

The Association Between Upper Limb Function and Muscle and Bone Properties in Youth with Osteogenesis Imperfecta

Georgia Powell

Department of Experimental Surgery

Faculty of Medicine

McGill University

Montreal

February 2022



A thesis submitted to McGill University in partial fulfillment of the requirement of the degree of
Master of Science in Experimental Surgery

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ABSTRACT

Osteogenesis imperfecta (OI) is a rare, congenital disorder characterized by bone fragility due to mutations affecting collagen type I. In addition to bone related deficits, previous research has established that individuals with OI have decreased muscle size and muscle strength, as well as upper and lower extremity functional deficits. Typically, for individuals with moderate to severe OI, the upper extremities contribute to mobility function, as many rely on their upper limbs for the use of ambulation aids. Therefore, upper limb function is critical for activities of daily living for individuals with OI. The literature indicates that individuals with OI who had stronger upper extremity function at five to six years of age, had improved mobility at skeletal maturity. However, at present it remains unclear whether muscle and bone properties at an early age contribute to adulthood upper extremity function. Hence, this study aims to investigate the association between upper limb function and upper limb muscle and bone properties in individuals with moderate to severe OI, from prepuberty to skeletal maturity.

A retrospective medical chart review of individuals with moderate (type IV) and severe (type III) OI, who have been followed at the Shriners Hospitals for Children®-Canada, was conducted. Data was collected at two time points: (T1) at prepubertal age (5-11 years old) and (T2) at skeletal maturity. The following parameters were included for analysis: anthropometric measurements, grip strength, forearm muscle cross-sectional area (CSA), upper limb function as measured by the PEDI mobility domain, and bone parameters measured at 65% of the proximal radius by peripheral quantitative computed tomography: total radius CSA and total radius bone mineral content (BMC). Stepwise regression analyses were conducted with the following T2 parameters set as dependent variables: bone CSA, BMC, muscle CSA, grip strength, and PEDI Mobility. Prepuberty, T1, muscle and bone parameters were set as independent variables.

Sixty-three individuals with OI type III ($n = 13$; females = 7, males = 6) and type IV ($n = 50$; females = 31, males = 19) were included. The mean age (SD) at T1 and T2 was 9.37 (1.30) years old, and 17.21 (2.41) years old, respectively. Stepwise regression analyses showed that T1 muscle size (CSA), OI type, and sex, all predicted T2 BMC ($r^2 = 0.41$, $p < 0.001$). Bone mineral content at T1, OI type, and sex, all predicted muscle strength ($r^2 = 0.50$, $p < 0.001$) and muscle size (CSA) ($r^2 = 0.32$, $p < 0.001$) at T2. Mobility, as measured by PEDI, was determined by T1 muscle size (CSA) and OI type ($r^2 = 0.24$, $p = 0.016$), whereas there was no effect of muscle strength.

The results from this study showed that prepuberty muscle size and muscle strength were positively associated with bone mass at skeletal maturity, and muscle size was further associated with mobility function at skeletal maturity. This suggests that an increase in muscle strength and muscle size during prepubertal growth are likely to improve upper limb functional mobility and bone strength in adulthood. Following the results of this study, it would be of interest to develop new therapeutic interventions, targeting muscle size and muscle strength during the prepubertal growth period, as well to determine whether these interventions generate functional benefits in adulthood.

ABRÉGÉ

L'ostéogenèse imparfaite (OI) est une maladie congénitale rare caractérisée par une fragilité osseuse due à des mutations affectant le collagène de type I. En plus des déficits osseux, des recherches antérieures démontrent que les individus atteints d'OI présentent une diminution de la taille et de la force musculaires, ainsi que des déficits fonctionnels des membres supérieurs et inférieurs. En général, chez les personnes atteintes d'une OI modérée à sévère, les membres supérieurs sont responsables de la fonction de mobilité, car beaucoup d'entre elles comptent sur leurs membres supérieurs pour l'utilisation des aides à la mobilité ou pour les transferts. Par conséquent, une bonne capacité fonctionnelle des membres supérieurs est essentielle à la vie quotidienne des personnes atteintes d'OI. À ce sujet, la littérature suggère que les personnes atteintes d'OI qui présentent une meilleure capacité fonctionnelle des membres supérieurs à l'âge de cinq à six ans ont également une meilleure mobilité une fois la maturité squelettique atteinte. Cependant, nous ignorons pour le moment si ces capacités fonctionnelles et la mobilité sont influencées par les propriétés musculaires et osseuses des patients ayant l'OI. Cette étude vise donc à examiner l'association entre la capacité fonctionnelle des membres supérieurs les propriétés musculaires et osseuses chez les personnes atteintes d'une OI modérée ou sévère de la pré-puberté à la maturation squelettique.

Une étude longitudinale rétrospective des dossiers médicaux des personnes atteintes d'OI modérée (type IV) et sévère (type III), qui ont été suivies aux Hôpitaux Shriners pour enfants®-Canada, a été menée. Les données ont été recueillies à deux moments : (T1) à la pré-puberté (5 à 11 ans) et (T2) à la maturité squelettique. Les paramètres suivants ont été inclus dans l'analyse : les mesures anthropométriques, la force de préhension, la section transverse des muscles de l'avant-bras, la capacité fonctionnelle des membres supérieurs, telle que mesuré par le PEDI et les paramètres

osseux (la section transverse et la teneur minérale osseuse du radius à 65% de la portion proximale du radius). Des analyses de régressions pas à pas ont été effectuées avec les paramètres suivants, du temps T2, définis comme variables dépendantes : CSA osseux, BMC, CSA musculaire, force de préhension et mobilité PEDI. Les paramètres musculaires et osseux au niveau pré-puberté i.e., T1, ont été définis comme des variables indépendantes.

Soixante-trois participants ont été inclus, dont 13 ayant l'OI de type III (7 filles; 6 garçons) et 50 ayant l'OI de type IV (31 filles; 19 garçons). L'âge moyen (écart-type) aux T1 et T2 était respectivement de 9,37 (1,30) ans et de 17,21 (2,41) ans. D'après les analyses de régression pas à pas (stepwise), la taille musculaire (section transverse) au temps T1, le type d'OI et le sexe prédisaient tous la teneur minérale osseuse au T2 ($r^2 = 0,41$, $p < 0,001$). De plus, la teneur minérale osseuse au T1, le type d'OI et le sexe prédisaient tous la force musculaire ($r^2 = 0,50$, $p < 0,001$) et la taille musculaire ($r^2 = 0,32$, $p < 0,001$) au T2. Finalement, la mobilité mesurée par le PEDI dépendait de la taille musculaire au T1 ($r^2 = 0,24$, $p = 0,016$) et du type d'OI, mais pas de la force musculaire.

Les résultats de cette étude ont montré que la force et la taille musculaire à la pré-puberté est positivement associé à la masse osseuse et à la mobilité fonctionnelle à maturité squelettique. Suite aux résultats de cette étude, il serait intéressant de développer des nouvelles interventions thérapeutiques visant l'hypertrophie et le renforcement musculaire durant la période de croissance pré-pubertaire, et de déterminer si ces interventions amènent des bénéfices fonctionnels à l'âge adulte.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Dr. Louis-Nicolas Veilleux. It has been a pleasure and privilege to work alongside such an inspiring and dedicated clinician scientist over the last two years. Thank you for providing me with guidance, encouragement, and with the environment and resources that were imperative for the completion of this thesis. Having the opportunity to work in Dr. Veilleux's lab meant I had access to an interdisciplinary team of kinesiologists, physiotherapists, biomedical engineers, and clinical researchers, which not only exposed me to a holistic approach to patient care, but additionally to innovative research that directly impacts patients. Thank you, Dr. Louis-Nicolas Veilleux, for making this thesis possible with your continuous support.

As well, I am grateful for Dr. Frank Rauch's support of the research project and for giving me privileged access to his decades of expertise in osteogenesis imperfecta. I would like to thank all the individuals at the Shriners Hospitals for Children®-Canada who helped foster an encouraging and inspiring environment to conduct my masters research over the last two years.

Moreover, I am especially grateful for the invaluable friendships of Sofia Addab and Jean-Gabriel Lacombe, who are both also extraordinary colleagues. I am incredibly appreciative to have had the opportunity to learn from you both while working together. Thank you for having my back and for all the laughs along the journey.

Finally, I would like to express my utmost gratitude to my family, who has always provided me with immense support, patience, and encouragement throughout my education. Growing up with my mother and sister, two strong women by my side, has pushed me to reach for my dreams and lead my projects with a strong work ethic.

PREFACE

Contribution to Original Knowledge

I certify that this thesis contains no material previously published, unless where references or acknowledgements have been made.

Contribution of Authors

The current thesis is the product of a master's research study, please find the respective contributions of the student and supporting staff as follows:

- i. Conception and design of the study: Ms. Georgia Powell, Dr. Frank Rauch, and Dr. Louis-Nicolas Veilleux
- ii. Ethics submission: Ms. Georgia Powell, Ms. Sena Tavukcu, and Dr. Louis-Nicolas Veilleux
- iii. Data collection: Ms. Georgia Powell and Ms. Sena Tavukcu
- iv. Data management, analysis, and interpretation: Ms. Georgia Powell and Dr. Louis-Nicolas Veilleux
- v. Drafting of the thesis: Ms. Georgia Powell
- vi. Review of the thesis: Dr. Louis-Nicolas Veilleux

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ABBREVIATIONS

OI	Osteogenesis Imperfecta
PEDI	Pediatric Evaluation of Disability Inventory
SHC-C	Shriners Hospitals for Children®-Canada
IRB	Institutional Review Board
pQCT	Peripheral Quantitative Computer Tomography
CSA	Cross-Sectional Area
BMC	Bone Mineral Content
ROM	Range of Motion
T1	Prepuberty Skeletal Maturity
T2	Skeletal Maturity

CHAPTER I: INTRODUCTION

1.1 Background

The World Health Organization states that a disorder is considered rare, when it affects less than one in every 2,000 individuals (1). The treatment of rare disorders present fundamentally different challenges from those of more common disorders, as their diagnosis and management are often more complex (1). Osteogenesis imperfecta (OI) is a congenital skeletal disorder that is prevalent in one in every 10,000 individuals, and thus qualifies to be considered as a rare disorder (2, 3).

Osteogenesis imperfecta is among the most debilitating bone disorders in children and adolescents (4) and is characterized by low bone mass, bone fragility, dental anomalies, short stature, and the presence of scoliosis (5). The clinical severity of OI varies from being nearly asymptomatic with a mild predisposition to frequent fractures, as well as, normal stature to profoundly disabled and can even be fatal in the perinatal period (6). Moreover, the severity of bone fragility varies widely amongst the different types of OI (7). In addition to bone fragility, previous research has shown that OI is further associated with muscle deficits and weaknesses (8-10). Given both the positive relationship between muscle force and bone strength, and how bone tissue adapts to mechanical loads imposed by forces directly generated by muscles (8), muscle weaknesses are likely a contributing factor of bone mass deficits in individuals with OI (9). Additionally, muscle weaknesses may have further functional implications in those with moderate to severe OI, as these individuals often have restricted mobility despite multidisciplinary treatment with pharmacological therapies, surgical interventions, and rehabilitation (11).

Despite the increasing evidence of both bone and muscle anomalies in children and adolescents with OI, there remains a gap in the literature with respect to investigating the

relationship between upper limb muscle and bone properties and mobility function, at prepubertal and post-pubertal growth.

1.2 Study Objectives and Hypothesis

The aim of the current thesis is to: (i) investigate the extent to which upper limb muscle strength and bone size during prepubertal growth are associated with muscle strength and bone size at skeletal maturity in individuals with moderate to severe OI, (ii) determine if upper limb muscle strength and muscle size at prepubertal growth are related to bone size and bone mass at skeletal maturity, in individuals with moderate to severe OI, and (iii) assess if muscle strength and muscle size at prepubertal skeletal maturity are associated with upper limb function at skeletal maturity in individuals with moderate to severe OI.

Given the aims of the present study, it is hypothesized that in individuals with moderate to severe OI: (i) bone size and muscle strength during prepubertal growth will be positively associated with bone size and muscle strength at skeletal maturity, (ii) upper limb muscle strength and muscle size at prepubertal growth will be positively associated with bone size and bone mass at skeletal maturity, and (iii) prepuberty upper limb muscle strength and muscle size will be positively associated function at skeletal maturity.

CHAPTER II: LITERATURE REVIEW

2.1. *Osteogenesis Imperfecta*

2.1.1. *Genetic Overview*

Osteogenesis imperfecta (OI) is typically caused by a dominant mutation in one of the two genes that code for the alpha chains in collagen type I, *COL1A1* and *COL1A2* (4, 12). These genetic mutations are associated with bone fragility, as collagen type I is the main component of the organic bone matrix, playing an instrumental role in the integrity of bone tissue (13-16). Furthermore, mutations in eighteen additional genes have been identified and associated with OI phenotypes (13). These additional genes have been shown to be expressed in osteoblast activity, with the majority of the genes directly involved in collagen type I metabolism (13). Some of these genes play an essential role in the function of osteoblasts, such as in the Wnt signaling pathways, which are cellular molecule transduction pathways (13, 14). The most common genetic sequence abnormality associated with OI is a point mutation, affecting the glycine residue on either the *COL1A1* or *COL1A2* genes, generating a combination of both normal and abnormal collagen (17). The resulting phenotype varies from mild to fatal, depending on (i) which of the two alpha chains is affected, (ii) the position in the triple helix at which the substitution arises, and (iii) the amino acid that is substituted for glycine (17).

Lindhahl et al. (2015), conducted a study examining the genetic mutation in 43 children with moderate to severe OI, and found that 31 had mutations in the *COL1A1* or *COL1A2* genes (18). Additionally, Bardai et al. (2016) studied genetic mutations in 598 individuals with OI. In individuals with OI type I, mutations in the *COL1A1* and *COL1A2* genes were detected in 100% of patients, whereas, in OI types III and IV, mutations in the *COL1A1* and *COL1A2* genes were

detected in less than 80% of patients (7). For the remaining type III and type IV patients, mutations in twelve different genes were identified (7). Other than the *COL1A1* and *COL1A2* genes, the *IFITM5* gene, a gene involved in protein coding, was the most frequently observed mutation in moderate to severe OI (7). As well, mutations in the *SERPINF1* and *CRTAP* genes, both involved in the coding of proteins, have been identified as the most common link to recessive OI (7). Recessive OI is relatively common in more severe OI compared to mild OI (7). Nonetheless, based on linkage studies on families with dominant OI, it is assumed that over 90% of individuals with OI have a *COL1A1* or *COL1A2* mutation (19-21). Some individuals with moderate to severe OI do not have a positive family history, meaning the genetic mutation was not passed down from a family member, thus initiated by a spontaneous genetic mutation (7). However, almost all individuals with a known OI phenotype have pathogenic variants in one of the known OI-associated genes.

2.1.2 Clinical Classification of OI

The most widely used clinical classification of OI is the Sillence classification, which separates OI into four distinct phenotypic types (4). OI type I is the mildest form and is usually non-deforming and often associated with normal mobility (Figure 1) (22-24). The typical features of OI type I include normal height or mild short stature and occasionally blue sclera. The genetic mutation most commonly associated with OI type I is a premature stop codon in the *COL1A1* gene (17). OI type II is fatal in the perinatal period and is associated with multiple rib and long bone fractures at birth, pronounced deformities, broad long bones, and dark sclera (4). Type III is the most severe non-fatal form of OI, and is characterized by very short stature, a triangular face, severe scoliosis, and blue sclera (4). Individuals with severe OI typically have secondary bone

deformities due to both long bone and vertebral compression fractures (25). The result of these fractures can lead to respiratory difficulties, which has been identified as the leading cause of death in this patient group (17). As well, individuals with OI type III have restricted mobility and limited ambulation (22). Chronic constipation is a gastrointestinal complication that can be severe in individuals with OI type III who have pelvic deformities (26-28). Moderate OI, classified as OI type IV, encompasses all individuals who are not clearly part of the first three types. Type IV is characterized by moderate bone deformities and variable short stature, thus the severity of OI type IV is intermediate between OI types I and III (13). The typical genetic mutation associated with OI types II, III, and IV is a glycine substitution on either of the *COL1A1* or *COL1A2* genes (17). The severity of bone fragility increases throughout the following order: type I, type IV, type III, and type II (17).

Three separate clinical entities based on distinct clinical and bone histological features, have been further delineated: OI types V, VI, and VII (29-31). OI type V and type VI are both moderate to severe forms of OI, whereas, OI type VII is a recessive form (17). These three additional rare types of OI often resemble OI type IV in regard to the severity of bone fragility. However, they are associated with specific clinical characteristics and are caused by mutations in the genes: *IFITM5*, *SERPINF1*, and *CRTAP*, respectively (13, 22).



Figure 1. Lower extremity radiographs of children with OI. (A) a young boy with OI type I. (B) a young girl with OI type III. (C) a young boy with OI type IV. (D) a young boy with OI type V. Adapted from Tauer et al. (2019) (13).

2.1.3 Additional Findings on OI

Folkestad et al. (2016) conducted a population-based study in Denmark and demonstrated that individuals with OI have an increased risk of death at any age, which can lead to a decreased life expectancy (32). The median age of death was 72.4 years for males and 77.4 years for females, which was ten and seven years earlier compared to the control population, respectively (32). Additionally, respiratory issues are a well-documented complication associated with OI. In several OI mouse models, lung histology has appeared abnormal (33-35). As such, lung function can be affected by scoliosis, which is a common feature of severe OI (34, 36, 37).

Sleep Apnea, characterized by pauses in breathing, affects less than 5% of the general population (38), however, survey results from Tosi et al. (2015) found that Sleep Apnea was present in 32% of adults with severe OI, 17% with moderate OI, and 9% with mild OI (39). Another study by Arponen et al. (2018), found that 15% of adults with OI (all types combined) had been previously diagnosed with Sleep Apnea and used a positive airway pressure ventilator during sleep (40). Nonetheless, Sleep Apnea is not a well-researched aspect OI, though it may have serious effects for individuals with moderate to severe OI.

Dental and craniofacial anatomy can be affected in individuals with OI. In the previously mentioned study from Tosi et al. (2015), survey results indicated that 75% of participants, which included more severely affected individuals with OI, noted that dental and craniofacial issues impacted their quality of life (39). Dentinogenesis imperfecta is present in several types of OI, occurring in approximately 80% of individuals with OI type III (21). Dentinogenesis imperfecta results in a discolouration of the teeth, tooth fractures, and abnormal formation of teeth. Dental

abnormalities may contribute to dysplasia of the mandible and maxilla, which frequently leads to malocclusion in individuals with OI type III and type IV (41, 42). Cranial based abnormalities are a serious complication of OI, with the potential to lead to further complications such as the compression of the structure of the posterior fossa, spinal cord syrinx formation, or hydrocephalus (43, 44). These abnormalities are uncommon in mild OI, but typically will develop in 50% of individuals with severe OI (45, 46).

2.2 Musculoskeletal Systems

2.2.1 Bone Tissue

Bone, a connective tissue that makes up the body's skeleton, provides shape and support for the body, storage of minerals, and protection of various organs. Bone marrow, the soft, spongy tissue found in the center of the bone, is involved in the development and storage of blood cells. There are three types of bone tissue: (i) compact bone, which is the harder, outer tissue, (ii) cancellous bone, which is the sponge-like tissue inside the bone, and (iii) subchondral bone, the smooth tissue at the ends of the bone, which is covered by cartilage, illustrated in Figure 2 (47).

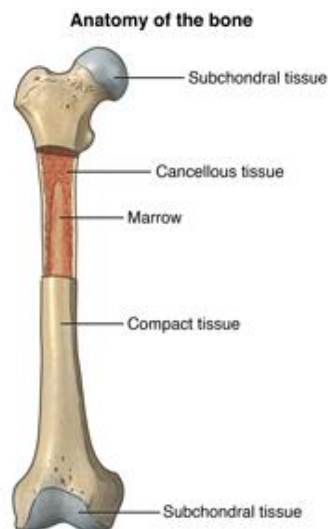


Figure 2. Anatomy of a long bone.

Adapted from: <https://www.hopkinsmedicine.org/health/wellness-and-prevention/anatomy-of-the-bone> (47).

The periosteum, a bone's tough and thin outer membrane, is replete with tunnels and canals through which bone nutrients are carried by hematic and lymphatic vessels. Bone classification originates with shape: long, short, flat, or irregular, and is also cellular: osteoblasts, osteoclasts, osteocytes, and osteoprogenitor cells (48). Osteoblasts, specialized fibroblast-like cells, synthesize the components of the extracellular matrix of the bone, such as collagen type I. Osteoclasts, large multinucleated phagocytic cells, are involved in the reabsorption of bone matrix, contributing to bone remodeling in response to growth or mechanical stress (48). Osteocytes are involved in bone turnover and the exchange of waste materials and nutrients from the bone to the bloodstream (49). Finally, osteoprogenitor cells, are mesenchymal stem cells which differentiate into osteoblasts.

2.2.2 Muscle Tissue

Muscle tissue is composed of cells that can shorten or contract, ultimately producing movement. Muscle tissue, highly vascularized, typically has long and slender cells, arranged in bundles or layers surrounded by connective tissue. The three types of muscle tissue are: smooth, skeletal, and cardiac, and are either striated or non-striated. Striated muscle cells, having filaments of actin and myosin, the contractile proteins within the muscle tissue, are organized into repeating arrays, or sarcomeres, which gives the striated appearance (50). Whereas non-striated muscle cells do not have any cross striations. Smooth muscle, non-striated, is found in the walls of various organs such as the gastrointestinal tract, bladder, uterus; and it plays a role in the regulation of blood pressure, respiration, childbirth, and digestion (51). Smooth muscle, regulated by the autonomic nervous system, contracts slowly and rhythmically, and involuntarily, thus cannot be

controlled consciously. Striated cardiac muscle is found in the walls of the heart, is also under control of the autonomic nervous system and is involuntary, non-fatiguing, and rhythmic (52). Finally, skeletal muscle, also striated, is attached to bones and responsible for skeletal movement. Skeletal muscle is under control of the peripheral component of the central nervous system and is under voluntary control (52).

Bone and muscle are functionally and anatomically interdependent making them fundamental to the movement of the human body. On an anatomical level, skeletal muscles in the extremities are attached to at least two bones, having an insertion and origin through a tendon (53). Functionally, skeletal muscle and bone mass are both regulated by several factors, some of which are shared by both systems and include: genetics, nutrition, hormones and growth factor, and mechanical stimuli (54). Muscles and bones interact through physical forces such as gravity, locomotion, or exercise, causing mechanical strain on the tissue sensed by adhesion molecules, which is translated into a biochemical response (55). These changes in mechanical loading play a crucial role in the regulation of both bone mass and strength. Schoenau et Frost (2002), defined the muscle-bone unit as the mechanical relationship between muscle and bone (56), with which a change in muscle strength should and often does have a predictable and corresponding effect on bone strength (56-62). Building upon the muscle-bone unit, and focusing on mechanical loading of both muscle and bone tissue, mechanostat is a widely researched theory originally conceptualized by Frost (1987), describing the adaptation of bone tissue to mechanical stimuli (63).

2.2.3 Mechanostat Mechanism

The mechanostat is a mechanism which monitors the adaptation of bone tissue from mechanical usage by a negative feedback loop (Figure 3) (63). The mechanostat model describes

how bone tissue adapts to mechanical forces in an optimal way to keep the maximum strain on the bone during physiological movement close to a predetermined set point (64). The largest direct force that acts on the bone is the force generated from muscles, indicating that bone tissue adapts to local muscle forces. The implication is that strong muscles should lead to strong bones and weak muscles should lead to weak bones (64).

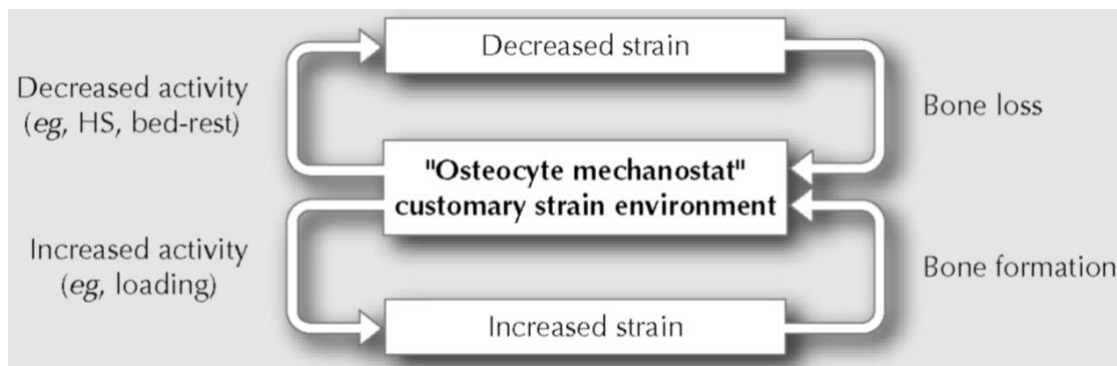


Figure 3. Schematic Overview of the Mechanostat Feedback Mechanism. Adapted from Suva et al. (2005) (65).

Exercise is an integral part of the mechanostat model. Exercise has the potential to increase peak muscle forces, imparting mechanical strain which leads to a proportional increase in bone strength (66). Nikander et al. (2005), compared the difference in the effect on bone between sports with high impact (ex: hurdles), odd impact (ex: soccer), low impact (ex: cross-country skiing), and non-impact (ex: swimming), and found that high impact sports were associated with the highest bone mineral density, while the lowest bone mineral density was found in non-impact sports (1.092g/mm^2 and 0.897g/mm^2 , respectively) (67). As well, the femoral bone cross-sectional area was significantly higher in high impact sports (407.2mm^2) and declined as the level of impact decreased to non-impact sports (294.0mm^2). As such, high impact mechanical loading and impact from atypical loading directions can be an effective method for bone strengthening (67).

Furthermore, Anliker et al. (2013) studied the differences between dominant and non-dominant leg muscle forces and bone mass in high level soccer players and found significant side-to-side differences in bone mass and geometry between the two legs (68). However, no proportional difference between muscle force and bone mineral content was found. Though, soccer is a well-balanced sport, where the non-dominant leg supports the dominant leg, thus the loading of the bone is experienced in both legs (68). This concept has been further reinforced by the comparison of dominant and non-dominant upper limbs in racket sport players (69-75). Ducher et al. (2005) studied the geometric bone changes of the dominant and non-dominant arm in response to long-term tennis playing. The results showed that total bone volume was higher in the dominant radius ($2,862.0\text{mm}^3$) compared to the non-dominant radius ($2,504.0\text{mm}^3$) and bone mineral density in the dominant and non-dominant radius was 631.3g/mm^2 and 613.0g/mm^2 , respectively (76).

In contrast, during growth, immobilization or malnutrition can result in a reduction in longitudinal bone length as well as decreased bone mass (66). Previous research has shown that periods of extended bed rest lead to a reduction in bone formation (decreased quantity of osteoblasts and mineral apposition rates) and increased bone reabsorption (increased quantity of osteoclasts and bone reabsorption makers in urine samples) (77-79). Additionally, hormones and nutrition have an influence on the mechanical load on the bone during growth. Both hormones and nutrition influence the mechanostat set point by contributing to aspects of the activity of osteoblasts and osteoclasts (80). As the mechanostat mechanism is a highly regulated function, individuals with either bone or muscle deficits may have a compromised mechanostat mechanism.

2.3 Musculoskeletal Properties in Osteogenesis Imperfecta

Considering the intricate connection between muscle and bones, it is not surprising that disorders affecting one of these tissues, typically will have an influence on both tissues (53). Given Frost's mechanostat mechanism, disorders affecting bone growth and development in children and adolescents may have an impact on muscle function (64).

2.3.1 Skeletal Deficits in Osteogenesis Imperfecta

Mendelian bone fragility disorders are associated with genetic variants which can be inherited in an autosomal dominant, autosomal recessive, or in an X linked manner (81). These genetic variants have the potential to have adverse effects on bone strength, leading to fractures caused by minimal trauma or even without any observable trauma (82). Generally, the more damaging the genetic defect is, the earlier the first fracture will occur, which typically will happen during bone growth (82). Children and adolescents with OI will often have eleven times (1,100%) more fractures compared to the general population of the same age and sex (82, 83). OI is associated with a particularly high relative risk of femur and lower leg fractures, as not only are fractures more frequent in OI, but also more severe compared to the general population (13). The rate of femur fractures in children and adolescents with mild OI, is increased 90-fold (83, 84). As such, the most common type of fracture in individuals with OI is a transverse diaphyseal femur fracture, a fracture occurring in an approximate horizontal line across the femoral shaft (85). Mutations in the *COL1A1* and *COL1A2* genes are by far the most common monogenic link to fractures in children with OI (7, 86).

There are many other genetic defects that have been identified to interfere with the production of collagen type I and have further been associated with bone fragility phenotypes (82).

As previously discussed, the typical clinical presentation of OI not only includes bone fragility but also joint hyperlaxity, discoloration of the sclera in the eye, and dentinogenetic imperfecta (87). In the more severe forms of OI, it is common for the clinical presentation to include deformities of the long bones, craniofacial skeleton, pelvis, and spine (Figure 4) (82).

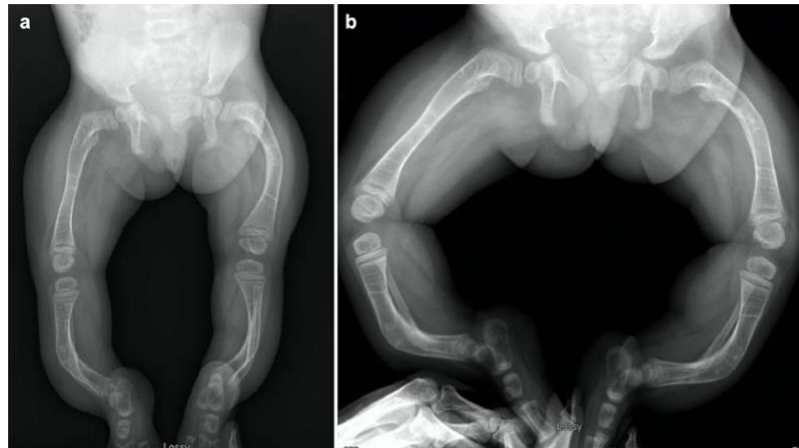


Figure 4. Lower extremity radiographs of a two-year-old girl with OI type III. (A) lateral view, and (B) bilateral view. Adapted from Wallace (2021) (88).

Short stature is a hallmark of moderate to severe OI. In OI type III, short stature may be explained by lower extremity deformities and fractures, vertebral compression fractures, and scoliosis, as these clinical observations are highly prevalent in severe OI (89). Although, a further explanation are the mutations in collagen type I that can have a direct effect on growth plate activity during bone development, leading to an overall decrease in bone length (90). Previous studies have investigated the length of the second metacarpal in individuals with OI, and the results of the studies showed normal bone length (91-93). However, these studies either had a small sample size and exclusively focused on OI type I (92) or did not compare the discrepancies between the different types of OI (91, 93). In a recent study by Rauch et al. (2020), investigating the length of all nineteen tubular hand bones in 144 individuals with OI, and with a confirmed

COL1A1 or *COL1A2* genetic mutation, it was determined that the tubular hand bones in individuals with OI type I were mostly normal, however in type III and type IV the bone length was significantly decreased (89). The results of this study highlighted the contribution of the *COL1A1* and *COL1A2* genetic mutations effect on bone growth. These mutations are not only affecting bone growth by inducing fractures and deformities, but also through deficiencies in longitudinal bone growth in bones that don't typically fracture or deform (89).

Mutations in collagen type I may play a role in irregular growth plate activity in those with OI. Growth plate abnormalities have been observed in a few individuals with OI (94, 95). From a physiological point of view, collagen type I is found in the perichondrium, a layer of dense, irregular connective tissue surrounding cartilage of developing bone, therefore mutations in collagen type I could contribute to altered growth plate activity (96).

It has been determined that compared to age-matched controls, OI bone showed a higher average mineralization density than normal bone (97). Disturbances in organic and mineral bone compounds can be associated with altered biochemical behaviour. Although mineralized OI bone may be harder at the material level (98), it is known to break much more easily when deformed, and damage from fatigue accumulates much faster on repetitive loading (99, 100). Moreover, OI is also characterized by an insufficient amount of bone, as both cortical thickness and the amount of trabecular bone is low in individuals with OI (101). At the cellular level, in OI, osteoblasts produce less bone than normal, however, the overall bone formation rate in the trabecular compartment is amplified, due to the elevated number of osteoblasts (17). Nevertheless, the increased number of osteoblasts does not lead to a net gain in trabecular bone mass as the activity of bone resorption is also enhanced (17).

Although bone fragility is the leading clinical manifestation of OI, investigations have been made into muscle weaknesses in both humans and mouse models, which has revealed altered muscle properties. Understanding the mechanisms responsible for OI muscle weakness is critical, especially considering the extensive connection between muscle and bone through mechanotransduction and biochemical signaling (102).

2.3.2 Muscle Weakness in Osteogenesis Imperfecta

While OI is primarily a bone disorder with the main clinical feature being pathological fractures, Boot et al. (2006) reported a patient case of OI type IV, with the presenting symptom being lower limb muscle weakness and the following symptom being vertebral fractures (103). A muscle biopsy was conducted and the muscle tissue was found to have increased acid phosphatase and swollen mitochondria (103). As the etiology of decreased muscle force in patients with OI is vague, these muscle weaknesses may be due to an intrinsic muscle defect. Muscle abnormalities have been reported in both OI mouse models as well as in children and adolescents with OI. The genetic mutations affecting collagen type I may have a direct impact on muscle tissue, as collagen type I is a component of the extra-cellular matrix, which surrounds muscle fibers (53, 104). There have been several clinical studies demonstrating decreased muscle strength in children and adolescents with OI (105-109). Englebert et al. (1997) showed that muscle strength differs significantly between OI types I, III, and IV (105). Type I patients had normal muscle strength but had weaker periarticular hip muscles, type III patients had significantly decreased muscle strength, which was particularly apparent in the lower extremities, and type IV patients had decreased muscle strength in the proximal muscles of both the upper and lower extremities (105). Additionally, a muscular imbalance was observed between hip extensor-flexor muscles in patients

with OI type III, hip extensors and abductors were weaker compared to hip flexors which the authors of the study suggested that in type III, this imbalance may be increased as these individuals are typically born with severely bowed legs (105). As well, factors such as (i) fractures leading to periods of physical inactivity, causing muscle atrophy or (ii) restricted mobility leading to reduced physical activity, limiting muscle development (53).

2.3.2.1 Muscle Weaknesses in the OI Mouse Model

The *oim* mouse is the most frequently used animal model of OI, with a frameshift mutation in the *COL1A2* gene, giving rise to a dysfunctional alpha-two chain (110). The heterozygous *oim/+* mouse has a mild bone phenotype (111) and Gentry et al. (2010) reported normal muscle mass in this mouse model (112). Whereas the homozygous *oim/oim* mouse, used to model severe OI, is characterized by spontaneous fractures and restricted growth, and was found to have low muscle mass, relative to body mass (112). When comparing the homozygous *oim/oim* mouse to wild type mice, the *oim/oim* mouse had less fibrillar collagen and a lower peak tetanic force relative to muscle cross-sectional area (112). However, both muscle fiber size and type distribution appeared to be normal (112). The *oim/+* mice presented with much milder functional abnormalities compared to the *oim/oim* mouse. Furthermore, results from two recent mice model studies suggest there may be a reduced physiological response to physical exertion in OI. The two studies were completed with two different OI mice models. The first by Gremminger et al. (2019), compared the difference between *oim/oim* and wildtype mice in response to weight-bearing and non-weight bearing exercise (102). The results demonstrated that *oim/oim* mice had severe mitochondrial dysfunction, which likely contributes to compromised muscle function and reduced physical activity levels (102). The second study by Tauer et al. (2021), compared the difference between

OI mice (*Col1A1*^{Jrt/+}, a dominant severe form of OI) and wildtype mice in response to wheel-running, and found the OI mice showed very mild improvements in muscle force and tolerance to fatigue following multiple weeks of exercise (113). Nevertheless, further research is needed as findings from OI mouse model studies may not be transferable to humans.

2.3.2.2 Muscle Weaknesses in Mild OI

Researchers have observed that children with OI have muscle weaknesses which can interfere with therapeutic aims to improve mobility (114). Takken et al. (2004), investigated muscular differences in seventeen children and adolescents with mild OI compared to healthy age- and sex-matched controls (115). The results of this study showed that those with OI had lower isometric force of the hip flexors, dorsiflexors, shoulder abductors, and grip force compared to healthy controls (115). As well, Caudill et al. (2010), studied ankle strength and functional limitations in twenty children with OI type I and observed plantar flexor muscle weakness compared to the control group (116). To build upon previous research, Veilleux et al. (2014) conducted a study examining lower extremity muscle function and muscle anatomy of the calf in fifty-four children and adolescents with OI type I (8). The results showed that those with OI type I had a smaller muscle size, but normal muscle density as compared to healthy age- and sex-matched controls. To assess muscle force, a mechanography was used and showed that the OI group had both lower average peak force and peak force relative to muscle cross-sectional area (8). However, the results also showed that many children with OI type I had normal muscle function, demonstrating that muscle abnormalities in OI can vary with mutations in the *COL1A1* and *COL1A2* genes (8).

The origin of muscle mass and functional deficits in OI remains unclear despite previous research efforts. Lack of physical activity may contribute to decreased muscle function in individuals with OI. However, a study from Pouliot-Laforte et al. (2015) assessing physical activity in fourteen children with OI type I was performed and showed that physical activity levels were similar between those with OI type I and healthy controls (117). The results of this study suggested that although possible, the reduction in physical activity contributes to muscle weakness in children with OI, it is unlikely to play a significant role (117).

As the previously mentioned studies provide evidence for muscle weakness in OI and given the close correlation between muscle force and bone strength (63, 118), muscle weakness and low muscle mass may contribute to bone deficits in OI (9). However, the source of the muscle phenotype in OI remains poorly understood (13). One study by Veilleux et al. (2015), assessed the muscle-bone relationship in thirty children and adolescents with OI type I, and demonstrated that those with OI type I had 17% lower peak muscle force and 22% lower tibia bone mineral content compared to age- and sex-matched controls (9). The results of this study shed light onto the muscle-bone relationship in individuals with OI type I. In addition to the clinical presentation of muscle weakness in individuals with OI, the positive correlation between muscle force and bone strength, may suggest that bone fragility could be exacerbated by muscle weakness (9). Therefore, muscle strength is an ideal therapeutic target for individuals with OI.

2.3.2.3 Muscle Weaknesses in Moderate to Severe OI

Typically, individuals with severe OI (type III) are not able to perform standard muscle function tests as they do not have the level of functional mobility necessary for many of these tests. Additionally, individuals with severe OI typically have frequent fractures, limiting their ability to

perform muscle tests, even the fear of fracturing for patients is a consideration for isometric muscle tests (53). Many individuals with severe OI have had orthopedic interventions, such as intramedullary rodding surgery, where metal rods are implanted in the spine or extremities. These metal rods limit the ability to perform both whole body scans using dual-energy x-ray absorptiometry and peripheral quantitative computed tomography, which are both widely used practices in determining lean mass (53). However, most rodding surgeries are in the spine and lower extremities, and few children have major deformities or permanent metal rods in their forearms, making the upper limb more accessible (53).

Palomo et al. (2016) performed a study with 266 children and adolescents with OI types I, III, and IV and compared the cross-sectional area of subcutaneous fat and muscle to healthy controls (119). It was determined that muscle cross-sectional area and the length of the forearm were lower in OI types I and III compared to healthy controls, however fat cross-sectional area was similar between the OI groups and healthy controls. Thus, children and adolescents with OI may have low muscle size but a normal amount of subcutaneous fat at the forearm (119). In addition, it was shown that the forearm muscle cross-sectional area provides a reasonable estimate for total lean mass in children with OI (119). Impaired upper extremity function is often associated with reduced mobility in individuals with moderate to severe OI (11). Individuals with OI type IV, are typically ambulatory, but require assistive devices such as walkers or crutches, which can be physically demanding for their upper extremities (11). The increased use of the arms for mobility may have a beneficial effect on both upper extremity muscle mass and function. Veilleux et al. (2017) assessed upper and lower extremity muscle function in twenty-seven children and adolescents with OI type IV (10). The results indicated both maximal muscle force and power were significantly lower in individuals with OI type IV compared to individuals with OI type I and

healthy controls (10). The authors of the study determined that the history of fractures was a significant negative predictor of lower limb muscle function in OI type IV, as fractures typically lead to periods of inactivity and can interfere with muscle development (10). Despite multidisciplinary treatment with bisphosphonates, intramedullary rodding surgery, and rehabilitation, muscle function deficits may contribute to reduced mobility faced by individuals with OI (11).

2.3.2.4 Additional Considerations

Collagen type I is present in bone, tendons, ligaments, skin, dentin, the sclera of the eye, and other connective tissues (120). Specifically, in tendons and ligaments, collagen type I plays a significant role in both the functional and anatomical properties, thus mutations in collagen may influence both structural and mechanical musculoskeletal properties (121, 122). Joint hyperlaxity has been described as a clinical feature of OI, further predisposing individuals with OI to ligament and tendon injuries (109). McKiernan (2005) conducted a study on the musculoskeletal impairments in 111 adults with mild OI and found that ligament weakness or instability contributed to joint hypermobility in 67% of the patients and 33% reported a previous tendon rupture (123). Tendon pathology has been investigated in the OI mouse model. Tail tendons from *oim/oim* mice were chosen for investigation as the main component of the tendon is collagen type I (122). The ultimate stress and strain for the tail tendons from *oim/oim* mice were found to be 50% weaker compared to control mice, indicating a significant reduction of the ultimate tensile strain of collagen type I in the *oim/oim* mice (122). Furthermore, ligament laxity is one of the skeletal manifestations that varies with disease severity in OI (120, 124).

2.4 Upper Extremity Function in Osteogenesis Imperfecta

Muscle weaknesses may have further functional implications in individuals with moderate to severe OI. Children with OI type III and type IV often have restricted mobility despite multidisciplinary treatments (11). A recent study from Montpetit et al. (2021), investigated the early clinical characteristics of predicting functional ambulation at skeletal maturity in 88 individuals with OI. Ambulation score was assessed at the age of five to six years old and then again at final height, between the ages of fifteen and twenty-four years old. The ability to ambulate independently at skeletal maturity was predicted by independent ambulation at the first time point, highlighting the importance of maximizing functional movement at a young age in order to have improved functional abilities throughout adulthood (22).

In previous research, functional outcomes have been evaluated through the Pediatric Evaluation of Disability Inventory (PEDI), a comprehensive clinical assessment of key capabilities and performances for functional evaluations of children with disabling conditions (125). PEDI measures function in three domains: social, self-care, and mobility. The assessment specifically measures upper extremity functional skills (ex: toileting, feeding, brushing teeth, walking with crutches, or propelling a manual wheelchair). PEDI is one of the most reliable methods for evaluating comprehensive function of the upper extremities (126). Previous research from Land et al. (2005) and Ruck et al. (2011) used PEDI as a validated outcome measure to determine functional skills of individuals with OI (127, 128). In one study by Amako et al. (2004), PEDI was used to assess upper limb functional outcomes in 159 children with OI (129). The results of this study showed that children with OI type III were the least independent in self-care and mobility, and individuals with type IV had the second lowest score in both self-care and mobility compared to OI type I and type V (129). There was a significant correlation between upper limb long bone

deformity angle and PEDI score. Mild and unilateral deformities limited mobility but not self-care, but severe deformities limited both mobility and self-care (129). Moreover, the results from this study led researchers to further investigate if correction of upper limb deformities could improve function in individuals with OI. Ashby et al. (2018) conducted a chart review on nineteen children with moderate to severe OI, all of whom underwent twenty-two corrective forearm procedures. Functional ability was assessed preoperatively and every year postoperatively using the PEDI self-care and mobility domains (130). Corrective surgery on the upper limbs in those with OI produced significant short-term functional improvements, with most maintained in the long term (130). Improved long term function was likely a result of a combination of several factors, including a reduced fracture risk, the child's increased confidence in using the arm, improved grip strength, and improved functional arm length (130). Overall, a reduction in upper limb function can significantly impair practical activities of daily living for individuals with OI.

2.5 Current Treatments

Physiotherapy, rehabilitation, pharmacological therapy, and orthopedic surgery are the mainstay of treatment for patients with OI (106, 131). The therapeutic goals in OI can vary with phenotype and mobility status. Typically, orthopedic and rehabilitation treatments for individuals with OI type I, focus on fracture management (87). In mild OI, medical follow-up focuses on screening for complications, such as vertebral compression fractures, which may prompt for intravenous bisphosphonate treatment (132-134). As the disease severity varies for moderate to severe OI, type III and type IV are often associated with long bone deformities, scoliosis, and restricted mobility, therefore treatment is typically focused on rehabilitation and orthopedic interventions. Rehabilitation efforts aim to increase mobility, improve physical functioning, and

other functional capabilities (106, 135). Physiotherapy will typically focus on muscle strengthening, increasing joint flexibility, and bone mass. As well, physical activity programs are encouraged to prevent contractures and immobility-induced bone loss (131). Furthermore, orthopedic measures such as intramedullary rodding, bracing, splints, and shoe insertions, are all common in the treatment of OI. Intramedullary rodding surgery is used to straighten bones and sometimes standing and walking is only possible after rods have been placed, illustrated below in Figure 5 (131, 136, 137). Intramedullary rodding can be successful, though it does not alter the extreme bone fragility, therefore, medical interventions aiming to strengthen skeletal parameters are still essential (17).



Figure 5. Various rod implants in a young girl with OI throughout growth. Adapted from Biggin et Munns (2017) (138).

2.5.1 Pharmacological Treatments

In the medical management of OI, the most widely used treatment modality is bisphosphates therapy, which aims to decrease pain and increase bone mineral density in children and adolescents with both mild and severe OI (25). Bisphosphonate is a family of drugs, that are

potent antiresorptive agents, acting by inhibiting osteoclasts, thereby preventing bone resorption (139). There are two different types of bisphosphonates, nitrogenous and non-nitrogenous. Nitrogenous bisphosphonates disrupt osteoclast formation, survival, and cytoskeletal dynamics, and are drugs such as alendronate, pamidronate, or zoledronate (139). Whereas, non-nitrogenous bisphosphonates initiate osteoclast apoptosis, and are drugs such as clodronate or etidronate (139). It has been heavily reported that bisphosphonate treatment in OI leads to an increase in areal bone mineral density of the spine and other skeletal sites and a reduction in fracture rates (87, 139). Moreover, previous research from Montpetit et al. (2003), demonstrated that in children and adolescents with severe OI, maximal isometric grip force increased after a single cycle of intravenous pamidronate, and this increase in grip force was maintained for at least two years (140). Subsequently, Land et al. (2006), studied the effect of a three-year treatment of intravenous pamidronate therapy on functional abilities in children with moderate to severe OI (127). The results from this study showed that functional mobility and grip force was significantly higher in patients who received treatment compared to age- and disease severity matched controls (127). A history of bisphosphonate treatment can be an indicator of disease severity, as patients with mild OI typically will not receive bisphosphonate treatment (87). Even though there is no cure for the genetic mutation causing OI, many longitudinal studies in children with severe OI have found that intravenous bisphosphonate therapy can be associated with increased bone mass, reshaping of compressed vertebral bodies, and decreased fracture rates (127, 141-144).

Ensuring that vitamin D serum levels remain sufficient is a frequently cited goal in the medical management of OI (21, 145, 146). Previous research from two cross-sectional retrospective studies showed a positive association between vitamin D status and bone mineral density (147, 148). Additionally, research from Plante et al. (2016) conducted a randomized

control trial of 60 children with OI that compared two doses of vitamin D supplementation: 400 vs 2000 international units (IU). The increase in mean vitamin D serum levels was significantly higher in the group that received the 2000IU supplementation compared to the 400IU (149).

The treatment of OI is not limited to pharmacological approaches, as often a multidisciplinary approach is required. Typically, the overall treatment goal for children with moderate to severe OI is to improve functional outcomes, such as mobility or self-care, thus enabling patients to live more independently throughout adulthood (150).

2.6 Research Questions

The literature review presented above sheds light onto the impact muscle strength has on bone properties. Thus, there is a need to explore the interaction between the upper limb muscle-bone relationship and mobility function in individuals with OI. As such, it could lead to the identification of new conservative therapeutic targets. While previous research has demonstrated that individuals with OI have both low bone density and muscle weaknesses, there remains a gap in the literature regarding the association between bone and muscle properties from prepuberty to post-puberty and upper limb function in those with moderate to severe OI. Hence, here lies our interest in conducting a retrospective study to investigate the association between bone and muscle properties and upper limb function in individuals with moderate to severe OI. Thus, this study will systematically address the following research questions:

- (i) To what degree is upper limb muscle strength and bone size, during childhood, associated with muscle strength and bone size at adulthood in individuals with moderate to severe OI.

- (ii) Does upper limb muscle strength and muscle size at prepuberty have an impact on upper limb bone mass and bone size at skeletal maturity in individuals with moderate to severe OI.
- (iii) Does upper limb muscle strength and muscle size at prepubertal growth provide valuable insight into mobility function at skeletal maturity, for individuals with moderate to severe OI.

CHAPTER III: METHODOLOGY

3.1 Study Design

This is a retrospective medical chart review of individuals with osteogenesis imperfecta, type III and type IV, analyzing muscle and bone properties and upper limb function at two time points. The study population is a consecutive case review, including all patients meeting inclusion criteria to minimize bias.

3.2 Ethics Committee Approval

The study protocol was presented to the Shriners Hospitals for Children®-Canada's (SHC-Canada) Clinical Research Committee, which consists of clinicians from various departments and the hospital's director of research. The committee reviewed the study, assessed the feasibility and resources, and granted approval in June 2021. Furthermore, study approval from the SHC-Canada hospital administrator was granted in July 2021. Several documents including the (i) study protocol, (ii) study delegation log, and (iii) request for headquarter review were prepared and submitted to SHC Headquarters, Department of Research Programs in July 2021. All study personnel were included on the study delegation log, which comprised of the principal investigator, co-investigator, clinical research coordinators, and the student. Prior to the initiation of the study, all study personnel were required to complete the necessary training and applications, which included: (i) Ethics/Human Subject Protection, (ii) Good Clinical Practice-GCP, Collaborative Institutional Training Initiative, (iii) Hospital administrator's approval of the Shriners Hospital Advanced Practice Professional application (curriculum vitae, Tri-Council Policy Statement: Ethics Conduct for Research Involving Humans Course on Research Ethics (TCPS 2:CORE),

education certificates, application documents, and two reference letters), (iv) Medical Research Confidentiality Statement, (v) Medical Research Security Access, and (vi) KnowBe4 Security Awareness Training. The study documents were verified by SHC Headquarters, Department of Research Programs and approval was granted in August 2021. The final step in obtaining study approval was a new study submission to the McGill University, Faculty of Medicine and Health Sciences, Institutional Review Board (IRB). The new study submission consisted of the completion of: (i) Initial Review Form, (ii) Study Protocol, (iii) Study Documents (data collection documents), (iv) Scientific Review Form completed by an expert in the field with no conflict of interest, (v) A letter detailing the study and rationale, and (vi) Approval letter from the SHC Headquarters. As this study involved minimal risk to participants, it qualified for an expedited review. McGill IRB granted study approval in August 2021.

Following both SHC Headquarters and McGill IRB ethical approval, the Request of Medical Records was submitted to the Health Information Services and Medical Imaging Department at the SHC-Canada, approved by the hospital administrator, and was granted approval in August 2021.

During data collection, a study amendment was submitted in early November 2021 to McGill's IRB. As the study looks to compare data from two time points, a substantial amount of patient data from the first time point had not been uploaded onto the electronic medical record system and remained in paper medical charts. As such, an amendment was submitted to expand data collection to not only include retrieving data from patient's electronic medical records, but as well, from paper medical charts requested from the necessary departments. Data collection resumed immediately after acquiring IRB approval in November 2021.

3.3 Study Eligibility Criteria

In order to be deemed eligible to be included in this study, patients must have met the inclusion criteria, which consisted of the following: (i) Patients who are followed at the SHC-Canada, with a clinical diagnosis of OI, type III or type IV, and (ii) Patients who have had at least two peripheral quantitative computer tomography (pQCT) scans: (1) between the ages of five and eleven years old and (2) at skeletal maturity, which is defined by a change in height that is less than two centimeters per year. There were no exclusion criteria for this study. As the study population was a consecutive case review, it entailed all eligible pediatric patients of all genders and ethnic backgrounds.

3.4 Study Procedures

3.4.1 Overview

Patient data was retrieved by examining previously collected data from patients with OI, who have been followed at SHC-Canada, that meet the study eligibility criteria. Patient data was extracted from their electronic medical records or paper medical charts requested from the appropriate department by study personnel. All patient data was de-identified and recorded on a password protected document and stored on a Shriners Hospital computer in the principal investigator's office. Patient data was collected at two time points: (T1) between the age of five and eleven years old and (T2) at skeletal maturity (for females approximately over the age of fourteen years old and for males approximately over the age of sixteen years old). Skeletal maturity was defined by a change in height that is less than two centimeters per year. Patient data collected at both time points included: (i) anthropometric data, (ii) radius pQCT data, measured at the 65% site of the proximal radius, (iii) upper limb muscle strength, (iv) upper limb range of motion, and

(v) upper limb function. The period of data collection of medical information is from January 1st, 2003 – July 26th, 2021. All other medical chart information was not used from data sources outside of this study period.

3.4.2 Subject Selection

The department of Health Information Services and Medical Imaging at the SHC-Canada provided study personnel with a comprehensive list of previous in-patients with a OI diagnosis from January 2003 – July 2021. Study personnel did a preliminary screening for eligible patients, based on clinical diagnosis, and identified all OI type III and type IV patients. A secondary screening based on the study eligibility criteria was completed. All available data on patient's electronic medical records was collected, and when available, missing data was extracted from paper medical charts from the rehabilitation department and the clinical biomedical laboratory.

3.4.3 Data Storage

Individuals that met the study inclusion criteria were de-identified and assigned a study ID number. Direct subject identifiers were stored as key codes and were kept separately from the study data set. Patient's medical record number, date of birth, and corresponding study ID number were saved in a password protected Excel file which was stored on a Shriners Hospital computer in the office of the principal investigator. The key code is the only link that re-identifies the study participant to their health information, all other patient data has been de-identified. All study management information was recorded in the Shriners Hospital's clinical trial management system, OnCore. All study records will be retained and stored in the principal investigator's office for seven years as per the *Clinical Research Records Retention and Storage* policy at the SHC-Canada.

3.5 Data Collection

The “Minimum Necessary” standard has been applied to this study, indicating that only the reasonably necessary amount of data required to answer the research questions has been extracted (151). The collected data elements are outlined below is Table 1.

Table 1. Elements of data collection.

Data Collection Parameters:			
Patient Characteristics	Anthropometric Data	(I)	Date of birth
		(II)	Sex
		(III)	Height
		(IV)	Clinical diagnosis
Treatment	Bisphosphonate Treatment	(I)	Treatment status
		(II)	Time under treatment
Bone and Muscle	pQCT Data: at the 65% site of the radius	(I)	Total cross-sectional area of the radius
		(II)	Total bone mineral content of the radius
		(III)	Cross-sectional area of the forearm muscle
Joint Amplitude	Range of Motion	(I)	Elbow
		(II)	Wrist
Muscle Strength	Grip Strength	(I)	Dominant hand
		(II)	Non-dominant hand
Function	PEDI	(I)	Mobility domain
		(II)	Self-care domain

3.5.1 Peripheral Quantitative Computed Tomography (pQCT)

Peripheral quantitative computed tomography (pQCT) is a non-invasive tool for examining cross-sectional images of long bones as well as bone size, shape, mineral density, and muscle size. Radius pQCT is performed at the non-dominant forearm using Stratec XCT2000 equipment (Stratec Inc., Pforzheim, Germany) and the manufacturer’s software package (version XCT 6.00B) (152). Two sites on the radius are assessed, located at 4% and 65% of the forearm length proximal

to the reference line at the distal radius (152-154). These locations represent metaphysis and diaphysis, the 4% and 65% sites, respectively (Figure 6). At both locations, a single tomographic slice of 2.0mm thickness is taken at a voxel size of 0.4mm x 0.4mm x 2.0mm (153). The speed of the translational scan movement is typically set at 15mm/s (153). At the metaphysis, the 4% site, the outer bone contour is detected at the default threshold of 280 mg/cm³. The diaphysis, the 65% site, is analyzed at a threshold of 710 mg/cm³, using the equipment's default settings (153). Total cross-sectional area (CSA), total volumetric bone mineral density, and trabecular volumetric bone mineral density are calculated using the software's CALCBD routine (153). Whereas bone mineral content (BMC) is calculated as the product of the total cross-sectional area and total volumetric bone mineral density (153). Results of radius pQCT analyses are transformed to age-specific z-scores using published reference data (152-154).

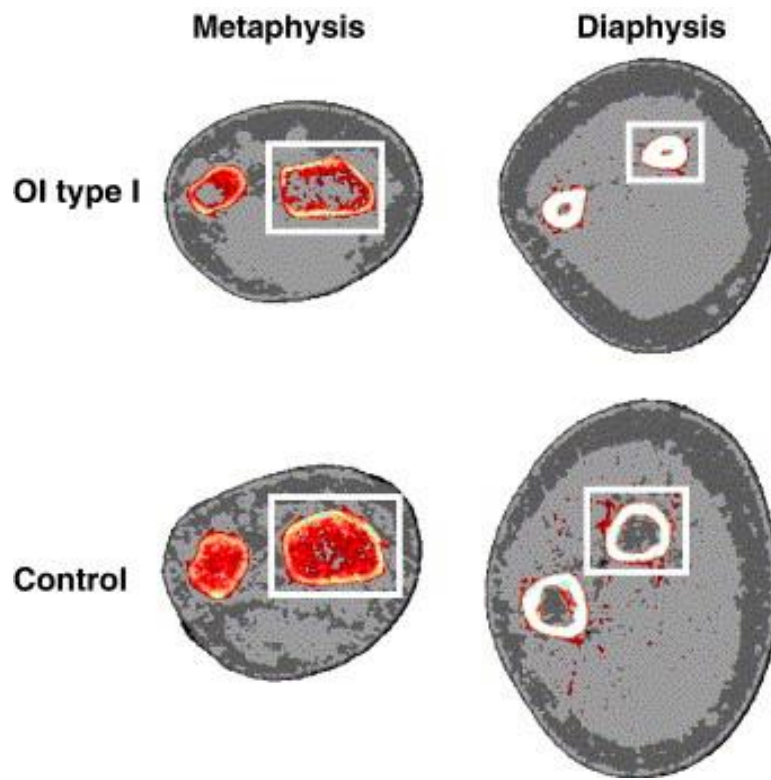


Figure 6. pQCT images of both the metaphysis (4% site) and diaphysis (65% site) of the radius. The radius is specified by the white square boxes. The top images are results taken from an 8-year-old girl with OI type I and the lower images are from an age-and-sex-matched control. Adapted from Rauch et al. (2005) (92).

All pQCT data is reviewed and verified by the director of the clinical biomedical laboratory at the hospital prior to being uploaded onto the electronic medical record system. This secondary verification step ensures all pQCT scans are accurate and incorrect data entry is minimal. Moreover, the positioning of patient's forearm for radius pQCT scans ensures that scans are of high quality with minimal artifacts, as the patient's wrist and elbow are both secured, see Figure 7 below.

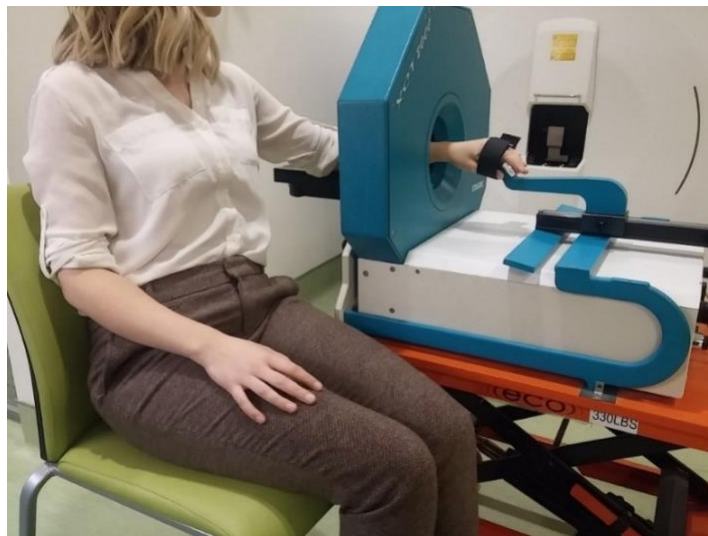


Figure 7. Radius pQCT positioning. The forearm is held in a secured position with minimal ability to move throughout the scan.

3.5.2 Rehabilitation

Nearly all patients at the SHC-Canada are followed by a rehabilitation program, consisting of regular assessments of developmental and self-care milestones, range of motion, ambulation

status, and strength measurements of the upper and lower extremities (22). Treatment interventions depend on the needs of each patient. Furthermore, family education regarding strengthening of upper and lower extremities and gentle stretching is a crucial component of physiotherapy for the OI patient population (22). Upper limb muscle strength is evaluated by the grip strength test. Grip strength is assessed using a Jamar hydraulic hand-held dynamometer (Preston, Jackson, Michigan, USA). Patients are typically seated and instructed to squeeze the hand-held dynamometer with maximal effort. The test is repeated three times on both the dominant and non-dominant side. The maximum value of the three tests for each side is taken as the final score per side and is measured in pounds (lbs). Results are further transformed into age- and sex-specific z-scores.

Additionally, range of motion (ROM) is part of the standard assessment for patients with OI at the SHC-Canada. Typically, upper limb ROM is assessed using a goniometer by therapists during annual appointments. Upper limb ROM is assessed at various joints including the shoulder, elbow, and wrist. As the elbow and wrist are the joints encompassing the radius, these are the measurements of interest. The therapist instructs the patient to move each joint in a series of movements, depending on the joint and the individual's mobility level. For the elbow the movements are flexion (0-150 degrees), extension (0-150 degrees), pronation (0-90 degrees), and supination (0-90 degrees) for both arms in passive and active measurements. Passive ROM is when the therapist assists in the movement, whereas active ROM is when the patient carries out the movement by themselves. For the wrist the typical movements are flexion (0-80 degrees) and extension (0-70 degrees), in both passive and active measurements. The results are recorded as either the degree of motion or '*within normal limits*' or '*limited*'.

Finally, occupational therapists work closely with patients to develop self-care skills, provide the appropriate aids for mobility, and work to incorporate developmentally appropriate

activities into home programs (22). The PEDI questionnaire is administered annually by occupational therapists through a combination of parent and patient interviews and observations of the patient's performance (22). The items of the self-care and mobility domains require the use of the upper extremities and therefore, scores are considered as a proxy for upper limb function. The use of the upper limbs are also critical for performing activities of daily living for this patient population. Each item is scored as either zero or one, indicating unable or able to perform the task, respectively. A raw score is tabulated by summing up the numbers of tasks performed (22). The scoring ranges from 0-73 on the PEDI-self-care domain, indicating no-function to full function and for the PEDI-mobility domain the scoring range is between 0-59, denoting no mobility to full mobility.

3.6 Research Endpoints

3.6.1 Primary Endpoints

The primary outcome of interest of this study is the association among muscle strength and bone size between (T1) Prepubertal skeletal maturity and (T2) Skeletal maturity in individuals with moderate to severe OI. To assess the relationship between muscle and bone properties between both time points, the primary endpoints are as follows:

- i. Cross-sectional area of the total radius at 65% (mm²)
- ii. Grip strength (lbs)

3.6.2 Secondary Endpoints

The secondary outcomes of interest are the association between muscle and bone properties and function between (T1) Prepubertal skeletal maturity and (T2) Skeletal maturity in individuals with moderate to severe OI. To evaluate this relationship the secondary endpoints are as follows:

- i. Cross-sectional area of the total radius at 65% (mm²)
- ii. Bone mineral content of the total radius at 65% (mg/mm)
- iii. Cross-sectional area of the forearm muscle at 65% (mm²)
- iv. Grip strength (lbs)
- v. Range of motion of both the elbow and wrist (degrees)
- vi. PEDI Mobility domain scores (self-reported questionnaire)

3.7 Statistical Considerations

Descriptive statistics are presented as means and standard deviations. Based on previous research from Montpetit et al. (2021), of functional predictive relationships between growth and skeletal maturity in children OI (22), and from Veilleux et al. (2014) and Veilleux et al. (2015), on the muscle-bone relationship in children with OI (8, 9), stepwise regression analyses will be used.

To determine which factors to input into the regression models, bi-variate correlations were conducted with height, muscle properties (grip strength and muscle CSA), bone properties (bone CSA and BMC), and function parameters (PEDI) at both time points. To assess the relationship between muscle parameters (grip strength and muscle CSA) and bone mass, additional correlations were computed. Specifically, to assess the association between both bone and muscle properties and upper limb function at T1 and T2, independent stepwise linear regression analyses were performed. Various linear regressions were computed with the following parameters set as dependent variables: bone CSA, BMC, muscle CSA, grip strength, and PEDI Mobility. Bisphosphonate treatment status was not included in the analyses as amongst the study cohort at both time points, there was a high percentage of patients receiving treatment. To determine if grip strength and bone CSA during prepuberty growth were associated with grip strength and bone

CSA at skeletal maturity, multiple regression models were generated with T2 grip strength and T2 bone CSA set as dependent variables. Independent predictors were set as: T1 grip strength, T1 bone CSA, sex (male: 0, female:1), OI type (0: type III, 1: type IV), and height (expressed as age- and sex specific z-scores; a disease severity marker in OI (9)). Additional regression analyses were performed to assess the relationship between T1 muscle properties (grip strength and muscle CSA) and T2 bone parameters (bone CSA and BMC), with T2 bone parameters set as dependent variables. Independent predictors were T1 muscle properties (grip strength and muscle CSA), sex (male: 0, female:1), and OI type (0: type III, 1: type IV). Finally, to assess if muscle strength and muscle size at prepubertal growth were associated with upper limb function at skeletal maturity, regression analyses were conducted with T2 PEDI Mobility and T1 muscle properties (grip strength and muscle CSA). T2 PEDI Mobility was set as the dependent variable and the independent predictors were T1 muscle properties (grip strength and muscle CSA), sex (male: 0, female:1), and OI type (0: type III, 1: type IV). Z-scores of the included parameters were incorporated into statistical computations when available.

A general linear model was conducted to determine if there were significant differences in muscle, bone, and functional parameters between both the OI type III and type IV study cohorts. A one-way ANOVA was conducted to evaluate if there were significant differences in z-scores between T1 and T2 of the following parameters: height, bone CSA, BMC, muscle CSA, and grip strength.

All statistical analyses were carried out with a significance level (alpha) of 0.05. Statistical analyses were conducted using the statistical analysis software SPSS, version 25 (SPSS, Inc., Chicago, IL, USA).

Assuming an effect size of 0.15, which is considered as medium according to Cohen (1988) (155), a significance level of 0.05, a power of 0.80, and setting the number of predictors to four (muscle size, muscle strength, range of motion, and function), the estimated sample size required is 55. The sample size was calculated using G-Power (156). As this is a retrospective study, which included patient data from 2003 – 2021, this sample size was obtainable given the vast OI patient population treated at the SHC-Canada.

CHAPTER IV: RESULTS

4.1 Sample Characteristics

In total, 63 patients (39 females, 24 males) were eligible to be included in this study. Of the 63 patients, 13 patients (7 females, 6 males) had a diagnosis of OI type III and 50 patients (31 females, 19 males) had a diagnosis of OI type IV. At T1, patient's age ranged from 7 to 11 years old, with a mean age of 9.37 years old (SD = 1.30). At T2, patient's age ranged from 12 to 21 years old, with a mean age of 17.21 years old (SD = 2.41). The mean height measured at T1 was 114.84 cm (SD = 12.02), with a mean z-score of -3.35 (SD = 1.94). At T2, the mean height was 135.39 cm (SD = 16.09) with a mean z-score of -4.05 (SD = 1.78). The number of study participants who received treatment of bisphosphonates at T1 was 51 patients, and at T2 was 25 patients. Sample characteristics of the OI type III and type IV groups are outlined below in Tables 2 and 3, respectively.

Table 2. OI type III T1 and T2 sample characteristics.

	T1 Mean (SD)	T2 Mean (SD)	Δ
N (male/female)	13 (6/7)		
Age (years)	9.23 (1.36)	18.54 (2.11)	9.31
Height (cm)	103.15 (9.47)	120.12 (14.35)	16.97
Height Z-score	-5.26 (1.94)	-6.02 (2.16)	-0.76
Bisphosphonate Treatment Status (N)	10	8	—

Note. Δ = delta values.

Table 3. OI type IV T1 and T2 sample characteristics.

	T1 Mean (SD)	T2 Mean (SD)	Δ
N (male/female)	50 (18/32)		
Age (years)	9.40 (1.30)	16.86 (2.38)	7.46
Height (cm)	117.44 (10.93)	138.80 (14.55)	21.36
Height Z-score	-2.93 (1.67)	-3.73 (1.51)	-0.80
Bisphosphonate Treatment Status (N)	41	17	—

Note. Δ = delta values.

4.2 Correlations

Various bi-variate correlations were conducted with height, bone, muscle, and function parameters at T1 and T2. Taken together, the Pearson correlation between T1 and T2 height for both OI types is $R = 0.77$ ($P < 0.001$), and between T1 and T2 height z-score is $R = 0.83$ ($P < 0.001$). For the OI type III group, the Pearson correlation between T1 and T2 height is $R = 0.84$ ($P = 0.001$) with the T1 and T2 height z-score correlation equal to $R = 0.88$ ($P = 0.01$). For the OI type IV group, the correlation between T1 and T2 height is $R = 0.70$ ($P < 0.001$) with the T1 and T2 height z-score correlation equal to $R = 0.76$ ($P < 0.001$).

To determine the muscle-bone relationship between total BMC and both muscle CSA and grip strength, correlations were computed at both T1 and T2, as illustrated in Figures 8 and 9 below, respectively.

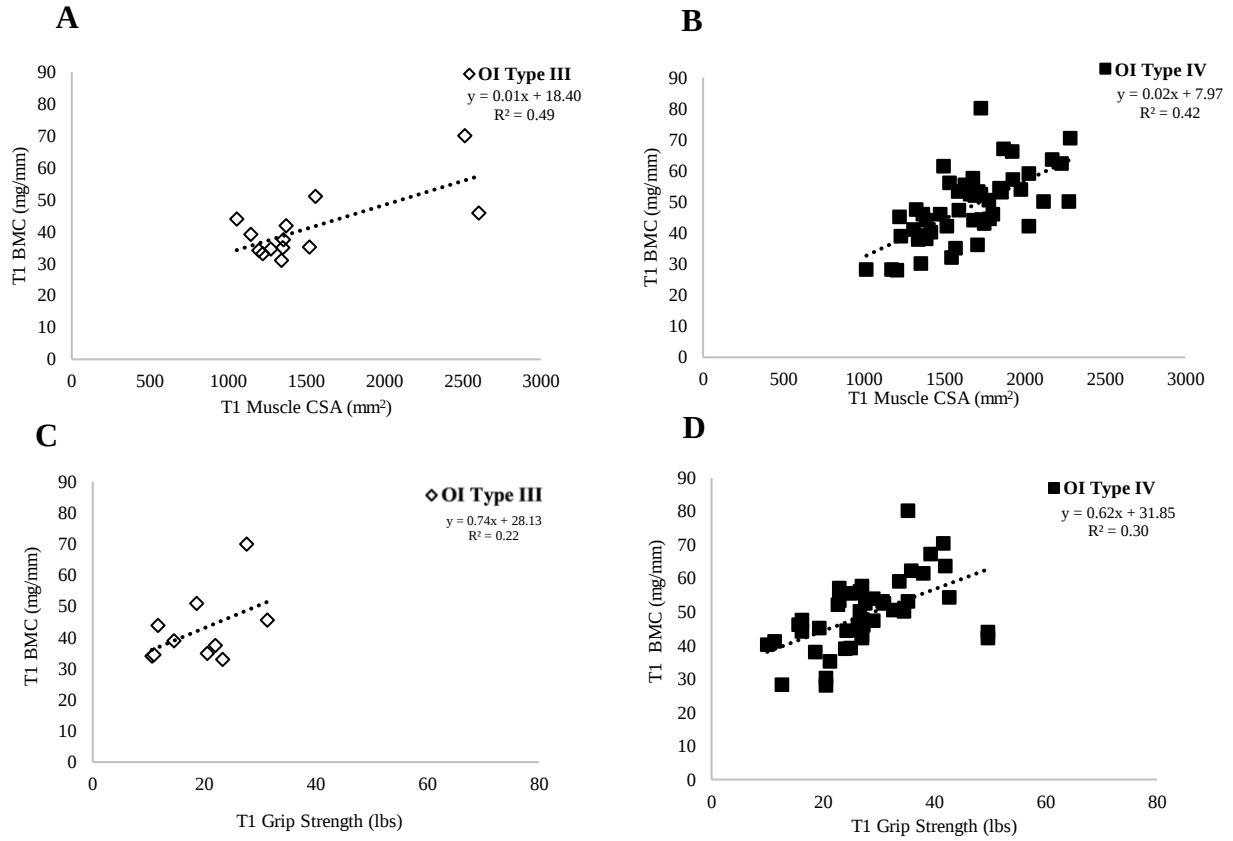


Figure 8. Illustration of the muscle-bone relationship at T1 between total BMC and muscle properties. (A) OI type III total BMC (mg/mm) and total forearm muscle CSA (mm²). (B) OI type IV total BMC (mg/mm) and total forearm muscle CSA (mm²). (C) OI type III total BMC (mg/mm) and grip strength (lbs). (D) OI type IV total BMC (mg/mm) and grip strength (lbs).

Note. All BMC (mg/mm) and CSA (mm²) parameters were measured at the 65% site of the radius by pQCT imaging.

At T1, for the OI type III group, there was a positive association between total BMC (mg/mm) and both forearm muscle CSA (mm²) ($R = 0.71$, $P = 0.01$) and grip strength (lbs) ($R = 0.47$, $P = 0.17$). As well, for the OI type IV group, there was a positive association between total BMC (mg/mm) and both forearm muscle CSA (mm²) ($R = 0.65$, $P = 0.58$) and grip strength (lbs) ($R = 0.55$, $P < 0.001$).

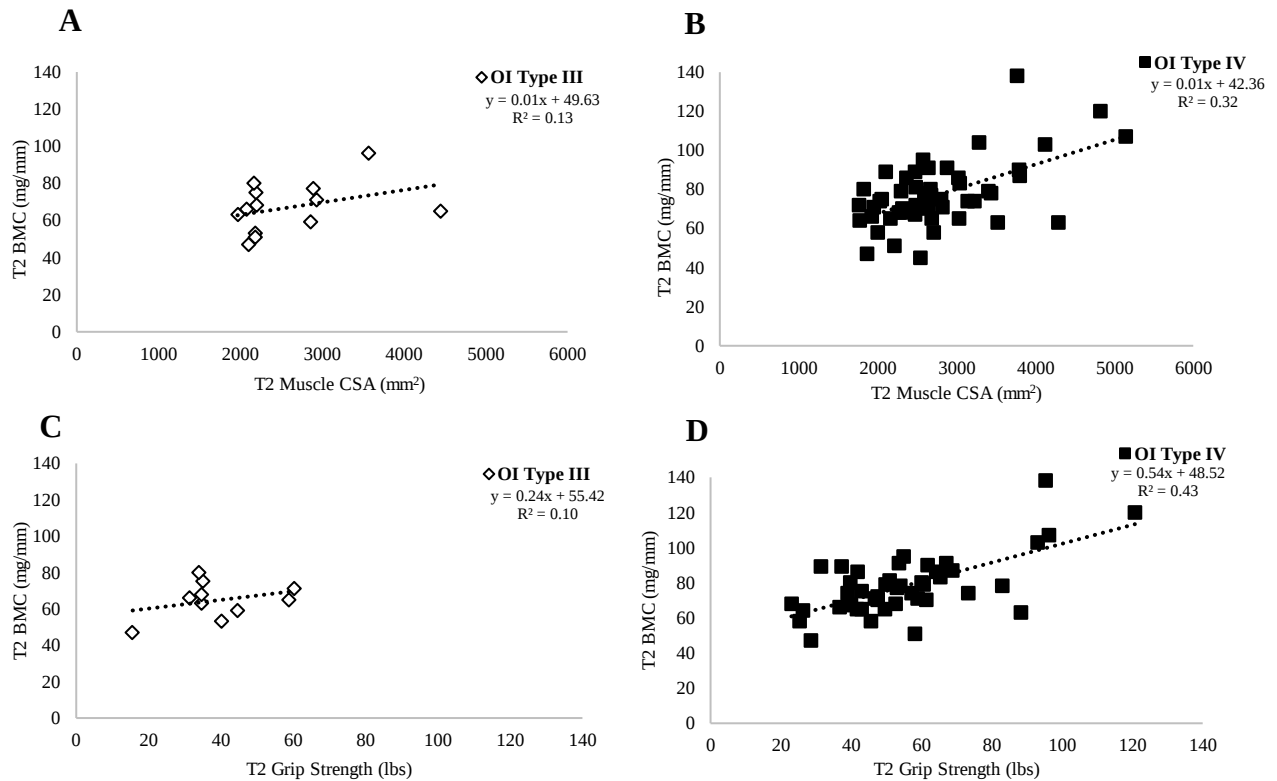


Figure 9. Illustration of the muscle-bone relationship at T2 between total BMC and muscle properties. (A) OI type III total BMC (mg/mm) and total forearm muscle CSA (mm²). (B) OI type IV total BMC (mg/mm) and total forearm muscle CSA (mm²). (C) OI type III total BMC (mg/mm) and grip strength (lbs). (D) OI type IV total BMC (mg/mm) and grip strength (lbs). *Note.* All BMC (mg/mm) and CSA (mm²) parameters were measured at the 65% site of the radius by pQCT imaging.

At T2, for the OI type III group, there was a positive association between total BMC (mg/mm) and both forearm muscle CSA (mm²) ($R = 0.37$, $P = 0.22$) and grip strength (lbs) ($R = 0.32$, $P = 0.58$). For the OI type IV group, there was a positive association between total BMC (mg/mm) and both forearm muscle CSA (mm²) ($R = 0.57$, $P < 0.001$) and grip strength (lbs) ($R = 0.66$, $P < 0.001$).

To determine the muscle and bone parameter associations with mobility function, Pearson correlations with PEDI Mobility were conducted and resulted in low and moderate, positive

correlations at T1 and T2. Pearson correlations with T1 PEDI Mobility and T2 PEDI Mobility are outlined below in Tables 4 and 5, respectively.

Table 4. Pearson correlations with T1 PEDI Mobility.

	Variable	R	P
T1 PEDI Mobility	T1 total CSA z-score	0.49	<0.001
	T1 total BMC z-score	0.50	<0.001
	T1 muscle CSA z-score	0.29	0.03
	T1 grip strength z-score	0.45	0.001
	T2 PEDI mobility	0.36	0.04

Table 5. Pearson correlations with T2 PEDI Mobility.

	Variable	R	P
T2 PEDI Mobility	T2 total CSA z-score	0.32	0.05
	T2 total BMC z-score	0.38	0.02
	T2 muscle CSA z-score	0.43	0.01
	T2 grip strength z-score	0.36	0.03
T2 PEDI Mobility	T1 total CSA z-score	0.27	0.10
	T1 total BMC z-score	0.37	0.02
	T1 muscle CSA z-score	0.39	0.02
	T1 grip strength z-score	0.31	0.08

4.3 Regressions

To determine the association between T1 and T2 bone properties, stepwise regression models were generated with T2 total CSA and BMC z-scores set as dependent variables. Based on the previous results of the bi-variate correlations, for all models, the following variables were set as predictors: T1 total radius CSA and BMC, z-scores. The regression analyses indicated that T2

total CSA was predicted separately by (i) T1 total CSA, independent of OI type and sex and (ii) T1 total BMC, OI type, and sex. T2 total BMC was determined separately by (i) T1 total BMC, independent of OI type and sex and (ii) T1 total CSA, OI type, and sex (Table 6).

Table 6. Skeletal predictors of T2 bone parameters at the 65% site of the radius.

	Regression Equation	R²	N	P
T2 Total CSA (z-score)	-1.11 + 0.67 (T1 total CSA; z-score)	0.49	60	<0.001
T2 Total CSA (z-score)	- 2.60 + 0.65 (T1 total BMC; z-score) + 0.80 (OI type; 0,1) - 0.15 (sex; 0,1)	0.54	62	<0.001
T2 Total BMC (z-score)	- 0.77 + 0.70 (T1 total BMC; z-score)	0.56	62	<0.001
T2 Total BMC (z-score)	- 2.40 + 0.35 (T1 total CSA; z-score) + 1.16 (OI type; 0,1) + 0.81 (sex; 0,1)	0.40	60	<0.001

Note. Abbreviations: CSA: cross-sectional area, BMC: bone mineral content. OI type (0: type III, 1: type IV), sex (0: males, 1: females).

To assess the association between T1 and T2 muscle parameters, stepwise regression models were generated with T2 muscle parameter (grip strength and forearm muscle CSA) z-scores set as dependent variables and analyzed separately according to sex (Table 7). For each of these models, the following parameters were set as predictors: T1 grip strength and muscle CSA, z-scores. For females, the regression analyses indicated that T2 grip strength was predicted separately by (i) T1 grip strength, independent of OI type and height and (ii) OI type, independent of T1 forearm muscle CSA and height. T2 forearm muscle CSA was determined separately by (i) T1 forearm muscle CSA and (ii) T1 grip strength, both independent of OI type and height. For males, T2 grip strength was predicted separately by (i) T1 grip strength and height and (ii) T1 forearm muscle CSA and height, both independent of OI type. T2 forearm muscle CSA was separately determined by (i) T1 forearm muscle CSA and OI type and (ii) T1 grip strength and OI type, both independent of height.

Table 7. Muscle predictors of T2 muscle parameters.

	Regression Equation	R²	N	P
<i>Female</i>				
T2 Grip Strength (z-score)	- 0.44 + 0.39 (T1 grip strength; z-score)	0.29	27	0.003
T2 Grip Strength (z-score)	-2.24 + 0.98 (OI type; 0,1)	0.12	33	0.043
T2 Muscle CSA (z-score)	- 0.05 + 0.76 (T1 muscle CSA; z-score)	0.60	37	<0.001
T2 Muscle CSA (z-score)	- 0.48 + 0.40 (T1 grip strength; z-score)	0.16	30	0.022
<i>Male</i>				
T2 Grip Strength (z-score)	- 0.22 + 0.85 (T1 grip strength; z-score) – 0.37 (T1 height; z-score)	0.73	17	<0.001
T2 Grip Strength (z-score)	- 1.79 + 0.36 (T1 muscle CSA; z-score) – 0.41 (T1 height; z-score)	0.60	18	0.002
T2 Muscle CSA (z-score)	- 1.49 + 0.78 (T1 muscle CSA; z-score) + 1.51 (OI type; 0,1)	0.64	21	<0.001
T2 Muscle CSA (z-score)	0.63 + 1.19 (T1 grip strength; z-score) + 0.57 (OI type; 0,1)	0.45	19	0.006

Note. Abbreviations: CSA: cross-sectional area. OI type (0: type III, 1: type IV).

To evaluate the associations between prepuberty and post-puberty muscle and bone properties, regression models were produced with post-puberty bone z-scores (T2 total CSA and BMC) set as dependent variables (Table 8). For these analyses, the predictors were set as prepuberty muscle z-scores (T1 grip strength and forearm muscle CSA). T2 total CSA was predicted by (i) T1 forearm muscle CSA and OI type, independent of sex and height and (ii) T1 grip strength, independent of OI type, sex, and height. T2 total BMC was determined by (i) T1 forearm muscle CSA, OI type, and sex, independent of height and (ii) T1 grip strength and sex, independent of OI type and height. Further regression models were generated with post-puberty muscle z-scores (T2 grip strength and muscle CSA), set as dependent variables. For these analyses, the inputted predictors were prepuberty bone z-scores (T1 total CSA and BMC). T2 grip strength was predicted by (i) T1 total CSA, OI type, and sex and (ii) T1 total BMC, OI type, and sex. T2

forearm muscle CSA was determined by (i) T1 total CSA, OI type, and sex and (ii) T1 total BMC, OI type, and sex.

Table 8. Predictors of T2 bone and muscle properties.

	Regression Equation	R²	N	P
T2 Bone Parameters				
T2 Total CSA (z-score)	- 3.33 + 0.50 (T1 muscle CSA; z-score) + 1.22 (OI type; 0,1)	0.34	59	<0.001
T2 Total CSA (z-score)	- 1.49 + 0.73 (T1 grip strength; z-score)	0.26	49	<0.001
T2 Total BMC (z-score)	- 2.96 + 0.41 (T1 muscle CSA; z-score) + 1.29 (OI type; 0,1) - 0.90 (sex; 0,1)	0.41	59	<0.001
T2 Total BMC (z-score)	- 1.32 + 0.52 (T1 grip strength; z-score) - 0.87 (sex; 0,1)	0.26	49	0.002
T2 Muscle Parameters				
T2 Grip Strength (z-score)	- 1.31 + 0.25 (T1 total CSA; z-score) + 0.88 (OI type; 0,1) - 0.43 (sex; 0,1)	0.33	50	<0.001
T2 Grip Strength (z-score)	- 1.02 + 0.43 (T1 total BMC; z-score) + 0.62 (OI type; 0,1) - 0.12 (sex; 0,1)	0.50	52	<0.001
T2 Muscle CSA (z-score)	- 1.50 + 0.30 (T1 total CSA; z-score) + 0.78 (OI type; 0,1) - 0.53 (sex; 0,1)	0.23	60	0.001
T2 Muscle CSA (z-score)	- 1.27 + 0.45 (T1 total BMC; z-score) + 0.71 (OI type; 0,1) - 0.13 (sex; 0,1)	0.32	62	<0.001

Note. Abbreviations: CSA: cross-sectional area, BMC: bone mineral content. OI type (0: type III, 1: type IV), sex (0: males, 1: females).

Finally, to determine the contribution of prepuberty muscle and bone properties to post-puberty upper limb function, regression models were generated with T2 PEDI Mobility set as the dependent variable (Table 9). Prepuberty bone (T1 total CSA and BMC) and muscle (T1 grip strength and forearm muscle CSA) z-scores were set as predictors. T2 PEDI Mobility was predicted by (i) T1 total BMC, OI type, and sex and (ii) OI type and sex, independent of T1 total CSA. T2 PEDI Mobility was determined by (i) OI type, independent of T1 grip strength and sex and (ii) T1 forearm muscle CSA and OI type, independent of sex.

Table 9. Muscle and bone property predictors of T2 function.

	Regression Equation	R²	N	P
T2 PEDI Mobility	45.03 + 1.53 (T1 total BMC; z-score) + 10.90 (OI type; 0,1) - 2.39 (sex; 0,1)	0.24	38	0.02
T2 PEDI Mobility	39.29 + 13.57 (OI type; 0,1) - 1.78 (sex; 0,1)	0.22	38	0.01
T2 PEDI Mobility	39.71 + 12.98 (OI type; 0,1)	0.20	32	0.008
T2 PEDI Mobility	43.92 + 1.64 (T1 muscle CSA; z-score) + 10.38 (OI type; 0,1)	0.24	38	0.016

Note. Abbreviations: CSA: cross-sectional area, BMC: bone mineral content. OI type (0: type III, 1: type IV), sex (0: males, 1: females).

4.4 Comparisons Amongst OI Type III and Type IV

4.4.1. Comparison of Bone, Muscle, and Function Parameters

To determine the differences in muscle and bone properties between the OI study cohorts, comparisons between OI type III and type IV at T1 and T2 were computed. The mean comparison of bone properties between OI type III and type IV at the 65% site total radius CSA T1 ($P = 0.09$) and T2 ($P < 0.001$) and total radius BMC T1 ($P = 0.04$) and T2 ($P = 0.03$) is illustrated below in Figure 10. At the 65% site, total radius CSA was approximately 18% higher at T1 and 25% higher at T2 in the OI type IV group compared to the OI type III group. As well, total BMC, at the 65% site, for the OI type IV group was approximately 18% higher at T1 and 16% higher at T2 compared to the OI type III group.

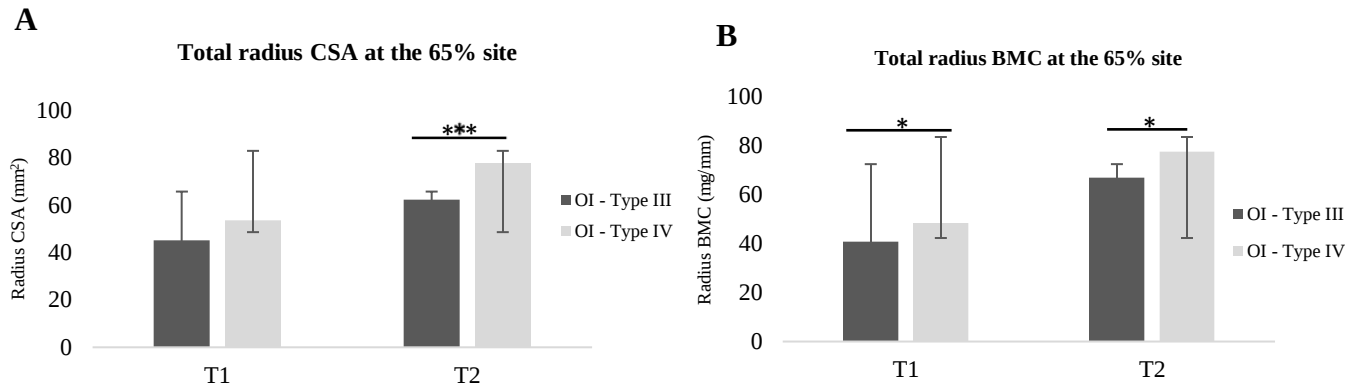


Figure 10. Bone property comparison between OI types III and IV at T1 and T2.

(A) Total radius CSA comparison at the 65% site. (B) Total radius BMC comparison at the 65% site.

Note. Error bars represent $\pm$ standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Both grip strength and forearm muscle CSA, at the 65% site, were compared based on OI type and separated according to sex between T1 and T2. The difference in female grip strength of the dominant hand at T1 ($P = 0.05$) and T2 ($P = 0.04$), male grip strength of the dominant hand at T1 ($P = 0.06$) and T2 ($P = 0.006$), female forearm muscle CSA at T1 ($P = 0.58$) and T2 ($P = 0.50$), and male forearm muscle CSA at T1 ($P = 0.40$) and T2 ($P = 0.08$) is shown below in Figure 11. For grip strength, the female OI type IV group was 72% higher at T1 and 41% higher at T2 compared to the OI type III group. For the male OI type IV group, grip strength at T1 was 45% higher and at T2 was 62% higher than the OI type III group. For forearm muscle CSA, at T1, the female OI type IV group was 19% higher and at T2, was 0.31% higher compared to the female OI type III group. For males, the OI type IV group, forearm muscle CSA was 16% higher at T1 and 32% higher at T2 compared to the OI type III group.

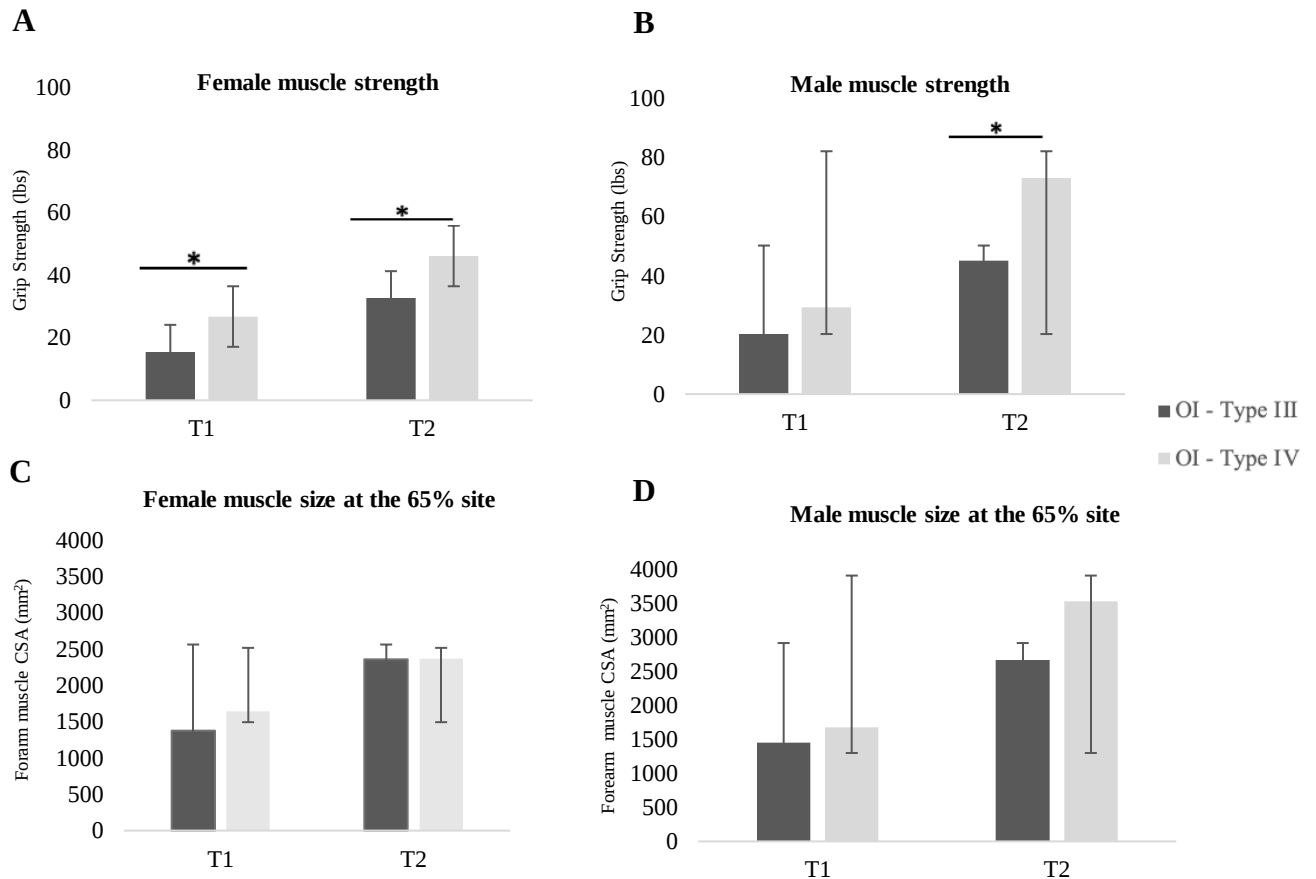


Figure 11. Muscle property differences at T1 and T2. (A) Female grip strength. (B) Male grip strength. (C) Female muscle CSA at the 65% site. (D) Male muscle CSA at the 65% site. Note. Error bars represent $\pm$ standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Specific force was computed to further investigate the comparison in muscle properties between female and males, OI type III and type IV, and outlined below in Figure 12. In the OI type III group, for males, specific force was 24% higher at T1 ($P = 0.33$), and 16% higher at T2 ($P = 0.57$) compared to females. For the OI type IV group, males specific force was 4% higher at T1 ($P = 0.56$) and 15% higher at T2 compared to females ($P = 0.58$).

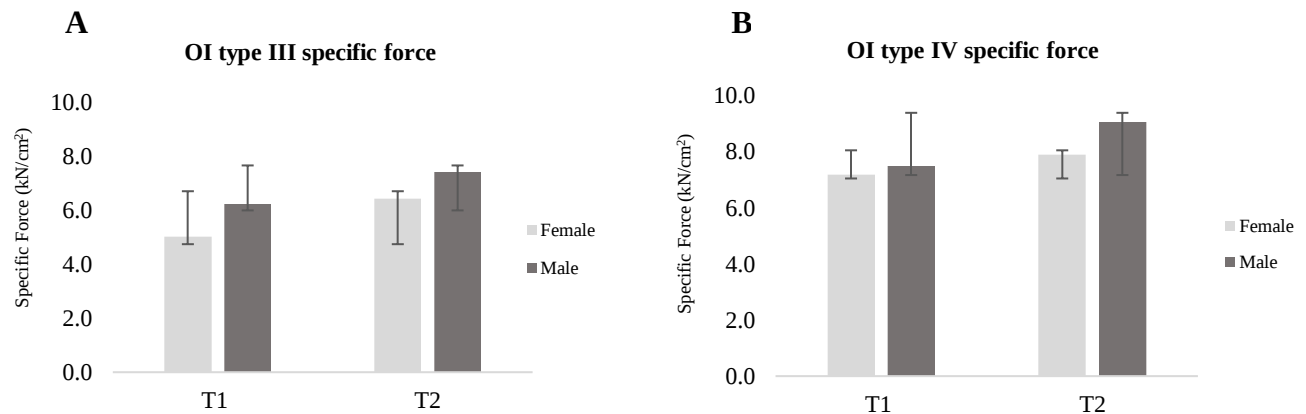


Figure 12. Specific force comparison between OI types III and IV. (A) Specific force comparison between OI type III female and males. (B) Specific force comparison between OI type IV female and males. *Note.* Error bars represent $\pm$ standard deviation.

Finally, to better understand the difference in function between OI types, PEDI Mobility was compared between OI type III and type IV at T1 ($P = 0.02$) and T2 ($P = 0.001$) and is shown below in Figure 13. The OI type IV group had a PEDI Mobility score 18% higher at T1 and 35% higher at T2 compared to the OI type III group. The results showed that PEDI Mobility function score did not change significantly from T1 to T2 for both the OI type III ($P = 0.33$) and OI type IV study cohorts ($P = 0.62$).

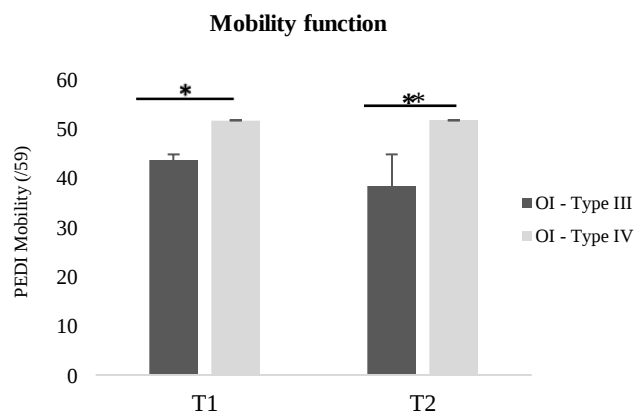


Figure 13. Comparison of PEDI Mobility at T1 and T2. *Note.* Error bars represent $\pm$ standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

4.4.2. Comparison of Z-scores Between T1 and T2

To determine the change in muscle and bone parameters from prepuberty to post-puberty, comparisons in z-scores were computed. Comparisons were separated based on OI type, the OI type III and type IV groups are outlined in tables 10 and 11 below, respectively. A one-way ANOVA was conducted to determine significance between T1 and T2 in each parameter. One-sample t-tests were performed with mean z-scores at each time point and resulted in a significance level of $P < 0.001$, other than when indicated. In both OI groups, the largest decrease in z-scores from T1 to T2 was in height. However, for the remaining parameter z-scores, for both OI groups, the difference from T1 to T2 stayed within ± 1 z-score.

Table 10. Mean z-score differences in the OI type III group between T1 and T2.

	T1	T2	Δ in Z-score	P
Height	-4.10 (1.50)	-5.27 (2.92)	-1.17 (2.40)	0.001
Total CSA	-4.26 (1.87)	-4.41 (1.68)	-0.15 (1.87)	0.59
Total BMC	-2.86 (1.84)	-3.37 (2.10)	-0.51 (1.68)	0.22
Forearm Muscle CSA	-2.43 (2.03)*	-2.81 (2.22)*	-0.38 (1.67)	0.88
Grip Strength	-3.45 (0.95)	-2.51 (1.05)	0.94 (1.08)	0.02

Note. Results are presented as mean (SD). * $p < 0.005$.

Table 11. Mean z-score differences in the OI type IV group between T1 and T2.

	T1	T2	Δ in Z-score	P
Height	-2.76 (2.77)	-3.79 (1.65)	-1.03 (2.99)	0.008
Total CSA	-3.18 (1.68)	-3.11 (1.61)	0.07 (1.16)	0.47
Total BMC	-1.88 (1.65)	-1.89 (1.36)	-0.01 (1.01)	0.94
Forearm Muscle CSA	-1.78 (1.22)	-1.33 (1.26)	0.45 (0.95)	0.002
Grip Strength	-2.15 (1.05)	-1.23 (1.02)	0.92 (0.98)	<0.001

Note. Results are presented as mean (SD).

CHAPTER V: DISCUSSION

Previous research has established that in addition to bone related deficits, children and adolescents with OI experience muscle weakness, decreased muscle size, and upper and lower extremity functional deficits (8-10, 117, 119). As muscles and bones are interdependent, muscle deficits may contribute to bone mass deficits in individuals with OI (9). For individuals with moderate to severe OI, upper extremity function is critical for activities of daily living for this patient population, as many require the use of mobility aids, which rely heavily on the upper limbs for mobility function. As such, the literature has demonstrated that individuals with OI who had stronger upper extremity function at five to six years of age, had improved mobility at skeletal maturity (22). However, there remains a gap in the literature regarding the contribution of muscle and bone properties at an early age to adulthood mobility function. Hence, the present study investigated the association between upper limb function and muscle and bone properties in individuals with moderate to severe OI, at both prepuberty and skeletal maturity.

Given the aim of the current study, it was hypothesized that in individuals with moderate to severe OI: (i) bone size and muscle strength during prepuberty growth would be positively associated with bone size and muscle strength at skeletal maturity, (ii) prepuberty upper limb muscle strength and muscle size would be positively associated with bone size and bone mass at skeletal maturity, and (iii) prepuberty upper limb muscle strength and muscle size would be positively associated with function at skeletal maturity. As such, the first two hypotheses were confirmed, and the final hypothesis was partially confirmed. The results of the present study did reflect a positive association between bone size and muscle strength during prepuberty growth and skeletal maturity. A positive association was found between prepuberty muscle strength and size and skeletal maturity bone size and mass. Contrary to our third hypothesis, prepuberty muscle

strength did not contribute to mobility function at skeletal maturity, however prepuberty muscle size did.

5.1 The Upper Limb Muscle-Bone Relationship

The present study showcased the association between various muscle and bone properties at two time points, during prepuberty growth and at skeletal maturity. The results demonstrated that both muscle size (CSA) and muscle strength were positively associated with total radius bone mass (BMC) at both prepuberty and skeletal maturity. This positive association indicates that larger muscle size (CSA) or higher muscle strength, is associated with a higher bone mass (BMC). These findings are consistent with previously reported muscle force deficits in OI being paralleled by a deficit in bone mass (9, 10). However, on an individual level, it is unclear whether the association between bone mass and muscle parameters will remain constant throughout adulthood, as in the present study, analyses were conducted at two time points.

Prepuberty bone mass (BMC) z-score was the only positive independent predictor of post-puberty bone mass (BMC) z-score. Both OI type and sex had significant independent influences on the relationship between prepuberty bone mass (BMC) z-score and post-puberty bone size (CSA) z-score. These independent influences showed that those with OI type IV had higher post-puberty bone size (CSA) compared to those with OI type III and post-puberty bone size (CSA) was lower in females compared to males. These results imply that prepuberty bone mass (BMC) plays an integral role in the contribution to post-puberty skeletal parameters. Hald et al. (2016) reported profound differences in bone mass and architecture in adults with OI type III compared to adults with OI type I (157). Both bone deformities and deficits are long term limitations for patients with OI. Given the results that prepuberty bone mass (BMC) contributes to post-puberty

bone mass (BMC) and bone size (CSA), increases in bone mass (BMC) during prepuberty growth may be especially important for individuals with moderate to severe OI for improved bone properties throughout adulthood.

Between prepuberty and post-puberty muscle parameters the results revealed, for females, prepuberty muscle size (CSA) z-score was a significant positive independent predictor of post-puberty muscle size (CSA) z-score. For males, prepuberty muscle strength z-score was a significant predictor of post-puberty muscle strength z-score, with height having a significant independent influence on the relationship between prepuberty and post-puberty muscle strength z-scores. This suggests that males who had a lower prepuberty height z-score had a lower post-puberty muscle strength z-score compared to those who had a higher height z-score at prepuberty. Compared to prepuberty muscle strength z-score, the results indicated that prepuberty muscle size (CSA) z-score was a stronger predictor of post-puberty bone property z-scores. OI type had a significant independent influence on the relationship between prepuberty muscle size (CSA) z-score and post-puberty bone mass (BMC) and bone size (CSA) z-scores. Whereas sex had a significant independent influence on the relationship between prepuberty muscle size (CSA) z-score and post-puberty bone mass (BMC) z-score. This indicates that the OI type IV study cohort had higher post-puberty bone mass (BMC) and bone size (CSA) z-scores compared to the OI type III study cohort. Further, females had a lower post-puberty bone mass (BMC) z-score in comparison to males. As well, prepuberty bone mass (BMC) z-score was found to be a significant predictor of post-puberty z-scores of muscle size (CSA) and muscle strength. Both OI type and sex had a significant independent influence on the relationship between prepuberty bone mass (BMC) z-score and post-puberty muscle size (CSA) and muscle strength z-scores. As such, individuals with OI type IV had higher post-puberty muscle size (CSA) and muscle strength z-

scores compared to individuals with OI type III. As well, females had lower muscle strength and muscle size (CSA) z-scores at post-puberty compared to their male counterparts. These results further strengthen the ever-growing evidence of the relationship between muscle and bone properties in individuals with OI (8, 9, 64, 113, 119). Given that prepubertal muscle size (CSA) and muscle strength are predictors of post-pubertal bone mass (BMC) and bone size (CSA), the results of the current study suggest that improving muscle strength and size (CSA) during prepubertal growth may lead to an increase in bone mass and size and thus, to long-term skeletal benefits.

As previously discussed, the mechanostat mechanism, is a theory which describes the adaption of bone tissue to the largest physiological load to which it is exposed (158). The largest physiological load on the skeletal system is generated from muscle forces (158, 159). Previous research from Frost (1987) (2003) suggested that collagen deficits in OI may led to an abnormally elevated mechanostat set point due to a higher strain-dependent threshold, limiting the bone remodeling response of the load-bearing bones (158, 160). However, recent findings from Veilleux et al. (2015), revealed that the mechanostat setpoint in patients with OI type I was in fact normal, and tibia bone mass adapted well to the surrounding calf muscle forces (9). Consistent with Veilleux et al. (2015), the results of present study provided mechanistic data on the upper limb muscle-bone interactions and demonstrated that the mechanostat set point was normal in individuals with moderate to severe OI at both prepuberty growth and skeletal maturity. Radius bone mass (BMC) seemed to adapt to the adjacent forearm muscle forces. Taken together, the observation of a normal muscle-bone relationship in individuals with OI, coupled with the abnormally low muscle strength and muscle size, suggests muscle weakness contributes to low

bone mass and bone size in OI. This is important, as muscle properties are targets which can be modified through appropriate therapies (9, 64).

From prepuberty to skeletal maturity, muscle and bone parameters remained within approximately one z-score from T1 to T2. These results suggest once puberty is reached, gains in muscle and bone strength, and potentially function, may be limited. Therefore, prepubertal growth appears to be a critical time point to implement interventions in hopes of effecting long term benefits.

The results presented above provide insight into upper limb bone mass (BMC) and muscle size (CSA) during childhood growth to be key therapeutic aims for improving adulthood muscle and bone strength. This is crucial for individuals with moderate to severe OI, as muscle weaknesses and bone deformities and fractures, ensuing in nonunion of the bones, typically further impact functional mobility despite multidisciplinary treatments with pharmacological therapies, surgical interventions, and rehabilitation (150).

5.2 Upper Limb Function

Present study findings showcased that post-puberty upper limb function was predicted by prepuberty muscle size (CSA) and bone mass (BMC) z-scores. OI type had a significant independent influence on the relationship between post-puberty upper limb function and prepuberty muscle size (CSA) and bone mass (BMC) z-scores. As well, sex had a significant independent influence on the relationship between prepuberty bone mass (BMC) z-score and post-puberty upper limb function. This suggests that the OI type IV study cohort had higher post-puberty upper limb function when compared to the OI type III study cohort. Also, post-puberty upper limb function was lower for females than males. These findings suggest that for individuals

with moderate to severe OI, early interventions targeting muscle size (CSA) and bone mass (BMC), as mentioned above, would not only be beneficial for improving long-term bone and muscle parameters, but also upper limb functional mobility. This is essential for this patient population, as these long-term improvements may increase the quality of life for individuals with moderate to severe OI. Prepuberty muscle strength and bone size (CSA) z-scores were not found to be predictors of post-puberty upper limb function. However, other factors which were not inputted into the regression models may have a greater contribution to post-puberty mobility function, such as bisphosphonate treatment, body mass, or surgical intervention outcomes. Montpetit et al. (2021) reported independent ambulation at five to six years of age was the main predictor of ambulation at skeletal maturity in individuals with moderate to severe OI (22), further highlighting the importance of providing targeted interventions during prepuberty growth to improve adulthood mobility function. Results from previous research reported that individuals with more severe types of OI, had greater limitations in mobility and restrictions in daily activities throughout adulthood compared to those with mild OI (161). Improvements in functional status at skeletal maturity was contingent on long term advances in the clinical management of the upper limbs for patients with severe OI (11). In conjugation with the findings from the present study and the results from previous literature highlighting mobility limitations experienced during adulthood by individuals with OI, it is increasingly evident that early therapeutic interventions aiming at improving muscle and bone parameters could contribute to long-term benefits of upper limb function and mobility.

5.3 Comparisons in Bone and Muscle Properties Between OI Types and Sex

The results indicated that total radius bone mass (BMC) and bone size (CSA) were higher in the OI type IV group, at both prepuberty and post-puberty, compared to the OI type III group. These findings were anticipated, as type III is the most severe form of OI, classified by the most profound bone fragility, low bone mass, and bone deformities (4, 17, 119, 162).

Muscle strength at prepuberty was 72% higher for females and 45% higher for males in the OI type IV group compared to the OI type III group. At post-puberty, muscle strength was 41% higher for females and 62% higher for males in the OI type IV group compared to the OI type III group. Muscle size (CSA) for both males and females were higher at prepuberty and at skeletal maturity for the OI type IV group compared to the OI type III group. These results are consistent with previous research from Palomo et al. (2016), that found children and adolescents between the ages of five and twenty years old, the OI type III study participants had smaller forearm muscle size (CSA), at the 65% site, compared to participants with OI type IV (119). However, the present results further revealed, for females at skeletal maturity, the OI type IV group only had a 0.31% larger muscle size (CSA) compared to the OI type III group, whereas for males, the OI type IV group was 32% higher than the OI type III group. Individuals with OI type III typically have impairments affecting their lower extremities, which requires support from the upper limbs to be able to lift themselves to a standing position and for the use of assistive devices such as a walker or wheelchair (22). Whereas the level of mobility can vary for individuals with OI type IV, as many are able to ambulate without a mobility aid. Previous research compared the difference in use of mobility aids between individuals with OI type III and type IV, and found that 100% of the OI type III study participants required a mobility aid, while 88% of the OI type IV study

participants were community ambulators (22). Another consideration is the treatment of bisphosphate status. At the post-puberty time point, 57% of OI type III females were receiving treatment, compared to 39% of the OI type IV female group. Bisphosphonate treatment is typically administered to more severely affected OI patients and has been previously reported that intravenous bisphosphate treatment not only targets bone mass, but also increases muscle strength in children and adolescents with OI (17, 127, 140, 142, 162). The small percent difference in muscle size (CSA) between females with OI types III and IV may be attributed to the use of ambulation aids and bisphosphonate treatment status at skeletal maturity. From a clinical perspective, the findings may suggest that females with OI type IV are potentially more severely affected than males at the upper limbs. As a result, females may be more likely to benefit to a greater extent from early therapeutic interventions than their male counterparts. At present, there is no available explanation as why females forearm muscle size does not differ between OI types, whereas it does for males. One potential explanation could lie in the hormonal status of males and females during post-puberty. However, further studies are needed to provide clarification.

Specific force, which is a reflection of the intrinsic force producing capacity of a muscle (163), was higher for the OI type IV group, at both time points, compared to the OI type III group. For both the OI type III and type IV groups, males had a higher specific force than females. This indicates, the OI type III group produces lower amounts of muscle force by units of muscle area than the OI type IV group, as well as for females compared to males. Previous research from Veilleux et al. (2014) and Veilleux et al. (2015), examined specific force to gain insight into the intrinsic muscle properties in OI type I (8, 9). In both studies, the results revealed per unit of muscle surface (CSA), the force produced by the OI type I group was lower compared to age- and sex-matched controls (8, 9). Given that OI type III and type IV are more severe than type I, it is

reasonable to assume that specific force may be lower in individuals with moderate to severe OI compared to individuals with mild OI and healthy controls. To the best of our knowledge, at present, the origin of reduced specific force in patients with OI is unknown. Previous results from OI mouse model studies demonstrated that in severe OI mouse models (*oim/oim* and *Col1a1^{Jrt/+}* mouse models) myofiber size was smaller, which may contribute to a reduction in specific force (112, 164). Muscle fiber composition has been shown to have a lower proportion of slow-twitch muscle fibers and a higher proportion of fast-twitch muscle fibers in the severe dominant OI mouse model (*Col1a1^{Jrt/+}* mouse model) compared to wild type mice (164). These results are unanticipated given that fast-twitch muscle fibers are typically stronger compared to slow-twitch muscle fibers. However, findings from OI mouse model studies may not necessarily be transferable to humans.

Mechanical properties of musculoskeletal structures, which are vital for the generation and transmission of muscle force, may be affected by mutations in collagen type I encoding genes (8, 64). There is a copious amount of collagen type I found in tendons, ligaments, and intramuscular connective tissue (122). The extracellular matrix surrounding muscle fibers has also been found to contain collagen type I (64, 104, 165), which plays an integral role in the transmission of muscle force to tendons (166). Results from Sims et al. (2003), showed that in the OI mouse model of severe OI (*oim/oim* mouse model), tendons contained an abnormally low amount of collagen type I and were biomechanically compromised (121). Reduced tensile strength leads to increased elasticity of the tendons, decreasing the efficiency of muscle contractions (64). Further detailed studies on the association between collagen structure and muscle strength are required provide clarification on this matter.

5.4 Comparison in Mobility Function Between OI Types

The comparison of function, expressed in the PEDI Mobility domain, between prepuberty and post-puberty, illustrated that the OI type IV group remained consistent between the two time points. However, for the OI type III group, mobility function decreased from prepuberty to post-puberty, although the reduction was not significant. Previous research from Montpetit et al. (2021), found that 13% of the study patient population (OI type III and type IV) had lower mobility scores at skeletal maturity than they had at the age of five to six years old (22). OI is not considered as a progressive disorder, therefore mobility function acquired during childhood can be expected to be maintained at skeletal maturity (22). Exceptions do occur, as fractures and upper limb deformities, both of which are common in individuals with severe OI, can have detrimental effects on mobility function at any age. The accumulation of bone fractures and the progression of upper extremity bone deformities can lead to limb immobilization, bone nonunion, and muscle atrophy (167). These repeated episodes of immobilization can have negative impacts on the upper extremity musculature, further contributing to reduced upper limb function. Although not a parameter measured in the current study, an increase in body mass at post-puberty compared to the prepuberty time point may also contribute to reduced function. Obesity and muscle weakness are both frequently mentioned as factors limiting mobility in severe OI (24, 168).

5.5 Study Limitations

The first limitation of the current study is that the study cohort was exposed to multiple treatment modalities simultaneously, as patients received bisphosphonate treatments, orthopedic interventions (such as intramedullary rodding), and rehabilitation, all of which are therapeutic

efforts that may have contributed to upper extremity function at skeletal maturity. However, the present data does not allow for the evaluation of the individual treatment effect for each modality.

Another limitation of the present study is its retrospective design. Patient data extracted from medical charts may be subject to bias, as only patients who maintained long-term follow-up care at the SHC-Canada were included. Additionally, even with the immense OI patient population database at the SHC-Canada, there were limitations regarding the availability of patient data. As the period of data collection for this study was from 2003 to 2021, patient data prior to 2007 was limited as this data was on a previous electronic medical record system and therefore inaccessible to study personnel. Range of motion was a variable of interest in the present study. However, in rehabilitation reports, range of motion data was scarce, and when documented, inconsistencies were observed. As such, when reported, range of motion would be documented with the exact degree of motion or written as '*within normal limits*' or '*limited*' and both active and passive range of motion measurements would be rarely reported.

Body mass was not an anthropometric measurement collected, which presented as a limitation to the current study. This limitation restricted the ability to investigate relative peak muscle force, which is defined as the ratio between absolute peak force and the patient's body weight. This would have allowed for the comparison of peak force across the OI type III and type IV study cohorts by removing the influence of body mass.

A final limitation of the current study is the wide age range set for T1. The prepuberty growth period was set between the ages of five and eleven years old. However, a seven-year age range is a wide range given the musculoskeletal growth and development which occurs during that timeframe. A study participant at the age of eleven years old will have completed a significant amount of bone and muscle growth compared to a study participant at five years of age.

Nevertheless, this retrospective study design allowed for the rigorous assessment of upper extremity musculoskeletal properties and function between two time points, in individuals with OI type III and type IV. To the best of our knowledge, this study was the first to produce an enriched understanding of the association between upper limb function and muscle and bone parameters between prepubertal growth and at skeletal maturity in individuals with moderate to severe OI. This study was conducted at a tertiary pediatric hospital, specializing in musculoskeletal care. The SHC-Canada is a global healthcare center for the treatment and management of pediatric bone disorders, with patients traveling from around the world to receive specialized treatment for OI. The OI healthcare team at the SHC-Canada is comprised of various pediatricians, orthopedic surgeons, nurses, rehabilitation therapists, and clinician scientists, all of whom are experts in the diagnosis, treatment, and management of pediatric bone disorders. With decades of expertise and research in OI, these specialists completed a systematic review of the study concept and design and further verified the scientific validity of the present study. The SHC-Canada annually provides care to approximately 350 patients with OI. As such, conducting this study at this specialized healthcare center allowed for access to a vast and extensive database of an OI patient population. This database included patients with moderate to severe OI, who do not typically seek treatment at other institutions.

5.6 Recommendations for Future Research

The results of the present study highlighted the importance of improving bone mass (BMC), muscle strength, and muscle size during the prepubertal growth period in order to enhance adulthood muscle and bone strength and functional mobility for individuals with moderate to severe OI. To build upon the current study findings, future studies should be longitudinal in design,

assessing the contribution of early musculoskeletal improvements to bone mass and upper limb function throughout adulthood. Next, studies should include the implementation of rehabilitation interventions, targeting muscle size and muscle strength, as early as possible during prepuberty for individuals with OI type I, type III, type IV, and healthy controls. In addition to the early intervention, researchers should assess longitudinal measurements of study participant's daily activity levels and the impact of muscle atrophy if exercise is not maintained. This recommendation for future research would allow for the comparison of the long-term association between upper limb function and the muscle-bone relationship in individuals with mild to severe OI and healthy controls. On an individual level, researchers may evaluate if long-term improvements of bone and muscle parameter z-scores during childhood growth continue into adulthood.

Results from the current study demonstrated that specific force was lower in the OI type III group compared to the type IV group. Future research should investigate the cellular and systemic physiological origin of the specific force differences between individuals with OI type III and type IV and compare to healthy controls.

Future studies should include a stringent measurement for the determination of skeletal maturity. For the present study, skeletal maturity was defined by a change in height that was less than two centimeters per year. An accurate method for establishing skeletal maturity would be to examine bone age by assessing growth plate closure. This would confirm skeletal maturity has been reached and ensure no further growth will occur.

CHAPTER VI: CONCLUSION

Finally, the present study showcased the association between upper limb function and muscle and bone properties in individuals with moderate to severe OI, at prepuberty and at skeletal maturity. Upper limb function is especially imperative for daily living for individuals with moderate to severe OI, as typically in this patient population, the upper extremities contribute to mobility function for the use of ambulation aids. To be proficient with a mobility aid, it requires strong upper limb function. Thus, upper extremity functional mobility is essential for improving the quality of life of individuals with moderate to severe OI. The current findings may aid in the development of advanced multidisciplinary rehabilitation approaches, targeting muscle size and strength during prepuberty growth to improve lifelong mobility function and bone strength for individuals with OI. Overall, this study contributes evidence supporting the benefits of early muscle strengthening programs for children and adolescents with OI.

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