17-18), which has an 18-Amp battery and allows for 15 miles of use. There is no need for a license for these bicycles in the United States, as the law requires that no electronic bike travel faster than 20 mph.

Figure 17. The Electric Bike Kit by the Electric Bike Factory.

Figure 18. The Electric Bike Kit incorporated onto a tricycle.

Powered Toy Ride On Cars & Trucks

Studies have shown that children with motor disabilities may experience emotional, social and cognitive problems due to their inability to adequately explore their environment with their peers.[30] Providing children the opportunity to explore with their friends will aid in their normal development. Scientists at the University of Delaware are actively involved in enhancing the recreational play of children with disabilities. They have developed a program entitled "GoBabyGo!" in which they take off-the-shelf ride on cars for children and redesign them for children with disabilities (Figure 19). Their senior designers, Drs. Cole Galloway, Michele Lobo and Sam Logan believed that giving children with difficulties in crawling and walking a mode of mobility that was fashionable and kid friendly would allow for an improved social interaction. The children would be able to obtain mobility with an exciting looking toy car versus a wheelchair.

The GoBabyGo! program's main mission is to provide mobility to all children, with and without disabilities. Their research goal is to determine if the toy

cars can provide the type of mobility that drives and improves socialization for children with disabilities. The scientists at the University of Delaware are attempting to normalize the social dynamics between the child and the family with their modified power wheel type toy vehicles.

Figure 19. Dr. James Cole Galloway, Lead Designer of the GoBabyGo! Program*. Photo courtesy of University of Delaware, Office of Communications and Marketing.*

Their future goal is to incorporate more electronics into the cars, such as webcams, GPS systems and sensors. They are actively recruiting research assistants and children to help with their research. The GoBabyGo! program encourages other designers to become involved as they offer some of their design manuals online at their website: http://www.udel.edu/gobabygo/. Their website also shows other researchers and designers how to bring a GoBabyGo! workshop to their respective location. For more information about the GoBabyGo! program you may contact them at udgobabygo@gmail.com.

The Internet is full of information on modifications to radio controlled and toy motorcars. One such forum is the Modified Power Wheels website http://www.modifiedpowerwheels.com. Their forum hosts developers who offer online manuals and do-it-yourself guides for parents of children with

and without disabilities. They also offer tutorials on designing personal power ride on cars for children.

Recreational Sports

Recreational play is important in normal childhood development and is important for children with disabilities. There are different activities that are available for members of the power wheelchair community including bowling and soccer. Companies such as Manufacturing Genuine Thrills, Inc. make wheelchair accessories such as the Ikan Bowler (Manufacturing Genuine Thrills, Inc., Brandon, FL) and the Power Soccer Guard (Manufacturing Genuine Thrills, Inc., Brandon, FL).

Power wheelchair bowling may occur with attachments such as the Ikan bowler or able-bodied participants can use their own hands to bowl. There are retractable bowling balls available for children who cannot place their fingers into the bowling ball holes, which provide a handle that retracts into the bowling ball when it is released. Wheelchair bowling is very popular and there are national organizations such as the American Wheelchair Bowling Association, which host national events. Bowling is a very good recreational activity for children with mobility problems.

Usually power soccer is a four-on-four event played on a regulation basketball court with a 22" soccer or physio ball. The goal zone is set up with goal posts or cones that are set 25 feet apart from each other with lines and tape placed 12 feet around to form a box. The United States Power Soccer Association has 60 teams across the country.

Wheelchair dancing is also a great exercise and social activity (Figure 20). Many adolescent and teenagers will have the desire to participate in school and community dances including the prom. There are many wheelchair dance clubs and classes nationwide. Also, there are professional wheelchair dance teams such as the Walk and Roll Dance Team who perform nationwide (Figure 21-22).

Figure 20. Walk and Roll Wheelchair Dance Team.

Figure 21. Walk and Roll Wheelchair Dance Team.

Figure 22. Walk and Roll Wheelchair Dance Team. Walk and Roll Foundation exists to provide education, inspiration, and guidance to those living with and without a different ability.

ADVICE FOR FAMILIES

Positioning and mobility equipment may be very expensive and certain items may benefit your child while others may not, therefore, when considering positioning and mobility equipment, please be sure to test and try the items out before you buy them. Also, seek out a physical therapy facility to aid you in this process, such as your local Shriners Hospital for Children. Please feel free to communicate your questions and concerns via email: tcaruso@shrinenet.org.

More Resources for Families

For more information about positioning and mobility products as well as wheelchair recreational activities, please visit the following websites:

Osteogenesis Imperfecta Foundation
804 W. Diamond Ave., Ste. 210
Gaithersburg, MD 20878
(800) 981-2663
(301) 947-0083
Fax: (301) 947-0456
www.oif.org

Shriners Hospitals for Children
https://www.shrinershospitalsforchildren.org

Rehabilitation Engineering and Assistive Technology Society of North America
http://www.resna.org/

National Registry of Rehabilitation Technology Suppliers
http://www.nrrts.org/

AbleData
Assistive technology information resource
http://www.abledata.com

Ginny Paleg PT, MPT, DScPT
http://www.paleg.com/wordpress/

Innovation in Motion, Inc.
http://www.mobility-usa.com/

GoBabyGo
https://www.udel.edu/gobabygo/

POWER BOWLING

American Wheelchair Bowling Association:
http://awba.org/awbaweb/

POWER SOCCER

The United States Power Soccer Association:
http://powersoccerusa.net/
http://www.uspsateams.org/

WHEELCHAIR DANCING

http://www.mobility-advisor.com/wheelchair-dancing.html
www.adaptivedancing.com
www.walkandrollfoundation.org

MORE SPORTS AND ACTIVITIES

American Association of Adapted Sports Programs:
http://www.mobility-advisor.com/wheelchair-sports-activities.html

We acknowledge that once a publication goes to print, it becomes immediately outdated. That being said, we hope that this chapter has sparked some interest in the provision of equipment for these children. We are happy to communicate via email and will remind the reader that a piece of adapted equipment for a child can often mean the difference between a life of limitations and a life of independence. tcaruso@shrinenet.org

ABBREVIATIONS

OI Osteogenesis imperfecta
DME Durable medical equipment

REFERENCES

1. Engelbert RH, Pruijs HE, Beemer FA, Helders PJ. Osteogenesis imperfecta in childhood: treatment strategies. *Archives of Physical Medicine and Rehabilitation.* Dec 1998;79(12):1590-1594.
2. American Physical Therapy A. *Guide to physical therapist practice.* Alexandria, Va: American Physical Therapy Association; 2001.
3. Cintas H, Gerber L., Danoff J., Strickland D. Perception of Competence in Walking and Nonwalking Children with Osteogenesis Imperfecta. *Pediatric Physical Therapy* 1998;10(4).
4. Graf A, Hassani S, Krzak J, et al. Gait characteristics and functional assessment of children with type I osteogenesis imperfecta. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Sep 2009;27(9):1182-1190.
5. Bly L. *Motor skills acquisition checklist.* San Antonio, TX: Therapy Skill Builders; 2003.
6. National IOH. Therapeutic Strategies for Osteogenesis Imperfecta: Publisher: 1001 Property Solutions LLC; 2011.
7. Bly L. *Motor skills acquisition in the first year: an illustrated guide to normal development.* Tucson, Ariz.: Therapy Skill Builders; 1994.
8. Campbell SK, Palisano, Robert J., Vander, Linden Darl W. *Physical therapy for children.* St. Louis, MO: Elsevier Saunders; 2006.
9. Bly L. *The components of normal movement during the first year of life and abnormal motor development.* Chicago, IL; Birmingham, Ala.: Neuro-Developmental Treatment Association; Pittengen and Associates; 1983.
10. *Leckey Sleepform*. www.leckey.com. Accessed May 21, 2015.
11. American Academy of Pediatrics AAP Task Force on Infant Positioning and SIDS: Positioning and SIDS. *Pediatrics.* Jun 1992;89:1120-1126.

12. Products PT. Continuing to Stand Tall. 2006; www.ptproductsonline.com/2006/10/continuing-to-stand-tall. Accessed Sepember 27, 2010.
13. Stand E. To stand or not to stand. www.easystand.com/case-studies/storyL.cfm. Accessed September 24, 2010.
14. Rehabilitation TIJo. Stand for health 2008; www.rehabpub.com/issues/articles/2008-08_02.asp. Accessed September 27 2010.
15. Advance. Rise and Conquer 2008; physical-therapy.advanceweb.com/Article/Rise-and-Conquer.aspx. Accessed September 24 2010.
16. DLF Factsheet Choosing children's mobility equipment. 2010; www.dlf.org.uk/sites/default/files/Choosing_childrens_mobility_equipment_sponsored.pdf
17. Abledata. Standing aids 1999; www.abledata.com/abledata_docs/standaid.pdf. Accessed September 24 2010.
18. Adolph K, Vereijken, B., Shrout, P. What changes in infant walking and why. *Sage Family Studies Abstracts.* 2004;26(2).
19. Stout J. Gait: development and analysis. In: Campbell SK, Vander Linden Darl W., Palisano Robert J., ed. *Physical Therapy for Children*. 4th ed. St. Louis: Mosby; 2012.
20. O'Shea RK, Shirley J. Charlson, Carole Ramsey. Assistive Technology. In: Campbell SK, Palisano Robert J., Vander Linden Darl W., ed. *Physical Therapy for Children*. 3rd ed. St. Louis, MO: Elsevier Saunders; 2006.
21. Tefft D, Guerette P, Furumasu J. Cognitive predictors of young children's readiness for powered mobility. *Developmental Medicine and Child Neurology.* Oct 1999;41(10):665-670.
22. Jones MA. MI, Hansen L. Use of power mobility for a young child with spinal muscular atrophy. *Physical Therapy.* 2003;83(3):253-262.
23. Deitz J, Swinth Y, White O. Powered mobility and preschoolers with complex developmental delays. *The American journal of occupational therapy: official publication of the American Occupational Therapy Association.* Jan-Feb 2002;56(1):86-96.
24. Furumasu J, Guerette P., Tefft D. The development of a powered wheelchair mobility program for young children. *Technology and Disability.* 1996;5(1):41-48.
25. Axelson P, Zollars JA. Presentation on assistive technologies for the seating and mobility needs of persons with osteogenesis imperfecta. *Connective Tissue Research.* 1995;31(4):S45-47.
26. Garcia-Mendez Y, Pearlman JL, Boninger ML, Cooper RA. Health risks of vibration exposure to wheelchair users in the community. *The Journal of Spinal Cord Medicine.* Jul 2013;36(4):365-375.
27. Ding D, Cooper R. A. Electric-Powered Wheelchairs. *IEEE Control Systems Magazine.* 2005;25(2):22-34.
28. Geu MJ, Tuffner FF, Madsen RO, Harman WM, Barrett SF. Safety enhancement of a specialized power assisted tricycle for a child with osteogenesis imperfecta type III. *Biomedical sciences instrumentation.* 2005;41:352-357.

29. Geu M, Madsen R, Weber E, Burnett M, Barrett S. Further safety enhancement of a specialized power assisted tricycle for a child with osteogenesis imperfecta type III and design of an adjustble hand power tricycle. *Biomedical Sciences Instrumentation.* 2006;42:102-107.
30. Church SJ, Saskatchewan School Trustees' Association Research Centre. *The student with a physical disability in the regular classroom : a handbook for the classroom teacher and school counsellor.* Regina, Sask.: Research Centre, Saskatchewan School Trustees Association; 1991.

31 QUALITY OF LIFE OUTCOME ASSESSMENT IN NON-SURGICALLY TREATED CHILDREN WITH OSTEOGENESIS IMERFECTA AND SCOLIOSIS USING THE SF36

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INTRODUCTION

Osteogenesis imperfecta (OI) is a heterogeneous group of inherited congenital connective tissue diseases responsible for varying degrees of bone fragility and ligamentous laxity attributed to a deficiency in collagen synthesis. The incidence of OI is reported as approximately 1 in 10,000;[1] and is typically classified into four clinical types (types I, IV, III, II) in order of severity according to genetics, symptoms and radiological criteria established by Sillence et al.[2] Recently, additional types of OI have been noted in literature and as many as 8 different types of OI have been described. In addition to brittle bones, OI also presents with a range of clinical characteristics including fractures and osteoporosis, bluish/grey sclera, dentinogenesis imperfecta, impaired hearing, and spinal deformities. The most prevalent spinal deformity observed in OI patients is scoliosis. The incidence of scoliosis in OI patients has been reported to vary between 39% and 90% in the literature, and higher incidences of scoliosis tend to be associated with more severe OI types.[3-6]

The etiology of scoliosis in OI is not fully understood, but studies have attributed vertebral instability and abnormal curvature seen in OI to many factors such as vertebral ligament laxity, vertebral body shape deformity, damage to vertebral growth plates, vertebral compression fractures, muscular weakness, and limb length discrepancy.[3,6,7] Furthermore, scoliotic curves in OI typically progress rapidly with age. Management of scoliosis in

children with OI is of critical importance beginning at an early age to curtail curve progression and its impact on pulmonary function and quality of life. Unfortunately, standard methods for correction and stabilization of scoliosis are quite problematic for children with OI. Bracing is often unsuccessful in correcting or managing spine curvature in children with OI. A brace can often deform the chest and ribs and it is often not tolerated by these children. On the other hand, spine fixation surgery stabilizes the spine and limits further curve progression, but is extremely risky and problematic due to bone fragility associated with OI.[8,9] To minimize risk, the key goal of surgical fixation in OI scoliosis is to fuse and instrument the spine without necessarily correcting or straightening the brittle spine.

Given the risk factors and limitations associated with managing scoliosis in OI children, some children with OI and scoliosis either opt out of surgery or are high risk candidates for surgery. This may be further inflated when we consider less resourced kids with OI scoliosis that are not afforded these options for a variety of reasons such as limited funds, limited transportation, and limited information and education about OI. As a result, many children with OI and scoliosis live with progressive curves as they develop and this impacts their quality of life in various ways.[10] At present, numerous studies have extensively explored the molecular basis of OI, but very few studies have addressed function and quality of life in individuals with OI.[11] There are few studies, however, that have thoroughly explored how different aspects of quality of life are influenced by degree of scoliosis curvature in children with OI. Since OI is a chronic condition that endures through childhood and into adulthood, it is important to understand how specific features and characteristics of OI, such as scoliosis, affect different aspects of quality of life in developing children.

The quality of life components that may be affected in individuals with OI and scoliosis include areas of both physical functioning and mental functioning. The physical functioning component includes areas of self-care, hygiene, walking, stair climbing, bending/lifting as well as exercise. Additionally, this area includes an individual's ability to perform work related activities, accomplish what one desires, pain limitations and overall general health. Quality of life also includes mental functioning areas, which include such things as feeling full of energy, being worn out, social relations, happy vs. sad, and overall feelings toward themselves and others. Accordingly, the purpose of this study is to determine if scoliosis curve

magnitude is associated with quality of life in children with OI and scoliosis, and specifically which aspects of quality of life are affected the most.

METHODS

This study included twenty-two adolescents to young adults with a diagnosis of OI (14.4±2.5 years, 16 males, 6 females) who were consented to participate in this Health Insurance Portability and Accountability Act (HIPAA) compliant, Institutional Review Board (IRB) approved protocol. Inclusion criteria consisted of individuals with OI over the age of 11 years with a diagnosis of OI and a scoliosis measurement of 10 degrees or greater. The participants comprised of those with type I OI (7), type III OI (7), type IV OI (6), type VI OI (1) and Bruck Syndrome (1). Of the type I OI participants, all were primarily ambulatory with the exception of one participant who reportedly used a wheelchair for longer distances. All of the type III OI participants used a wheelchair as their primary means of mobility. Of the type IV OI participants, 5 were primarily wheelchair users and 1 participant was able to ambulate most distances, only using a wheelchair for longer distances. Both the individuals with type VI OI and Bruck syndrome used only a power wheelchair for all mobility.

Following the study protocol, each participant completed a series of evaluations. Once all the proper consents and assents were signed, the participant underwent radiological evaluation to determine their Cobb angle as well as pulmonary function testing. Additionally, quality of life questionnaires including the Short Form 36 Health Survey (SF-36) and Revised Oswestry Low Back Pain Questionnaire were completed at each visit. Pain was assessed using the Visual Analogue Pain Scale.

This chapter will focus primarily on the SF-36 assessment which is a multi-purpose, generic measure health survey that inquires about eight separate categories which are divided into a physical and mental component. The 8 subscales of the SF-36 are as follows: Physical Function, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health.

Statistical Analysis

Descriptive statistics were calculated for the Cobb angle as well as the SF-36 outcome scores. Scores from the SF-36 were calculated using a norm-based scoring approach where the raw scale score is converted to a standardized

mean score of 50 and standard deviation (SD) of 10 that is relative to the 2009 U.S. general normative population scores. This is referred to as a norm-based scoring (NBS) approach. Using the NBS approach for our SF-36 scores from our study allows for easier statistical comparison with the normative SF-36 scores.

The relationships between Cobb angle and each SF-36 outcome scores were determined using Pearson Correlation Coefficient. For all correlations, an *r* value of 0.75 to 1.00 suggested a strong to very strong relationship, 0.50 to 0.75 was considered moderate to strong relationship, 0.25 to 0.50 was considered a weak to moderate, and 0.00 to 0.25 indicated a poor or weak to no relationship. The p-value of each correlation was also calculated to determine if the relationship trends observed were significant, i.e. $p<0.05$.

RESULTS

A total of 22 subjects with OI participated in this study. The average Cobb angle for this study was 56.4°, which is quite severe. SF-36 scores were obtained and compared to those of the 2009 U.S. general normative population. A summary table comparing average NBS SF-36 scores in this study to NBS SF-36 normal U.S. population data is presented in Table 1. With the exception of physical function, role-physical, and vitality, the mean values for the other SF-36 scores were within the normative range. Role-physical and physical function were 0.4SD (4.2 T-score points) and 2SD (21 T-score points) below the U.S. general population norm respectively, while vitality was 0.7SD (6.8 T-score points) above the U.S. general population norm.

Table 1. Average NBS SF-36 scores and Cobb angle for OI children in current study and the reported U.S. normal NBS SF-36 scores.

	Current OI study group	Reported U.S. Normal
Physical Function	29	50
Role-Physical	45.8	50
Bodily Pain	50.2	50
General Health	52.2	50
Vitality	56.8	50
Social Functioning	48.5	50
Role-Emotional	50.7	50
Mental Health	51.9	50

The relationship between Cobb angle and SF-36 outcome metrics are shown in the correlation coefficient table in Table 2. As indicated in Table 2, a

strong significant ($p < 0.01$) inverse relationship is seen between Cobb angle and physical function with a correlation coefficient of -0.633. Graphic representation of the relationship between physical function and Cobb angle is shown in Figure 1. Other SF-36 metrics do not show a significant relationship ($p>0.05$) with Cobb angle.

Table 2. Correlation Coefficient Table showing relationship between Cobb Angle and SF-36 metrics.

SF-36 metrics	Correlation Coefficient	p-value
Physical Function	-0.633 **	0.002
Role-Physical	-0.124	0.581
Bodily Pain	-0.318	0.149
General Health	-0.065	0.774
Vitality	0.115	0.609
Social Functioning	0.047	0.837
Role-Emotional	-0.067	0.768
Mental Health	0.221	0.324

** indicates correlation is significant at $p < 0.01$

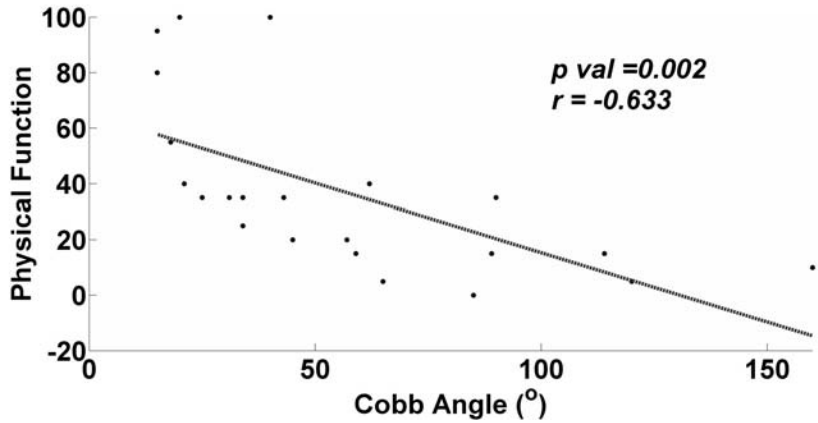

Figure 1. Scatter plot showing correlation between Physical Function score and Cobb Angle. The solid trend line represents the linear regression fit.

DISCUSSION

The current study was aimed at determining what quality of life features are specifically influenced by scoliosis curve magnitude in children with OI. Results suggest that besides physical function, other SF36 quality of life

measures do not appear to be significantly impacted by Cobb angle. Physical function tends to decrease as the magnitude of Cobb angle increases.

The average physical function and role-physical scores for all OI subjects in the study were below the normative range of U.S. general population. Interestingly, the average vitalitywas above the normative range of U.S. general population. These findings are not completely unusual, as previous quality of life studies involving adult OI subjects have also reported similar isolated decreases in physical function.[11] In this study of adults with more severe OI by Widmann, they also found that a significant difference was only noted in Physical Function, Bodily Pain and Role Physical. In the less severe subjects with OI the only significant difference noted was in their Physical Function while this group scored higher than the US population in General Health, Vitality, Social Function, Role Emotional and Mental Health (although not significantly).[11]

Interestingly, despite the deterioration observed in physical function, role-physical function was however minimally impacted by Cobb angle magnitude. This suggests that even though Cobb angle may limit the ability to perform basic activities of daily living (physical function), it doesn't appear to directly impact societal role limitations due to physical health (Role-physical function). Many individuals with OI are able to make adaptations in their work and home environment to continue to be able to accomplish what they would like to do and are very good self-advocates. Being able to make these adaptations to their environments and being great at self-advocacy allows individuals with OI to continue to be independent in their home and work which is important to allow them to have a good to excellent quality of life and be able to accomplish their goals.

CONCLUSION

It is known that children, adolescents and young adults with osteogenesis imperfecta have an increased risk of developing scoliosis due to their brittle bones, ligamentous laxity and muscular weakness. It is important for individuals with OI to have a physician monitor their spine in early childhood to allow for appropriate medical management. Early medical management can prevent complications later in life and allow for minimal limitations in physical functioning. While an increase in scoliosis may impact an individual's ability to perform certain physical tasks such as ambulation, standing, running, transfers and sometimes sitting, often individuals with OI continue to lead a good quality of life with little to no limitations in achieving

their goals and maintaining appropriate social functioning. Despite the physical limitations often seen in individuals with OI, specifically the more severe types of OI, such as type III and IV, people with OI typically lead a life with normal or often above normal psychological and social roles in society. They are quite adaptable and are able to formulate strategies, both functionally and emotionally, to allow for high levels of achievement despite often severe physical limitations.

REFERENCES

1. Vetter U, et al. Osteogenesis imperfecta: a clinical study of the first ten years of life. *Calcif Tissue Int.* 1992;50(1):36-41.
2. Byers PH, Steiner RD, Osteogenesis imperfecta. *Annu Rev Med*. 1992;43: 269-282.
3. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet*. 1979;16(2):101-116.
4. Benson DR, Newman DC. The spine and surgical treatment in osteogenesis imperfecta. *Clin Orthop Relat Res.* 198;159:147-53.
5. Falvo KA, Root L, Bullough PG. Osteogenesis imperfecta: clinical evaluation and management. *J Bone Joint Surg Am*. 1974;56(4):783-93.
6. Renshaw TS, Cook RS, Albright JA, Scoliosis in osteogenesis imperfecta. *Clin Orthop Relat Res*. 1979;145:163-167.
7. Ishikawa S, et al. Vertebral body shape as a predictor of spinal deformity in osteogenesis imperfecta. *J Bone Joint Surg Am.* 1996;78(2);212-9.
8. Norimatsu H, Mayuzumi T, Takahashi H, The development of the spinal deformities in osteogenesis imperfecta. *Clin Orthop Relat Res*. 1982;162:20-25.
9. Hanscom DA, et al. Osteogenesis imperfecta. Radiographic classification, natural history, and treatment of spinal deformities. *J Bone Joint Surg Am.* 1992;74(4):598-616.
10. Janus GJ, et al. Operative treatment of severe scoliosis in osteogenesis imperfecta: results of 20 patients after halo traction and posterior spondylodesis with instrumentation. *Eur Spine J*. 2000;9(6):486-491.
11. Engelbert RH, et al. Osteogenesis imperfecta in childhood: perceived competence in relation to impairment and disability. *Arch Phys Med Rehabil*, 2001;82(7):943-948.
12. Widmann RF, et al. Quality of life in osteogenesis imperfecta. *Int Orthop*. 2002;26(1):3-6.

32 PAIN IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder that affects individuals from birth across the lifespan. Characteristics of OI can include frequent fractures, average to short stature, blue sclera, joint hypermobility, ligamentous laxity, hearing loss, dentinogenesis imperfecta, abnormal curvature of the spine, muscle weakness, limited ambulation and acute or chronic pain. 1 in 10,000 individuals are affected by OI, which is primarily an autosomal dominant condition. Individuals may inherit this condition as a new mutation as well, which accounts for approximately 35% of those individuals with OI. The severity of the disease is extremely variable and is evident secondary to decreased bone quality and quantity as well as variable deformity of the long bones and vertebrae. Genetic testing is often recommended to determine the diagnosis and type of OI.

Currently, there are eight known types of osteogenesis imperfecta ranging in severity. Bone fragility results from poor quality of bone structures, disorganization of bone tissue, altered bone geometry and/or decreased production of normal bone/impaired bone formation. This can result in frequent fractures, which leads to impaired mobility, decreased ambulation, muscle weakness, limited independence in functional activities of daily living and overall deconditioning. A secondary condition resulting from the above factors is the development of pain, both acute pain resulting from a fracture and chronic bone/joint/muscular pain.

Pain is described as the unpleasant sensation occurring in varying degrees of severity as a consequence of injury, disease or emotional disorder. The

International Association for the Study of Pain's widely used definition of pain states, "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] It is the body's way of responding to damaged tissue.

There are two types of pain, chronic pain and acute pain. Chronic pain is usually considered to be pain that lasts more than 6 months, or beyond the expected time for healing, and acute pain is pain that lasts less than 30 days.[2] Additional feelings of frustration and fear can make chronic pain more intense. With OI, causes of acute and chronic pain can be a result of multiple fractures, muscle strain, vertebral collapse (compression fractures of the spine), joint misalignment or deformity, contractures and osteoarthritis.

Oftentimes pain in OI is overlooked. Increased focus is put on the fractures themself and less attention is given to the pain resulting from these fractures. There are limited published studies describing the prevalence, severity and characteristics of pain experienced by individuals with OI. Additionally, there is little mention of pain management in the treatment of OI.

Pediatric clinical research trials can be more difficult to perform than on adults, this can cause obstacles in pediatric pain management. Pharmaceutical companies in the past have been hesitant about performing pediatric clinical studies, due to its small market as compared to adult medicine.[3] Osteogenesis imperfecta qualifies as an orphan disease due to the limited amount of individuals with the disease.[4] This amplifies the problem of adequate medical research concerning this condition, making pain management specifically for children with OI a challenging prospect.

Both fracture pain and non-fracture pain are commonly reported by individuals with OI. Zach et al reports that pain is a common occurrence for children with OI that can be both acute and chronic in nature, interfering with a child's activities of daily living.[5] Those that are affected by either acute or chronic pain may also experience impairments in attention control, memory, processing new information, and problem solving.[6] Additionally, an increase in depression, anxiety, fear and anger may also be seen in individuals with acute and chronic pain.[7]

Many painful experiences may be associated with a cue, that children may remember, which may cause avoidance behavior or evoke profound emotions in the future.[8] Post-Traumatic Stress Disorder (PTSD) commonly

affects pediatric patients who suffer trauma related injuries.[9] PTSD can substantially affect the ability of the patient to function and adapt post-injury to activities of daily living.[9] Children with OI who fracture while simply taking a step and walking may remember the pain and, therefore, may avoid walking. Due to the amount of times a child with OI may experience a fracture; this pain will become very well known to them. Many have to overcome mental obstacles to regain their previous level of independent functional mobility following a fracture. It is often beneficial to be involved with a physical therapist during post-fracture rehabilitation to strengthen and progress safely under trained supervision and to avoid further pain as much as possible.

The assessment of pain can be challenging. Even with guidelines in place, the subjective nature of pain itself can pose potential problems in providing adequate pain management. It is important to explore the many different characteristics of pain, quality of pain, as well as how the pain affects an individual's quality of life. A person's self-report of pain is the most important and reliable measure of pain, and interestingly, health care professionals tend to underestimate its' severity.[10] Misinterpretation of the severity of the pain that the child is experiencing may be due to multiple factors. The communication between patient and clinician can be difficult to relay, even with the help of collateral information from the parent. Clinicians can be placed at a disadvantage of completely misunderstanding the intensity of the pain, because communication may only be able to come from the parent, due to the age of the child.

This chapter will provide a description of the physiology of pain and an overview of pain experienced by 28 children who participated in a larger study titled "Gait Characteristics and Functional Assessments of Children with Osteogenesis Imperfecta". Additionally, pain management options will be reviewed.

PHYSIOLOGY OF PAIN

Pain involves various neurological structures. Pain receptors, or nociceptors, are free nerve endings found in various tissue including the skin, periosteum and joint surfaces.[11] In the absence of a painful stimulus, nociceptor neurons (small diameter primary afferent neurons) are inhibited from activation by glycinergic and GABAnergic interneurons (Figure 1).[12] In the presence of a painful stimulus such as heat, noxious chemical or mechanical trauma, this

inhibition is removed allowing nociceptors to become active in pain signaling.

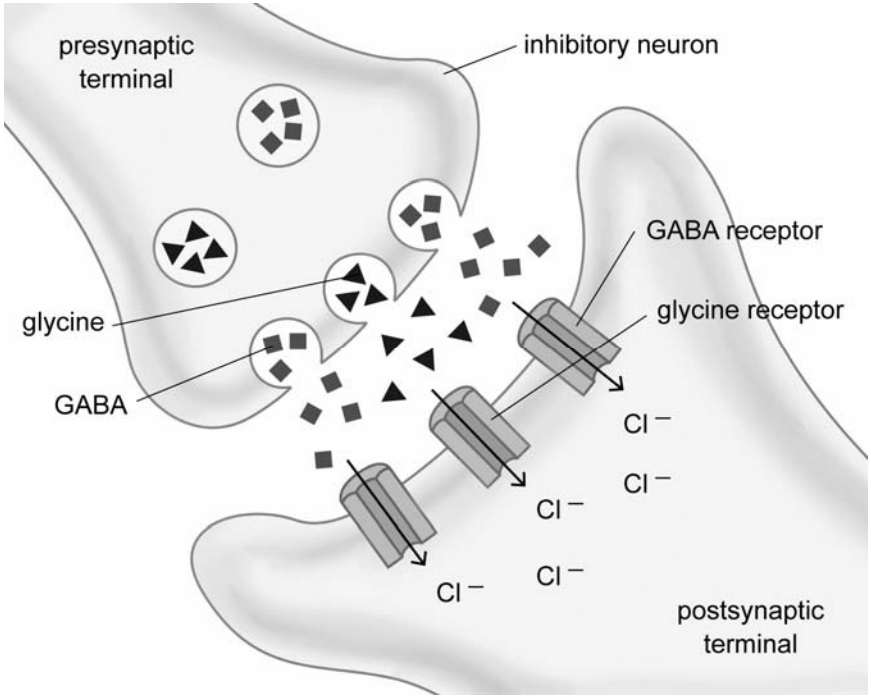

Figure 1. Inhibition of nociceptors.

Pain signals, or nerve impulses, are transmitted from the injured peripheral tissues (skin, periosteum and joint surfaces) by the nociceptive primary afferent neurons and eventually synapse with pain communicating pathways in the dorsal horn of the spinal cord.[13] When the nerve impulse reaches the terminal end of the nociceptive neuron in the dorsal horn, neurotransmitters are released which communicate pain information to the nociceptive pathways in the spinal cord.[14] The pain signal then travels from the dorsal horn through the nociceptive pathway called the lateral spinothalamic tract within the spinal cord (Figure 2). The signal is then projected to the brain allowing pain to be perceived.[15]

Neurotransmitters such as glutamate and substance P aid in facilitating the transmission of pain. Glutamate acts quickly and has a transient duration. Substance P is slow in response but functions for a longer period of time.[11] Finally, the intensity of pain as a result of tissue damage is directly related to the rate at which the tissue damage is occurring.[11]

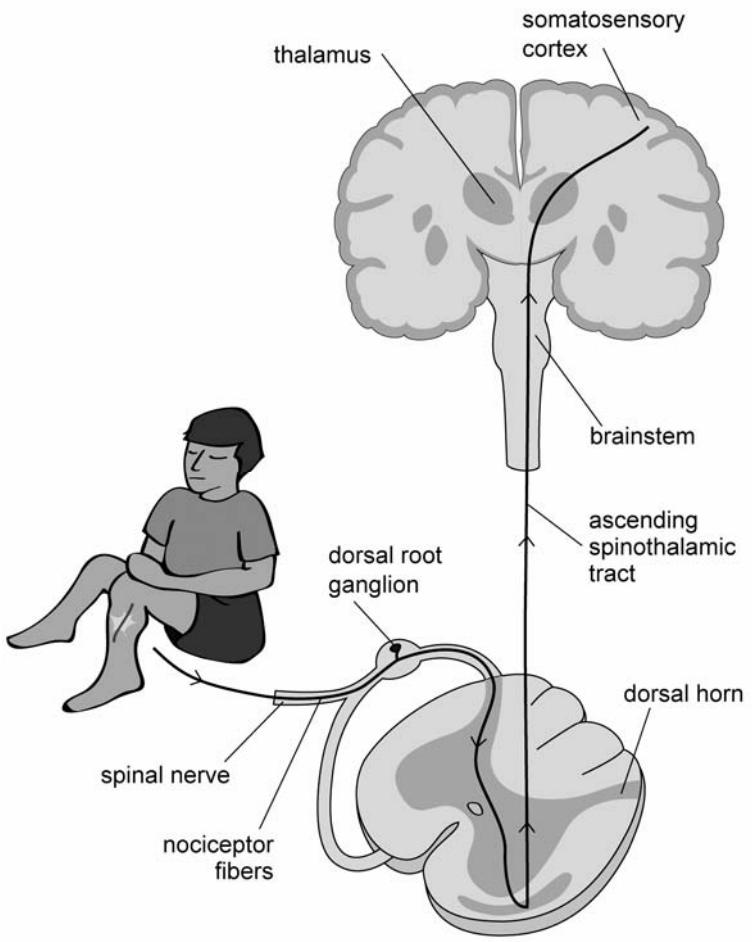

Figure 2. Neurological pain signaling.

A STUDY OF PAIN IN OSTEOGENESIS IMPERFECTA

Children and adults with OI may be limited in their functional mobility and activities of daily life due to pain. When assessing pain in children with OI it is necessary to consider the many different causes of pain, such as a fracture of any type, muscular pain, bone pain and/or joint pain. It is important to become familiar with how the individual's pain is affecting their functional mobility and daily living to be able to properly develop an approach to decrease their pain. The following study referred to in this chapter focused on the relationships between pain (complaint of pain, as well as intensity of

pain) and functional outcomes/quality of life in children with OI. The outcome tools used in this study include the Gillette Functional Assessment Questionnaire (FAQ score),[16] the Functional Mobility Scale (FMS score),[17] and the Pediatric Outcomes Data Collection Instrument (PODCI score).[18] Overall, functional mobility and functional activities can be largely affected by pain. The aim of this study was to gain an understanding of pain experienced by children with OI and what type of impact this pain had on their functional abilities as well as the limitations that resulted from this pain.

Methods

The relationship between pain and different types of factors such as intensity, type of pain, duration of pain, pain alleviation, FMS scores, PODCI scores, activity limitation and duration of activity limitation was analyzed in 28 children with either Type I, III, or IV OI over 18 months. Each participant's parent/guardian gave their informed consent to participate in this study, which was Health Insurance Portability and Accountability Act (HIPAA) compliant and Institutional Review Board (IRB) approved. Fourteen of the participants were being treated with oral or IV bisphosphonate medications. None of the participants had experienced a fracture or surgery for at least one year prior to participating in this study. All participants that consented to be included in the study were able to ambulate with or without an assistive device and were evaluated in the Motion Analysis Laboratory. Pain was assessed weekly through email/telephone contact with each participant or participant's caregiver. A journal for each participant was kept by recording various pain characteristics including: complaint of pain, location of pain, type of pain, fracture pain, missed activities, missed school, and activity limitations. A total of 18 months of pain characteristics for each study participant was collected. On occasion, weekly contact was unable to be made, however, information about each participant's pain was recorded at a minimum of every month for 18 months. In addition, each participant completed the Gillette Functional Assessment Questionnaire (FAQ), the Functional Mobility Score (FMS), the Pediatric Outcomes Data Collection Instrument (PODCI) and the Faces Pain Scale on four occasions, separated by approximately six months at each assessment. A DXA scan of the lumbar spine was taken at each visit as well. Z-scores, which are a comparison of a person's bone density with that of a typically developing individual of the same age and sex, was recorded at each visit. A z-score of 0 would mean that child had the same bone density as a typically developing child his/her same

age. A z-score of -1.0 or further away from zero would mean that a decreased bone density was detected.

Following is a description of the functional assessment tools used in this study. The FAQ, developed at Gillette Children's Specialty Healthcare, is a 10-level, parent-report walking scale encompassing a range of walking abilities from non-ambulatory to ambulatory in all community settings and terrains. The higher the score on the FAQ the more independence with walking and running a child possesses. The FMS is a useful tool for identifying children with varying levels of disabilities and functional mobility over three distinct distances, chosen to represent mobility in the home, at school and in the wider community. Again, the higher number achieved in each category, 0-6, the more independent a child is with ambulation. The PODCI is an outcome tool that looks at physical function over 6 domains; upper extremity function, transfers and mobility, sports participation, pain and comfort, global function, and happiness with physical condition. Finally, the Faces Pain Scale is a self-report measure used to assess the intensity of children's pain by identifying a face that represents how much pain they are in.[19]

Data Analysis

Descriptive statistics (frequencies, percentages) were used to describe the responses to each journal entry for each category stated above: complaint of pain, location of pain, intensity of pain, pain duration, pain type, what was used to treat the pain, activity limitations and duration of the activity limitation. Missing observations were eliminated in calculating the percentages for each question. When calculating percentages, only those participants who complained of pain were included.

To analyze the relationship/association between pain complaint and the outcome measures (FAQ, PODCI, etc), a Generalized Estimating Equations (GEE) analysis method was implemented using the 'complaint of pain' scores as the response variable. A GEE was used because there were repeated measurements (i.e. measures were collected during each visit over the course of the study for each participant), and the response variable (i.e, complaint of pain) was qualitative. Because all individuals without complaint of pain had OI Type I, no activity limitation, and no duration of activity limitation, the GEE was not applicable for these three predictor variables. Thus, the Fisher's Exact Test was used for them instead of the GEE.

To analyze the relationship/association between pain intensity and the outcome measures, a mixed model analysis method was implemented using the 'pain intensity' scores as the response variable. A mixed model was used because there were repeated measurements (i.e. measures were collected during each visit over the course of the study for each participant), and the response variable was quantitative.

Results

Table 1 depicts all aspects of pain that were analyzed. 96.4% of the participants complained of pain throughout the study. The most common location of pain was multiple joints (63.8%) followed by back pain (10.1%). When looking at pain intensity (rated between 0 – 10 as indicated on the International Association for the Study of Pain/Faces Pain Scale – Revised (FPS-R),[19] the most common response was a **5** (21.7%), followed by a **4** (18.8%), and then a **6** (14.5%). Pain duration response indicated that pain experienced by the children/adolescents in this study most commonly lasted more than one month (56.5%). The most common type of pain was aches/stiffness (44.9%) with the most common way of treating the pain being no treatment at all (42%). For most of the participants, the types of activity limitation were both recreational and school limitations (31.9%) followed by only recreational limitations (30.4%) and then no limitations at all (27.5%).

Results of the GEE analysis are given in Table 2. The results indicate that DXA Z score and Day of Visit are not significant factors when the participants reported on their pain. However, FAQ Score and FMS Score have significant associations with the participant's complaints of pain. This means the higher the functional score on the above listed outcome tool (FAQ and FMS), the lower the probability of the participant actually reporting a pain.

Table 1. Descriptive statistics for frequency questions.

Variable	Response	Frequency	Percentage
Complaint of pain	Yes	27	96.4%
	No	1	3.6%
Location of pain	Foot/ankle	2	2.9%
	Knee	2	2.9%
	Hip	4	5.8%
	Back	7	10.1%
	Shoulder/upper arm	2	2.9%
	Lower arm/wrist and hand	6	8.7%
	Multiple	44	63.8%
	Other	2	2.9%
Pain duration	<1 week	10	14.5%
	1-2 weeks	12	17.4%
	2 weeks-1 month	8	11.6%
	>1 month	39	56.5%
Pain type	Fracture related	14	20.3%
	Aches/stiffness	31	44.9%
	Surgery related	5	7.2%
	Injury related	19	27.5%
Pain intensity	0	1	1.4%
	1	1	1.4%
	2	6	8.7%
	3	6	8.7%
	4	13	18.8%
	5	15	21.7%
	6	10	14.5%
	7	3	4.3%
	8	9	13.0%
	9	0	0
	10	5	7.2%
Pain treatment	None	29	42.0%
	Rest	25	36.2%
	Thermal agents	0	0
	Medication	15	21.7%
Activity limitation	No limitation	19	27.5%
	School	5	7.2%
	Recreation	21	30.4%
	Both (i.e. school and recreation)	22	31.9%
	Sleep	2	2.9%
Limitation duration	None	19	27.5%
	<1 week	13	18.8%
	1-2 weeks	12	17.4%
	2 weeks-1 month	6	8.7%
	>1 month	19	27.5%

Table 2. Results of analyses using complaint of pain as the response variable.

Variable	Odds ration estimate	95% confidence interval	P-value
DXA Z-score	0.769	(0.463, 1.276)	0.3099
FAQ	0.589	(0.393, 0.883)	0.0103
FMS	0.513	(0.372, 0.707)	<.0001
PODCI Sports and Physical Function	0.975	(0.951, 0.995)	0.0145
PODCI Pain and Comfort	0.933	(0.875, 0.994)	0.0339
VISIT	0.886	(0.542, 1.450)	0.6304

When the predictor of pain was OI type, activity limitation or duration of activity limitation, the GEE was not applicable. Instead the Fisher's Exact Test was used. Complaint of pain was initially modified by taking the average for each participant in order to eliminate the within subject variation. It was then divided into two groups – 'always complain' and 'not always complain'. More specifically, 'always complain' means that a participant complained whenever she/he visited the hospital for study testing. 'Not always complain' means that a participant didn't complain at least once among the three visits to the hospital for study testing. OI type, activity limitation and duration of activity limitation were also redistributed into two groups based on different criteria. See Tables 3-5 for details.

Table 3. Results of Fisher's exact test for OI type vs. complaint of pain.

Complaint of pain	OI type I	OI type III and type IV
Always	14	6
Not always	8	0

Fisher's exact test P-value: 0.1412

Table 4. Results of Fisher's exact test for activity limitation vs. complaint of pain.

Complaint of pain	Activity limitation less than 2	Activity limitation more than 2
Always	10	10
Not always	7	1

Fisher's exact test P-value: 0.0987

Table 5. Results of Fisher's exact test for duration of activity limitation vs. complaint of pain.

Complaint of pain	Activity duration less than 2	Activity duration more than 2
Always	9	11
Not always	8	0

Fisher's exact test P-value: 0.0097

The results indicate that OI type is not a significant factor for pain complaint. Activity limitation is marginally significant, but is still not as strongly significant factor for pain complaint. However, the duration of activity limitation has a strong association with whether the patient always complained of pain or not. This means for those who always complained of pain and for those who didn't, the distributions in levels of their durations of activity limitations were significantly different. In other words, the 'always complained' group is more likely to have more activity limitations compared to the 'not always' group.

Mixed models were built to examine the effect of activity limitation, duration of activity limitation, DXA Z-score, FAQ and FMS score, and PODCI scores on intensity of pain. Results are given in Table 6. The results indicate that OI Type, DXA z-score, and day of visit are not significant factors for intensity of pain. However, activity limitation and duration of activity limitation have significant associations with intensity of pain, which means that with higher level of activity limitation and/or longer duration of activity limitation, the intensity of pain tends to be higher. FAQ score and FMS score also have significant associations with intensity of pain, which suggests that with higher functional scores, the intensity of pain tends to be lower.

Table 6. Results of analyses using Intensity of Pain as the response variable.

Variable	Estimate	95% confidence interval	P-value
OI type	0.4284	(-0.2672, 1.1240)	0.2168
DXA Z-score	-0.4503	(-0.9867, 0.0861)	0.0961
Activity limitation	1.2115	(0.8568, 1.5572)	<0.0001
Duration of activity limitation	0.8613	(0.6055, 1.1171)	<0.0001
FAQ score	-0.3286	(-0.6165, -0.0407)	0.0269
FMS	-0.3354	(-0.6418, -0.0291)	0.0331
PODCI Sports and Physical Function	-0.0263	(-0.0505, -0.0020)	0.0353
PODCI Pain and Comfort	-0.0269	(-0.0531, -0.0005)	0.0460
VISIT	-0.1670	(-0.6654, 0.3314)	0.4977

Discussion

Individuals with OI commonly experience both chronic and acute pain, exacerbated by frequent fractures that interfere with a child's daily living and activity involvement. Pain can also affect a child's growth and development, peer and family relationships and overall quality of life. In this study it appears that pain was most significantly reported at multiple joints as well as back pain, with the most common intensity of pain rated a 5. This indicates the pain was quite significant and should not be overlooked. Pain most often lasted longer than one month and consisted primarily of aches/stiffness. Most commonly these children did nothing to treat their pain and the limitations that were present involved recreation and school activities.

Limited published studies are available that describe the nature and prevalence of pain in OI. Additionally, the medical management of pain in OI is often overlooked in medical reviews. Most of the focus in the medical management of OI is related to treating the fractures and the low bone density, while often missing from the complete puzzle is the treatment of pain itself. Increased awareness is needed for these children to evaluate and manage their chronic and acute pain.

A study by Zach et al evaluated pain, both fracture related pain and non-fracture pain, in children with OI using specific pain outcome tools as the main objective or primary outcome.[5] Zach et al developed specific self-report pain questionnaires to evaluate pain following a fracture as well as to

quantify weekly non-fracture pain, such as chronic aches and pains.[5] The Pain Coping -Questionnaire (PCQ) was also used.[5] This questionnaire asked children to rate their responses to previously painful situations. He noted there are ways to cope with pain that may help children with OI manage their discomfort. There are three different coping strategies called the approach strategy, the distraction strategy and the emotion-focused strategy. When using the approach strategy, an individual views the pain with a problem solving approach, seeking social support and using positive self-statements. The distraction strategy uses mental strategies to avoid pain. Finally, the emotion-focused approach uses soothing thoughts or soothing activities such as listening to calming music, meditating or talking to an emotionally supportive friend. Zach et al reported that children with OI who were dealing with fracture pain used the approach coping strategies most commonly. Similarly, the most often used strategy when dealing with non-fracture pain in children with OI was the distraction strategy.[5] Being aware of these strategies to help children deal with pain can be beneficial in their overall medical management and quality of life.

Analgesia use for acute fracture pain may be underutilized. Zach et al noted that those children with OI who experienced non-fracture pain rarely used analgesics, possibly because they were not affective for them or because the children became so accustomed to the pain and instead used their coping strategies so effectively that they did not ask for or desire to use analgesia.[5] There are different options for treating pain, and finding the right method for an individual is unique to that specific person and what works for them. Following is a description of some of the approaches one may take in treating pain along with the pros and cons of the approach.

THE MANAGEMENT OF PAIN

The management of pain in the pediatric population can be a difficult task. There are many painful conditions where simple pain relievers will not suffice. Management of muscle soreness in OI may be different than the pain that follows a fracture or aching bone pain. Clinicians utilize many medications and treatments that will be discussed in this chapter. These medications have different analgesic properties and strength. The World Health Organization developed a step wise system called the analgesic ladder, which is a treatment protocol that increases the strength of analgesic medication prescribed, based upon the severity of the injury and complaint of pain given by the child.[20] The analgesic ladder was originally created in order to treat children with oral cancer, however, many clinicians have

adopted this method for treating pain in other medical situations. The stepped approach is as follows: 1) simple analgesics such as non-steroidal anti-inflammatory drugs, 2) weak opiods, 3) strong opiods and 4) adjuvants.[20] Adjuvants include medicines that are not originally developed to treat pain, however, have been found to be effective in difficult to manage pain.

Non-Steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDS) are seen throughout the analgesic ladder either as a primary medication for patients that present with mild pain, or as an adjunct to stronger therapy to treat pain of increased severity. NSAIDS have shown efficacy in the treatment of musculoskeletal pain.[21] At the molecular level, when trauma occurs through fractures or bruising, inflammatory mediators including prostaglandins, are produced by immune cells to provide protection and prevention of further injury. NSAIDS decrease inflammation, and as a result decrease pain. These prostaglandins also remove the inhibition of nociceptors allowing them to transmit pain signals to the central nervous system. NSAIDs then reduce the production of prostaglandins by inhibiting cyclooxygenase, an enzyme that is a catalyst for prostaglandin formation.[22,23] However, caution must be observed when prescribing NSAIDs for use as an analgesic medication. Prostaglandins contribute to the protective mucosal barrier in the gastrointestinal tract.[24] Consequently, ulceration of the gastrointestinal tract may occur with an increased ingestion of NSAIDs.[25]

Acetaminophen

Acetaminophen works similarly by stopping the synthesis of prostaglandins while blocking cyclooxygenase, however, studies have shown that it may also block the reuptake of anandamide, an endocannaboid. Endocannaboid functions as an analgesic agent and preventing its reuptake will prolong its action.[26,27] Acetaminophen also causes inhibition of vanilloid receptor activation in nociceptors.[28] Vanilloid receptors are involved in generating pain signals originating from chemical, thermal and mechanical stimuli.[29] Clinicians must be careful to ensure that the proper dosage of acetaminophen is being prescribed, especially in the pediatric population. In an earlier report, the Food and Drug Administration found that in many cases of unintentional acetaminophen overdose, the wrong pediatric formula was administered, or adult dosages were used instead of age appropriate formulation, or weight appropriate doses were not calculated properly, or

the wrong dosing device was used in administering the medication such as tablespoon versus teaspoon, or using a dropper instead of a syringe.[30,31]

Acetaminophen is metabolized mainly by the liver with a small portion excreted unchanged in the renal system (<5%) and the remainder excreted in bile (2.6%). As stated, clinicians must be careful to ensure proper dosing when prescribing acetaminophen, as overdosing has demonstrated toxic effects on the liver.[32] The liver provides detoxification of many harmful substances through a biotransformation process called conjugation, in which toxic substrates are converted into nontoxic compounds allowing them to be excreted by the body.[33] During acetaminophen metabolism, a toxic intermediate N-acetyl-p-benzoquinone-imine (NAPQI) is created and detoxified by the liver through the interaction with the tripeptide glutathione. Glutathione is composed of three amino acids: glutamic acid, cysteine, and glycine which chemically allows it to conjugate toxic substances.[33] However, this conjugation is limited by the amount of glutathione available in the liver. As acetaminophen overdose occurs, the amount of the toxic intermediate produced is increased and consumption of glutathione is accelerated. Once 70% of the glutathione is consumed, NAPQI will no longer be detoxified and liver damage will occur. Therefore, careful monitoring of acetaminophen use in children is important, as glucuronide conjugation occurs less in children than adults.[34]

Opioids

Opioids are a much stronger class of analgesia used to treat pain of increased severity.[35] The binding of opioids to the opiate receptor inhibits nociceptor activity in both the central and peripheral nervous systems. Molecularly this is accomplished because opioids decrease the release of neurotransmitters responsible for pain by closing calcium channels on presynaptic neurons. Opioids also cause increased membrane permeability of potassium in pain conducting neurons of the central nervous system. This causes hyperpolarization of these neurons resulting in reduced conduction of pain signals.[36]

Opioids do however have a respiratory side-effects that may cause reluctance in their usage, especially in the pediatric population. Both the rate and depth of breathing are decreased with opioid usage. Depression of the rate and depth of respiration, chest and abdominal wall rigidity along with a reduction in upper airway patency have been observed. Opioids also blunt respiratory responsiveness to carbon dioxide and hypoxia.[37]

Opioids activate the mesolimbic reward system allowing dopamine to be released, which causes the individual to experience pleasure.[38] Consequently, the dopamine pathway may motivate a patient to seek these rewards in the absence of pain, which may lead to dependence. Many parents may express concern over the potential of their child becoming addicted to opioids, which may cause pediatricians to be reluctant in prescribing this class of drugs, however, the pain being experienced by the child may warrant the use of an opioid as an analgesic agent.

Codeine, which is a weak opiate, is often prescribed for pain in children. Many clinicians view codeine as a "safer" opioid because patients experience less respiratory side effects.[39] However, codeine use has come under scrutiny concerning its efficacy. The analgesic effect of codeine is mainly due to its metabolism into the opioid, morphine, by the liver enzyme P450.[40] A study performed in London found that up to 47% of children ages 3 to 12 had a reduction in the P450 enzymatic activity necessary to convert codeine into morphine.[40] Consequently, many pediatric patients may not experience sufficient analgesia with the use of codeine.

Bisphosphonates

Many individuals with OI report that the use of osteoclast inhibitor drugs (bisphosphonates), which assist in improving bone density also are associated with the reduction of chronic aching pain, however, this is not well documented.[41-46] Bisphosphonates have been used to aid in fracture prevention in patients with most forms of OI except Type VI where bone mineralization is defective.[4] Jakubowska-Pietkiewicz et al found a decrease in bone pain following the use of cyclic intravenous infusions of pamidronate, a type of bisphosphonates, in 8 children with Type III OI, ages 1 month to 6 years.[47] Additionally, Wagner et al observed a clear decrease and even total relief from pain after twelve children with OI were studied for a total of 50 pamidronate intravenous infusions.[48] An increase in bone mineral density was also noted. However, a study performed by Chevrel G et al involving adults who received the bisphosphonate, alendronate, observed that the subjects reported slightly increased pain levels by the 36th month of administration.[49] Therefore, there is more to learn concerning the effects that bisphosphonates have on the pain experienced by individuals with OI.

Massage and Transcutaneous Electrical Neural Stimulation

Massage therapy and TENS, transcutaneous electrical nerve stimulation, have both been used to provide pain relief for many individuals. The analgesic benefit of massage and TENS therapy is typically attributed to the concept of the gate control therapy of pain,[50] in which small diameter nociceptors that carry pain signals to the CNS can become inhibited by the stimulation of larger non-noxious neurons. Many of these large, non-noxious neurons are located in the skin and are activated by mechanically stimulation such as touching or rubbing the skin. Massage takes advantage of this concept through controlled patterns of vigorous rubbing of the skin, which stimulates these large non-noxious fibers, allowing inhibition of smaller pain fibers. This gate mechanism is an endogenous pain modulating mechanism in the human body that allows for reduction in the intensity of experienced pain.

Massage can also relax stiff muscles and ease muscle knots by increasing blood supply to the area. However, caution must be taken during massage treatment to avoid applying too much pressure due to the fragility of bones, which is characteristic of all individuals with OI. An experienced and knowledgeable massage therapist is necessary when exploring this option of pain treatment. TENS uses this same gate control theory mechanism; however, this technique uses a high frequency electric current through the use of electrodes that are placed on the skin to stimulate these larger, inhibiting, non-noxious neurons. The TENS machine sends small impulses directly to certain parts of the body, which block pain signals from being transmitted to the brain.

Heat and Ice

Applying hot and cold therapy is an effective means to reduce pain in the musculoskeletal system.[51] An ice pack or cold compress applied to the affected area thermodynamically reduces the flow of ions inside nerve cells causing a decrease in the ability of nociceptors to provide pain signals to the central nervous system.[52,53] Additionally, cold temperature alleviates swelling, inflammation and reduces the rate of agonist association with receptors.[54]

Thermal therapy has been used as an analgesic in medical practice. Warm temperature has been shown to provide a soothing affect to newborns when

undergoing painful injections.[55] Studies have shown that infrared thermal therapy decreases cytokines related to inflammation and pain including IL-6 and endothelin-1 respectively.[56,57,58]

Heat or ice is typically applied for 20 minutes at a time, directly at the site of pain. It is recommended that a towel be placed between the hot or ice pack to protect the skin. Sometimes, it is beneficial to alternate heat with cold to provide greater pain relief.

Acupuncture

Acupuncture causes the release of endorphins, analgesic endogenous, opioid peptides, into the central nervous system to provide pain relief.[59] Acupuncture is an ancient Chinese medical practice, in which needles are inserted at specific points on the body to reduce pain.[60] It is believed that the needle pricks stimulate the nerve endings and cause the release of endorphins, which are natural painkillers produced in the brain. Acupuncture has been studied in the pediatric population for its treatment of migraine headaches.[61] It has also been useful in treating children who suffer from sickle cell anemia during pain crisis.[62] Although acupuncture has been shown to be effective in providing sufficient analgesia, clinicians in Western medicine have been slower in adopting it as a means of treatment. There may be reluctance to using this method since many children are adverse to needles. However, current literature supports the use of acupuncture in pediatric pain management.[60]

Exercise and Physical Therapy

General deconditioning can lead to pain in any individual and therefore, having a supervised exercise program set up for someone with OI can provide pain relief benefits. The pain relief stems from improved muscle strength, improved endurance, and gaining a greater positive outlook on life. Exercise raises the level of endorphins and can be as simple as moving joints through its physiological range of motion in a repetitious manner. The most highly recommended form of exercise for individuals with OI, in order to improve muscle strength and reduce pain is pool therapy, particularly in warm water.

Other Pain Management Methods

In addition to the above treatments for pain, various psychological approaches are available to try to manage both acute and chronic pain.[63] These methods include biofeedback which teaches individuals how to relax, lower their heart rate and release tension from their muscles. This involves training from a professional and the use of special electronic machines to alert the patient when they have achieved such a state. Often, biofeedback and relaxation training work together, learning to breathe slowly and deeply and relax the muscles. Hypnosis can also be used, which involves a therapist or, on occasion, an individual can be taught to do this themselves. Finally, distraction, imagery and individual or family therapy can be useful tools when dealing with pain.

Pain relief can be achieved with older children (12 years or older) through the use of the salicylate class of NSAIDs, which are topical pain relievers. These pain relievers are in the form of a gel or cream, which is rubbed over the affected area, penetrating the skin, in order to provide pain relief. This primarily works best for musculoskeletal pain. Skin patches that release small amounts of medicine through the skin, such as the opioid or fentanyl, have been useful and usually require a prescription to allow for the physician to oversee the effectiveness and use over time. Occasionally, treatment with antidepressants is effective, however, more research is needed with this class of drugs to determine which antidepressants may help children with OI.

CONCLUSION

Rare conditions such as OI are referred to as orphan diseases. Orphan diseases receive less attention by pharmaceutical and research companies, due to the limited number of people affected by these conditions.[64,4] This poses a potential obstacle in the treatment of pain that children with OI experience, and ultimately leads to issues such as limited data concerning the efficacy of certain pain management therapies.

Pain can significantly alter a person's quality of life and overall functional mobility. Individuals with OI are more susceptible to experiencing pain, both acutely and chronically, due to their increased frequency of fractures, immobilization, and low bone density. With more specific research focused towards pain in OI, it is our hope that we can become more aware of pain experienced by children with OI and offer more structured and efficient treatment strategies for pain management. Further research is needed in

evaluating pain in the pediatric population and identifying which treatments work best in avoiding both chronic and acute pain.

Pain assessment and management should be routinely performed during the medical evaluation of all children with OI. It is important for a child to be able to report his/her pain and that the medical staff value and listen to their input concerning their pain management. Coping strategies are a useful tool for children to learn, as well as how to pace their activities in order to keep pain to a minimum. It may also be beneficial for children to keep a journal for themselves, which will allow them to monitor their pain, learn pain patterns and possibly avoid certain activities that increase pain.

It is important that parents and clinicians are in mutual communication. Providing education to parents is essential to the health and wellbeing of children with OI. Accurate and current medical records should be available to health care providers involved in the care of children with OI. OI can often be misdiagnosed as child abuse due to the presence of multiple fractures related to the disease. If a child presents to an unfamiliar provider with a chief complaint of pain accompanied by multiple healed fractures, which are discovered on a skeletal radiograph, it may be assumed that the pain is due to child abuse. Proper documentation can mitigate this occurrence.

Pain management in children and adults with OI is best addressed with a multi-disciplinary approach. Good communication between the patient, caregivers and medical care providers is essential in developing a plan of care to address pain issues in a person with OI. With good communication and treatment plans developed across the multi-disciplinary medical team, it is the ultimate goal to decrease or eliminate any pain and allow for the most optimal quality of life and mental well-being for children with OI.

REFERENCES

1. Bonica JJ. The need of a taxonomy. *Pain*. 1979;6(3):247-8.
2. Thienhaus O, Cole BE. Classification of pain. In: Weiner R. Pain management: a practical guide for clinicians. Boca Raton: CRC Press; 2002:28.
3. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *The New England Journal of Medicine*. Nov 2002;347(14):1094-1103.
4. Marion DW. Osteogenesis Imperfecta. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA; 2012.
5. Zack P, Franck L, Devile C, Clark, C. Fracture and non-fracture pain in children with osteogenesis imperfecta. *Acta Paediatrica*. Sep 2005;94(9):1238-42.

6. Hart RP, Wade JB, Martelli MF. Cognitive impairment in patients with chronic pain: the significance of stress. *Current Pain and Headache Report*. Apr 2003;7(2):116-126.
7. Bruehl S, Burns JW, Chung OY, Chont M. Pain-related effects of trait anger expression: neural substances and the role of endogenous opioid mechanisms. *Neuroscience and Biobehavioral Reviews*. Mar 2009;33(3):475-491.
8. Rothman RH, Simeone FA. The Spine. Philadelphia: Saunders; 1982.
9. Wallace M, Puryear A, Cannada LK. An Evaluation of Posttraumatic Stress Disorder and Parent Stress in Children With Orthopaedic Injuries. *Journal of Orthopaedic Trauma*, Apr 2012;1.
10. Prkachin KM, Solomon PE, Ross J. Underestimation of Pain by Health-Care Providers: Towards a Model of the Process of Inferring Pain in Others. *The Canadian Journal of Nursing Research - Revue Canadienne De Recherche En Sciences Infirmières*, Jun 2007;39(2):88-106.
11. Guyton AC, Hall JE. Textbook of medical physiology. Philadelphia: Saunders; 2000.
12. Takazawa T, MacDermott A. Glycinergic and GABAergic tonic inhibition fine tune inhibitory control in regionally distinct subpopulations of dorsal horn neurons. *Journal of Physiology*, Jul 2010;588(14):2571-2587.
13. Slipman CW. Interventional spine: An algorithmic approach. Philadelphia, PA: Saunders/Elsevier; 2008.
14. Kliegman R, Nelson WE. Nelson textbook of pediatrics. Philadelphia, PA: Saunders/Elsevier; 2011.
15. Seidel HM. Mosby's guide to physical examination. St. Louis, Mo: Mosby/Elsevier; 2011.
16. Novacheck TF, Stout JL, Tervo R. Reliability and Validity of the Gillette Functional Assessment Questionnaire as an Outcome Measure in Children with Walking Diabilities. *Journal of Pediatric Orthopaedics*. Jan/Feb 2000;20(1):75.
17. Graham HK, Harvey A, Rodda J, Nattrass GR, Pirpiris M. The Functional Mobility Scale (FMS). *Journal of Pediatric Orthopaedics.* 2004;24(5):514-520.
18. Haynes R., Sullivan E., The Pediatric Orthopedic Society of North American Pediatric Orthopedic Functional Health Questionnaire: An Analysis of Normals. *Journal of Pediatric Orthopaedics*. 2001;21:619-621.
19. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. *Pain*, May 1990;41(2):139-150.
20. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management: Stepping up the quality of it's evaluation. *Journal of the Americal Medical Association*. Dec 1995;274(23):1870-1873.
21. Derry S, Moore RA, Rabbie R. Topical NSAIDS for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews.* Jan 2012;9.
22. Vane JR, Botting RM. (March 30, 1998). Mechanisms of action of nonsteroidal anti-inflammatory drugs. *The American Journal of Medicine*. Mar 1998;104(3A):2S-8S.
23. Brody TM, Larner J, Minneman KP. Human pharmacology: Molecular to clinical. St. Louis: Mosby; 1998.
24. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn't the stomach digest itself? *Physiological Reviews*. Oct 2008;88(4):1547-1565.
25. Klatt EC, Robbins SL, Cotran RS. Robbins and Cotran atlas of pathology. Philadelphia, PA: Saunders Elsevier; 2006.

26. Ruggieri V, Vitale G, Pini LA, Sandrini M. Differential involvement of opiodergic and serotonergic systems in the antinociceptive activity of N-arachidonoyl-phenolamine (AM404) in the rat: comparison with paracetamol. *Naunyn-schmiedeberg's Archives of Pharmacology*. Jan 2008;377(3):219-229.
27. Nazarian A, Are D, Tenayuca JM. Acetaminophen modulationof hydrocodone reward in rats. P*harmacology, Biochemistry, and Behavior*, Jan 2011;99(3):307-310.
28. Youmans JR, Winn HR. Youmans neurological surgery. Philadelphia, PA: Saunders; 2011.
29. Kissin I. Vanilloid-induced conduction analgesia: selective, dose-dependent, long-lasting, with a low level of potential neurotoxicity. *Anesthesia and Analgesia*. Jan 2008;107(1):271-281.
30. Food and Drug Administration. Science background: Safety concerns associated with over-the-counter drug products containing analgesic/antipyretic active ingredients for internal use. 2004; www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM171901.pdf
31. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated Periodically.
32. Argentieri J, Morrone K, Pollack Y. Acetaminophen and ibuprofen overdosage. *Pediatrics in Review*. Apr 2012;33(4):188-189.
33. Marx JA, Hockberger RS, Walls RM, Adams J, Rosen P. Rosen's emergency medicine: Concepts and clinical practice. Philadelphia: Mosby/Elsevier; 2010.
34. Alam SN, Roberts RJ, Fischer LJ. Age-related differences in salicylamide and acetaminophen conjugation in man. *The Journal of Pediatrics*. Jan 1977;90(1):130-135.
35. Hatch JP. Wall and Melzack's Textbook of Pain. 5th Edition. Elsevier/Churchill Livingstone; 2006.
36. Shen KZ, Johnson SW. Presynaptic modulation of synaptic transmission by opioid receptor in rat subthalamic nucleus in vitro. *Journal of Physiology*. May 2002;541:219-230.
37. Lalley PM. Opioidergic and dopaminergic modulation of respiration. *Respiratory Physiology and Neurobiology*. Dec 2008;164(1-2):160-167.
38. Kosten TR, George, Tony P. The Neurobiology of Opioid Dependence: Implications for Treatment. National Institute on Drug Abuse. *Science and Practice Perspective*. Jul 2002;1(1):13-20.
39. Stark RD, Morton PB, Sharman P, Percival PG, Lewis JA. Effects of codeine on the respiratory response to exercise in healthy subjects. *British Journal of Clinical Pharmacology*. 1983;15(3):355-359.
40. Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *British Journal of Anaesthesia*. Jan 2002;89(6):839-845.
41. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *The New England Journal of Medicine*. Jan 1998;339(14):947-952.
42. Glorieux FH. Bisphosphonate therapy for severe osteogenesis imperfecta. *Journal of Pediatric Endocrinology & Metabolism*. Jan 2000;13:989-992.
43. González E, Pavía C, Ros J, Villaronga M, Valls C, Escolá J. Efficacy of low dose schedule pamidronate infusion in children with osteogenesis imperfecta. *Journal of Pediatric Endocrinology & Metabolism*. Jun 2001;14(5):529-533.
44. Banerjee I, Shortland GJ, Evans WD, Gregory JW. Osteogenesis imperfecta and intravenous pamidronate. *Archives of Disease in Childhood*. Dec 2002;87(6): 562-563.

45. Zacharin M, Bateman J. Pamidronate treatment of osteogenesis imperfecta – Lack of correlation between clinical severity, age at onset of treatment, predicted collagen mutation and treatment response. *Journal of Pediatric Endocrinology & Metabolism*. Feb 2002;15:163-74.
46. Aström E, Söderhäll S. Beneficial effect of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Archives of Disease in Childhood*. May 2002;86(5):356-364.
47. Jakubowska-Pietkiewicz E, Młynarski W, Klich I, Fendler W, Chlebna-Sokół D. Vitamin D receptor gene variability as a factor influencing bone mineral density in pediatric patients. *Molecular Biology Reports*. May 2012;39(5):6243-6250.
48. Wagner S, Poirot I, Vuillerot C, Berard C. Tolerance and effectiveness on pain control of Pamidronate® intravenous infusions in children with neuromuscular disorders. *Annals of Physical and Rehabilitation Medicine*. Sep 2011;54(6):348-358.
49. Chevrel G, Schott AM, Fontanges E, Charrin J, Lina-Granade G, Duboeuf F, Garnero P, Arlot M, Raynal C, Meunier P. Effects of Oral Alendronate on BMD in Adult Patient's with Osteogenesis Imperfecta: A 3-Year Randomized Placebo-Controlled Trial. *Journal of Bone and Mineral Research*. Feb 2006;21(2):300-306.
50. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. Nov 1965;150(3699):971-979.
51. Nadler SF, Weingand K, Kruse RJ. The physiological basis and clinical applications of cryotherapy and thermotherapy for the pain practitioner. *Pain Physician*. Jan 2014;7:395-99.
52. Chung MK, Wang S. Cold suppresses agonist-induced activation of TRPV1. *Journal of Dental Research*. Sept 2011;90(9):1098-1102.
53. Grandl J, Kim SE, Uzzell V, Patapoution A, Bursulava B, Petrus M, Bandell M. Temperature induced opening of TRPV1 ion channel is stabilized by the pore domain. *Nature Neuroscience*. June 2010;13(6):708-714.
54. Szallasi A, Blumberg PM. [3H] resiniferatoxin binding by the vanilloid receptor: species related differences, effects of temperature and sulfhydryl reagents. *Naunyn Schmiedeberg's Archives of Pharmacology*. Jan 1993;347(1):84-91.
55. Gray L, Lang CW, Porges SW. Warmth is analgesic in healthy newborns. *Pain*. May 2012;153(5):960-966.
56. Wong CH, Lin LC, Lee HH, Liu CF. The analgesic effect of thermal therapy after total knee arthroplasty. *The Journal of Alternative & Complementary Medicine*. Feb 2012;18(2):175-179.
57. Zanjani TM, Sabetkasai M, Karimian B, Labibi F, Farokhi B, Mossafa N. The attenuation of pain behaviour and serum interleukin-6 concentration by nimesulide in a rat model of neuropathic pain. *Scandinavian Journal of Pain*. Oct 2010;1(4):229-234.
58. Gokin AP, Fareed MU, Pan HL, Hans G, Strichartz GR, Davar G. Local injection of endothelin-1 produces pain-like behavior and excitation of nociceptors in rats. *The Journal of Neuroscience*, Jul 2001;21(14):5358-5366.
59. Hans JS. Acupuncture and endorphins. *Neuroscience Letters*, May 2004;361(1-3):258-261.
60. Twycross A, Dowden S, Bruce E. Managing pain in children: A clinical guide. Chichester, U.K: Wiley-Blackwell; 2009.
61. Pintov S, Lahat E, Alstein M, Vogel Z, Barg J. Acupuncture and the opioid system: implications in management of migrane. *Pediatric Neurology*. Jan 1997;17(2): 129-133.

62. Co LL, Schmitz TH, Havadala H, Reyes A, Westerman MP. Acupuncture: an evaluation in the painful crises of sickle cell anaemia. *Pain*. Oct 1979;7(2):181-185.
63. Osteogenesis Imperfecta Foundation and National Institutes of Health – Osteoporosis and Related Bone Diseases. www.oif.org/site/PageServer?pagename=PainMgmt.
64. Brewer GJ, Special Issue on Personalized Medicine. Drug development for orphan diseases in the context of personalized medicine. *Translational Research*. Dec 2009;154(6):314-322.

33 TRANSITION INTO ADULTHOOD: DRIVING WITH OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Driving is highly valued in the United States and learning to drive is one of the first major milestones in transitioning from a teenager to a young adult. Driving provides independence and autonomy. Personal transportation affects activities of daily living and community participation by allowing engagement in school, work, shopping, social activities and medical appointments.[1] In 1994, four federal agencies jointly performed a survey (National Health Interview Survey on Disability, NHIS-D) and reported roughly one-third of the respondents with disabilities had no public transportation available in their area.[2] Furthermore, transportation is a key barrier to community participation among individuals with disabilities.[3,4] Primarily, people with disabilities rely on friends and family for transportation and social networking.

Having a medical condition or disability does not necessarily mean a person cannot drive. However, the ability to drive safely requires both motor and mental skills. Motor skills are required to control the direction of the vehicle, accelerate, decelerate and operate ancillary devices such as indicators, headlights, and windshield wipers. Mental skills are necessary to make good safe decisions based on changing road and traffic conditions. A driver's situational awareness is critical when trying to avoid accidents. Developing these skills to become a proficient driver takes practice and training. For those with moderate and severe osteogenesis imperfecta (OI), short stature, muscle weakness, severe scoliosis, bone fragility, hearing loss and use of a wheelchair creates more challenges to drive a vehicle.[5-7] Fortunately,

certified driver rehabilitation programs and new technologies have broadened the opportunity for those with OI to drive vehicles safely.

ROLE OF THE CLINICIAN

The level of severity of OI can impact a person's level of function, activity and quality of life.[8-10] Montpetit[8] reported adults with OI type III had significantly lower activity scores in aspects of mobility and domestic life activities, and lower levels of participation in employment and transportation. Based on these findings, it is important for the physician to promote and facilitate involvement in the community in young adults with moderate to severe OI. If the physician believes their patient may qualify to drive based on medical, psychological and functional abilities, they should inform their patient of potential driving opportunities.[11] They should also explain the necessity of taking professional driver training when operating a vehicle with adaptive equipment.

The physician and other members of the rehabilitation team can help prepare a person with OI to drive by providing physical therapy and training, recommendations and prescription of durable medical equipment. Since people with OI fracture frequently, recovery times may hinder the person's ability to drive. Rehabilitation is critical in helping the person become as independent as possible.[12] Most driving programs require a physician's referral for a driving evaluation. The physician must also state the patient's medical stability, the effects of medication, and any planned surgeries.

ACQUIRING A DRIVER'S PERMIT

Since each state has different requirements to obtain a driver's (learner's) permit and license, potential drivers should contact their local Driver and Vehicle Licensing Agency (DVLA). They can assist with state policies and regulations for driving with a disability. The OI community and the OI Foundation are also valuable resources when referring potential drivers to certified rehabilitation driving programs and vendors for adaptive driving equipment.

In the United States, a person must pass all required driving tests - vision, written, and road test to obtain a driver's license. Persons with disabilities may be required to submit a medical report form signed by a licensed physician attesting that their medical condition does not impair their ability to operate a motor vehicle. A driving rehabilitation course may be required

for those with moderate to severe OI. The leading organization for driving evaluators is the Association of Driver Educators for the Disabled (ADED).[13,14] The course can improve driver safety, increase longevity of a driving career, and minimize the cost for car modifications and maintenance of adaptive equipment.

The driving rehabilitation course helps assess a person's driving needs based on their impairment.[15] The driver evaluator is typically an occupational therapist who works with a driving instructor and rehabilitation engineer.[16] A complete evaluation includes: vision testing, muscle strength assessment, joint range of motion, hand function, balance, muscle tone, endurance, coordination and reaction time, judgment and decision making abilities, and the ability to drive with the adaptive equipment. The vision testing assesses acuity, depth perception, and field of vision. All the test assessments administered create a baseline from which the team can appraise the safe driving potential of the driver.

Following the evaluation, behind-the-wheel skills are evaluated with or without adaptive equipment. The goal of the evaluation is to determine if the potential driver can process important road and traffic conditions and execute the required response in a timely manner. Following the examination, the driver rehabilitation specialist will provide specific recommendations on driving restrictions, a complete list of recommended vehicle modifications, type of vehicle and/or alternative transportation.

CHOOSING THE RIGHT VEHICLE

Great care must be taken when selecting a vehicle to accommodate the driver's function and the necessary vehicle modifications. A certified rehabilitation driving instructor can assist the driver with selecting the right car/van or modifying an existing vehicle. The functional ability and safety of the driver is impacted by the driver's seat height, width of the door opening, head clearance when entering and exiting the vehicle using a wheelchair, seat width, and leg room. The driver must also consider the method of storing the wheelchair. A manual wheelchair can be folded and stored in the trunk or the foot space between the front and back seats or a roof rack; while a power wheelchair may require a platform lift.[14]

If a driver is not able to transfer from a wheelchair to a car seat and/or uses a power wheelchair, a van will be necessary. Minivans may require a

combination of a lowered floor and rear suspension that lowers the vehicle for loading and raises it for driving through the use of a ramp.

Full-sized vans require a wheelchair lift to raise the driver and wheelchair from ground level to the van's floor level. Side entry allows more functional passenger seating and require almost eight feet next to the van for the driver to enter and exit. Wireless controls are available to control the lifting device and doors.

Once the vehicle is modified, the driving instructor needs to ensure the driver can use the equipment safely. A final mechanical inspection should be based on national standards by the Society of Automotive Engineers. Since the vehicle is customized for the person's specific disabilities, the vehicle is not designed for other drivers with disabilities.

ADAPTIVE EQUIPMENT

Vehicle modifications should be done by vehicle modifiers who follow guidelines established by the National Equipment Dealers Association (NMEDA).[17] Costs can range from several hundred dollars to $80,000 or more depending on the needs of the driver. Vehicle modifications can include: hand controls (for braking and accelerating), seats that swivel, vehicle lifts and ramps for entry, reduced effort steering systems, touchpad controls for internal functions of car, six point transfer seats, joystick driving systems which allow for one hand operation of brake, airbag on-off switches, restraint systems, and gas and brake pedal extensions (Figures 1,2,3,4).[18]

Typically, drivers with less function will require more complex driving systems and replace the Original Equipment Manufacturer (OEM) system Less complex systems are often installed in parallel to the OEM systems (Figure 5). The four areas of modifications that enable people with OI to drive include: modifications to provide access to the vehicle and steering wheel, modifications to control the speed and direction of the vehicle, safety modifications to protect the driver in the event of an accident, and modifications to control secondary controls

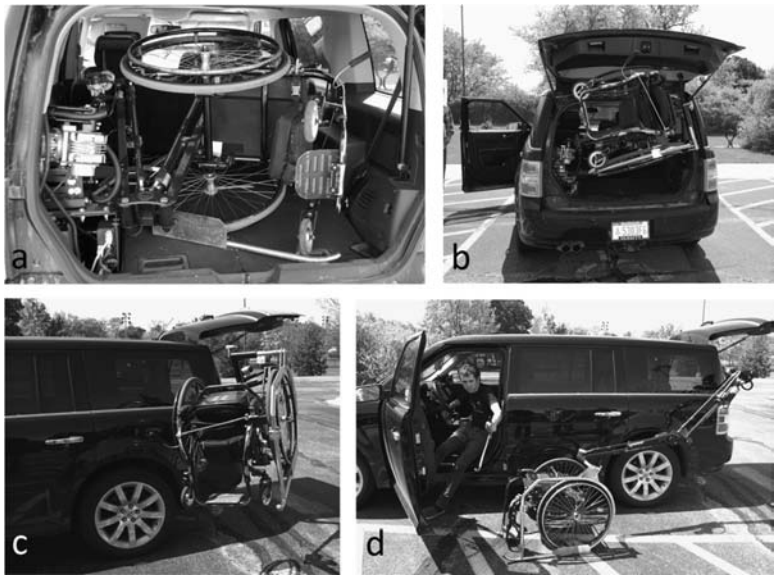
Figure 1. Adaptive driving equipment allows for independence and autonomy

Figure 2. Hand controls for braking and accelerating.

Figure 3. Once she enters the van using the lift, she can transfer from her wheelchair to the driver's seat.

BEHIND THE WHEEL

Once inside the van, the driver may need to transfer from their wheelchair into the driver's seat using a transfer seat. The transfer seat reduces the horizontal and vertical distance required during transfers. If the driver can't use a transfer seat, he must drive from the wheelchair. The wheelchair needs to be secured to hold the wheelchair and driver during operation. While safety experts recommend drivers must sit at least 10 inches from an activated airbag (measured from the steering wheel to the driver's breastbone), people with OI may need to sit closer to the steering wheel and shut off the airbag system. Please note: authorization from the National Highway Traffic Safety Administration is required prior to making any modifications to the airbag system. Detailed information on air bags and on/off switch applications is available from the State Motor Vehicle Departments, AAA clubs and the NHTSA.[19,20]



Figures 4. A motorized wheelchair lift transfers wheelchair from trunk to driver.

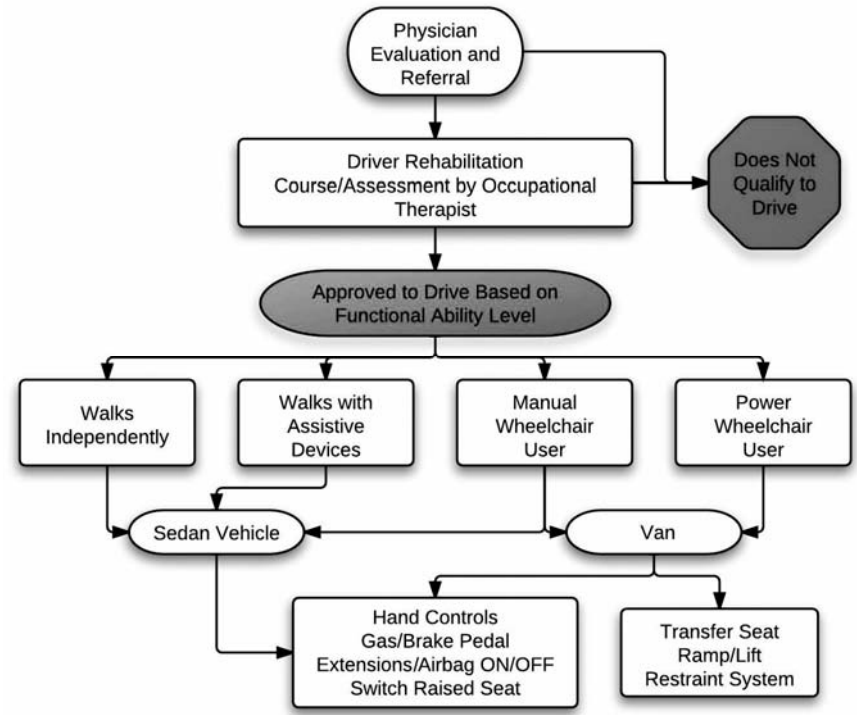


Figure 5. Adaptive driving flowchart.

Hand Controls

For drivers with short stature or limited leg function, hand controls can be used to operate the gas and brake pedals (Figure 2). There are several varieties of hand controls that sell for $1,200- 2,000 installed.[21] The push-right angle-pull hand control system is mounted underneath the steering column and the driver pushes forward on a handle to operate the brakes. For gas, the handle is pulled down toward the leg. If the driver has limited grip strength, a terminal device can be used to allow the driver to push forward to brake and pull back to accelerate. Powered hand controls are also available for those with weak upper extremity strength. The cost of powered hand controls typically ranges between $6,000 - 20,000. In addition, portable hand controls may be an option and cost between $200 - 600. The direction of the vehicle is controlled by the OEM steering wheel. For those using hand controls, a terminal device attached to the steering wheel is warranted such as a knob, a cuff, or tri-pin. If the driver lacks strength in one arm and/or has diminished range of motion in the elbow and wrist, a complete one-hand control system (e.g. tri-pin, joy-stick) is needed to operate both the gas/brake and steering systems.

Safe Driving Practices

Driving involves complex coordination of visual, cognitive, and musculoskeletal movements. The incidence of fractures is very high in people with OI; especially during motor vehicle collisions. Innovative education techniques for new drivers can help reduce traffic deaths and serious injuries of 15 – 19 year olds.[22]

Training is necessary to become a safe and proficient driver, especially when using adaptive equipment. To safely control the adapted vehicle and reduce the chance of a motor vehicle collision, an effective course in safe driving should encourage drivers to use the following safe driving techniques:[23,24]

- Make sure your mind is ready and focused on driving before you start to drive.
- Always keep your central vision up to take in a view of the road as far ahead as possible.
- Practice being aware of vehicles and objects in your peripheral vision.
- Avoid all internal vehicle distractions such as any kind of phone use, eating or emotional conversations. Thousands of fatal accidents have been linked to distractions. Never write, read or send text messages while driving like texting.

- Be aware of the side-effects of prescription medications before driving.
- Use your side and rear-view mirrors every five to seven seconds.
- Seeing who is coming up behind you, or who might not be paying attention, could save your life.
- Always have a safety zone or safety hole: a space to your left or right to drive into during an emergency. Your safety zone can also be the cushion of space in front of your vehicle when a tailgater follows too closely. Scan the space you are driving in by moving your eyes left and right to get a sense of your surroundings.
- Use your mirrors frequently.
- Respect the speed limits and pay special attention to slow down in school and work zones.
- Keep your eyes up. Look as far ahead as you can see.
- Always use the appropriate adaptive driving equipment.
- Inspect hand controls and other adaptive equipment periodically to ensure the equipment is working properly and tighten any loose bolts.

Drivers need to be aware of brake lights, changing traffic signals, pedestrians and potential dangers of any kind. New drivers are more likely to focus too long when using their central vision. For example, focusing on rear tail lights, license plates, billboards, pedestrians, another vehicle, or another driver for more than a second or two may lead to collisions. This can result in missed opportunities to detect road hazards. Moving our central view every second or two is known as eye scanning and is a great skill for new drivers to learn, practice and use.

EXPENSE

While programs and adaptive options exist, most individuals might find them to be relatively expensive and unfortunately, a majority of insurance companies will not pay for vehicle modifications. However, rebate programs from major car manufacturers are available in adapting new cars for drivers with disabilities. Also, grant aid maybe available through government financial aid programs, foundations and charity groups.

CASE EXAMPLES

Case#1. Jessica is a twenty-one year old female with OI type IV who is an independent ambulator at school but requires a manual wheelchair for distances greater than 50 meters. She is currently a college student who lives off-campus with friends and drives to school and work. Before she could

drive, her father reached out to her physician and the OI community to learn more about driving with OI. He learned that people with OI can drive safely with the use of adaptive equipment and professional drivers training. One of the biggest challenges was finding a drivers rehabilitation program in their region. After she received physician approval, she enrolled in a certified rehabilitation driving course at the age of sixteen. She was evaluated by an occupational therapist. Based on her physical abilities, the therapist recommended she drive with either an adaptive foot pedal or hand controls. She opted for hand controls as her legs frequently fractured (more than 25 times), while her arms had fractured twice. She wanted to drive as much as possible without being hindered by fractures and long recovery periods.

She also uses a knob on the steering wheel to assist in maneuvering the car while she uses the hand controls. She is required to use both hands while driving at all times. Since she is of short stature, a foam cushion seat is necessary to safely view the road. The airbags are turned off to prevent fracturing from airbag deployment. Once she received her driver's permit, she spent four months practicing with a driving instructor. She acquired her driver's license a year later at the age of seventeen. She currently drives a Buick Rendezvous sedan to accommodate her needs. She folds her manual wheelchair in her trunk and independently ambulates to the driver's seat. Jessica stresses the importance of driving for people with OI as it allows them to be independent. She encourages others to outreach to the OI foundation and their community for guidance as they can provide valuable knowledge and potentially help drivers save money and time.

Case #2. Jamie is a forty-one year old female with OI type III who uses a manual wheelchair and scooter. When she was sixteen, her family initially tried to enroll her in the Public High School driving program but she was turned down due to her disability. Knowing that driving will provide independence for his daughter, Jamie's father enrolled her in the Michigan Rehabilitation Services (MRS), who provided Drivers Rehabilitation Training. Her training included 50 hours on the road where she drove with an instructor for 2 hours every Saturday for 25 weeks. She took her test at the DMV using hand controls and steering knob.

Jamie purchased a used van and added hand controls, lift, swivel chair, booster seat and adaptive steering. The cost of adding the adaptive devices was approximately $15,000. Since her husband also has OI type III but varies

in height, strength and function; he is unable to use her adapted van and had to purchase a separate vehicle to accommodate his needs.

Once she enters the van using the lift, she transfers from her wheelchair to the swivel seat allowing her to take possession of the steering wheel. She has been driving for 23 years and describes driving as second nature. When she broke her pelvis, she was unable to drive until the bone healed three months later. Her inability to drive for three months was a challenge as her husband and two children relied on her for transportation to work, shopping and school.

CONCLUSION

Driving plays a significant role in the quality of life in people with OI. Clinicians are encouraged to inform families with OI on driving opportunities. Since people with OI fracture frequently and exhibit physical disabilities, it is important to provide the necessary rehabilitation drivers training and appropriate adaptive driving equipment. Once the driver receives their license, training and practice is essential to become a skilled driver.

With these examples in mind, it is possible to drive with moderate to severe OI. The type of adaptive equipment and vehicle is based on the driver's level of disability. Drivers with mild musculoskeletal impairments may require minimal adaptations to a car. Those with severe impairments will require more extensive adaptive equipment and a larger vehicle such a full sized van.

ABBREVIATIONS

ADED Association of Driver Educators for the Disabled
DVLA Driver and Vehicle Licensing Agency
NMEDA National Equipment Dealers Association
OEM Original Equipment Manufacturer
OI Osteogenesis imperfecta

ONLINE RESOURCES

www.nhtsa.gov
www.nsc.org
www.safekids.org
www.shrinershospitalsforchildren.org

www.andypilgrimfoundation.org
www.acura.com/MobilityOverview.aspx
www.chryslergroupllc.com/community/automobility/Pages/Automobility.aspx
www.fordmobilitymotoring.com/mainpage.mob
www.GMMobility.com
automobiles.honda.com/information/mobility-assistance.aspx
www.lexus.com/models/LS/accessories/mobility_program.html
www.toyotamobility.com/
vwmobility.com/vwmobilityrebate.html
www.vpgautos.com/
www.disableddealer.com/
www.disaboom.com/mobility
www.braunability.com/
www.christopherreeve.org/site/c.mtKZKgMWKwG/b.4453469/k.8F9D/Cars_ www.Driving.htm

REFERENCES

1. Brownstein CA, Wicks P. The potential research impact of patient reported outcomes on osteogenesis imperfecta. *Clin Orthop Relat Res.* Oct 2010;468(10):2581-2585.
2. Section B, Transportation, of the 1994 Disability Phase II Adult Public Use File available on the website of the Centers for Disease Control and Prevention; 1994; wonder.cdc.gov/wonder/sci_data/surveys/nhis/ type_txt/dfs94-b.htm.
3. Gray DB, Hollingsworth HH, Stark SL, Morgan KA. Participation survey/mobility: psychometric properties of a measure of participation for people with mobility impairments and limitations. *Arch Phys Med Rehabil.* Feb 2006;87(2):189-197.
4. 2004 NOD Annual Report. 2004; nod.org/about_us/our_history/annual_reports/2004_annual_report/.
5. Widmann RF, Bitan FD, Laplaza FJ, Burke SW, DiMaio MF, Schneider R. Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. *Spine (Phila Pa 1976).* Aug 15 1999;24(16):1673-1678.
6. Engelbert RH, Gulmans VA, Uiterwaal CS, Helders PJ. Osteogenesis imperfecta in childhood: perceived competence in relation to impairment and disability. *Arch Phys Med Rehabil.* Jul 2001;82(7):943-948.
7. Spegel J. Learning How to Drive with OI. Paper presented at: National Conference on OI2006.
8. Montpetit K, Dahan-Oliel N, Ruck-Gibis J, Fassier F, Rauch F, Glorieux F. Activities and participation in young adults with osteogenesis imperfecta. *J Pediatr Rehabil Med.* 2011;4(1):13-22.
9. Tosi LL. Osteogenesis imperfecta. *Curr Opin Pediatr.* Feb 1997;9(1):94-99.
10. Amako M, Fassier F, Hamdy RC, Aarabi M, Montpetit K, Glorieux FH. Functional analysis of upper limb deformities in osteogenesis imperfecta. *J Pediatr Orthop.* Nov-Dec 2004;24(6):689-694.
11. Adams A. Should family physicians assess fitness to drive?

YES. *Can Fam Physician.* 2010;12(56): 1264–1266.
12. Montpetit k. Rehabilitation Through the Years. In: Chiasson R-M, ed. *Interdisciplinary Treatment Approach For Children with Osteogenesis Imperfecta*. Quebec: Shriners Hospitals for Children; 2004:115-136.
13. ADED. The Association for Driver Rehabilitation Specialists.
14. van Roosmalen L, Paquin GJ, Steinfeld AM. Quality of life technology: the state of personal transportation. *Phys Med Rehabil Clin N Am.* Feb 2010;21(1):111-125.
15. Gomez-Talegon MT, Fierro I, Vicondoa A, Ozcoidi-Val M, Alvarez FJ. [Fitness-to-drive assessment in drivers with neurological and neuromuscular disorders at the driving test centres]. *Rev Neurol.* Nov 1-15 2007;45(9):526-531.
16. Unsworth CA. Using social judgment theory to study occupational therapists' use of information when making driver licensing recommendations for older and functionally impaired adults. *Am J Occup Ther.* Sep-Oct 2007;61(5):493-502.
17. NMEDA. National Mobilitity Equipment Dealers Association. www.nmeda.org/members/member-pdfs/nmedia_guidelines.pdf)
18. Paquin GS, Norman, Lindblom, Laurie. Driving with Spinal Cord Disorder. *Spinal Cord Medicine-Priniciples and Practice*. Second Edition ed. New York: Demos Medical; 2010.
19. BCAA. Front Air Bag Safety Technology Made Simple. www.bcaaroadsafety.com/resources/vehicle-technology/front-air bag-safety-technology.
20. NHTSA. Deactivation of Airbags. www.nhtsa.gov/people/injury/ airbags/airbags03/page8.html.
21. Reichenberger A. A Licensed motor vehicles for handicapped drivers. Paper presented at: National Academy of Sciences 1975.
22. CDC. Injury Prevention & Control: Motor Vehicle Safety. 2012; www.cdc.gov/Motorvehiclesafety/Teen_Drivers/.
23. NHTSA. Get The Facts. www.distraction.gov/content/get-the-facts/index.html.
24. NSC. White Paper: Understanding the Distracted Brain. 2010; distracteddriving.nsc.org.

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While OI remains a challenging condition, it is hoped that this work will contribute to an improved understanding of the condition as we strive to provide better transitional care from the pediatric to adult environment.

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