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Bone fracture incidence, measurement and adaptation: An exploration through the continuum from incidence to measurement and adaptation

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Bone fracture incidence, measurement and adaptation: An exploration through the continuum from incidence to measurement and adaptation

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ABSTRACT

Bone fracture incidence, measurement and adaption: An exploration through the continuum from incidence to measurement and adaptation.

This research encompasses four studies exploring bone adaptation, fracture incidence, and preventative measures to decrease fracture risk and increase bone health. Study one was a clinical audit exploring incidence rates for appendicular fractures in children in Western Australia over ten years. Diagnostic and remedial approaches were explored in studies two, three and four by examining the between-day reliability of upper limb scans; reliability of the osteogenic index (OI) for upper-body strength and power exercises; and the diagnostic value or utility of using pQCT in disease profiling, respectively. Fracture rates in the limbs of children were found to be increasing each year, particularly in the forearm, and regardless of gender, between 2005 and 2015, similar to international trend data. pQCT was established as a reliable tool for quantifying upper limb diaphyseal measurements. The OI had varying reliability depending on the equation used, exercise type and exercise intensity when measured using accelerometers at multiple locations. Lastly, paediatric populations with low motor competence and/or neuromuscular disorders were disease profiles which had a measurably negative influence on bone when compared to unaffected controls. The increase in fracture incidence in Western Australia is a concerning trend for bone health in children and adolescents that requires lifestyle and population-based interventions to arrest this incremental problem. pQCT may be a valuable tool for disease profiling with area measurements for bone and some muscle variables more reliable than volumetric measurements in the upper limbs. The OI is a more reliable tool when measuring strength exercises than power exercises; and individuals with a greater risk of weaker bones should apply more daily load to increase their overall bone health. Interventions should be put into place to rehabilitate individuals with already weaker bones, such as targeted and well-designed exercise programs supported by good nutritional practices.

DECLARATION

I certify that this thesis does not, to the best of my knowledge and belief:

(i) *Incorporate without acknowledgement any material previously submitted for a degree or diploma in any institution of higher education;*

(ii) *Contain any material previously published or written by another person except where due reference is made in the text; or*

(iii) *Contain any defamatory material.*

Signed.....Mark Jenkins.....  ...

Dated.....16th October, 2018.....

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PREFACE

Study One: Appendicular fracture epidemiology of children and adolescents: A 10-year case review in Western Australia (2005 to 2015) has been **published** in *Archives of Osteoporosis* on the 15th of May, 2018: https://www.ncbi.nlm.nih.gov/pubmed/29860609

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Study Two: Reliability of upper-limb diaphyseal mineral and soft-tissue measurements using peripheral Quantitative Computed Tomography (pQCT) has been published to the Journal of Musculoskeletal and Neuronal Interactions on the 10th of August, 2018.

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Study Three: Reliability of determining osteogenic indices using inertial measurement units for upper-body resistance exercises.

Study Four: Characterisation of peripheral bone material, structure and strength in youth at risk of secondary osteoporosis

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GLOSSARY

Cortical Bone: Cortical bone is solid in nature and comprises up of approximately 80% of the adult skeleton (Clarke, 2008).

Endosteum: The endosteum encompasses trabecular bone and contains osteoblasts, osteoclasts and blood vessels (Brandi, 2009).

Haematopoiesis: Haematopoiesis is blood cell formation (Marieb, & Hoehn, 2010).

Haversian Systems: Haversian systems are also referred to as cortical osteons (Clarke, 2008). Haversian canals run longitudinally in cortical bone with blood flowing through them, and this blood flow supports osteocytes (Pazzaglia, Congui, Raspanti, Ranchetti, & Quacci, 2009). Haversian canals, along with Volkmann canals, create the majority of cortical porosity along with the intracortical surface where remodelling occurs (Seeman, 2013).

Isokinetic strength training: Strength training performed at controlled and constant velocities (Ratamess et al., 2016).

Mechanosensitivity: Mechanosensitivity is the level of osteogenic response and stimuli detection to mechanical load (Kamkin, & Kiseleva, 2005).

Mechanostat: The mechanostat is the combination of all the necessary features bone requires in order to maintain a healthy state (Frost, 1987).

Mechanotransduction: Mechanotransduction is the process by which mechanical stimuli is transduced into a biological response (Robling, & Turner, 2009).

Oestradiol: Oestradiol is a steroidal hormone (Durante, & Li, 2009) that supresses bone turnover which increases cortical bone thickness at the endocortical surface (Davies, Evans, & Gregory, 2005).

Osteoblasts: Osteoblasts add new bone tissue to existing bone (Zernicke, MacKay, & Lorincz, 2006).

Osteoclasts: Osteoclasts break down and remove bone (Zernicke, MacKay, & Lorincz, 2006).

Osteocytes: Osteocytes are cells inside the bone matrix which modulate osteogenesis (Schaffler, & Kennedy, 2012).

Osteogenic: A tissue is regarded as osteogenic if it is involved in the process of bone growth or repair (Dorland's Medical Dictionary for Health Consumers, 2007).

Osteons: Osteons are cylindrical structures, typically several millimetres long and around 0.2 mm in diameter, found within cortical bone and trabecular bone (Brandi, 2009).

Osteopetrosis: Osteopetrosis causes bones to become weak due to the bone not being able to undergo the remodelling process (Boyce, Rosenberg, de Papp, & Duong, 2012).

Osteopenia: A mild form of osteoporosis (Seeman, 1997).

Osteoporosis: Osteoporosis is a bond disease that causes bones to become weak and increases the chance of fracture (Sugiura, & Bhatia, 2011).

Periosteum: The periosteum encompasses cortical bone in all places (Brandi, 2009) except for the joints, and contains osteoblasts, osteoclasts, nerve endings, and blood vessels which nourish the bone (Brandi, 2009; Clarke, 2008**).**

Strain: A measure of bone deformation which is represented as a microstrain (με) (Yang, Brüggemann, & Rittweger, 2011).

Stress: The internal resistance an object has when force is applied, and is measured in Pascals or Newtons per metre squared (N/m^2) (Yuehuei, & Draughn, 1999).

Stress-strain index: The stress-strain index of bone is a calculated predicted strength of the bone in accordance with a maximal failure three-point bending test (Kokoroghiannis et al., 2009).

Testosterone: Testosterone is an androgen (hormone) in the body (Chuu et al., 2011) that is a hormonal / endocrine factor driving osteogenic adaptations (Lang, 2011).

Trabecular Bone: Trabecular bone, also known as cancellous bone, is perforated and spongy in nature and comprises up of approximately 20% of the adult skeleton (Clarke, 2008).

Volkmann Canals: Volkmann canals are connected to Haversian canals transversally with blood flowing through them, and this blood flow supports osteocytes (Pazzaglia, Congui, Raspanti, Ranchetti, & Quacci, 2009). Volkmann canals, along with Haversian canals, create the majority of cortical porosity along with the intracortical surface where remodelling occurs (Seeman, 2013).

Wolff's Law: Wolff's Law states that there are mathematical rules which oversee the process of bone adapting over time due to mechanical loading, specifically in relation to trabecular orientation development in long bones (Wolff, 1892; translated in Wolff, 1986; Ruff, Holt, & Trinkaus, 2006).

ABBREVIATIONS

aBMD	Areal Bone Mineral Density
BM	Bone Mass
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMU	Basic Multicellular Unit
BSI	Bone Strength Index
BUA	Broadband Ultrasound Attenuation
CI	Confidence Interval
CoA	Cortical Area
CoD	Cortical Density
CV	Coefficient of Variation
DHEA	Dehydroepiandrosterone
DMP1	Dentin Matrix Protein 1
DXA	Dual-energy X-ray Absorptiometry
ED	Emergency Department
EDIS	Emergency Department Information System
EnR	Endocortical Radius
EnvBMD	Endocortical Volumetric Bone Mineral Density
EXCL	With Hand and Foot Fractures Excluded
FGF 23	Fibroblast Growth Factor 23
GH	Growth Hormones
GLM	Generalized Linear Model
GRF	Ground Reaction Force
HR-pQCT	High-resolution peripheral Quantitative Computed Tomography
ICC	Intraclass Correlation Coefficient
ICD-10	International Classification of Diseases, Tenth Revision
IGF-1	Insulin-Like Growth Factor 1
IGF-2	Insulin-Like Growth Factor 2
INCL	With Hand and Foot Fractures Included
MCSA	Muscle Cross-Sectional Area
MD	Muscle Density
MeA	Non-Cortical Area
MEPE	Matrix Extracellular Phosphoglycoprotein
MivBMD	Mid-Cortical Volumetric Bone Mineral Density

MRI	Magnetic Resonance Imaging
MRTA	Mechanical Response Tissue Analyser
MUA	Muscle Area
MUD	Muscle Density
OI	Osteogenic Index
OI-ADAPTED	The First Osteogenic Index Formula (Rantalainen et al, 2011)
OI-ORIGINAL	The Second Osteogenic Index Formula (Turner & Robling, 2003)
OR	Odds Ratio
PeR	Pericortical Radius
PevBMD	Pericortical Volumetric Bone Mineral Density
PMH	Princess Margaret Hospital
pQCT	peripheral Quantitative Computer Tomography
PTH	Parathyroid Hormone
PvBMD	Polar Volumetric Bone Mineral Density
QCT	Quantitative Computed Tomography
SERMs	Selective Oestrogen Receptor Modulators
SD	Standard Deviation
SOS	Speed of Sound
SSI	Stress-Strain Index
ToA	Total Area
TrA	Trabecular Area
TrD	Trabecular Density
vBMD	Volumetric Bone Mineral Density
vGRF	Vertical Ground Reaction Force
WA	Western Australia

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CHAPTER ONE – INTRODUCTION

1.1. Background

Several identified gaps in the literature are present concerning the overarching theme of bone fracture incidence to measurement and adaptation of bone. Specifically, this thesis sought to examine the contemporary trends in Australian paediatric fracture incidence are scarcely reported in the literature, the reliability of upper limb bone and soft-tissue pQCT assessments, the assessment of the osteogenicity of various upper limb exercises, and phenotypic characteristics of long bones of various paediatric populations at risk of secondary osteoporosis.

1.2. Purpose

The overall purpose of this thesis was to assess upper limb bone health, and determine a reliable way to quantify osteogenic adaptation. A detailed look into the bone fracture incidence of children and adults, the measurement of bone characteristics, and the process of osteogenic adaptation was assessed.

1.3. Research Questions

1. Has the fracture epidemiology of children and adolescents changed over 10-years in Western Australia (2005 to 2015)?
2. What is the reliability of upper-body diaphyseal mineral and soft-tissue measurements using peripheral Quantitative Computed Tomography?
3. What is the reliability of determining osteogenic index using inertial measurement units during upper-body resistance exercises?
4. Are there unique upper and lower limb bone structural profiles in different disease-specific sites?

1.4. Hypothesis

1. Appendicular fracture incidence of children and adolescents has increased over 10-years in Western Australia (2005 to 2015).
2. Peripheral quantitative computed tomography for the upper body diaphyseal mineral and soft-tissue measurements will be reliable for between-day scans.

3. The osteogenic index will be reliable from data gathered by inertial measurement units during each exercise, and there will be varying reliability between different osteogenic equations.
4. There will be unique upper and lower limb bone structural profiles for different disease-specific sites.

1.5. Significance

The four studies provided a detailed insight into bone fracture incidence, measurement, and adaptation. The fracture audit provided the first reported data for Western Australia (WA) and provided comparative data to international trends. If fracture incidence rates are increasing as hypothesised then this study provides evidence towards a 'call to action' for intervention to target increasing fracture incidence. Reliability assessment of pQCT for the upper limb adds insight into the reliability of variables never tested for upper limb reliability before, while also determining the ICC values to variables which have only been tested for CV values. The significance of study three is that this study determined if the OI is a reliable calculation when assessed using inertial measurement units. Assessment of this reliability allows research to establish if the OI is a valid tool for determining the osteogenic potential of exercises. This can assist in developing targeted training programs for athletes, or people with bone diseases. The significance of study four is that by determining unique upper and lower limb bone structural profiles for different disease-specific groups, we can identify groups who are susceptible to specific decreased bone characteristics which will inform future targeted interventions.

1.6. Limitations and Delimitations

The outcome of this thesis are delimited to the cohorts of subjects used in the clinical audits and experimental studies performed. *Study One*: appendicular fracture sites and incidence rates of children to adolescents are delimited to Western Australia. *Study Two*: pQCT reliability of measured sites are delimited to adult males only; with future research to repeat the process using adult females, and/or child and adolescent populations accordingly. *Study Three*: OI reliability results are delimited to the upper-body strength and power exercises performed, in recreationally active males only, where reliability may improve for moderately or highly trained individuals, or differ in female participants performing the same exercises. *Study Four*: Disease-specific comparisons to non-affected controls are delimited to the clinical groups defined, and the bone sites measured. This study was also limited by the small sample sizes evident in some of the disease-specific

clinical cohorts. This is, however, unavoidable given the prevalence of such disease types dictates the availability of data to describe them accordingly.

1.7. Outline of the Thesis

The subsequent chapters of thesis comprise of a literature review (Chapter 2), four experimental chapters that examined the aforementioned research questions (Chapters 3 – 6), an overall conclusion that re-evaluates all the findings within a single context of the current thesis (Chapter 7), future research topics that were highlighted as a result of the current thesis (Chapter 8) as well as auxiliary information that may be of interest to the reader (Appendices).

CHAPTER TWO – LITERATURE REVIEW

2.0. Overview

This literature review provides a background into the anatomical features of bone, the physiological processes of bone remodelling, the mechanisms commonly used to measure bone parameters, the bone adaptation response to skeletal loading, fracture causation, and the optimisation of bone adaptation through mechanical loading using osteogenic indices.

2.1. Bone Function

The functions of bones are to support the body (e.g. spine), provide movement (e.g. forearm), and to protect the organs (e.g. rib cage) (Flynn, 2003). Bones attach to muscle by tendons (Marieb, & Hoehn, 2010) and assist with muscle movement by providing the muscles with levers (Hart et al, 2017; Clarke, 2008), that permit the body part to move (Seeman, 2008). A metabolic function of bone is to act as a storage area for calcium and phosphate, and these are required to sustain serum homeostasis (Hadjidakis, & Androulakis, 2007). Other functions are to regulate the bone marrow (Boyce, Rosenberg, de Papp, & Duong, 2012), and to undergo haematopoiesis (Anthony, & Link, 2014). Haematopoiesis is referred to as blood cell formation and red blood cell (erythrocytes) production occurs in the red bone marrow (Marieb, & Hoehn, 2010). Red bone marrow (haematopoietic tissue) is located in all areas of trabecular bone and in the medullary cavities of the diaphysis in newborns and by adulthood is found in the axial skeleton, the girdles, and the proximal epiphysis of the femurs and humerus (Marieb, & Hoehn, 2010). Yellow bone marrow which is fat, is found in adults in the medullary cavity (Marieb, & Hoehn, 2010).

2.2. Bone Anatomy

There are over 200 bones in the human body, and over the course of a lifetime bones are constantly adapting in response to internal and external factors (Clarke, 2008). There are four different types of bones, defined as long bones, flat bones, short bones, and irregular bones (Marieb, & Hoehn, 2010). Long bones are bones which have an elongated middle portion, along with two ends, such as the humerus, radius, ulna, femur, tibia and fibula (Marieb, & Hoehn, 2010). Flat bones are flatter bones which are often curved, such as the scapulae and the majority of bones in the skull (Marieb, & Hoehn, 2010). Cube shaped bones in the wrists and ankles are examples of short bones (Marieb, & Hoehn, 2010).

Irregular bones are bones which have different shapes to the three prior classes, such as vertebrae (Marieb, & Hoehn, 2010) and the sacrum (Clarke, 2008).

The skeleton comprises of approximately 80% cortical bone and 20% trabecular (cancellous) bone (Seeman, 2013). However, the composition of bone is often considered at the macroscopic level (e.g. structure of the bone or such as the parts of the diaphysis, epiphysis, metaphysis, articular cartilage, etc.) or microscopic level (e.g. composition of extracellular matrix, cells and size of spaces). Individual bones are comprised of different proportions of cortical and trabecular bone, thus having different mechanical properties and mechanical behaviour through-out (Hart, Nimphius, Rantalainen, Ireland, Siafarikas & Newton, 2017). Cortical bone is also known as compact bone (Brandi, 2009) and is made up of 70% mineralised bone matrix with the other 30% extracellular fluid-filled void volume (Seeman, 2013). Trabecular bone which is also known as spongy bone (Jiménez-Mendoza, 2013) is less dense than cortical bone as it has 30% mineralised bone matrix with the other 70% extracellular fluid-filled void volume (Seeman, 2013). Cortical bone is situated in the shafts (diaphysis) of various long bones along with the outer surfaces of flat bones, while trabecular bone is located predominantly at the ends (metaphysis and epiphysis) of long bones and at the internal parts of flat bones (Brandi, 2009). Irregular bones and short bones are similar to flat bones in their composition, in that a thin layer of cortical bone encompasses trabecular bone (Marieb, & Hoehn, 2010). Cortical bone is solid in nature, while trabecular bone is perforated (Clarke, 2008). Blood is supplied to bone through nutrient arteries (Marenzana, & Arnett, 2013) (Figure 1).

During childhood, a hyaline cartilage disc called an epiphyseal plate, grows in order to lengthen bone (Marieb, & Hoehn, 2010). During growth, the length of bone increases by the metaphysis being moved away from the diaphysis by endochondral bone formation (Wang et al., 2010). As an adult a remnant of the epiphyseal plate is referred to as an epiphyseal line (Marieb, & Hoehn, 2010). As young adults, the main reason males end up having more bone mineral content (BMC) and areal bone mineral density (aBMD) in the upper and lower diaphysis than females is that males undergo bone acquisition for a longer period of time during puberty, in conjunction with other factors, such as hormonal drive and the endocrine environment (Bonjour, & Chevalley, 2014).

On the microscopic scale, both cortical bone and trabecular bone are of similar mineralised collagen meshwork and present in either a lamellar formation (concentric

layers) or a woven formation (Clarke, 2008). Collagen fibres (which provide bone with its toughness (Wise et al., 2007)) are laid differently depending on which formation they are presented in (Clarke, 2008). A woven formation is weaker than lamellar bone as the collagen fibres are disorganised (Clarke, 2008). Woven bone is created during the initial formation of bone (Clarke, 2008) and during the bone healing process (Tarantino et al., 2009). Remodelling of the woven bone continues until lamellar bone is formed for both cortical and trabecular bone (Tarantino et al., 2009). During puberty, the largest amount of bone growth occurs (Gilsanz et al., 2011) with standing height growing at a faster pace than BMC and aBMD accumulation resulting in a period of relative bone weakness. This period of rapid skeletal development is thought to underpin the increased risk for and reported high incidence of fractures during puberty (Bonjour, & Chevalley, 2014).

The typical components of bone on a microscopic level are depicted in Figure 2, whereas Figure 1 displays the components of bone on a mostly macroscopic level. Both cortical bone and trabecular bone are composed of osteons (Brandi, 2009). Osteons are cylindrical with collagen fibres presented in a spiral formation (Ushenko, Ermolenko, Burkovets, & Ushenko, 2000). While these collagen fibres have dissimilar angles when compared to each lamella of the osteons, the fibres are presented in the same way within each lamella (Ushenko, Ermolenko, Burkovets, & Ushenko, 2000). This formation allows for the bone to endure twisting motion stresses (Marieb, & Hoehn, 2010), however pure compression on a bone can result in fractures due to shear stress (Bucholz, Heckman, & Court-Brown, 2006). Trabecular bone is positioned along stress lines which assists in stress resistance (Marieb, & Hoehn, 2010). Trabecular osteons are referred to as packets, while cortical osteons are referred to as Haversian systems (Clarke, 2008).

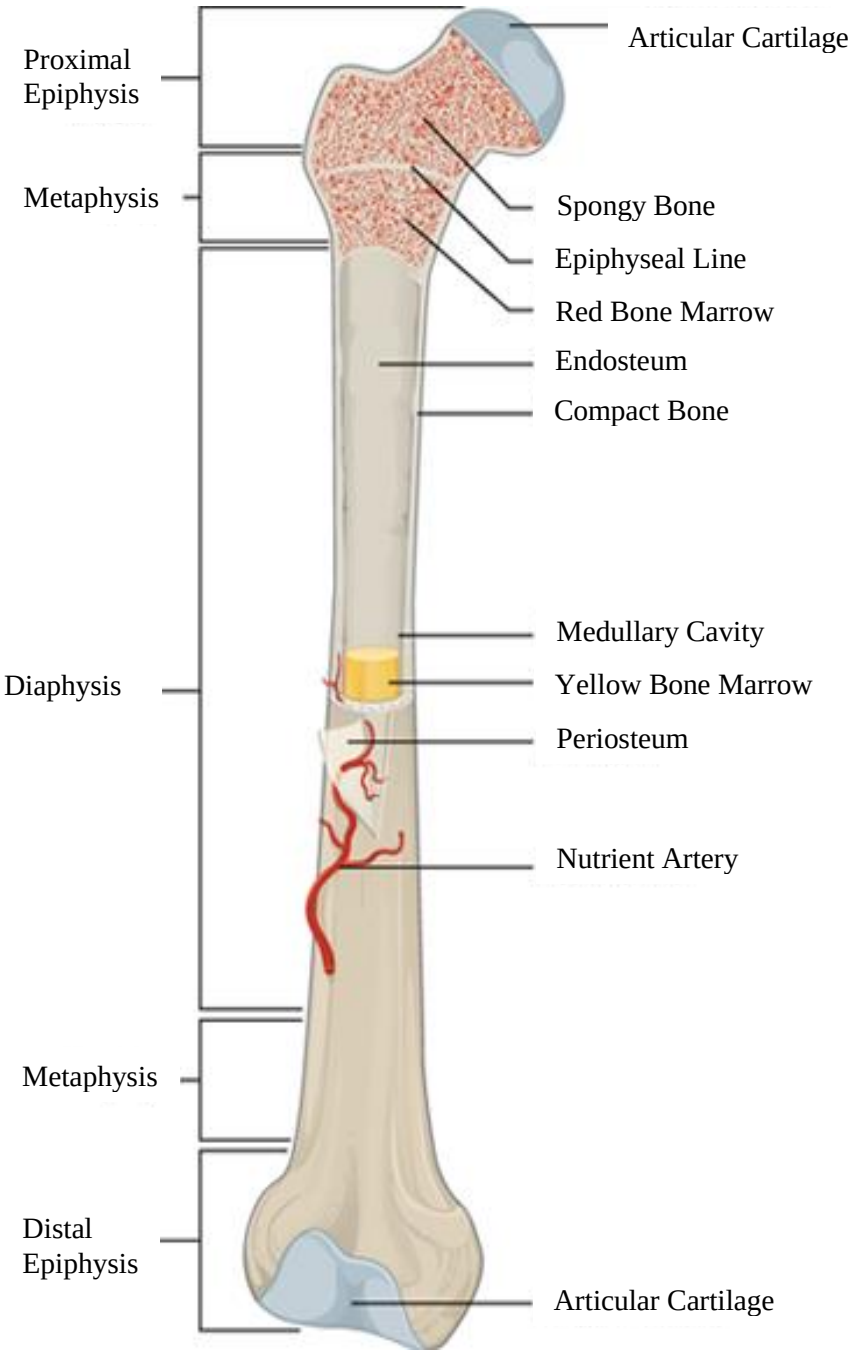

Figure 1. Anatomy of a long bone (adapted from OpenStax, 2013).

The periosteum is a fibrous construct which encompasses cortical bone (Brandi, 2009) in all places except for the joints which are covered by articular cartilage (Clarke, 2008). Articular cartilage which is at the end of an epiphysis, absorbs stress and provides a cushion between the ends of bones during movement (Marieb, & Hoehn, 2010). The periosteum contains osteoblasts, osteoclasts, nerve endings, and blood vessels which nourish the bone (Brandi, 2009). As more bone is added to the surface of the periosteum, the bending and twisting strength of bone is increased (Turner, & Robling, 2003). The periosteum is connected to the cortical bone by collagen fibres known as Sharpey's fibres

(Clarke, 2008). Like the periosteum, the endosteum also contains osteoblasts, osteoclasts and blood vessels (Brandi, 2009). The endosteum is a membranous construct which encompasses trabecular bone (Brandi, 2009). The endosteum contains three parts with the first being the endocortical surface which occurs between the medullary canal and the cortex (Seeman, 2013). The second part is the trabecular surface which occurs on both sides of the trabecular plates (Seeman, 2013). The third part is intracortical surface which is created due to the lining of the Haversian systems and Volkmann canals (Seeman, 2013).

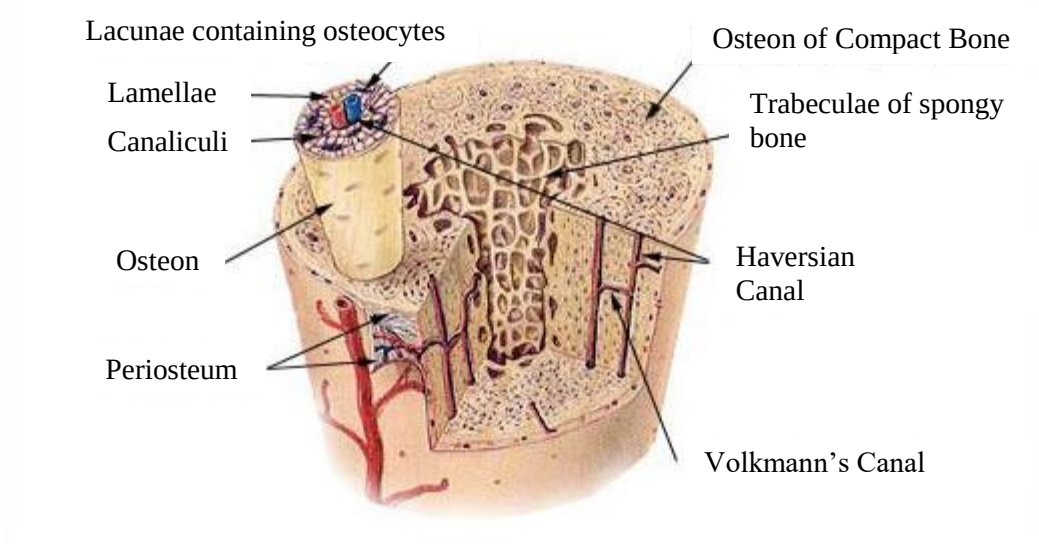

Figure 2. The inside of cortical (compact) and trabecular bone (Singh, n.a.).

Volkmann canals are connected to Haversian canals transversally, while Haversian canals run longitudinally in cortical bone (Pazzaglia, Congui, Raspanti, Ranchetti, & Quacci, 2009). These canals have blood flowing through them, and this blood flow supports osteocytes (Pazzaglia, Congui, Raspanti, Ranchetti, & Quacci, 2009). The volume of cortical bone within the periosteum and endosteum is made up of 70% mineralised bone matrix volume, with the remaining 30% made up of extracellular fluid-filled volume (Seeman, 2013). The cortical bone which is mineralised then joins together to create osteons, and osteons have an extracellular fluid-filled Haversian canal which is located centrally (Seeman, 2013). The Haversian canals and the Volkmann canals create the majority of cortical porosity, although they also create the intracortical surface where remodelling occurs (Seeman, 2013).

2.2.1. Bone Remodelling

Bone remodelling occurs for both cortical and trabecular bone types and is the process by which osteoclasts and osteoblasts work together in order to resorb bone and then lay down new bone respectively. Although the bone cells work closely together, and are physiologically coupled, each can work independent of the other (Hernandez, Beaupre, & Carter, 2000). There are three stages to bone remodelling: osteoclasts remove old bone by the process of resorption; followed by the process of reversal which is when mononuclear cells emerge on the surface of the bone; with the final stage formation where osteoblasts add new bone until the amount of bone which was resorbed is completely replaced (Hadjidakis, & Androulakis, 2007). Osteoblasts and osteoclasts which work together in this way are referred to as a basic multicellular unit (BMU) (Hernandez, Beaupre, & Carter, 2000).

Remodelling for cortical bone occurs in the Haversian canals, while for trabecular bone it occurs on the trabecular surface (Hernandez, Beaupre, & Carter, 2000). After osteoblasts have performed their roles, they embed themselves in the bone matrix and transform into osteocytes (Figure 2) (Zernicke, MacKay, & Lorincz, 2006). Osteocytes, which outnumber osteoclasts and osteoblasts by more than a ratio of 20 to 1 (Robling, & Turner, 2009), respond to mechanical loading (Robling, & Turner, 2009), and they modulate osteogenesis (Schaffler, & Kennedy, 2012) by regulating osteoblast and osteoclast activity and formation (Bellido, 2013). Osteocytes regulate osteoblasts by producing sclerostin which inhibits osteoblasts, and by decreasing the sclerostin amount osteocytes allow bone formation to occur (Schaffler, & Kennedy, 2012). Osteocytes which are apoptotic, undergo apoptosis due to nearby non-dying osteocytes increasing receptor activator of nuclear factor kappa-B ligand amount which activates osteoclasts (Schaffler, & Kennedy, 2012). Nuclear factor kappa-B ligand also produces osteoprotegerin, which binds to nuclear factor kappa-B ligand and does not allow receptor activator of nuclear factor kappa-B to bind to nuclear factor kappa-B ligand; this is a limiter of osteoclast formation (Boyce, Rosenberg, de Papp, & Duong, 2012).

Osteocytes also regulate local mineralisation into the bone matrix by producing dentin matrix protein 1 (DMP1) and matrix extracellular phosphoglycoprotein (MEPE) (Schaffler, & Kennedy, 2012). Osteocytes regulate systemic phosphate levels by producing the phosphaturic factor fibroblast growth factor 23 (FGF 23) (Schaffler, & Kennedy, 2012). Osteocytes are involved in sensing mechanical loads on bone by

detecting fluid movement in lacunar-canalicular spaces, and this results in osteocytes sending signals which regulate osteoclasts and osteoblasts (Schaffler, & Kennedy, 2012).

Osteoid, which is unmineralised bone, is laid down by osteoblasts (Westerlind et al., 1997), where it mineralises (Seeman, 1997). Osteoid bone is made up of 90% type I collagen, with the remaining 10% composed of ground substances (Kalfas, 2001; Wahl, & Czernuszka, 2006). Both type I collagen (Fonseca, Moreira-Gonçalves, Coriolano, & Duarte, 2014) and Hydroxyapatite (Seeman, 2013) are important for bone strength, providing bone with its toughness and stiffness respectively (Wise et al., 2007). Importantly, Vitamin D is a key factor in the correct mineralisation of osteoid. Vitamin D supplementation has been shown to increase bone mineral density (BMD) in prepubertal children (Davies, Evans, & Gregory, 2005) while a deficiency in Vitamin D has shown to lead to metabolic bone disease (Holick, 2004). As reported by Holick (2004), a deficiency can also cause a collagen matrix mineralisation defect, which increases the fracture rate. This can also lead to collagen expanding over the periosteum, which can result in increased pain.

Bone remodelling is important as it assists in repairing micro-damages in the bone matrix where osteoclasts resorb old bone, and newly stimulated osteoblasts concentrate in loaded areas, thus changing bone structure to meet the changing mechanical needs (Hadjidakis, & Androulakis, 2007). Imbalance in bone remodelling is associated with many deficits. If damage to the bone occurs at a rate faster than it can be repaired, then the micro-damage will spread to create a stress fracture (Robling, & Turner, 2009). For example, bone disease such as osteoporosis is associated with premature death in the elderly (Sugiura, & Bhatia, 2011). Osteoporosis causes bones to become weak and increases the chance of fracture, even to a minor bump (Sugiura, & Bhatia, 2011). In children, if osteoclast activity fails to occur during skeletal development, then a disease known as osteopetrosis can occur (Boyce, Rosenberg, de Papp, & Duong, 2012). Osteopetrosis, despite resulting in an increase in bone mass, causes bones to become weak due to the bone not being able to undergo the remodelling process (Boyce, Rosenberg, de Papp, & Duong, 2012). For untreated children with severe osteopetrosis, bone marrow will become suppressed and this can result in a decreased life expectancy (Stark, & Savarirayan, 2009).

Another useful function of bone remodelling is that it is a key in maintaining plasma calcium homeostasis (Hadjidakis, & Androulakis, 2007) which provides strength and

structure to bone (Flynn, 2003). Around 99% of calcium in the body is located in bone playing a role in the development, maintenance and growth of bone (Flynn, 2003). During growth stages an increased calcium level has a positive effect on bone mass (Davies, Evans, & Gregory, 2005), BMC and BMD (Anderson, 1996).

However, during early adolescence hormones dominate the bone remodeling growth process (Anderson, 1996). Hormonal regulation of bone remodelling is through systemic and local means (Hadjidakis, & Androulakis, 2007). The main systemic regulators consist of parathyroid hormone (PTH), growth hormones (GH) (insulin-like growth factor 1 (IGF-1), and insulin-like growth factor 2 (IGF-2)), thyroid hormones, oestrogen, androgen, glucocorticoids, calcitriol, and calcitonin (Hadjidakis, & Androulakis, 2007). PTH is the key regulator of calcium homeostasis (Hadjidakis, & Androulakis, 2007) and also increases bone turnover (Fonseca, Moreira-Gonçalves, Coriolano, & Duarte, 2014) and can increase bone mass (Kuruvilla, Fox, Cullen, & Akhter, 2008). Both growth and thyroid hormones affect the regulation of bone resorption and formation, while oestrogen decreases osteoclast lifespan and increases the effectiveness of osteoblasts (Hadjidakis, & Androulakis, 2007). Androgen affects androgen receptors by inhibiting the action of nuclear factor kappa-B ligand on osteoclasts resulting in an increase in osteogenic adaptations (Lang, 2011). A tissue is regarded as osteogenic if it is involved in the process of bone growth or repair (Dorland's Medical Dictionary for Health Consumers, 2007). Glucocorticoids are a key part in osteoblast maturation, however they reduce osteoblast activity (Hadjidakis, & Androulakis, 2007). Calcitriol raises the bone mineralisation amount by increasing intestinal phosphorus and calcium absorption (Hadjidakis, & Androulakis, 2007).

2.2.2. Bone Development During Childhood

Childhood is the key period of growth and development (Cameron, & Demerath, 2002). Bone mass increases throughout childhood, with an acceleration of bone mass accrual during puberty (Davies, Evans, & Gregory, 2005). Before the onset of puberty, there are minimal gender differences in the mass and diameters of long bones (Seeman, 2008). However, during puberty periosteal apposition takes place at a greater rate in boys compared to girls, and this results in wider long bones in adult men (Seeman, 2008). Endocortical resorption however occurs at similar rates for both boys and girls (Seeman, 2008). Bone growth is dependent upon GH and IGF-1, with exercise being a stimulus for the secretion of GH (Bass et al., 1998). During puberty for boys and girls, the levels of

GH and IGF-1 increase, resulting in an increase in the number of osteoblasts (Davies, Evans, & Gregory, 2005). As a result, bone turnover accelerates during puberty (Davies, Evans, & Gregory, 2005).

Testosterone is the foremost androgen in the body (Chuu et al., 2011) and is a factor in osteogenic adaptations (Lang, 2011). During puberty, for boys, testosterone levels increase and result in large increases in trabecular bone (Lang, 2011). Dehydroepiandrosterone (DHEA), an adrenal androgen has a positive effect on the growth of bone strength pre-puberty for boys and girls (Davies, Evans, & Gregory, 2005). Oestradiol, a steroidal hormone found in the ovaries (Durante, & Li, 2009), increases cortical bone thickness at the endocortical surface by suppressing bone turnover (Davies, Evans, & Gregory, 2005).

The development of bone mass throughout childhood is important. Risk factors for low BMD values in girls include amenorrhea and the late onset of puberty (Boot, de Ridder, Pols, Krenning, & de Muinck Keizer-Schrama, 1997). The late onset of puberty has a higher chance of occurring in individuals with low body weight and low BMD who exercise (Seeman, 1997). For example, studies have shown that ballet dancers who have undergone late menarche and have amenorrhea have a reduced BMD and an increase in fractures (Boot, de Ridder, Pols, Krenning, & de Muinck Keizer-Schrama, 1997). It has also been shown that an increased fracture rate and a decrease in BMD is linked to people who have anorexia nervosa (Boot, de Ridder, Pols, Krenning, & de Muinck Keizer-Schrama, 1997). Once recovered from anorexia nervosa, adolescent girls have persistent osteopenia and a greater decrease in the BMD of the spine in comparison to adults who have anorexia nervosa (Davies, Evans, & Gregory, 2005).

2.2.3. Bone Mass During Adulthood

Bone mass continues to accumulate in children until their peak as adults in their mid to late twenties, upon where bone mass will begin to slowly decline (O'Flaherty, 2000). Different rates of bone loss per decade have been reported, with results ranging from 2% to 13% (O'Flaherty, 2000). Bone loss rates between men and women (pre-menopausal) are similar but are less for cortical bone (3% to 5% loss per decade) compared to trabecular bone (6% to 13% per decade) (O'Flaherty, 2000). For menopausal women, the rate of bone loss increases (O'Flaherty, 2000). The rate of BMD loss per year for women who were one to three years into menopause ranges from 3.1% to 4.0%, while women

who have been in menopause greater than thirteen years have shown to have an annual bone loss of 2.3% ± 2.1% (Okano et al., 1998). Bone loss in post-menopausal women is also exacerbated if deficient in oestrogen (Ahlborg et al., 2003) with oestrogen deficiency associated with extensive loses in trabecular bone (Hubal et al., 2005). Decreases in oestrogen levels leads to an increase in bone resorption and a decrease in mechanosensitivity (Lang, 2011).

Other factors can also play a role in bone mass accrual or loss throughout the lifespan. Studies have had varied results on the impact paralysis (either a paraplegic, or a quadriplegic) has on overall bone loss (Sievänen, 2010). Bone loss in the distal tibia has varied from less than 5% in around half a year, to nearly 60% in over eight years (Sievänen, 2010). During growth if a person does not apply mechanical load to their bones, they will only develop 30% to 50% of their normal bone mass (Robling, & Turner, 2009). Their long bones will become weak and thin, with a decreased periosteal circumference (Robling, & Turner, 2009). Astronauts undergo a rapid loss in bone mass due to the lack of loading in space due to being in a weightless environment (Robling, & Turner, 2009). Studies have shown that microgravity-induced BMD loss occurs mainly at weight-bearing locations, such as the tibia and the calcaneus (Nordström, Tervo, & Högström, 2011). Whereas the BMD amount in non-weight-bearing locations such as the radius, had no measurable loses (Nordström, Tervo, & Högström, 2011). The largest amount of bone loss for astronauts occurs in the endocortical region (Cervinka, Rittweger, Hyttinen, Felsenberg, & Sievänen, 2011). Bone mass decreases due to disuse at a faster rate than it increases due to loading (Sievänen, 2010). The deterioration of bone structure may become permanent if prior loading levels are not achieved (Sievänen, 2010). Likewise, bed rest is associated with bone loss in the endocortical region (Cervinka, Rittweger, Hyttinen, Felsenberg, & Sievänen, 2011), with the greatest BMD loss occurring in the legs, yet no decrease in BMD loss at the radius (Nordström, Tervo, & Högström, 2011), consistent with the rationale that the radius is a non-weight-bearing bone. In both the microgravity and best rest environments, recovery of bone loss is reported. After six months in space, it is possible to recover 50% of bone loss in less than a year, while after three months bedridden, it is possible to recover nearly all bone loss in less than a year (Sievänen, 2010).

Genetic characteristics also play an important role. People of different ethnicities having different genetic values of bone (O'Flaherty, 2000), with up to 80% of bone mass

characteristics accounted by genetics (Kanan, 2013; Ralston, & De Crombrugghe, 2006). African Americans have higher peak bone mass, cortical and trabecular bone density, and lower bone turnover in comparison to Caucasian Americans (O'Flaherty, 2000). Other studies have shown dark-skinned people to have higher bone density than Caucasian people, who have higher bone density than Asian people (Chinese and Japanese) (Boot, de Ridder, Pols, Krenning, & de Muinck Keizer-Schrama, 1997). African Americans also have more BMC than non-Hispanic Anglo-American, Hispanic and Asian people (Stults-Kolehmainen et al., 2013). It has been shown that Afro-Caribbean women have a lower chance of developing stress fractures when compared to Caucasian and Asian women (Aweid, Aweid, Talibi, & Porter, 2013). The skeletal size of dark-skinned people is also shown to be larger than people of Caucasian and Asian ethnicity (Seeman, 1997).

2.3. Measurement of Bone

Primarily measurement of bone comprises examining bone mineralisation to determine mass, density, content, strength and overall health. This is usually conducted using a bone densitometry scan (imaging) which helps determine the overall status of bones through non-invasive methods (Damilakis, Adams, Guglielmi, & Link, 2010).

Common methods for scanning bone include Dual-energy X-ray Absorptiometry (DXA) and peripheral Quantitative Computed Tomography (pQCT), which are discussed further below. Another bone scanning device is a mechanical response tissue analyser (MRTA) which is able to measure bone strength (Miller et al., 2007). However, MRTA can only be used to assess superficial bones such as the tibia and the ulna, and only provides information regarding the whole bone without nuanced detail on the distribution and quality of the bone (Miller et al., 2007) and is therefore not further discussed. Magnetic Resonance Imaging (MRI; Lee, Sagel, Stanley, & Heiken, 2006) and axial Quantitative Computed Tomography (QCT) scans can also measure bone properties; however due to higher radiation exposures for QCT scans, large cost barriers, the risk versus benefits arising for the latter, and the inability to evaluate tissue quality for the former, these are also not further discussed. A high-resolution peripheral quantitative computed tomography (HR-pQCT) is able to measure bone properties more precisely than pQCT, however due to the gantry length not being long enough for most models of HR-pQCT it is unable to scan proximal sites such as of the tibia (Lala, Cheung, Gordon, & Giangregorio, 2012). While more recent models of HR-pQCT are able to scan further up

the distal limbs (Kroker, Bhatla, Emery, Manske, & Boyd, 2018), the lack of accessibility for the newer models can be a limitation to using HR-pQCT for scanning proximal limb sites. Finally, bone assessments have also been undertaken with quantitative ultrasonography (broadband ultrasound attenuation [BUA] and speed of sound [SOS]), which can only be used to assess superficial bones, and provides only a localised assessment of the characteristics directly in the line of sound wave propagation, and is therefore not discussed further (Töyräs, Nieminen, Kröger, & Jurvelin, 2002).

2.3.1. Dual-energy X-ray Absorptiometry (DXA)

DXA is a widely used, two-dimensional scanning device (Figure 3) (Lee, Gilsanz, & Wren, 2007), which uses X-rays to scan the entire body aBMD (Damilakis, Adams, Guglielmi, & Link, 2010) and body composition of fat mass, lean mass, and total tissue mass (Suster, Leury, Hofmeyr, D'Souza, & Dunshea, 2004). Areal bone mineral density is regarded as the BMC divided by area (Dowthwaite, Flowers, & Scerpella, 2011), while BMD is regarded as bone mass which has been adjusted for its bone volume (Davies, Evans, & Gregory, 2005).

DXA is able to scan and collect data across the entire body in a single scan or can be used to provide more isolated scans of the femoral neck of the femur or lumbar as a diagnostic tool to identify people at risk of osteoporosis (Damilakis, Adams, Guglielmi, & Link, 2010). For example, a person with an aBMD at the femoral neck or lumbar below -2.5 standard deviations from healthy norms is classed as having osteoporosis, while a person with an aBMD of between -1 and -2.5 standard deviations is classed as having osteopenia (Seeman, 1997; Wright et al., 2014). Low bone mass can increase the chance of developing bone fractures (Nordström, Tervo, & Högström, 2011). Osteoporosis also results in a negative change in bone microarchitecture which causes an increase in bone fragility (Ammann, & Rizzoli, 2003). DXA is regarded as being the ‘gold standard’ for diagnosing osteoporosis and osteopenia (Salehi-Abari, 2017).

A limitation of DXA is the inaccuracy of aBMD and aBMC measurements due to changes in body fat (Lee, & Gallagher, 2009), although accuracy of scanning bone would only be affected by significant amounts of fat (Yu, Thomas, Brown, & Finkelstein, 2012). This is based on the location of fat (Lee, & Gallagher, 2009), with arms containing on average less fat than the legs and trunk (Stults-Kolehmainen et al., 2013). Another limitation is that DXA is only able to detect aBMD and not volumetric bone mineral density (vBMD)

or bone geometry (Dowthwaite, Flowers, & Scerpella, 2011). vBMD is regarded as BMC divided by volume (Dowthwaite, Flowers, & Scerpella, 2011).

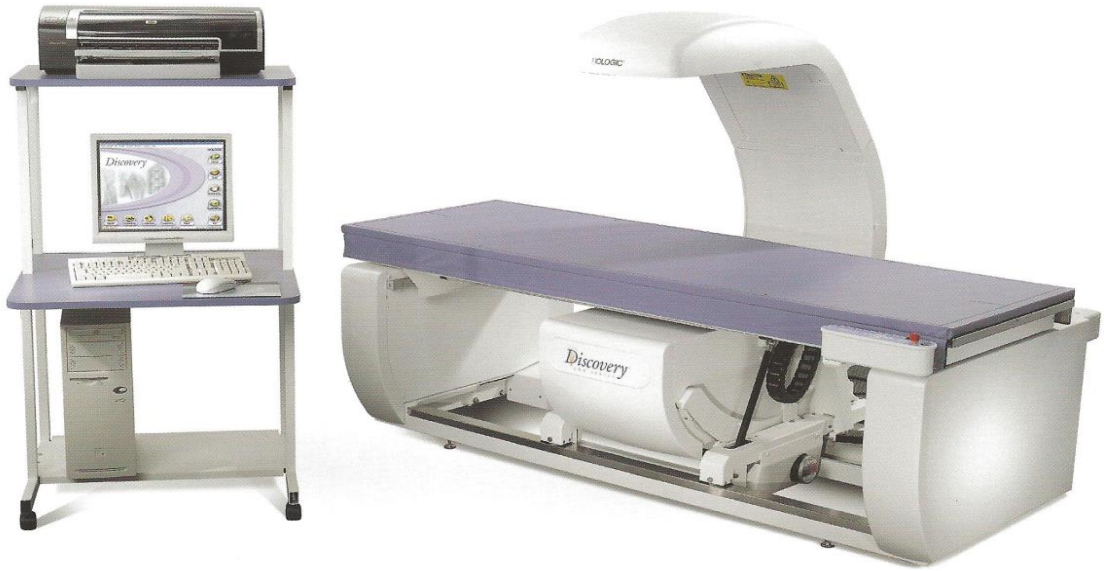

Figure 3. A fan-beam Hologic DXA (Discovery A) densitometry machine.

2.3.2. peripheral Quantitative Computed Tomography (pQCT)

The pQCT is a bone densitometry imaging device which scans bone in three dimensions collecting higher resolution images and more in-depth volumetric data than DXA (Lee, Gilsanz, & Wren, 2007) (Figure 4). The pQCT device is able to scan the one segment in detail at any given time (upper arm, forearm, thigh or shank) (Sievänen et al., 1998). A pQCT operates by subjecting the selected limb to a stream of X-rays (Sievänen et al., 1998). The XCT 3000, used for this research study, has specific operating features (*XCT 3000 manual software version 6.20*, 2009) which are subsequently described. The stream of X-rays are delivered by means of an X-ray tube with a small focal spot. A series of miniature-semiconductor-crystals make up a detector-system which allows for a reduced scanning time. Micro-controllers control the parallel evaluation of the detector measuring values, and also the internal control of the three axes. Bone is measured by a process known as filtered back-projection, a process by where an absorption profile of the scanned object is found by that said object absorbing X-rays. The resulting data is then corrected for beam hardening and dead time. Numerous absorption profiles are collected from different angular positions and then mathematically folded creating a cross sectional image of the original object to be.

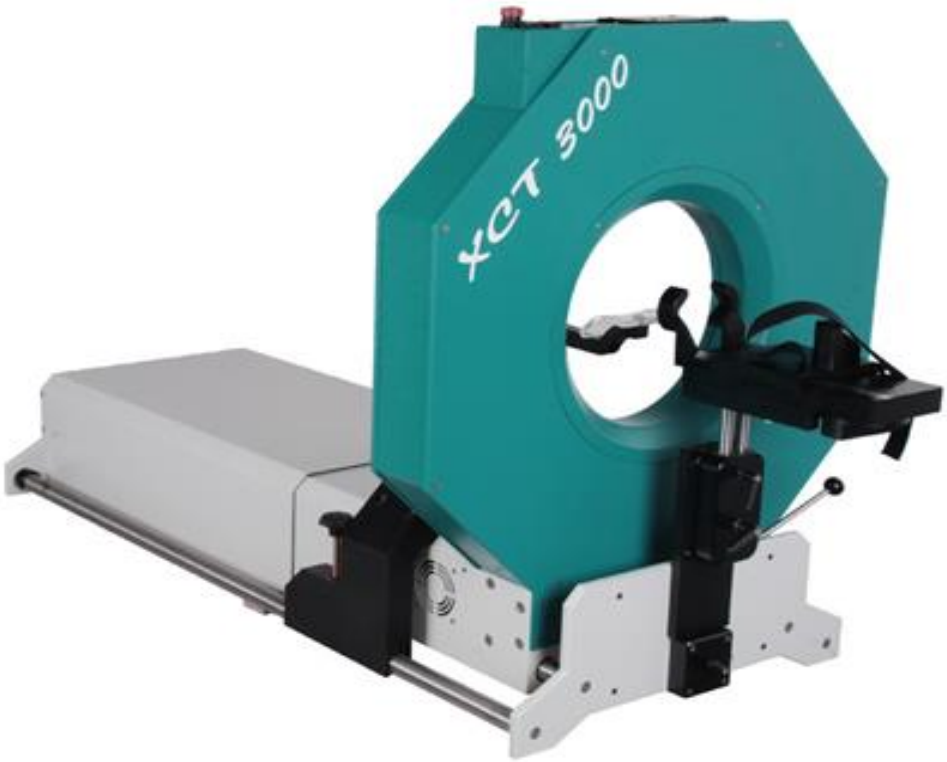

Figure 4. A pQCT machine. Figure adapted from Stratec Medizintechnik, 2017.

2.3.3. Comparison of DXA and pQCT

DXA and pQCT methods of scanning bone involve low doses of radiation and this allows a safe amount of repeated scans over a period of time (Damilakis, Adams, Guglielmi, & Link, 2010). A whole body DXA scan was found to have a radiation total from 0.0048 mSv to 0.0105 mSv, with Sv the unit of measurement, sieverts (Damilakis, Adams, Guglielmi, & Link, 2010). pQCT scans have been found to have radiation totals less than 0.01 mSv, and even less than 0.003 mSv (Damilakis, Adams, Guglielmi, & Link, 2010). As the worldwide average effective amount of background radiation over a year is 2.4 mSv, DXA and pQCT are well under that total and therefore the risk is considered to be low in their radiation doses per scan (Damilakis, Adams, Guglielmi, & Link, 2010). However, it should be noted that every dose of radiation accumulates and increases the chance of an adverse effect (Pogribny et al., 2005). Both DXA (El Maghraoui, & Roux, 2008) and pQCT can produce errant results if there is patient movement during scanning (Rantalainen et al., 2018; Sievänen et al., 1998). A pQCT scan typically takes longer than a DXA scan to complete (Binkley, Berry, & Specker, 2008). Although there may be more time for the patient to move during a pQCT scan, the pQCT has a securing mechanism to fixate the limb and minimise movement (Shaw, & Stock, 2009), whereas DXA is an unrestrained scan thus can result in a greater risk of movement during a DXA scan.

DXA is used to diagnose patients with osteoporosis and osteopenia (according to the cut-off points defined by Seeman, 1997, and Wright et al., 2014, which are mentioned above) and is regarded as being the 'gold standard' for diagnosing osteoporosis and osteopenia (Salehi-Abari, 2017). Hence for this reason DXA is more commonly used as a diagnostic tool than pQCT (Dowthwaite, Flowers, & Scerpella, 2011). However, the use of pQCT as a diagnostic tool may be limited by the lack of reliability and normative data available in comparison to DXA. However, there are some advantages to the pQCT that provide support for further research as to the usefulness for diagnostic purposes.

DXA scans two-dimensionally and is only able to interpret the structure of a three-dimensional limb with less accuracy than pQCT (Lee, Gilsanz, & Wren, 2007). DXA is able to determine BMC and aBMD, while pQCT is able to establish BMC along with vBMD (Dowthwaite, Flowers, & Scerpella, 2011). The vBMD is able to be measured by polar and radial distribution (Rantalainen, Nikander, Daly, Heinonen, & Sievänen, 2011). The benefit in measuring vBMD over aBMD is that vBMD allows within-bone differences to be measured and this allows bone growth and adaptation to be observed over time (Dowthwaite, Flowers, & Scerpella, 2011). A pQCT scan is also able to measure the bone structure, along with the amount of cortical and trabecular bone (Burrows, Liu, & McKay, 2010). Since DXA does not assess the structural properties of bone on the same level that pQCT does, the effects that exercise has on bone strength may be underestimated when assessed by DXA (Sievänen et al., 1998). DXA cannot differentiate between cortical bone and trabecular bone, measure bone strength, and is not able to measure bone geometry on the same specific level that pQCT can, hence bone growth cannot be as accurately portrayed as it would be from pQCT (Dowthwaite, Flowers, & Scerpella, 2011).

The primary advantage of pQCT is that it scans limbs two-dimensionally and combines those scans to produce three-dimensional images (Engelke et al., 2008). Another advantage of using pQCT over DXA is that pQCT is able to measure the stress-strain index (SSI) of bone which is a calculated predicted strength of the bone in accordance with a maximal failure three-point bending test (Kokoroghiannis et al., 2009). A three-point bending test is performed by using a universal testing machine (Marrelli, Maletta, Inchingolo, Alfano, & Tatullo, 2013), while bone strength is regarded as the amalgamation of the geometry and material properties of bone (Willnecker, 2006), (Cointry et al., 2014). pQCT also has advantages for measuring change over time. Of

particular interest is that a pQCT scan is effective in detecting bone loss in patients and monitoring their bone status over time (Sawada et al., 2006) because it has a much higher resolution than DXA. A pQCT has a higher resolution than DXA because pQCT is able to scan an image with a higher precision with fewer μm/ pixel (Briggs et al., 2010). The voxel size for pQCT has a standard value of 0.5mm, while it can go as low as 0.2mm (Lala, Cheung, Gordon, & Giangregorio, 2012). While the voxel size can go to 0.2mm, it does not improve the overall accuracy of the pQCT due to the associated higher level of noise compared to 0.5 mm voxels and therefore 0.5mm is the standard value used (Lala, Cheung, Gordon, & Giangregorio, 2012). A pQCT has been touted as a good measure for longitudinal studies. Current reliability information exists for cortical and trabecular vBMD along with SSI for the second metatarsal of cadavers and these variables were found to have excellent intraclass correlation coefficient (ICC) values and low coefficient of variation (CV) values (Chaplais et al., 2014). Excellent ICC values were also found for vBMD for the subchondral tibia (Wrigley, Creaby, & Bennell, 2007). Low CV values were found for vBMC, bone strength index (BSI), cortical density (CoD), cortical area (CoA), trabecular density (TrD), and trabecular area (TrA) for numerous locations in the upper and lower limbs (Sievänen et al., 1998).

Although pQCT offers much beyond the capability of DXA, no ICC values have been reported for many of the muscle and bone measurements. The CV values have been measured for muscle density (MuD) and muscle cross-sectional area (MSCA) in the lower leg (Wong, et al., 2015), however reliability values have not been reported for the measures of muscle in the upper limb. There is also a lack of information concerning the between-day reliability of pQCT. Furthermore, while DXA is more readily available to practitioners across the world, pQCT machines are increasingly more commonplace in hospital and academic institutions, and are recommended for preferential use where available, with comparable costs per limb scanned by pQCT relative to a whole-body scan by DXA depending on providers and their cost structures. However, the increased information and utility of data obtained through pQCT justifies its use within clinical populations. The cost of a DXA machine is lower than that of pQCT (Binkley, Berry, & Specker, 2008), however, as pQCT becomes more mainstream, its production cost may also reduce, as per economy of scale.

2.4. Bone Adaptation

Bone adaptation can occur in different ways. One way bones adapt is genetically, and both nutrition and hormones are important for osteogenesis (as previously discussed at 2.2.1. Bone remodelling) (Hernandez, Beaupre, & Carter, 2000). Bones will develop the characteristic shape due to genetics (Pazzaglia, Zarattini, Spagnuolo, Superti, & Marchese, 2012). Pharmaceutical agents (refer 2.4.1) and mechanical loading (refer 2.4.2.) and can also alter bone adaptation.

2.4.1. Pharmaceutical Agents for Bone Adaptation

Certain drugs such as bisphosphonates (Fonseca, Moreira-Gonçalves, Coriolano, & Duarte, 2014) are able to assist osteoporosis treatment by regulating the actions of osteoblasts and osteoclasts during the deposition or resorption stages of bone remodelling (Hernandez, Beaupre, & Carter, 2000). Selective oestrogen receptor modulators (SERMs) have also been shown to increase aBMD and decrease fracture risk (Ammann, & Rizzoli, 2003). Other pharmaceutical anti-resorptive or pro-formative agents include denusomab, parathyroid hormone, calcitonin, or hormone replacement therapies (Brandi, 2013).

Pharmaceutical agents can have either a positive or negative effect on bone adaptation, as observed with bisphosphonates in a study by Fonseca and colleagues (2014). While it does not occur often in patients undergoing bisphosphonate treatment, it is possible for increased bone mineralisation (due to blunted resorption) to increase the risk of atypical fractures, while also compromising bone mechanical behaviour and competency. Due to the decrease in bone turnover, older and more mineralised bone is accumulated. This can lead to an increase in the brittleness of bone, which causes bone to be unable to absorb any energy due to elastic deformation. Therefore, everyday loads will be dissipated by developing micro-cracks which ultimately lead to a complete fracture. Also, since older damaged bone is accumulated, an association has been formed between the long-term use of anti-resorptive treatments such as bisphosphonates, and the increase of sudden fractures along with the inability of fractures to heal.

2.4.2. Mechanical Loading for Bone Adaptation

Bone adapts over time in response to the presence or absence of mechanical loading (Hart et al, 2017), in accordance with Wolff's Law (Wolff, 1892; translated in Wolff, 1986). Wolff claimed that there were mathematical rules which govern this process, specifically

in relation to trabecular orientation development in long bones (Ruff, Holt, & Trinkaus, 2006). Wolff created the trajectory theory of trabecular bone architecture, which states that while under stress, trabeculae of trabecular bone will follow the same lines of trajectory along the stress lines in the bone (Skedros, & Baucom, 2007). Wolff developed this theory by observing Culmann's crane created by Karl Culmann in 1866 (Skedros, & Baucom, 2007), which theorises that trabecular trajectories in the proximal femur were alike to that of a curved crane (Robling, & Turner, 2009). However, this theory has subsequently been shown to be inaccurate (Currey, 1997), as the trajectory of the trabeculae is not as a consequence of stress lines.

Frost (1990) expanded on Wolff's Law and labelled this occurrence as bone remodeling and created the concept of the mechanostat, which is the combination of all the necessary features bone requires in order to maintain a healthy state (Frost, 1987). The mechanostat observes and controls factors which directly determine bone mass, such as bone modelling, longitudinal growth, and BMU remodeling activities (Frost, 1987). From this, the functional muscle-bone unit was termed, describing the relationship between bone and muscle and its comparison to the norm, as primary, secondary or mixed bone defect (Schoenau, 2005). Specifically, Schoenau (2005) described a primary bone defect when the amount of BMC is not adequate for the amount of muscle mass a person has. If the amount of BMC is adequate for the amount of muscle mass a person has, but that person has a lower amount of muscle mass in regards to their height, then they have a secondary bone defect. If both the muscle mass is not adequate for a person's height, and the amount of BMC is not adequate for the amount of muscle mass, then that person has a mixed bone defect (Schoenau, 2005).

Bone adaption through mechanical loading operates through mechanotransduction, a process by which mechanical stimuli is transduced into a biological response (Robling, & Turner, 2009). It is involved in bone repair and bone regeneration through four different phases (Huang, & Ogawa, 2010). These phases include mechanocoupling, biochemical coupling, signal transmission from the sensor cell to the effector cell, and the response of the effector cell (Huang, & Ogawa, 2010). Mechanocoupling involves a sensor cell (osteocyte) picking up a local mechanical signal which is the result of mechanical force being applied to the bone, while biochemical coupling involves the local mechanical signal transducing into a biochemical signal (Turner, & Pavalko, 1998).

2.5. Bone Loading

Bone loading is an important factor for osteogenic adaptation (Wolff, 1892; translated in Wolff, 1986). Hence, mechanical stimuli imparted onto the skeleton through various forms of exercise can result in osteogenic adaptations to bone (Hart et al, 2017; Judex, & Zernicke, 2000).

There are site-specific differences in osteogenesis for mechanical stimulus (Kuruvilla, Fox, Cullen, & Akhter, 2008). The osteogenic response to exercise is potentially determined by the training volume, the rate of mechanical stimuli, and the magnitude of mechanical stimuli (Hart et al, 2017; Turner, 1998). These potential determinants of osteogenic adaptation are based on three rules: bone adaptation is the result of dynamic loading and not static loading; an adaptive response in bone only requires a small amount of mechanical loading, while a decreased effect on bone can be caused by extensive loading; and customary mechanical loading environments result in more adaptive bone than routine mechanical loading environments (Turner, 1998).

As stress (internal resistance, Yuehuei, & Draughn, 1999) is applied to bone, a strain (bone deformation, Yang, Brüggemann, & Rittweger, 2011) occurs on the bone and this is referred to as the stress-strain relationship (Barry, & Kohrt, 2008). Faridmehr et al., (2014) described when loading is applied to a bone, elastic deformation/strain will occur, and during elastic deformation/strain bone will undergo non-permanent adaptations (Figure 5). During elastic deformation/strain, the relationship between stress and strain is demonstrated (Young's modulus) until loading passes a point known as the yield strength where permanent adaptation occurs (Faridmehr et al., 2014) (Figure 5). Uniform plastic deformation will occur until the ultimate tensile strength is produced and this point is referred to as necking, with any deformation after this point referred to as non-uniform plastic deformation, increasing until eventually a fracture occurs, referred to as the fracture strength (Faridmehr et al., 2014) (Figure 5).

A higher strain magnitude and a faster strain rate each result in an increased osteogenic response (Barry, & Kohrt, 2008) with isokinetic strength training an example shown to elicit a positive osteogenic response (Miller et al., 2007). Yang and colleagues (2011) describe four different types of strains which can be applied to bones. Axial strains occur in the same direction as the load which is applied to the bone; e.g. compressive and tensile strains. Shear strains occur when two planes slide over one another. Bending strains occur

when a bone bends, while torsion strains occur due to the rotation of bone (Yang, Brüggemann, & Rittweger, 2011). However, there is a point when the frequency of the exercise peaks will not further increase the osteogenic adaptations (Figure 5) (Turner, & Robling, 2003). Studies such as Rubin and Lanyon, (1984), have found that after approximately 40 loading cycles, the osteogenic adaptations will not significantly increase anymore. This is due to the bone cells becoming desensitised to prolonged mechanical loading (Turner, & Robling, 2003). It is also found that loading cycles produce smaller osteogenic adaptations compared to large magnitudes of stress applied to the bone (Whalen, Carter, & Steele, 1988). A study using accelerometers showed that higher vertical impacts are produced due to intensity rather than due to exercise frequency (Hannam et al., 2017).

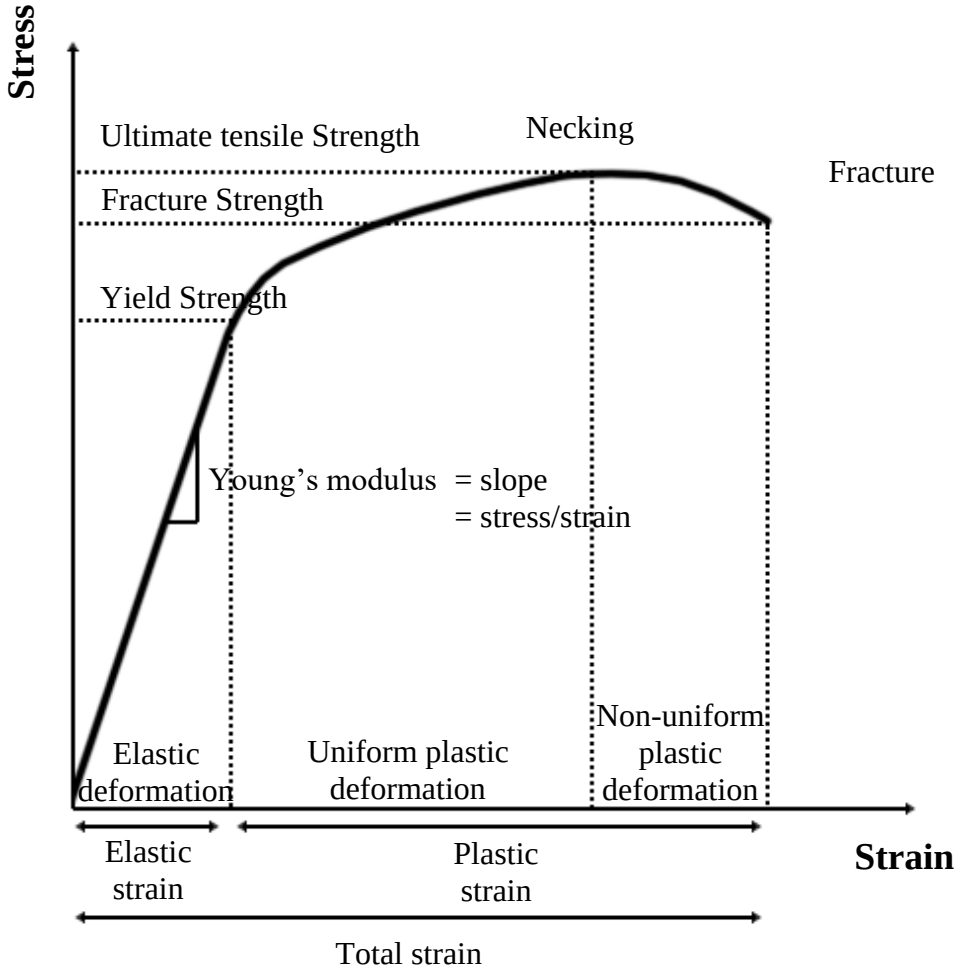

Figure 5. Stress-strain relationship showing yield strength, elastic deformation, plastic deformation, and the fracture point. Figure adapted Faridmehr et al., 2014.

The direction of load-specific adaptations also effects osteogenesis (Hert, & Lisková, 1971). Over time, athletes participating in particular types of sports exhibit contextually specific adaptational changes in bone which primarily strengthen bone in mechanically

optimal, routinely loaded sites (Rantalainen, Nikander, Daly, Heinonen, & Sievänen, 2011). These adaptations have been shown to occur in athletes aged 17 to 40 and demonstrates that if sport-specific exercises are performed then bone will adapt to the structurally optimum outcome regardless of age (Rantalainen, Nikander, Daly, Heinonen, & Sievänen, 2011). Bone loss occurs in areas of low stress as seen in a 90-day bed rest study by Cervinka, Rittweger, Hyttinen, Felsenberg, & Sievänen, (2011), (however individual typical loading was not measured), and bone added to areas of high stress (Rubin, & Lanyon, 1984). Athlete versus non-athlete differences have also been shown. For athletes, BMD is higher and bone strength is stronger compared to non-athlete (Nikander, Sievänen, Uusi-Rasi, Heinonen, & Kannus, 2006). Among athletic populations, there are differences in vBMD for both polar and radial distributions across different sports (Rantalainen, Nikander, Daly, Heinonen, & Sievänen, 2011). These studies highlight the need to identify the specific load-specific adaptation characteristics of different exercises in order to optimise bone growth and maintain bone health.

Bone loading mechanosensitivity is dramatically reduced right after loading (Miller et al., 2007), and it is important to take time to rest in order to replenish bone mechanosensitivity and fatigue. The greater the number of loading cycles, the greater mechanosensitivity decreases (Turner, & Robling, 2003) (Figure 6). After 24 hours of rest, 98% of bone loading mechanosensitivity returns (Miller et al., 2007). Therefore, exercise produces the greatest osteogenic adaptations when performed in short bouts with several hours break between sessions (Turner, & Robling, 2003).

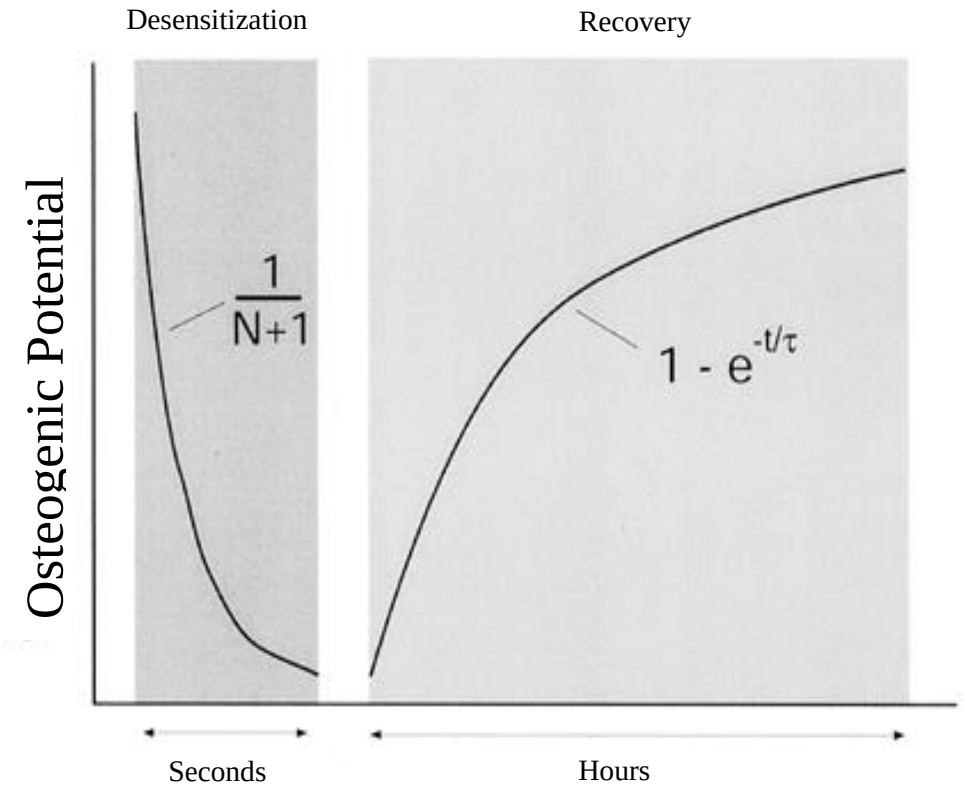

Figure 6. Osteogenic potential and mechanosensitivity. Bone desensitization to loading occurs quickly, while recovery can take hours. N represents the number of loading cycles. Figure adapted from Turner, & Robling, 2003.

2.5.1. Role of Exercise for Bone Loading

Exercise has been shown to be important for overall bone health, with bone loading shown to be an important factor (Barry, & Kohrt, 2008; Santos, Elliot-Sale, & Sale, 2017). The main forms of exercise that have been shown to be beneficial for bone loading include resistance training, plyometrics, running, jogging, walking, jumping, kicking, throwing and swift directional movement changes (Barry, & Kohrt, 2008; Guadalupe-Grau, Fuentes, Guerra, & Calbet, 2009). Specifically, these exercises involve ground-reaction forces resulting in a higher BMD increases than exercises that consist of unloaded exercises such as swimming and rowing (Guadalupe-Grau, Fuentes, Guerra, & Calbet, 2009). Running produces a strain on the tibia slightly higher than the strain from drop jumps, and far greater than walking (Yang, Brüggemann, & Rittweger, 2011), and a higher strain on the bone produces greater bone adaptation (Al Nazer, Lanovaz, Kawalilak, Johnston, & Kontulainen, 2012). Although swimming and rowing results in athletes with similar BMDs to those of a sedentary population (Guadalupe-Grau, Fuentes, Guerra, & Calbet, 2009), swimmers have been shown to gain higher bone strength in their humeri (Shaw, & Stock, 2009). Overall, exercise that elicits small changes in bone can

result in large increases in bone characteristics, as seen in a study by (Warden et al., 2005) which showed how a small increase in the structural properties of bone resulted in a large increase in skeletal fatigue resistance.

High acceleration impacts over a long period of time from daily living and activities such as running, jumping, stamping, and step exercises, can result in osteogenic effects (Ahola, Korpelainen, Vainionpää, Leppäluoto, & Jämsä, 2009). When considering vertical ground reaction force (vGRF), a measure of high acceleration impact, a study to predict parameters of bone strength by Weeks & Beck (2008) found drop jump, depth jump, and tuck jump had the greatest vertical vGRF on a force plate, while lunge, walk, and side lunge were found to have the lowest vGRF across 19 different activities selected to represent components of sporting and everyday physical activities (Weeks, & Beck, 2008). Bone adaptation through higher GRF's (ground reaction force) as just described is one mechanism for eliciting adaptation. Another is via the concept of the previously discussed mechanostat theory that loading on the bones based on the muscle-bone unit would also elicit bone adaptation (Schoenau, 2005). Therefore, instead of placing high rate of loading (e.g. GRF), high amounts of muscle loading may also elicit bone adaptation (Santos, Elliot-Sale, & Sale, 2017). The muscle loading concept can be demonstrated through vibration exercises, a form of training which has been shown to positively improve bone strength by developing positive osteogenic adaptations in individuals with cerebral palsy who lack muscular strength and control and a decrease in movement, hence are unable to acquire the necessary mechanical stimulation required for osteogenic adaptations (Wren et al., 2011).

For bone health, different exercises (Santos, Elliot-Sale, & Sale, 2017) and bone loading intensities have been recommended for varying age groups (Barry, & Kohrt, 2008). Large loading intensities are recommended for children and adults (Barry, & Kohrt, 2008; Burrows, 2007). In children and adolescents, large loading intensities are recommended for maximising the osteogenic adaptations (Burrows, 2007). Bone loading should be maintained during adulthood as bone mass will begin to decline from a person's mid to late twenties (O'Flaherty, 2000), and exercise will assist in maximising peak bone mass and ultimately decreasing the risk of osteoporosis (Santos, Elliot-Sale, & Sale, 2017). Sex specific loading regimens are warranted, as in post-menopausal women power training is associated with slower bone loss than strength training (Von Stengel, Kemmler, Lauber,

Kalender, & Engelke, 2007). For the elderly population it is recommended to remain as active as their health permits (Barry, & Kohrt, 2008).

2.6. Bone Fractures

Bones are rigid, stable structures of the body designed to withstand bending, however if the force is too great, a bone will break (fracture) (Abrahamyan, 2017). Fractures can be classed as open (the bone pierces the skin) and closed (the bone does not pierce the skin) (Altizer, 2002). Fractures can also be classed as complete (through the entire bone) and incomplete (not through the entire bone) (McKenna, Heffernan, Hurson, & McKiernan, 2014). There are 11 main types of fractures that occur: transverse fracture; oblique fracture; greenstick fracture; spiral fracture; avulsion fracture; compression fracture; buckle/torus fracture; intraarticular fracture; hairline fracture; comminuted fracture; displaced fracture (Altizer, 2002).

Transverse, oblique, spiral fractures (Courtney, Bernstein, & Ahn, 2011; Marieb, & Hoehn, 2010) and certain avulsion fractures, such as apophyseal avulsion fractures are commonly fractured playing sport (Imai, Kitano, Nakagawa, & Takaoka, 2007). A transverse fracture is a sideways fracture that occurs due to slight bending of a long bone, followed by a great force (Altizer, 2002). An oblique fracture is a diagonal fracture that occurs due to slight bending of a long bone, followed by a great force (Altizer, 2002). A spiral fracture, also known as a torsional fracture (MedicineNet.com, 2016) occurs due to excessive twisting forces which are applied to the bone (Marieb, & Hoehn, 2010). An avulsion fracture occurs due to a sudden pulling force on the bone (Altizer, 2002).

Some fractures occur more commonly in certain periods across the lifespan. A greenstick fracture occurs when only one side of the bone shaft fractures, while the other side of the bone shaft bends and are more common in children as their bones are more flexible than the bones of adults (Marieb, & Hoehn, 2010). A buckle, or torus fracture occurs when the bone buckles, and they are also common in young children (Altizer, 2002). An intraarticular fracture is a fracture that protrudes into the joint surface (Altizer, 2002). Intraarticular fractures in the distal radius often occur in young adults (Meena, Sharma, Sambharia, & Dawar, 2014). A hairline fracture, also known as a stress fracture (Uddin, & Rahman, 2016) is caused due to excessive stress placed upon a bone without the proper time for recovery as commonly observed in military recruits and athletes (Aweid, Aweid, Talibi, & Porter, 2013). Stress fractures can also be caused when weakened bone

experiences an injury under normal stress (Aweid, Aweid, Talibi, & Porter, 2013). A displaced fracture is a fracture where bone fragments have shifted and separated from the bone (Altizer, 2002). These fractures are often caused by high-impact forces (Courtney, Bernstein, & Ahn, 2011), such as with a traffic accident (Gao, Zhu, & Zhang, 2015).

The elderly and specific disease groups present their own predispositions to fractures with two specific fracture types. A comminuted fracture is when the bone breaks into fragments of three or more pieces and occurs more in the elderly due to their bones being more brittle (Marieb, & Hoehn, 2010). A compression fracture occurs when bone is crushed together, such as in the vertebrae and are common in people with osteoporotic bones (Marieb, & Hoehn, 2010).

2.6.1. Fracture Healing Process

Altizer (2002) describes the fracture healing process (Figure 7) as five main stages. Within 72 hours after the initial bone injury, a haematoma is formed. Fibrocartilage tissue forms from three days to two weeks after the injury. A callus is then formed anywhere from two weeks to six weeks after the injury. Osteogenesis will then occur anywhere from three weeks to six months after the onset of the fracture. The final stage in the fracture healing process is bone remodelling, and this may occur from six weeks to one year after the initial injury (Altizer, 2002).

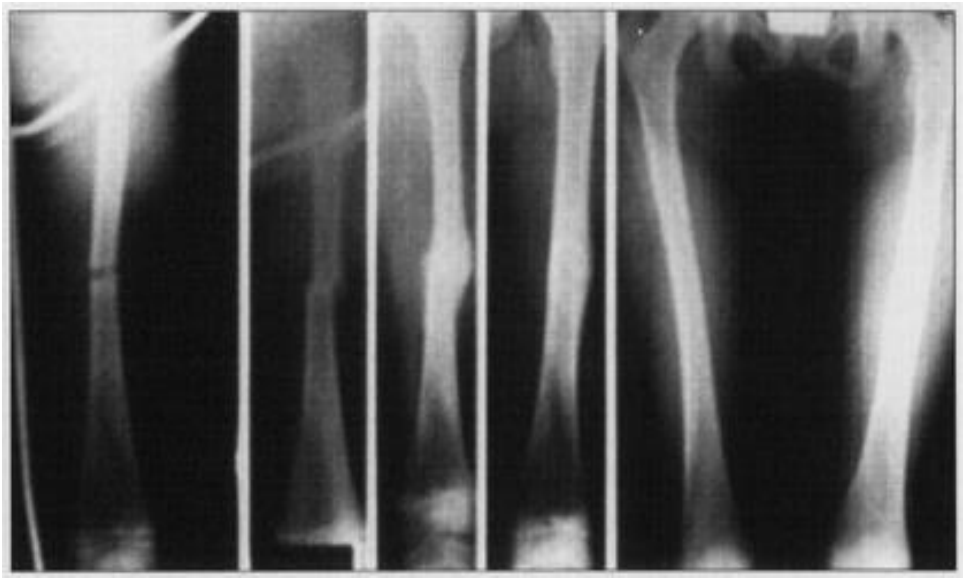

Figure 7. The bone healing process. From left to right: The day of the fracture; two weeks after injury; eight weeks after injury; six months after injury; eighteen months after injury. Figure adapted from Altizer, 2002.

In order for a fracture to heal properly, there must be no gap at the location of the fracture as too much movement and instability during fracture healing can lead to the non-union of the fracture site (Gaston, & Simpson, 2007). A fracture is regarded as non-union if the healing has not completed within four to six months after the onset of the fracture, with repetitive stress applied to the fracture site, and the lack of blood supply to the fracture site a leading causes of non-union (Altizer, 2002). Some fractures may heal incorrectly, over the normal period of time for healing, with bony deformities and are known as mal-union fractures (Altizer, 2002). These fractures occur due to unequal stress forces placed on the fracture site, or due to excess weight being placed on the fracture site before the bone is healthy enough to do so (Altizer, 2002). Delayed union fractures are fractures which take longer than normal to heal, and occur between three months and one year after the onset of the fracture and can be caused by internal fixation devices breaking, and also due to an infection (Altizer, 2002).

The rate of fracture healing is dependent upon previously mentioned factors, as well as the location of the fracture. Trabecular bone fractures often heal at a faster rate than cortical bone fractures (Iwegbu, 2012). Fractures in the humerus take on average less than five months to heal (Denard et al., 2010), while four to eight weeks healing is reported for ulna shaft fractures (Black, & Becker, 2009) and tibial shaft fractures (Aweid, Aweid, Talibi, & Porter, 2013). Distal radius fractures have varied healing rates reported from four to eight weeks (Black, & Becker, 2009) compared to eight to nine weeks (Rozental, Vazquez, Chacko, Ayogu, & Bouxsein, 2009). Fractures in both the radius and ulna concurrently have shown to heal in nine weeks on average (Ruhullah, Singh, Shrestha, Gupta, & Jha, 2016). Return to weight bearing activities after having a stress fracture varies according to fracture site. Stress fractures in the anterior tibia or the femoral shaft can take six to eight weeks (Kahanov, Eberman, Games, & Wasik, 2015), up to twelve weeks for a femoral shaft stress fracture (Aweid, Aweid, Talibi, & Porter, 2013), four to six weeks in the femoral neck, two to four weeks for a fibula stress fracture (Kahanov, Eberman, Games, & Wasik, 2015), and less than three weeks for a posteromedial tibial stress fracture (Kahanov, Eberman, Games, & Wasik, 2015).

2.6.2. Fracture Incidence

The incidence of fractures varies over the course of life (Donaldson, Reckless, Scholes, Mindell, & Shelton, (2008). The highest rates of fractures occur in childhood and old age

when the skeleton is at its weakest (Hedström, Svensson, Bergström, & Michno, 2010). The types of fractures also vary dependent upon age (Altizer, 2002; Meena, Sharma, Sambharia, & Dawar, 2014; Marieb, & Hoehn, 2010). The main types of fractures which occur during skeletal development include complete fractures, compression fractures, greenstick or bowing fractures, transverse fractures, oblique fractures, and spiral fractures (Kraus, & Wessel, 2010). Fractures in children are a common occurrence with the distil radius being the most common site of fractures (Boyce, & Gafni, 2011). Fractures in children in the upper limb represent 68% of fractures (Maasalu, Raukas, & Märtson, 2009) with approximately 25% of fractures in children and adolescents occurring in the forearm (Goulding, Jones, Taylor, Williams, & Manning, 2001). Approximately 50% of boys and 40% of girls experience a fracture during their childhood (Boyce, & Gafni, 2011). The main causes of fractures in children include the type of activity such as participation in contact sports (Peck, Johnston, Owens, & Cameron, 2013), along with falls which may be caused by an impaired balance due to obesity (Sahoo et al., 2015). Fractures in children are expected to heal at a faster rate than fractures in adults due to their bones still being in the formative growth stage (Malone, Sauer, & Fenton, 2011). Inactivity in children can also be associated with low BMD, aBMD, vBMD, and also an increased risk of forearm fractures (Goulding, Jones, Taylor, Williams, & Manning, 2001).

Worldwide, for individuals over the age of 50, one in three women will experience an osteoporotic fracture compared to one in five men (International Osteoporosis Foundation, 2017). Bone loss occurs in the elderly (Ensrud, 2013), particularly inactivity related decrease in BMD (Nordström, Tervo, & Högström, 2011) and combined with an increased risk of age related falling, leads to an increased risk of fracture (Ensrud, 2013, Nordström, Tervo, & Högström, 2011). Approximately 10% to 15% of falls in the elderly result in a fracture, the most common including fractures of the hip, wrist, pelvis, ankle, and multiple arm sites (Ensrud, 2013). Since inactivity is a leading cause of BMD loss, it is therefore important for older individuals to participate in activities that improve balance and decrease the risk of a fall (Nordström, Tervo, & Högström, 2011; Hill, 2018).

International fracture incidence data in children is well reported (Moon et al., 2016; Mäyränpää, Mäkitie, & Kallio, 2010; Randsborg et al., 2013), however no specific analyses exist in Australia to describe fracture incidence and trends in children or adolescents. The only published work reported fracture incidence in adults in the city of

Geelong on the east coast of Australia. Fracture incidence for individuals aged 35 years and above was reported and showed that the fracture incidence for women increased at a greater rate than men as people aged (Sanders et al., 1999). For the same cohort, it was found that individuals who live in an urban environment have a significantly greater fracture incidence per 10^4 than those who lived in a rural environment (99 and 89 respectively; $p = 0.01$) (Sanders et al., 2002).

2.7. Osteogenic Index

The OI is a formula which predicts the osteogenic potential of different loading exercises and is important as it allows individuals to determine and/or predict the amount of osteogenic adaptation from different exercises (Turner, & Robling, 2003). The larger the OI number, the larger the osteogenic potential of the given exercise (Turner, & Robling, 2003). An exact OI number to elicit osteogenic adaptation such as BMD is presently unknown (Lau, & Pang, 2009). Two different OI formula are commonly used.

The OI formula for Rantalainen et al., (2011) (OI-ADAPTED) considers the loading rate and the interval between loading and is regarded as:

$$\textit{Osteogenic Index (OI)} = \sum_{i=1}^{f_i \leq 50\text{Hz}} \varepsilon_i f_i$$

ε_i = the magnitude of the i^{th} frequency bin, and f_i = the frequency of the i^{th} frequency bin.

The OI formula for Turner & Robling (2003) (OI-ORIGINAL) is regarded as:

Osteogenic Index (OI) = Peak ground reaction force (in body weight) x ln (number of loading cycles + 1)

The OI-ADAPTED equation is different from the OI-ORIGINAL equation in that Rantalainen and colleagues (2011) calculate the OI of each individual repetition in an exercise set, while Turner and Robling (2003) calculate the highest OI value of a single repetition in a set and uses that value to represent all repetitions in the set. A comparison of reliability when utilising the different methods of calculating OI (Rantalainen et al., 2011; Turner, & Robling, 2003) has not been reported.

As mentioned previously, too many loading cycles will result in a dramatic loss of mechanosensitivity in a session (Turner, & Robling, 2003). Turner and Robling (2003) found that the OI can be increased by splitting a daily exercise (in this instance 120 jumps)

routine into half and performing those sessions with an eight hour gap in between. They reported that OI nearly doubled, from 14.4 to 21.4 as arbitrary OI units. For loading cycles of 150, 300, and 600 jumps per day, the optimal training regimen for the highest OI was training five days a week, with two sessions per day (Turner, & Robling, 2003). Although these gains and optimal loading cycles have been reported, there is no specific research to indicate how much change in bone does an increase in the OI represent.

A study by Lau and Pang (2009) has shown that exercises that contain higher GRFs such as jumping, stepping and walking, produce a greater OI than exercises with minimal GRF's such as sitting-to-standing. Exercises that have the potential to produce the greatest OI are hip extensions, long jumps, and knee flexions, whereas exercises that have the least potential to produce the greatest OI are hip adduction, sitting-to-standing, and step-ups (Martelli, Kersh, Schache, & Pandy, 2014). A high-impact lower body exercise study has shown that an increase in the intensity and number of impacts, quantitatively shows modification in bone geometry and strength over time (Vainionpää et al., 2007). The intensity and the number of impacts have a dependent relationship to osteogenic adaptations, with the number of impacts being the main predictor of bone circumference transformation (Jämsä, Ahola, & Korpelainen, 2011). These exercises with transient impact force spikes result in bone increasing strength at a greater level than if no transient impact force spikes occurred (Rantalainen et al., 2011). Therefore, it is important to perform exercises with transient impact force spikes in order to achieve a greater osteogenic adaptation. Based on the studies on lower body osteogenesis (Lau, & Pang, 2009; Martelli, Kersh, Schache, & Pandy, 2014; Vainionpää et al., 2007), the same outcomes could be presumed to occur in the upper body after a study of equivalent exercises however this has yet to be investigated. Further, the upper body may provide a unique model for understanding the accuracy of the OI and bone adaptation. There are no known studies where the OI is applied clinically.

2.7.1. Measurement of OI

The key element to determining OI is the measurement of the impact during each exercise repetition (peak GRF). One method of measuring this is by using accelerometers (Ahola, Korpelainen, Vainionpää, & Jämsä, 2010). Accelerometers are small and portable and are able to measure motion analysis on the x, y, and z-axes (Cuesta-Vargas, Galán-Mercant, & Williams, 2010). Data captured by accelerometers during exercise can be put into the OI equations in order to determine the OI. Force data for the OI equation can also be

calculated by using force plates (Turner, & Robling, 2003). Strain gauge force transducers can also be used, such as by positioning them on a treadmill (Kluitenberg, Bredeweg, Zijlstra, Zijlstra, & Buist, 2012).

Despite the potential of using OI as a method to determine and select exercises to maximise osteogenic adaptation, there is no known research evaluating the reliability of OI assessments of exercises. The investigation of reliability is critical to ensure training studies using exercise interventions based on osteogenic indices of exercises to maximise bone health are accurately determining or predicting the osteogenic potential for the duration of the study. This will allow researchers and coaches to determine which exercises and which OI equations result in consistent and dependable OI results (Sullivan, 2011). There has also yet to be a comparison of reliability when utilising the different methods of calculating OI.

2.8. Summary of the Literature Review

Bone ontogeny, response to mechanical loading, methods to assess bone health, and methods to evaluate osteogenicity of exercise were reviewed along with fracture mechanisms and fracture incidence. Four gaps in the literature were identified; 1) it was noted that contemporary trends in Australian paediatric fracture incidence are scarcely reported in the literature, which is due to barely any fracture incidence audits having being performed, 2) it was found that the reliability of upper limb bone and soft-tissue pQCT assessments are absent, which may be due to the lack of desire and/or technology available to research those assessments, 3) assessment of the osteogenicity of upper limb exercises were not to be found from the literature, which may be due to the OI being a somewhat novel technique, and 4) phenotypic characteristics of long bones of various paediatric populations at risk of secondary osteoporosis were missing from the literature, as this topic has not been researched before. Therefore, as described in the introductory chapter, the subsequent experimental chapters aimed to investigate these identified gaps in the literature.

APPENDICULAR FRACTURE EPIDEMIOLOGY OF CHILDREN AND ADOLESCENTS: A 10-YEAR CASE REVIEW IN WESTERN AUSTRALIA (2005 TO 2015)

Accepted for Publication, Archives of Osteoporosis - 15th May, 2018.

CHAPTER FOUR – STUDY TWO

RELIABILITY OF UPPER-LIMB DIAPHYSEAL MINERAL AND SOFT-TISSUE MEASUREMENTS USING PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

4.1. Abstract

Objectives: To quantify between-day reliability of upper-body diaphyseal measurements (radius, ulna, humerus) using peripheral Quantitative Computed Tomography (pQCT).

Methods: Fourteen males (age: 25.8 ± 2.3 years,) underwent repeat pQCT scans (one to two days apart) at mid-shaft ulna (60%), mid-shaft radius (60%) and mid-shaft humerus (50%) cross-sections of the non-dominant limb. Intraclass correlation coefficients (ICC) and coefficients of variation (CV) were determined for musculoskeletal morphology variables.

Results: Reliability was excellent (ICC: 0.76 – 0.99; CV: 1.3 – 7.3) at all sites for bone mass, stress-strain index, endocortical and pericortical radius, endocortical volumetric bone mineral density (vBMD), muscle area, total area, non-cortical area, and cortical area. Reliability was good to excellent (ICC: 0.58 – 0.80; CV: 0.6 – 3.7) for polar vBMD and mid-cortical vBMD; fair to excellent (ICC: 0.30 – 0.88; CV: 0.5 – 8.0) for muscle density and cortical density; and fair to good (ICC: 0.25 – 0.60; CV: 3.4 – 7.6) for pericortical vBMD. Average reliability across the three sites was excellent (ICC $\geq$ 0.77; CV $\leq$ 8.0).

Conclusions: Overall between-day reliability of pQCT was excellent for the mid-shaft ulna, radius and humerus. pQCT provides a reliable and feasible body composition and skeletal morphology assessment tool for upper limb longitudinal investigations in scientific and clinic settings.

4.2. Introduction

Peripheral Quantitative Computed Tomography (pQCT) produces a series of two-dimensional scans reconstructed to provide a three-dimensional image at specific cross-sections to determine volumetric measures of bone material, structure and strength, along with muscle and fat morphology of the upper and lower limbs (Hart et al., 2017; Lee, Gilsanz, & Wren, 2007; Engelke et al., 2008). The clinical utility of pQCT to assess segmental tissue composition, the effects of bone disease(s), and osteogenic adaptations due to exercise and growth is increasing (Lee, Gilsanz, & Wren, 2007), thus it is important to quantify the reliability of pQCT at various sites and across commonly assessed variables in order to determine which measures provide consistent and dependable results (Sullivan, 2011). If pQCT results are unreliable, incorrect measurements may lead to misdiagnoses, false-positive or false-negative outcomes due to scan variability, and may compromise the ability of clinicians and researchers to accurately assess the efficacy of interventions.

Few studies have described the reliability of pQCT measures (Chaplais et al., 2014; Wrigley, Creaby, & Bennell, 2007), principally focusing on isolated lower limb sites. Specifically, excellent reliability for cortical and trabecular bone mineral density and stress strain index (SSI) was observed when scanning the second metatarsal of cadavers (Chaplais et al., 2014); and for bone mineral density in the subchondral tibia of healthy individuals (Wrigley, Creaby, & Bennell, 2007); with another study measuring between-day reliability of upper limb and lower limb bone sites, demonstrating high reliability with low coefficients of variation (CV) (Sievänen et al., 1998). Although this single study focused on the CV's of multiple variables at several bone sites for each of the long bones in the limbs (Sievänen et al., 1998), there is a need for additional measures of reliability more generally, in particular with the upper-limbs and soft-tissue. Indeed, root mean squared coefficient of variation (CV_{RMS}) values for bone measures have been reported for the upper and lower limbs (Sievänen et al., 1998), however intraclass correlation coefficients (ICC) have not.

Similarly, low CV_{RMS} values for various pQCT muscle measures in the lower leg (Wong et al., 2015), and the upper-arm (Weatherholt et al., 2015) have also been reported, though have not yet been studied in the forearm or thigh segments to date. Similarly, there appears to be a lack of information concerning the between-day reliability of pQCT measures. Accordingly, the purpose of this investigation was to determine the between-

day reliability of pQCT on commonly measured bone and muscle diaphyseal variables for the upper limb (consisting of the upper arm and forearm).

4.3. Method

4.3.1. Participants

Fourteen male participants (age: 25.79 ± 2.27 years, height: 179.11 ± 6.66 cm, and weight: 86.41 ± 22.84 kg), aged between 20 to 30 years volunteered and completed the current study. Males were purposefully recruited as a voluntary sub-cohort of a larger study which involved an osteogenic training intervention limited to men (i.e. minimum strength level requirement). All participants were healthy in accordance with a pre-exercise medical questionnaire to ensure no pre-existing medical conditions (i.e. current or previous fractures in measured scan sites; and movement disorders or similar), no recent nuclear medicine or radiation exposure (within the prior month), and no contraindicated medications (i.e. patients on anti-resorptive medication, such as bisphosphonates or denusomab) were present at the time of study involvement. Individuals were also excluded from participation if there was a pre-existing or recent injury (within 6 months of recruitment) in the scanned limb; if they were unable to adopt the required scan position(s) due to pain or discomfort from an existing injury to a non-scan site, if they had ever fractured or broken the scanned bones being examined. The study was approved by the University Human Research Ethics Committee (ID: JENKINS-11690) and all participants read an information sheet and provided written informed consent.

4.3.2. pQCT

Reliability for several variables was determined by performing test re-test pQCT scans (XCT-3000; Stratec Medizintechnik, Pforzheim, Germany), 24 or 48 hours apart within the same hour as the initial testing day to control for any potential diurnal variation. The same technician performed all scans for every session. The non-dominant forearm and upper arm was scanned, determined as the opposite limb of each participant's preferred writing hand. Calibration was performed daily in accordance with manufacturer specifications (*XCT 3000 manual software version 6.20*, 2009). Participants were placed in a prone position on a massage table with their upper arm and/or forearm abducted 90 degrees from the torso with the elbow extended and palm face down and hand fixed inside the pQCT gantry (Figure 13). A prone position was chosen over a supine position to

ensure consistency in arm orientation between upper arm and forearm scans. Specifically, when an individual has their forearm scanned while being seated, their arm is in a prone position, plus the hand fixation device was contoured to the palm of the hand in a prone position, with a strap support around the back of the hand; which is routinely used for radial scans. This attachment was thus also used for the humeral scan (observable in Figure 13). The pQCT was height adjusted for each participant to ensure the arm remained in line with the torso.

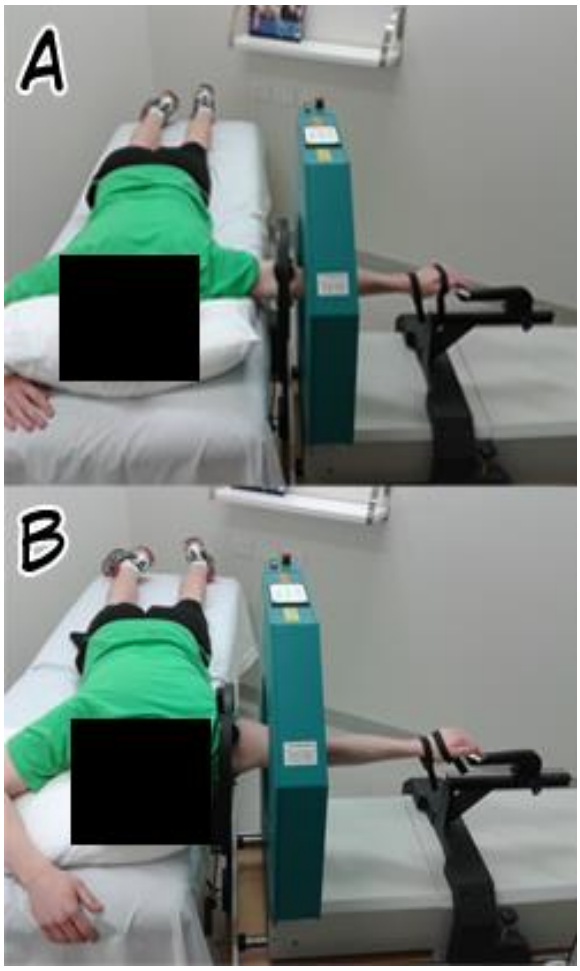

Figure 13. Positioning for pQCT scanning for (A) lower arm, and (B) upper arm.

Humeral and forearm lengths were measured in triplicate (Humerus: ICC: 0.99 (0.98 – 1.00), CV: 0.5 (0.4 – 0.7); Forearm: ICC: 1.00 (0.99 – 1.00), CV: 0.3 (0.3 – 0.5)), with the average of the measures taken for each region used to establish the cross-section locations to be examined. Specifically, humeral length was defined as the lateral epicondyle at the humeroradial joint (distal end) to the acromion process at the glenohumeral joint (proximal end), with scanning occurring at the 50% humeral site. Forearm length was defined as the cortical end plate of the radius (distal end) to the lateral

epicondyle at the humeroradial joint (proximal end), with scanning occurring at 60% of radial length and ulna length from the distal end. A voxel size of 0.5mm was used for all scans. To determine the scan commencement point for the radius and ulna, a 30mm scout view image was generated with the reference line positioned through the cortical end-plate at the distal radioulnar joint (Figure 14). To determine the scan commencement point for the humerus, the halfway location of the humerus was marked on the surface of the participant's skin, with the gantry manually positioned at the marked location. An example of the scanned bones can be viewed in Figure 15. As no conspicuous anatomical landmark is visible at the distal end of humerus using the scout view owing to the olecranon process of the ulna visually obstructing the humeral endpoint, and given the added complexity of positioning a participant to access the 50% humeral slice within the gantry's moveable limits, a scout view was not used for the humerus only. Instead, the research mask was used to manually position the gantry at 50% of humeral length, which was marked on the arm from the measurement of the upper arm length.

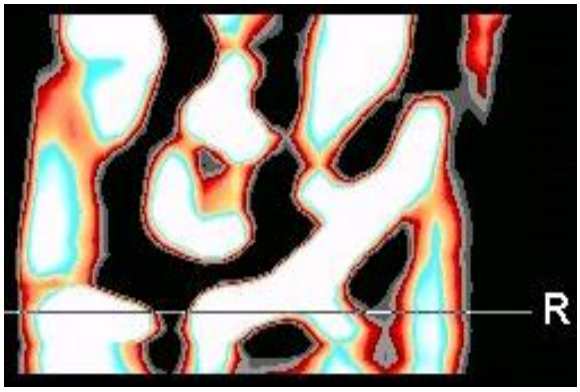

Figure 14. Scout view of the distal radioulnar joint for the forearm scan with the reference line (R) noted.

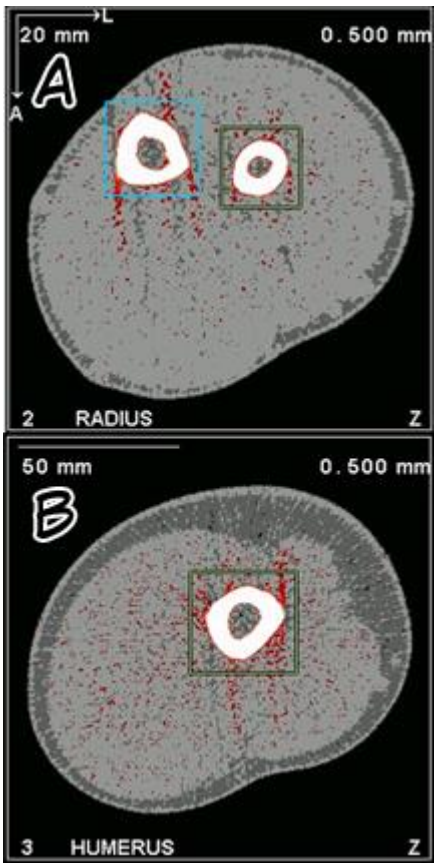

Figure 15. pQCT cross-sections (A) showing radius (green box) and ulna (blue box), and (B) Humerus.

Bone morphology was assessed using ImageJ (Version 1.48c; National Institute of Health, United States of America), BoneJ (Version 1.3.10; Imperial College London, United Kingdom) and the pQCT plug-in (National Institutes of Health, 2016; Rantalainen, Nikander, Daly, Heinonen, & Sievänen, 2011; Doube et al., 2010). Bone mass, endocortical radius, pericortical radius, polar volumetric bone mineral density (vBMD), endocortical vBMD and pericortical vBMD were distributed over 36 segments (two-dimensional images rotating at ten degrees to achieve 360 degrees) and then split into 90 degree portions (0-90°; 90-180°; 180-270°; 270-360°) to allow for comparison of reliability between the two scanning days and in order to replicate the approach of a previous study (Macdonald, Cooper, & McKay, 2009). The ICC and CV values for the four 90 degree portions for each variable were averaged to determine the overall reliability. Muscle density, muscle area, SSI, total area, non-cortical area, cortical area, and cortical density are unable to be broken into segmented portions, so reliability values were determined by comparing their overall values only. Additional variables (endocortical radius, pericortical radius, polar vBMD, endocortical vBMD, mid-cortical vBMD, pericortical vBMD, total area and non-cortical area) were included which had not

previously had reliability reported. Endo-, mid-, and pericortical vBMD were measured by contouring the cortex with a threshold of 220 mg/cm^3, and subsequently peeling away the outer-most and inner-most layers of pixels. Thereafter, the cortical ring was evenly divided into three concentric radial rings, labelling the inner-most portion as endocortical, outer-most portion as pericortical, and the middle portion as mid-cortical, as seen in Rantalainen et al., 2011. Bone area was contoured at 220 mm^2 and these pixels were used for structure-related measurements (CoA, ToA, SSI). Subsequently volumetric density was defined as all pixels within the bone envelope with density higher than or equal to 220 mg/cm^3. For density distribution analyses the dense cortex was contoured with 220 mg/cm^3 and the outermost layers of pixels were subsequently peeled away and disregarded. These contouring selections are the norm in the field. The lower threshold used for area-related measures ensures accurate area measures (Rittweger, Michaelis, Giehl, Wüsecke, & Felsenberg, 2004), and a higher threshold is used for volumetric density measures to minimise influence of the partial volume effect (defined as pixels that are partially filled with soft-tissues, and/or partially with hard-tissues).

4.3.3. Statistical Analysis

Between-day reliability of pQCT was assessed by using a reliability analysis spreadsheet (Analysis of Reliability Spreadsheet, Version 2012, SportScience, New Zealand) to determine the ICC and the CV with 90% confidence and upper and lower confidence limits (Hopkins, 2000; Sportscience, 2011). Data was assessed for outliers based on visual identification of acceptable scans from previous studies (Blew, Lee, Farr, Schiferl, & Going, 2014; Rantalainen et al., 2017). Two outliers were identified and removed for the radius and ulna analyses, while seven outliers were identified and removed for the humerus analysis. The most likely cause for the outliers is attributed to motion artefact. Statistical analyses were conducted with SPSS (Version 19.0.0; IBM SPSS Statistics, USA) and a reliability analysis program by Hopkins (2000) (Hopkins, 2000; Sportscience, 2011). An ICC value greater than 0.75 was regarded as having excellent reliability, an ICC value between 0.4 and 0.75 inclusive was regarded as having fair to good reliability, and an ICC value below 0.4 was regarded as having poor reliability (Fleiss, 1986). Further, a CV less than 10% was considered acceptable (Pedersen, & Liu, 2012).

4.4. Results

ICC and CV for variables assessed by pQCT at the three different sites (60% mid-shaft ulna; 60% mid-shaft radius; 50% mid-shaft humerus) across fourteen different variables (bone mass; SSI; endocortical radius; pericortical radius; polar vBMD; endocortical vBMD; mid-cortical vBMD pericortical vBMD; muscle area; muscle density; total area; non-cortical area; cortical area; cortical density) are summarised in Table 2. ICC and CV results for 90 degree segments are summarised in Table 3.

The overall ICC value for the radius was excellent with 0.77, with a CV value of 2.6%. For the radius, all ICC values for bone mass, SSI, endocortical radius, pericortical radius, total area, non-cortical area, and cortical area, were excellent and ranged from 0.95 to 0.99, with CV values ranging from 0.9% to 4.0%. Endocortical vBMD and mid-cortical vBMD both had excellent ICC values of 0.80, with CV values of 3.2% and 1.6% respectively. Polar vBMD had a fair to good ICC value of 0.63, and a CV value of 0.6%. Pericortical vBMD and cortical density had a fair to good ICC values ranging from 0.25 to 0.31, with CV values ranging from 4.3% to 8.0%.

The overall ICC value for the ulna was excellent with 0.78, and a CV value of 3.7%. For the ulna, all ICC values for bone mass, SSI, endocortical radius, pericortical radius, total area, non-cortical area, and cortical area were excellent and ranged from 0.92 to 0.99, with CV values ranging from 2.0% to 7.3%. Endocortical vBMD had an excellent ICC value of 0.76, and a CV value of 6.6%. Polar vBMD, mid-cortical vBMD, and cortical density had a fair to good ICC values ranging from 0.58 to 0.69, with CV values ranging from 1.7% to 3.7%. Pericortical vBMD had a poor ICC value of 0.34, and a CV value of 7.6%.

The overall ICC value for the humerus was excellent with 0.87, and a CV value of 2.5%. For the humerus, all ICC values for bone mass, SSI, endocortical radius, pericortical radius, polar vBMD, endocortical vBMD, total area, non-cortical area, and cortical area were all excellent and ranged from 0.77 to 0.99, with CV values ranging from 0.5% to 6.6%. Mid-cortical vBMD, pericortical vBMD, and cortical density had fair to good ICC values ranging from 0.60 to 0.74, with CV values ranging from 1.0% to 3.4%.

For soft-tissues, the muscle area for the forearm had an excellent ICC value of 0.99, and a CV value of 1.3%. The muscle density for the forearm had a poor ICC value of 0.30,

and a CV value of 0.7%. The muscle area for the upper arm had an excellent ICC value of 0.99, and a CV value of 2.0%. The muscle density for the upper arm had an excellent ICC value of 0.88, and a CV value of 0.5%.

For 90 degree segments, bone mass, endocortical radius, and pericortical radius had excellent ICC values for all segments (≥ 0.78), with low CV values (≤ 5.4%). Endocortical vBMD had ICC values ranging from fair to good, to excellent (0.51 ≤ 0.98), with low CV values (≤ 8.3%). Polar vBMD, mid-cortical vBMD, and pericortical vBMD had ICC values ranging from poor to excellent (-0.02 ≤ 0.98), with all CV values low (≤ 8.8%) except for one location for the pericortical vBMD (11.3%).

Table 2. Intraclass Correlation Coefficient (ICC) and Coefficient of Variance (CV) for peripheral Quantitative Computer Tomography with 90% confidence intervals for bone site variables.

	60% radius site		**60% ulna site**		**50% humerus site**	
	ICC (90% CI)	**CV% (90% CI)**	**ICC (90% CI)**	**CV% (90% CI)**	**ICC (90% CI)**	**CV% (90% CI)**
BM	0.96 (0.89 – 0.99)	2.8 (2.1 – 4.3)	0.99 (0.98 – 1.00)	2.0 (1.5 – 3.2)	0.99 (0.98 – 1.00)	2.0 (1.5 – 3.2)
SSI	0.98 (0.95 – 0.99)	2.7 (2.0 – 4.3)	0.97 (0.92 – 0.99)	4.3 (3.2 – 6.8)	0.82 (0.40 – 0.95)	6.6 (4.5 – 13.0)
EnR	0.98 (0.95 – 0.99)	2.8 (2.1 – 4.4)	0.97 (0.92 – 0.99)	4.8 (3.6 – 7.5)	0.98 (0.92 – 1.00)	2.5 (1.7 – 4.8)
PeR	0.95 (0.85 – 0.98)	1.6 (1.2 – 2.4)	0.92 (0.80 – 0.97)	2.3 (1.7 – 3.7)	0.91 (0.68 – 0.98)	2.4 (1.6 – 4.5)
PvBMD	*0.63 (0.29 – 0.14)*	*0.6 (0.5 – 0.9)*	*0.58 (0.20 – 0.82)*	*3.7 (2.7 – 5.7)*	0.77 (0.34 – 0.94)	1.6 (1.1 – 3.2)
EnvBMD	0.80 (0.54 – 0.92)	3.2 (2.4 – 5.0)	0.76 (0.47 – 0.91)	6.6 (4.9 – 10.4)	0.86 (0.54 – 0.97)	2.9 (2.0 – 5.7)
MivBMD	0.80 (0.56 – 0.92)	1.6 (1.2 – 2.5)	*0.69 (0.33 – 0.88)*	*1.7 (1.3 – 2.7)*	*0.66 (0.15 – 0.90)*	*1.0 (0.7 – 1.8)*
PevBMD	0.25* (-0.24 – 0.64)	4.3 (3.2 – 6.7)	0.34* (-0.09 – 0.68)	7.6 (5.6 – 12.0)	*0.60 (-0.01 – 0.88)*	*3.4 (2.3 – 6.5)*
MD	0.30* (-0.20 – 0.68)	0.7 (0.6 – 1.2)	0.30* (-0.20 – 0.68)	0.7 (0.6 – 1.2)	0.88 (0.58 – 0.97)	0.5 (0.3 – 0.9)
MuA	0.99 (0.98 – 1.00)	1.3 (1.0 – 2.1)	0.99 (0.98 – 1.00)	1.3 (1.0 – 2.1)	0.99 (0.98 – 1.00)	2.0 (1.4 – 3.9)
ToA	0.98 (0.94 – 0.99)	1.7 (1.2 – 2.6)	0.96 (0.89 – 0.99)	2.8 (2.1 – 4.4)	0.98 (0.90 – 0.90)	1.9 (1.3 – 3.7)
MeA	0.99 (0.97 – 1.00)	4.0 (2.9 – 6.2)	0.98 (0.95 – 0.99)	7.3 (5.4 – 11.6)	0.99 (0.97 – 1.00)	3.1 (2.2 – 6.1)
CoA	0.97 (0.91 – 0.99)	2.0 (1.5 – 3.1)	0.94 (0.84 – 0.98)	3.7 (2.7 – 5.7)	0.97 (0.87 – 0.99)	2.7 (1.9 – 5.3)
CoD	0.31* (-0.20 – 0.68)	8.0 (5.9 – 12.7)	*0.58 (0.15 – 0.83)*	*3.4 (2.5 – 5.3)*	*0.74 (0.21 – 0.93)*	*2.3 (1.6 – 4.5)*
Average	**0.77 (0.58 – 0.85)**	**2.6 (2.0 – 4.1)**	**0.78 (0.58 – 0.91)**	**3.7 (2.8 – 5.9)**	**0.87 (0.61 – 0.96)**	**2.5 (1.7 – 4.8)**

BM: bone mass; SSI: stress-strain index; EnR: endocortical radius; PeR: pericortical radius; PvBMD: polar volumetric bone mineral density; EnvBMD: endocortical volumetric bone mineral density; MivBMD: Mid-cortical volumetric bone mineral density; PevBMD: pericortical volumetric bone mineral density; MD: muscle density; MuA: muscle area; ToA: total area; MeA: non-cortical area; CoA: cortical area; CoD: cortical density. Italicised values represent fair to good ICC, * represents poor ICC values whereas all other values were considered excellent (ICC > 0.75).

Table 3. Intraclass Correlation Coefficient (ICC) and Coefficient of Variance (CV) for peripheral Quantitative Computer Tomography with 90% confidence intervals for 90 degree segments.

	60% radius site		60% ulna site		50% humerus site	
	ICC (90% CI)	**CV% (90% CI)**	**ICC (90% CI)**	**CV% (90% CI)**	**ICC (90% CI)**	**CV% (90% CI)**
BM 0-90°	0.96 (0.90 – 0.99)	2.2 (1.6 – 3.4)	0.99 (0.97 – 1.00)	2.2 (1.7 – 3.5)	0.97 (0.86 – 0.99)	3.4 (2.4 – 6.7)
90-180°	0.96 (0.90 – 0.99)	2.5 (1.9 – 3.9)	0.99 (0.98 – 1.00)	1.5 (1.1 – 2.3)	0.94 (0.78 – 0.99)	4.0 (2.7 – 7.7)
180-270°	0.95 (0.87 – 0.98)	2.7 (2.0 – 4.3)	0.99 (0.98 – 1.00)	1.8 (1.4 – 2.9)	0.98 (0.92 – 1.00)	2.9 (2.0 – 5.6)
270-360°	0.96 (0.89 – 0.98)	3.6 (2.7 – 5.7)	0.99 (0.97 – 1.00)	2.5 (1.8 – 3.9)	0.99 (0.94 – 1.00)	2.4 (1.6 – 4.6)
EnR 0-90°	0.97 (0.92 – 0.99)	3.2 (2.4 – 5.0)	0.97 (0.92 – 0.99)	4.4 (3.3 – 6.9)	0.98 (0.93 – 1.00)	2.3 (1.6 – 4.5)
90-180°	0.98 (0.95 – 0.99)	2.5 (1.9 – 3.9)	0.98 (0.94 – 0.99)	4.5 (3.4 – 7.1)	0.99 (0.94 – 1.00)	2.2 (1.5 – 4.2)
180-270°	0.98 (0.96 – 0.99)	2.5 (1.8 – 3.8)	0.97 (0.92 – 0.99)	4.9 (3.6 – 7.6)	0.99 (0.96 – 1.00)	1.7 (1.2 – 3.3)
270-360°	0.99 (0.96 – 1.00)	3.1 (2.3 – 4.9)	0.96 (0.88 – 0.98)	5.4 (4.0 – 8.4)	0.97 (0.86 – 0.99)	3.6 (2.5 – 7.1)
PeR 0-90°	0.94 (0.83 – 0.98)	1.7 (1.3 – 2.6)	0.98 (0.95 – 0.99)	1.5 (1.1 – 2.4)	0.96 (0.83 – 0.99)	1.7 (1.2 – 3.3)
90-180°	0.96 (0.89 – 0.99)	1.4 (1.0 – 2.1)	0.78 (0.48 – 0.92)	3.9 (2.9 – 6.1)	0.82 (0.41 – 0.96)	3.3 (2.2 – 6.3)
180-270°	0.89 (0.71 – 0.96)	2.1 (1.5 – 3.2)	0.97 (0.91 – 0.99)	2.0 (1.5 – 3.1)	0.90 (0.64 – 0.98)	2.4 (1.6 – 4.6)
270-360°	0.99 (0.97 – 1.00)	1.1 (0.8 – 1.7)	0.95 (0.86 – 0.98)	1.9 (1.4 – 3.0)	0.96 (0.82 – 0.99)	2.0 (1.3 – 3.8)
PvBMD 0-90°	0.94 (0.83 – 0.98)	1.8 (1.3 – 2.8)	0.88 (0.70 – 0.96)	2.4 (1.8 – 3.7)	0.86 (0.51 – 0.97)	0.5 (0.4 – 1.0)
90-180°	0.82 (0.56 – 0.93)	2.8 (2.1 – 4.3)	0.23* (-0.28 – 0.64)	5.2 (3.8 – 8.1)	*0.68 (0.10 – 0.91)*	*1.9 (1.3 – 3.7)*
180-270°	*0.48 (0.01 – 0.78)*	*2.8 (2.1 – 4.4)*	*0.55 (0.10 – 0.81)*	*3.1 (2.3 – 4.8)*	0.94 (0.77 – 0.99)	1.3 (0.9 – 2.4)
270-360°	0.28* (-0.23 – 0.67)	1.8 (1.3 – 2.8)	*0.65 (0.26 – 0.86)*	*3.9 (2.9 – 6.2)*	*0.61 (-0.02 – 0.89)*	*2.8 (1.9 – 5.5)*
EnvBMD 0-90°	0.94 (0.85 – 0.98)	4.2 (3.1 – 6.5)	0.88 (0.70 – 0.96)	8.1 (6.0 – 12.8)	0.89 (0.59 – 0.97)	1.1 (0.8 – 2.2)
90-180°	0.89 (0.72 – 0.96)	3.3 (2.4 – 5.1)	*0.51 (0.05 – 0.79)*	*6.5 (4.8 – 10.3)*	*0.73 (0.19 – 0.93)*	*3.8 (2.6 – 7.3)*

		60% radius site		60% ulna site		50% humerus site	
		ICC (90% CI)	**CV% (90% CI)**	**ICC (90% CI)**	**CV% (90% CI)**	**ICC (90% CI)**	**CV% (90% CI)**
	180-270°	*0.68 (0.31 – 0.87)*	*3.0 (2.2 – 4.7)*	0.81 (0.55 – 0.93)	3.3 (2.5 – 5.2)	0.98 (0.92 – 1.00)	2.4 (1.7 – 4.7)
	270-360°	0.67 (0.29 – 0.87)	2.3 (1.7 – 3.6)	0.83 (0.59 – 0.94)	8.3 (6.2 – 13.2)	0.84 (0.44 – 0.96)	4.4 (3.0 – 8.7)
MivBMD	**0-90°**	0.98 (0.94 – 0.99)	0.9 (0.7 – 1.5)	0.81 (0.54 – 0.93)	1.5 (1.1 – 2.4)	0.37* (-0.33 – 0.80)	1.3 (0.9 – 2.6)
	90-180°	0.91 (0.76 – 0.97)	2.2 (1.6 – 3.4)	*0.74 (0.40 – 0.90)*	*1.2 (0.9 – 1.8)*	0.94 (0.78 – 0.99)	0.6 (0.4 – 1.2)
	180-270°	0.77 (0.47 – 0.91)	1.4 (1.1 – 2.3)	*0.51 (0.04 – 0.79)*	*1.8 (1.3 – 2.8)*	*0.56 (-0.10 – 0.87)*	*0.9 (0.6 – 1.7)*
	270-360°	*0.53 (0.08 – 0.81)*	*1.9 (1.4 – 2.9)*	*0.70 (0.34 – 0.88)*	*2.3 (1.7 – 3.6)*	*0.75 (0.25 – 0.94)*	*1.0 (0.7 – 1.8)*
PevBMD	**0-90°**	*0.54 (0.08 – 0.81)*	*3.6 (2.7 – 5.6)*	0.83 (0.59 – 0.94)	2.0 (1.5 – 3.1)	*0.44 (-0.25 – 0.83)*	*2.8 (1.9 – 5.4)*
	90-180°	0.09* (-0.40 – 0.54)	4.0 (3.0 – 6.3)	-0.02* (-0.49 – 0.46)	11.3 (8.4 – 18.1)	0.82 (0.39 – 0.95)	2.9 (2.0 – 5.6)
	180-270°	0.31* (-0.19 – 0.69)	5.9 (4.4 – 9.2)	*0.44 (-0.05 – 0.76)*	*8.8 (6.5 – 13.9)*	*0.58 (-0.06 – 0.88)*	*3.5 (2.4 – 6.7)*
	270-360°	0.06* (-0.43 – 0.52)	3.6 (2.7 – 5.7)	0.09* (-0.40 – 0.54)	8.1 (6.0 – 12.9)	0.56 (-0.10 – 0.87)	4.2 (2.9 – 8.2)
Average		**0.77 (0.55 – 0.90)**	**2.6 (2.0 – 4.1)**	***0.75 (0.51 – 0.89)***	***4.1 (3.0 – 6.4)***	**0.82 (0.50 – 0.95)**	**2.4 (1.7 – 4.7)**

BM: bone mass; EnR: endocortical radius; PeR: pericortical radius; PvBMD: polar volumetric bone mineral density; EnvBMD: endocortical volumetric bone mineral density; MivBMD: Mid-cortical volumetric bone mineral density; PevBMD: pericortical volumetric bone mineral density. Italicised values represent fair to good ICC, an * represents poor ICC values whereas all other values were considered excellent (ICC > 0.75).

4.5. Discussion

The purpose of this investigation was to determine the between-day reliability of pQCT on commonly measured diaphyseal bone and muscle variables of upper-limb (upper-arm and forearm) cross-sections. We demonstrate between-day reliability of the pQCT for bone measures to be excellent for a majority of reported variables at all upper limb sites, however several variables at various sites only provided fair to good reliability with some variables providing poor reliability. The between-day reliability for upper limb muscle measures were excellent for all muscle area sites, and poor to excellent for all muscle density sites. This study reports, for the first time, reliability data for humeral soft-tissue analyses, as well as radial and ulnar diaphyseal bone material and density distribution (endo- and pericortical radii, polar vBMD, endo-, mid- and pericortical vBMD) and forearm muscle measures. These reliability results support the utility for pQCT to provide correct, accurate diagnostic measurements of bone and muscle assessments to be made by clinicians and researchers, with subsequent interventions able to confidently demonstrate efficacy. Although SSI reliability has not been previously reported in the forearm bones, the excellent reliability results are similar to a study by Chaplais et al., 2014 which focused on the second metatarsal, also reporting excellent ICC values (≥ 0.99) and very low CV values ($\leq 8.9\%$), suggesting broadly that SSI measures in the upper limbs are reliable (Chaplais et al., 2014). The excellent reliability results are also similar to a study by Weatherholt et al. (2015), which had very low CV values (1.4%), also suggesting that SSI measures in the upper limbs are reliable.

Area measurements of endocortical radius and pericortical radius had excellent ICC values for all bones (≥ 0.91) and very low CV values for all bones ($\leq 4.8\%$). This is in contrast to the volumetric bone measurements of polar vBMD, endocortical vBMD, mid-cortical vBMD, and pericortical vBMD which demonstrated good reliability with low CV values ($\leq 7.6\%$), though had ICC values ranging from poor (0.25) to excellent (0.86) across sites. Area measurements of muscle were also excellent for all upper limb sites (ICC = 0.99), while poor to excellent for muscle density across sites (ICC = 0.30 - 0.88), with high reliability demonstrated in the upper arm versus low reliability in the forearm. This is similar to the bone variables, such that area measurements exhibit high ICC values and low CV values while density measurements exhibited moderate ICC values and low CV values. A possible reason for the excellent reliability observed in area measures versus reduced reliability in density measures could be due to slight patient positioning

discrepancies between visits with regards to manual positioning of the cross-section examined or parallax error due to subtle variations of the limb perpendicular to the gantry. Inherently, measures of area may be less sensitive to movement artefact or subtle positional differences between days and scans relative to density measures. Positively, no current studies, to the authors' knowledge, have measured ICC values for muscle variables, which strengthens the current study, particularly as CV's measure the standard deviation as a percent of the mean, and is suitable for within-subject variation; though an ICC takes into account both within and between-subject variation, thus appropriately strengthens the value of reliability analyses (Sportscience, 2000; Sportscience, 2009).

CV reliability results for upper limb bone mass, cortical area and cortical density are similar to the multiple reliability findings previously reported by Sievänen et al., 1998. Indeed, bone mass results at all three bones for both studies reported very low CV values (≤ 4.9%) (Sievänen et al., 1998), with similarly low CV values between studies for cortical area and cortical density values (≤ 8.0%) (Sievänen et al., 1998). Cortical area and cortical density for this study (Radius ≤ 8.0%, Ulna ≤ 3.7%; Humerus ≤ 2.7%) are comparable to Sievänen et al, 1998 (Radius ≤ 6.5%; Ulna ≤ 2.1%; Humerus ≤ 4.6%) (Sievänen et al., 1998). While the CV results for cortical area and cortical density may slightly vary between the studies, all CV values are very low and considered excellent. Furthermore, muscle area CV values for the upper-limb sites of this study (≤ 2.0%) are very low and similar to the muscle area CV values in the calf region reported by Wong et., al, 2017 (≤ 2.9%), and muscle density values in the forearm by Frank-Wilson et al, 2015 (≤ 5.3%) (Wong et al., 2017; Frank-Wilson, Johnston, Olszynski, & Kontulainen, 2015). The CV values are also similar for muscle density values between our study (≤ 0.7%) and the same studies by Wong et. al., 2017 (≤ 4.1%), Frank-Wilson et al, 2015 (≤ 2.6%), and Weatherholt et al, 2015 (0.7%) (Wong et al., 2017; Frank-Wilson, Johnston, Olszynski, & Kontulainen, 2015; Weatherholt et al, 2015 (0.7%). The CV values for the upper arm are also similar for total area between our study (1.9%) and a study by Weatherholt et al, 2015 (1.0%). There are possible reasons for differences in CV between muscle density and muscle area (which are two separate measurements in the first instance). Muscle area is cross-sectional area (outer circumference) of the muscle; whereas muscle density factors in the amount of muscle within the cross-sectional area defined, inclusive of intramuscular fat and other factors. In addition, CV is calculated as SD/Mean. If the scale does not start from zero (as is the case with volumetric density), a CV does not provide a reasonable description of variability. This is why we also report

ICC, which does not suffer from this scale-related anomaly. CV is reported because that is what is routinely reported in the bone field to represent reliability.

Increased reliability at the 60% mid-shaft radius site and the 60% distal ulna site compared to the 50% humerus site may be due to the commencement point for the scans of the forearm being selected by a scout view of the pQCT, while the 50% humerus site was located manually and positioned manually. While the manual selection of the 50% humerus site did result in an excellent average ICC value, it is possible that determining the scan location manually may be less precise than it would be by determining the scan location using scout view. This is because errors in the manual measurements of the limbs may lead to errors in the scan locations (Shields et al., 2006). While this may lead to errors with or without a scout view, previous reference lines from scout views may be used for subsequent scans and this will allow for more precise scans with the scout views; subsequent manual measurements do not have previous reference lines to use (Shields et al., 2006). Another possible reason for the lower average ICC values for the 50% humerus site is due to the clamping and fixation of the arm during scanning. For forearm scans, a clamp can be used to prevent movement (Szabo et al., 2011). For the humerus scans, a clamp was not used due to the 50% humerus site being unable to reach the scan location of the pQCT whilst ensuring participant comfort. This may have resulted in slight movement artefact or subtle arm relocation which would have resulted in lower ICC value between days and scans. However, the methodological aspects to securing limbs for scanning was not evaluated in our study and certainly warrants further investigation, particularly with respect to improving reliability and minimising motion artefact. While small motion artefact may not have a large effect on the results, a large amount of motion artefact can affect the results negatively (Shields et al., 2006); and these may have differential effects on area variables relative to density variables. Lastly, an additional limitation and potential reason for the varying ICC values could be due to the positional expertise and measurement of the technician performing the pQCT scans.

4.6. Conclusion

The overall reliability of pQCT is excellent for the three scanned upper limb long bones as reported by both ICC values and low CV values. Humerus 50% scans are more reliable than radius and ulna 60%, and the humeral reliability could be improved by creating new limb clamping methods to prevent arm movement during the scanning process. Area

measurements for bone and some muscle variables were more reliable than volumetric measurements across upper-limb sites.

CHAPTER FIVE – STUDY THREE

RELIABILITY OF DETERMINING OSTEOGENIC INDICES USING INERTIAL MEASUREMENT UNITS DURING UPPER-BODY RESISTANCE EXERCISES

5.1. Abstract

This study investigated the reliability of two osteogenic indices (OI) when assessed using inertial measurement units (IMU) positioned in various locations across upper-body resistance training exercises. Eight males (age: 24.4 ± 2.7 years) performed upper-body strength (bench press, prone row, biceps curl, triceps extension) and power (bench press throw, ballistic prone row) resistance exercises, repeated across three days. Intra-class correlation coefficients (ICC) and coefficients of variation (CV) of wrist and bar IMU locations were assessed for two different osteogenic index calculations (OI-ADAPTED accounting for rate and magnitude; OI-ORIGINAL accounting for magnitude). Strength exercises (ICC: 0.62; CV: 15.3%) had greater OI reliability than power exercises (ICC: 0.39; CV: 31.0%). The wrist site (ICC: 0.64; CV: 16.8%) had a greater reliability than the bar site (ICC: 0.53; CV: 18.4%, while OI-ORIGINAL (ICC: 0.60; CV: 16.0%) had a greater reliability than OI-ADAPTED (ICC: 0.57; CV: 19.1%). Strength exercises were generally more reliable, however the theoretical osteogenic benefit (in accordance with OI value) was much less than power exercises. The OI-ADAPTED equation is a more complex equation, however the OI-ORIGINAL equation is more reliable and easier to use, thus making it more practical and meaningful for practitioners measuring OI when using IMU's.

5.2. Introduction

Optimising osteogenic adaptation through mechanical loading programs requires three key elements: dynamic loading behaviour; brief bouts of repetitious mechanical loading cycles interspersed with rest periods (i.e. minimising mechano-saturation); and variable mechanical loading environments (i.e. variations in strain magnitude, rate and gradient) (Hart, Nimphius, Rantalainen, Ireland, Siafarikas & Newton, 2017). Together, these loading parameters produce larger adaptive responses in bone than customary mechanical loading environments (Turner, 1998). To quantify the potential for a mechanical loading program to induce osteogenesis to target skeletal tissue, the Osteogenic index (OI) was established. OI is a mathematical model based on a series of animal experiments (Turner & Robling, 2003; Robling, Castillo, & Turner, 2006) that quantifies the expected osteogenic adaptation from a particular mechanical loading event or program.

Osteogenic indices are explicitly used as a surrogate, indirect tool to evaluate total osteogenic loads experienced, and osteogenic potential acquired through-out the fulfilment of a designed mechanical loading program, OI can be expressed in several ways with multiple formulas in existence (Whalen, Carter and Steele, 1988; Turner 1998; Ahola, Korpelainen, Vainionpää, & Jämsä, 2010), though one of the formulations most closely aligned with what is known about bone mechanoresponsivity is Rantalainen et al (2011)'s adaptation of Turner's OI equation, defined herein as *OI-ADAPTED* = $\sum_{i=1}^{f_i \leq 50\text{Hz}} \varepsilon_i f_i$ x ln(N), where ε_i = the magnitude of the i^{th} frequency bin, and f_i = the frequency of the i^{th} frequency bin, N = number of loading cycles. Importantly, Rantalainen and colleagues' (2011) adapted OI formula, while more complex in construction, critically includes load rate in addition to load magnitude, which together form the two most potent mechanical drivers of osteogenesis (Barry, & Kohrt, 2008). Comparatively, Turner and Robling (2003) reported a simplified estimate of OI, which appears to have more practical utility, presumably due its ease of implementation (Ahola, Korpelainen, Vainionpää, & Jämsä, 2010; Santos-Rocha, Oliveira, & Veloso, 2006), and is defined herein as *OI-ORIGINAL = Peak GRF (bwt) x ln (N + 1)*, where *GRF (bwt)* = ground reaction force in body weight; N = number of loading cycles (Turner, & Robling, 2003).

Despite OI showing practical utility in predicting osteogenic outcomes (Ahola, Korpelainen, Vainionpää, & Jämsä, 2010) and potential to determine and select exercises to maximise bone development (Turner, & Robling, 2003), there is no known research

evaluating the reliability of OI assessments of exercises, or the comparison of reliability when utilising the different methods of calculating OI. The exploration of reliability is critical to ensure training studies using exercise interventions based on osteogenic indices of exercises to maximise bone health are accurately predicting or determining the osteogenic potential for the duration of the study. Subsequently, this will allow researchers and coaches to determine which exercises and which OI equations result in consistent and dependable OI results (Sullivan, 2011).

Resistance exercises (i.e. strength and power exercises) are known to elicit positive osteogenic adaptations (Nickols-Richardson, Miller, Wootten, Ramp, & Herbert, 2007; Von Stengel, Kemmler, Lauber, Kalender, & Engelke, 2007). However, no published research describes the OI of upper body strength and power exercises commonly used in resistance training programs nor the reliability of different formulate in determining the osteogenic potential of these exercises. Indeed, OI can be determined by fixating inertial measurement units (or accelerometers) to the body of individual performing exercise, or the equipment used during exercise. Accelerometers can provide reliable results with human motion, however the degree of reliability will depend on the task being performed and the site the accelerometer is located (Cuesta-Vargas, Galán-Mercant, & Williams, 2010); the stability of fixation to minimise movement artefact (Flores, Sedano, de Benito, & Redondo, 2016); and the movement speed produced by the individual themselves (Horner, Rayson & Bilzon, 2011).

Accordingly, the purpose of this pilot study was to: 1) determine the between-day reliability of OI calculated using two different osteogenic index equations (Rantalainen et al., 2011; Turner, & Robling, 2003) and 2) determine the reliability of an accelerometer placed on the bar or wrist, for various upper body strength and power exercises.

5.3. Method

5.3.1. Experimental Approach to Problem

To assess the between-day reliability of determining OI, participants were required to attend three testing sessions. The initial testing session was used to determine the maximal strength (one repetition maximum; 1RM) for bench press, prone row, biceps curl and triceps extension exercises in order to determine the relative submaximal intensities for the subsequent strength and power exercises to be assessed. The final two testing sessions involved the performance of a bench press throw and ballistic prone row (power

exercises), bench press, prone row, biceps curl, and triceps extension (strength exercises), performed in this stated order, and repeated within 2 to 7 days to allow recovery between repeated assessments.

5.3.2. Participants

Eight male participants (age: 24.4 ± 2.7 years, height: 183.4 ± 6.2 cm, weight: 98.4 ± 20.3 kg) volunteered and completed this study. All participants were healthy in accordance with a pre-exercise medical questionnaire. Participants were excluded if they had a prior and/or current injury in the upper limbs; were taking medication that would contraindicate exercise; did not have at least one year of resistance training experience; or could not bench press a 1RM (repetition maximum) of at least 75 kilograms.

The study was reviewed and approved by the University Human Research Ethics Committee (HREC Approval 11690), and all participants provided written informed consent after reading an information sheet explaining the study requirements, risks and benefits.

5.3.3. Maximal Strength Assessment

Participants performed a five minute warm-up on a cycle ergometer (Monark Ergomedic 828E, Vansbro, Sweden) followed by 1RM testing in accordance with Scott et al. (2014). Specifically, participants estimated their predicted 1RM for each exercise (based on their resistance training experience) to use for baselines for determining the weight for the warm-up sets (Scott et al., 2014). There were three warm-up sets for each exercise: 1) ten repetitions of the exercise at 50% of their predicted 1RM; 2) five repetitions of the exercise at 70% of their predicted 1RM; and 3) one repetition of the exercise at 90% of their predicted 1RM (Scott et al., 2014). All warm-up sets were completed with two minutes rest provided between each set, for each exercise prior to the specific 1RM exercise test. Following the warm-up and rest period, ~5% of the overall weight lifted in the last warm-up set was added (Scott et al., 2014). Following each successful 1RM lift, ~5% was added until the participant was unable to lift any larger weight (Scott et al., 2014), with three-minute breaks provided between all 1RM attempts for a given exercise.

Following the completion of 1RM testing per exercise, the subsequent warm-up set occurred after a five-minute passive recovery period to minimise the effect of fatigue. It is important to note that when multiple exercises are assessed for their 1RM in a single

session, exercise order is not a notable confounding factor when exploring different muscle groups, therefore no other exercise order other than the one chosen for the 1RM testing would have produced significantly greater 1RM results (Neto et al., 2015). Bench press was performed as previously described by Graham (2003), however the exercise was performed using a Smith machine to control for horizontal movement. Prone row was performed as described by Darrall-Jones, Jones, & Till (2015). Biceps curl was performed while standing, using a barbell as described by Kostek, & Knortz (1980). Triceps extension was executed while lying supine (Stiggins, & Allsen, 1986). Participants were shown the technique of how to perform each exercise, along with how to perform a bench press throw while using the Smith machine, and a ballistic prone row, as familiarisation for these exercises to be performed on reliability assessment days (Figure 16).

5.3.4. Exercise Reliability Assessment

The first testing session was conducted a minimum of two days after the familiarisation session with participants performing the exercise repetitions, rest and loads (Table 4). The testing session was then repeated on a non-consecutive day. The maximum time between testing sessions was seven days, which only occurred when the participants could not attend an earlier training session. During each of the testing sessions, a light dynamic exercise-related movement was performed as a warm-up before all exercises. An inertial measurement unit (IMU; 34.5 mm x 57.8 mm x 14.5 mm in dimension, 0.027 kg in weight; MTx XSENS Motion Tracker, Netherlands) was fixated to each participant's non-dominant wrist (Figure 17a), and the barbell (Figure 17b) used during each exercise. Both wrist and barbell data were recorded at the same time using two different IMU's. The IMU's used were the same for each participant and placed on the same side near the weight plates for each exercise in order to avoid contact with the participant or the underside of the prone row bench (participant safety and to avoid any IMU contact noise). Each IMU collected acceleration data in all three orthogonal axes while sampling at 100 Hz. Data from each IMU was collected using MT Manager Version 3.8.1 (XSENS, Netherlands).

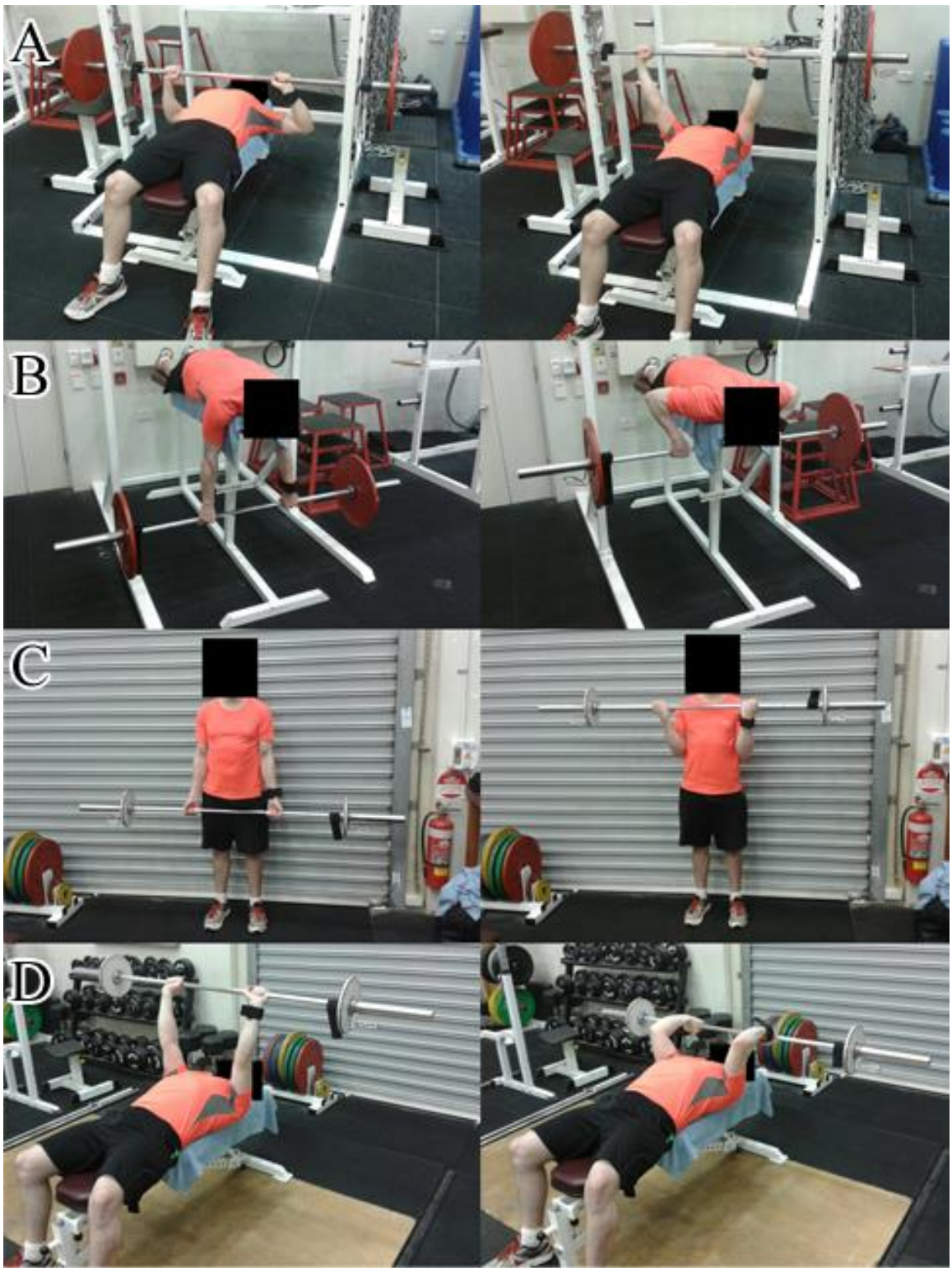

Figure 16. Execution of the bench press (A), prone row (B), biceps curl (C), and triceps extension (D).

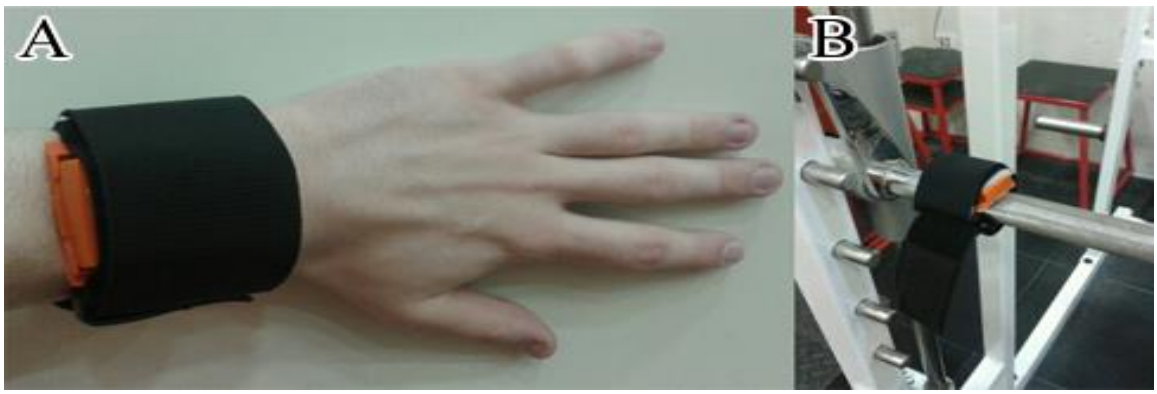

Figure 17. Positioning of the accelerometers on the wrist (A) and on the barbell (B).

Table 4. Exercise training schedule, including load, rest between sets, the repetitions per set, and the tempo per repetition.

Exercise order	Exercise	Load	Rest (minutes)	Repetitions	Tempo*
1	Bench press throw	30% 1RM	3	5	2 0 X
2	Ballistic prone row	30% 1RM	3	5	2 0 X
3	Bench press	50% 1RM	3	5	2 0 2
4	Bench press	70% 1RM	3	5	2 0 2
5	Bench press	90% 1RM	3	3	2 0 2
6	Prone row	50% 1RM	3	5	2 0 2
7	Prone row	70% 1RM	3	5	2 0 2
8	Prone row	90% 1RM	3	3	2 0 2
9	Bicep curl	50% 1RM	3	5	2 0 2
10	Bicep curl	70% 1RM	3	5	2 0 2
11	Bicep curl	90% 1RM	3	3	2 0 2
12	Triceps extension	50% 1RM	3	5	2 0 2
13	Triceps extension	70% 1RM	3	5	2 0 2
14	Triceps extension	90% 1RM	3	3	2 0 2

* The first digit is the time (s) on the eccentric phase, the second digit is the time (s) spent between transition of eccentric and concentric phase of the lift, and the final digit is the time (s) on the concentric phase. An X refers to a maximal intent velocity.

5.3.5. Measurement and Calculation of Osteogenic Index

The resultant acceleration was used for all osteogenic index analyses. In accordance with Rantalainen and colleagues (2011), the first osteogenic index formula (OI-adapted) was calculated in MATLAB Version 2011a (MathWorks, Natick, USA) as OI-ADAPTED =

$\sum_{i=1}^{f_i \leq 50\text{Hz}} \varepsilon f_i$ x ln(N+1). These results were compared to the original (OI-original) osteogenic index = Peak *ground reaction force (in body weight) x ln (number of loading cycles + 1)* (Turner, & Robling, 2003), also calculated in MATLAB. However, in place of peak ground reaction force, peak acceleration was used in order to be consistent with the OI-ADAPTED equation which uses acceleration as a measure (Rantalainen et al., 2011).

5.3.6. Statistical Analysis

Statistical analyses were conducted with SPSS Version 19.0.0 (IBM SPSS Statistics, Chicago, USA), OI calculation was determined with MATLAB Version R2011a, and reliability analysis was determined by using a Microsoft Excel (Microsoft, Redmond, USA) spreadsheet (Hopkins, 2011; Hopkins, 2000). Between-day reliability of OI was assessed using a reliability analysis spreadsheet to determine the intraclass correlation coefficient (ICC) and the coefficient of variation (CV) with 90% confidence upper and lower confidence limits (Hopkins, 2011; Hopkins, 2000). A 90% confidence interval was chosen as recommended by Hopkins, 2007. ICC values were reported as having excellent reliability (> 0.75); fair to good reliability (0.4 – 0.75); and poor reliability (< 0.4) (Oremus, Oremus, Hall, McKinnon, & ECT & Cognition Systematic Review Team, 2012). Coefficients of variation less than 10% was considered acceptable in accordance with other studies analysing biomechanical, strength and power based human movement data (Pedersen, & Liu, 2012; Augustsson et al., 2006; Cormack, Newton, McGuigan, & Doyle, 2008; Cronin, Hing, & McNair, 2004; Hunter, Marshall, & McNair, 2004). Dependent t-tests were used to determine if there were significant differences for the osteogenic index values between the strength bench press loads and the bench press throw, along with the strength prone row loads and the ballistic prone row. A Holm-Bonferroni Sequential Correction analysis was performed using a Microsoft Excel spreadsheet (Justin Gaetano, 2013).

5.4. Results

ICC and CV values of OI using the OI-ADAPTED formula, across the wrist and barbell for the six different exercises (bench press throw; prone throw ballistic; bench press; prone row; biceps curl; triceps extension) produced greater reliability at the wrist site than the barbell site (Table 5). ICC and CV values of OI using the OI-ORIGINAL

Table 5. Intraclass correlation coefficient, coefficient of variance and standardised typical error of measurement for the Osteogenic Index at the wrist and on the weight bar with 90% confidence intervals using the formula of OI-ADAPTED (Rantalainen et al., 2011).

	Wrist site ICC (90% CI)	CV% (90% CI)	Bar site ICC (90% CI)	CV% (90% CI)
Bench press throw	**0.88 (0.6 – 0.97)**	16.1 (11.1 – 30.7)	*0.45 (-0.18 – 0.82)*	16.7 (11.5 – 32)
Prone row ballistic	-0.07 (-0.63 – 0.53)	28.5 (19.4 – 56.9)	*0.52 (-0.08 – 0.85)*	35.2 (23.7 – 71.9)
Bench press 50%	**0.76 (0.31 – 0.93)**	18.4 (12.6 – 35.4)	*0.75 (0.29 – 0.93)*	17.1 (11.8 – 32.8)
Bench press 70%	*0.48 (-0.15 – 0.83)*	19.6 (13.4 – 37.9)	0.23 (-0.4 – 0.72)	22.6 (15.4 – 44.1)
Bench press 90%	0.02 (-0.57 – 0.6)	25.7 (17.5 – 50.8)	*0.47 (-0.15 – 0.83)*	19.7 (13.5 – 38.1)
Prone row 50%	*0.64 (0.09 – 0.89)*	20.1 (13.8 – 39)	0.19 (-0.44 – 0.7)	23.3 (15.9 – 45.7)
Prone row 70%	*0.70 (0.19 – 0.91)*	18.6 (12.8 – 36)	0.35 (-0.3 – 0.77)	19.5 (13.4 – 37.8)
Prone row 90%	**0.90 (0.65 – 0.97)**	12.9 (8.9 – 24.3)	**0.87 (0.59 – 0.96)**	12.5 (8.7 – 23.6)
Biceps curl 50%	*0.53 (-0.08 – 0.85)*	26.4 (18.0 – 52.4)	**0.79 (0.39 – 0.94)**	19.1 (13.1 – 36.9)
Biceps curl 70%	*0.68 (0.16 – 0.9)*	14.5 (10 – 27.6)	**0.93 (0.76 – 0.98)**	**7.7 (5.4 – 14.2)**
Biceps curl 90%	**0.83 (0.48 – 0.95)**	14.6 (10.1 – 27.7)	**0.83 (0.48 – 0.95)**	17.9 (12.3 – 34.4)
Triceps extension 50%	**0.8 (0.4 – 0.94)**	16.9 (11.6 – 32.4)	**0.85 (0.54 – 0.96)**	14.4 (9.9 – 27.3)
Triceps extension 70%	**0.79 (0.39 – 0.94)**	10.2 (7.1 – 19.2)	*0.71 (0.22 – 0.91)*	13.3 (9.2 – 25.1)
Triceps extension 90%	0.26 (-0.38 – 0.73)	23.7 (16.2 – 46.6)	-0.06 (-0.62 – 0.54)	29.2 (19.8 – 58.6)
Average	*0.59 (0.10 – 0.85)*	19.0 (13.0 – 36.9)	*0.56 (0.08 – 0.85)*	19.2 (13.1 – 37.3)

Bold values represent excellent reliability (ICC > 0.75). Italicised values represent fair to good reliability ($0.75 \geq 0.4$). All other values represent poor reliability (ICC < 0.4). Bold CV values which are less than 10% are considered acceptable.

Table 6. Intraclass correlation coefficient, and coefficient of variance for the Osteogenic Index at the wrist and on the weight bar with 90% confidence interval using the formula of OI-ORIGINAL (Turner, & Robling, 2003).

	Wrist site ICC (90% CI)	CV% (90% CI)	Bar site ICC (90% CI)	CV% (90% CI)
Bench press throw	**0.96 (0.84 – 0.99)**	11.0 (7.7 – 20.7)	0.06 (-0.54 – 0.62)	66.3 (43.1 – 149.4)
Prone row ballistic	0.01 (-0.58 – 0.59)	59.3 (38.9 – 130.9)	0.33 (-0.31 – 0.76)	14.6 (10.1 – 27.7)
Bench press 50%	**0.77 (0.33 – 0.93)**	10.9 (7.6 – 20.4)	*0.64 (0.09 – 0.89)*	14.8 (10.2 – 28.2)
Bench press 70%	*0.40 (-0.23 – 0.8)*	11.4 (7.9 – 21.5)	-0.11 (-0.65 – 0.5)	17.9 (12.3 – 34.4)
Bench press 90%	*0.48 (-0.14 – 0.83)*	14.2 (9.8 – 27.0)	-0.19 (-0.70 – 0.44)	27.4 (18.6 – 54.6)
Prone row 50%	**0.87 (0.58 – 0.96)**	14.0 (9.7 – 26.6)	*0.66 (0.13 – 0.90)*	22.6 (15.5 – 44.3)
Prone row 70%	*0.59 (0.02 – 0.87)*	26.5 (18.1 – 52.7)	*0.64 (0.09 – 0.89)*	24.2 (16.5 – 47.6)
Prone row 90%	*0.65 (0.11 – 0.89)*	20.7 (14.2 – 40.3)	*0.64 (0.09 – 0.89)*	23.2 (15.8 – 45.4)
Biceps curl 50%	*0.74 (0.29 – 0.93)*	**7.5 (5.3 – 13.9)**	**0.83 (0.49 – 0.95)**	**5.5 (3.9 – 10.2)**
Biceps curl 70%	**0.84 (0.51 – 0.96)**	**5 (3.5 – 9.2)**	*0.67 (0.15 – 0.90)*	**9.5 (6.6 – 17.8)**
Biceps curl 90%	**0.93 (0.76 – 0.98)**	**2.7 (1.9 – 4.8)**	**0.88 (0.6 – 0.97)**	**5.9 (4.1 – 10.8)**
Triceps extension 50%	**0.94 (0.80 – 0.98)**	**4.6 (3.2 – 8.4)**	**0.77 (0.34 – 0.93)**	**3.8 (2.6 – 6.9)**
Triceps extension 70%	**0.83 (0.47 – 0.95)**	**7.1 (5 – 13.2)**	0.31 (-0.22 – 0.76)	**4.7 (3.3 – 8.7)**
Triceps extension 90%	**0.79 (0.38 – 0.94)**	**8.3 (5.8 – 15.4)**	**0.81 (0.42 – 0.94)**	**5.4 (3.8 – 10)**
Average	*0.70 (0.30 – 0.90)*	14.5 (9.9 – 28.9)	*0.50 (0.00 – 0.81)*	17.6 (11.9 – 35.4)

Bold values represent excellent reliability (ICC > 0.75). Italicised values represent fair to good reliability (0.75 ≥ 0.4). All other values represent poor reliability (ICC < 0.4). Bold CV values which are less than 10% are considered acceptable.

formula, across the wrist and the barbell for the same six exercises also produced greater reliability at the wrist site than the barbell site (Table 6).

5.4.1. Bench Press Throw

The bench press throw had excellent ICC values at the wrist site for both equations with values of 0.88 (OI-ADAPTED) and 0.96 (OI-ORIGINAL). The bench press throw at the bar site for the ICC value for the OI-ADAPTED equation was fair to good (0.45), while the bench press throw at the bar site for the OI-ORIGINAL equation had a poor ICC value (0.06). All bench throw press CV values were over 10% (11.0% ≤ 66.3%). Dependent t-tests reported significant differences ($p < 0.05$) between the three strength bench press loads and bench press throw, at both the wrist and barbell sites for both the OI-ADAPTED and OI-ORIGINAL equations, except for at the 90% bar site for the OI-ORIGINAL equation ($p = 0.18$). A Holm-Bonferroni Sequential Correction analysis found all values to be significantly different for the OI-ADAPTED equation, and all values to be significantly different for the OI-ORIGINAL equation except for the 70% bar site (adjusted p value = 0.06) and the 90% bar site (adjusted p values = 0.18).

5.4.2. Ballistic Prone Row

The ballistic prone row had poor ICC values at the wrist site for both equations with values of -0.07 (OI-ADAPTED) and -0.01 (OI-ORIGINAL). The ballistic prone row at the bar site for the OI-ORIGINAL equation also had a poor ICC value (0.33), however the ICC value for the OI-ADAPTED equation was fair to good (0.52). All ballistic prone row CV values were over 10% (14.6% ≤ 59.3%). Dependent t-tests reported significant differences ($p < 0.05$) between the three strength prone row loads and ballistic prone row, at both the wrist and barbell sites for both the OI-ADAPTED and OI-ORIGINAL equations, except for at the 50% bar site for the OI-ADAPTED equation ($p = 0.74$). A Holm-Bonferroni Sequential Correction analysis found all values to be significantly different for the OI-ADAPTED equation except for the 50% bar site (adjusted p values = 0.74), and all values to be significantly different for the OI-ORIGINAL equation.

5.4.3. Bench Press

The bench press 50% at the wrist site for both equations (OI-ADAPTED: 0.76; OI-ORIGINAL: 0.77) were the only bench press loads to report an excellent ICC. Bench press loads to have fair to good ICC values for both equations were the bench press 70% at the wrist site (OI-ADAPTED: 0.48; OI-ORIGINAL: 0.40), and the 50% bar site (OI-

ADAPTED: 0.75; OI-ORIGINAL: 0.64), while the bench press 70% bar site for the OI-ADAPTED equation (0.47) and the bench press 90% wrist site for the OI-ORIGINAL equation (0.48) also had fair to good reliabilities. Poor ICC values for both equations were reported for the bench press 70% at the bar site (OI-ADAPTED: 0.23; OI-ORIGINAL: -0.11), while the bench press 90% wrist site for the OI-ADAPTED equation (0.02) and the bench press 90% bar site for the OI-ORIGINAL equation (-0.19) also had poor reliabilities. All of the CV values for the bench press loads were over 10% (10.9% ≤ 27.4%).

5.4.4. Prone Row

Prone row 90% at the wrist site for the OI-ADAPTED equation (0.90), prone row 90% at the bar site for the OI-ADAPTED equation (0.87), and prone row 50% at the wrist site for the OI-ADAPTED equation (0.87) were the only prone row loads to report an excellent ICC. The prone row had poor reliabilities for the 50% (0.19) and 70% (0.35) bar sites for the OI-ADAPTED equation, while all remaining sites had fair to good reliabilities (0.59 ≤ 0.70). All of the CV values for the prone row loads were over 10% (14.0% ≤ 26.5%).

5.4.5. Biceps Curl

The biceps curl 50% at the bar site for both equations (OI-ADAPTED: 0.79; OI-ORIGINAL: 0.83), both equations at the 90% wrist site (OI-ADAPTED: 0.83; OI-ORIGINAL: 0.93), both equations at the 90% bar site (0.83 ≤ 0.88), the OI-ADAPTED equation at the 70% bar site (0.93), and the OI-ORIGINAL equation at the 70% wrist site (0.84) were reported to have excellent ICC values. The biceps curl had fair to good reliability for both equations at the 50% wrist site (OI-ADAPTED: 0.53; OI-ORIGINAL: 0.74), for the 70% wrist site (0.68) for the OI-ADAPTED equation, and for the 70% bar site (0.67) for the OI-ORIGINAL equation. No poor ICC values were reported for the biceps curl. The CV values below 10% included the 70% bar site for the OI-ADAPTED equation (7.7%) and all of the bicep curl loads for the OI-ORIGINAL equation (2.7% ≤ 9.5%).

5.4.6. Triceps Extension

The triceps extension 50% at the wrist site for both equations (OI-ADAPTED: 0.80; OI-ORIGINAL: 0.94), both equations at the 50% bar site (OI-ADAPTED: 0.85; OI-ORIGINAL: 0.77), both equations at the 70% wrist site (OI-ADAPTED: 0.79; OI-

ORIGINAL: 0.83), the OI-ORIGINAL equation at the 90% wrist site (0.79), and the OI-ORIGINAL equation at the 90% bar site (0.81) were reported to have excellent ICC values. The triceps extension had fair to good reliability for the OI-ADAPTED equation at the 70% bar site (0.71). Poor ICC values were reported the OI-ADAPTED equation for the 90% wrist site (0.26), the OI-ADAPTED equation for the 90% bar site (-0.06), and the OI-ORIGINAL equation for the 70% bar site (0.31). The CV values for all OI-ADAPTED exercises and loads were over 10%, while the CV values for all OI-ORIGINAL exercises and loads were below 10 % (3.8% – 8.3%).

5.4.7. Overall Exercises

Excellent ICC values were reported for 6/14 loads at the wrist site and 5/14 loads at the bar site for the OI-ADAPTED equation, compared to 8/14 loads at the wrist site and 4/14 loads at the bar site for the OI-ORIGINAL equation. Poor ICC values were reported for 3/14 loads at the wrist site and 4/14 loads at the bar site for the OI-ADAPTED equation compared to 1/14 loads at the wrist site and 5/14 loads at the bar site for the OI-ORIGINAL equation. Biceps curl and triceps extension had excellent ICC values for a majority of loads (4/6 for each equation), while the ballistic prone row had the lowest proportion of excellent ICC values (0/2 for each equation). Ballistic prone row had the greatest proportion of poor ICC values (1/2 for the OI-ADAPTED equation, and 0/2 for the OI-ORIGINAL equation), while the biceps curl had the lowest proportion of poor ICC values (0/6 for each equation). The overall wrist site reported 14/28 loads with excellent ICC values, compared to 9/28 for the bar site. The overall

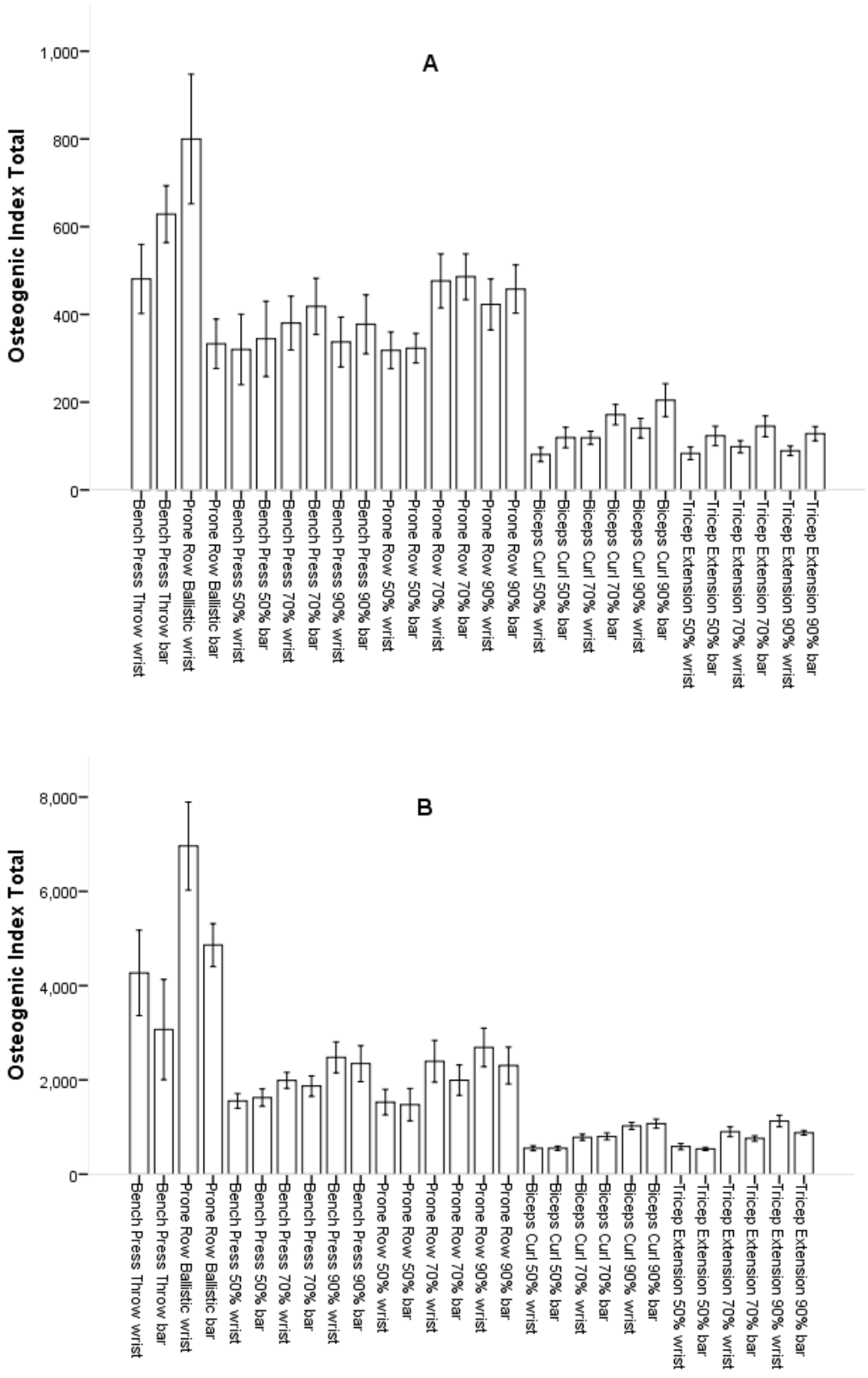

Figure 18. The mean Osteogenic Index for all exercises using (A) OI-ADAPTED (Rantalainen et al, 2011), and (B) OI-ORIGINAL (Turner & Robling, 2003). n = 8.

wrist site had an ICC value of 0.64 and a CV value of 16.8%, compared to an ICC value of 0.53 and a CV value of 18.4% for the bar site. The overall wrist site reported 4/28 of loads with poor ICC values, compared to 9/28 for the bar site. The mean ICC and CV values using the OI-ADAPTED equation, were 0.59 and 19.0% at the wrist site, and 0.56 and 19.2% at the bar site. The mean ICC and CV values using the OI-ORIGINAL equation, were 0.70 and 14.5% at the wrist site, and 0.50 and 17.6% at the bar site. The overall ICC and CV values per equation were 0.57 and 19.1% for the OI-ADAPTED equation, and 0.60 and 16.0% for the OI-ORIGINAL equation. Overall strength exercises had an ICC value of 0.62 and a CV value of 15.3%, compared to an ICC value of 0.39 and a CV value of 31.0% for power exercises. Overall OI values for power exercises (2674.88) produce 321.1% greater OI values than strength exercises (833.08) (Figure 18).

5.5. Discussion

The purpose of this pilot investigation was to determine the reliability of the osteogenic index (OI) when assessed using two different OI equations and two different IMU locations for various upper-body resistance training strength and power exercises and loads. Between-day reliability of the OI ranged from poor to excellent depending on the exercises, the loads and the site of the IMU. The OI reliability was greater for strength exercises compared to power exercises, and at the wrist site compared to the bar site. However, the overall OI value was significantly larger for power exercises compared to strength exercises.

Strength exercises had an overall greater ICC value and a lower CV value than power exercises, however no strength exercise had all excellent reliability values. For the strength exercises the biceps curl was the only exercise to have no poor ICC values for either equation. This is in contrast to a study by Seo et al., 2012, which while accelerometers were not used, found the reliability of 1RM testing for bench press, biceps curl, and triceps extension to all have excellent ICC values (≥ 0.98). However, the CV values were all larger than 10% (≥ 29%) (Seo et al., 2012), and this is in contrast to our study where the highest CV value for the biceps curl was 26.4%, while the highest overall strength CV value was 29.2%. The prone row for our study had no poor ICC values for the OI-ORIGINAL equation, with both OI equations having their prone row CV values (12.5% – 26.5%) lower than the CV values for the other three strength exercises found by Seo et al., 2012 (≥ 29%).

The greater reliability for strength exercises compared to power exercises may be explained by the degree of individual movement performing the exercise which has been shown to affect the degree of reliability (Horner, Rayson & Bilzon, 2011). An individual performing power exercises has less control over the weight bar compared to an individual performing strength exercises due to the speed at which the exercises are performed, and this decreases reliability. This is similar to a study which focuses on another power exercise, the vertical jump (Nibali, Tombleson, Brady, & Wagner, 2015). Just like when using a weight bar, vertical jump height when performing vertical jumps has been shown to be a factor with varying reliability (Nibali, Tombleson, Brady, & Wagner, 2015). A speed-accuracy relationship is shown in another study which exclaims that an increased velocity will lead to an increased movement error (Hsieh, Pacheco, & Newell, 2015). The force/time relationship which can be referred to as impulse, is important in order to maximise performance, and therefore the right balance between force and time is necessary (Danion, Bongers, & Bootsma, 2014). Also, for the bench press throw despite being in a Smith machine, control over the bar is decreased once it is thrown into the air, affecting the bar IMU. Along with the bench press bar potentially knocking the Smith machine when thrown, the ballistic prone row knocks the underside of the bench with considerable force which causes the bench to move slightly and thus may decreases reliability independent of the reliability associated with the loads that affect the person (or bone).

The wrist site had greater reliability values than the bar site, and this makes it the preferred location for accelerometer placement. A factor determining site reliability difference is that any unwanted contact to the bar results in decreased reliability. When an object using an accelerometer experiences a sudden bump, a spike in at least one of the axes will occur (Purushotham, & Kumar, 2014) and this will alter the OI reliability. As the reliability of accelerometers are site specific (Cuesta-Vargas, Galán-Mercant, & Williams, 2010), the bumping of the bar on equipment such as the Smith machine and the ballistic prone row is a reason why the overall bar reliabilities are smaller than the overall wrist reliabilities. Also, the further the distance the accelerometer on the bar is away from the wrist, the decreased chance of reliability, as the most stable points on the weight bar would be the points closest to the individuals' hands. While the wrists may move in synchronisation, one end of the bar could be slightly lower than the other end, results in decreased reliability. Also, from a practical standpoint a wrist accelerometer would be more

convenient as it is not required to be re-mounted when moving from one exercise to another.

By determining the reliability of the OI equations for different exercises, subsequent exercise routines can be put into place to increase osteogenic adaptation. The power resistance exercises produced far greater OI values than the strength exercises, and therefore when prescribing an exercise intervention to an individual the quickest method for them to increase osteogenic adaptation is through power resistance exercises. However, as strength exercises have a higher OI reliability than power resistance exercises, creating an exercise program incorporating strength exercises would allow an individual to know with greater accuracy just how much osteogenic adaptation will occur. Although, due to the varying reliability of certain strength and power exercises it may be difficult to prescribe an exercise program based on the OI and know just how much osteogenic adaptation will occur. For individuals who have poor bone characteristics, medical professionals can provide exercise interventions that include high OI valued exercises with excellent reliability in order to maximise the overall bone health. Impact exercises were not tested even though they are known to be more osteogenic than non-impact exercises (Barry, & Kohrt, 2008).

The OI-ADAPTED equation is a more complex equation and captures more of the loading characteristics than the OI-ORIGINAL equation, however the complexity of the OI-ADAPTED equation is why it produces lesser reliability than the OI-ORIGINAL equation. Just like there were differences in the reliability between the two equations, the osteogenic adaptations of the OI-ORIGINAL equation were higher than the OI-ADAPTED equation. Therefore, the OI-ORIGINAL equation may be a more practical solution for calculating the OI. Providing technique is correct, there shouldn't be significant between-participant OI differences for the exercises. There will only be between-participant differences for the exercises if certain participants are stronger than other participants and are thereby able to perform heavier and/or faster exercises. Also, if the technique of certain participants is greater than the technique of other participants, then that could impact the OI values as well.

This study was designed as a pilot study and hence limited by its small sample size. However this study aimed to determine the potential of incorporating the different OI equations for different exercises into future studies. Moreover, impact exercises (such as

punching a punching bag or catching a medicine ball) were not evaluated, although impact exercises are known to have high osteogenic potential. Impact exercises were not assessed due to the low sampling rate of the IMUs used in the present study. This study however provides important evidence for statistical powering for future studies involving these OI equations and exploring other exercises for osteogenic adaptation.

5.6. Conclusion

Strength exercises demonstrated greater reliability than power exercises, while power exercises produced greater osteogenic loads. If a more specific osteogenic load is sought after, such as prescribed by a doctor, then strength exercises can be used. While if a large osteogenic load is sought after, such as for the quickest gains possible like with an athlete, then power exercises can be used. The wrist site had greater reliability than the bar site and is a more practical location for accelerometer placement. The OI-ORIGINAL equation is a less complex equation with greater reliability than the OI-ADAPTED equation and is a simpler, more practical and reliable measure of osteogenic adaptation in exercises.

CHARACTERISATION OF PERIPHERAL BONE MATERIAL, STRUCTURE AND STRENGTH IN YOUTH AT RISK OF SECONDARY OSTEOPOROSIS

CHAPTER SEVEN – SUMMARY/CONCLUSION

The four clinical and applied studies of this thesis have provided a detailed insight into bone fracture incidence, measurement, and adaptation. Study one focused on the fracture epidemiology of children and adolescents at appendicular bone sites and if any changes occurred in WA over a lengthy period of time (2005 to 2015). Study two determined the reliability of using pQCT when measuring numerous upper body diaphyseal mineral and soft-tissue measurements for the humerus, radius and ulna. Study three focused on OI reliability for upper-body resistance (strength and power) exercises while using inertial measurement units at two measurement sites (bar and wrist). Study four determined the bone characteristics of children with different diseases and low motor competence when compared to unaffected children.

Study one confirmed the hypothesis that appendicular fracture incidence of children and adolescents in WA has increased from 2005 to 2015, but that the incidence rates are lower than reported for other countries around the world. This was controlled for gender and age, and provides a 'call to action' for an intervention in order to target the increasing fracture incidence. This is also the first study providing reported data on fracture incidence in WA comparing to international trends. While there is an increase in the fracture incidence in WA, the incidence is lower than other reported countries.

Study two confirmed the hypothesis that pQCT will be reliable for between-day scans for upper body diaphyseal mineral and soft-tissue measurements. The overall ICC values for the three sites were excellent, with low CV values. The study added more information to previously measured variables, while also adding new information to never before measured variables in the upper limbs.

The results of study three varied in comparison to the hypothesis. The OI equations were not reliable for all exercises when using inertial measurement units, however there was varying reliability between the two OI equations with the OI-ADAPTED equation having greater reliability at the bar site, while the OI-ORIGINAL equation had greater reliability at the wrist site. The OI is a valid tool for determining the osteogenic potential for certain exercises, and from this targeted training programs for athletes, or people with bone diseases can be implemented.

Study four confirmed the hypothesis that there will be unique upper and lower limb bone structural profiles depending on the disease or if individuals have low motor competence. Knowing that individuals with neuromuscular disorders and low motor competence are the groups most susceptible to decreased bone characteristics, targeted interventions can be put into place to increase the bone health of these individuals.

The key findings from this thesis are that the fracture incidence in WA is increasing, pQCT has shown excellent reliability for a variable of upper limb measurements, the OI is more reliable when measuring strength exercises compared to power exercises, and individuals with neuromuscular disorders or low motor competence are more susceptible to having compromised bone characteristics. Identifying the rising fracture incidence trend for children in WA, suggests that interventions should be put into place to increase the bone health of children in order to decrease the fracture risk and future risk of osteoporosis. Examination of between day reliability of never before scanned pQCT variables, informs subsequent research studies particularly longitudinal intervention-based studies. Therefore, any intervention put into place will be able to rely upon the reliability of pQCT as an accurate measurement tool of bone characteristics. Based on the OI, targeted interventions can be designed to optimise increases bone health. Interventions for children can focus on using strength exercises that are more reliable for eliciting more consistent osteogenic adaptation, or focus on using ballistic exercises which while they produce greater osteogenic adaptations, they are not as reliable as strength exercises. By undertaking an intervention and increasing the bone health of those children and adolescence at fracture risk (e.g. neuromuscular disorder, low motor competence, chronic disorders), this may optimise peak bone mass during the critical growth period, minimise risk of future osteoporosis and improve their overall quality of life into adulthood.

CHAPTER EIGHT – FUTURE RESEARCH

The findings from these studies have highlighted many areas for future research.

Study 1.

- Identify potential lifestyle factors that impact fracture incidence.
- Address lifestyle factors impacting bone health through targeted interventions to reverse the increasing incidence of fractures.

Study 2.

- Many of the variables examined in this study have not been measured in the lower limbs, and this information could give an insight into a more accurate portrayal of the bone structure of lower limbs.
- The same variables could be measured in children and adolescents.

Study 3.

- The OI of both equations can be incorporated into future exercise studies focusing on the exercises with high reliabilities, however future research should identify if it is necessary to examine OI individually during training studies to ensure efficacy of predicted OI of chosen exercises.
- Results from this study provides important evidence for statistical power required for future studies involving the OI equations, and for exploring other exercises that would suit an intervention for osteogenic adaptation.
- Future exercise studies involving the OI and children can also be implemented.

Study 4.

- A limitation in this study was the small samples available for some of the disease groups. Hence future research should examine these disease groups with a larger sample.
- A prospective research design would permit clear inclusion and exclusion criteria to be defined in addition to examining these findings in light of other confounding factors, such as physical activity levels.
- DCD has a relatively high prevalence (nearly 1 in 100 kids are affected), and individuals with DCD appear to be at risk of poorer bone health compared to non-affected peers. A randomised controlled study with exercise and nutrition

interventions would shed light on whether a life-style intervention could address this apparent risk.

- It should also be explored whether the suboptimal bone status associated with DCD persists into adulthood or not.

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APPENDICES

Supplementary Table 6. pQCT Fibula 4% Descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=535)			
Age (years)	12.34 (3.57)	12.91	12.04 – 12.65
Bone length (mm)	337.81 (58.88)	340.00	332.81 – 342.82
Cortical Density (cm^3) CoD ($mg.cm^3$)	469.16 (103.88)	461.71	460.34 – 477.98
Cortical Area (mm^3)	114.27 (44.92)	108.75	110.46 – 118.09
SSI (mm^3)	147.94 (78.84)	135.61	141.24 – 154.63
Total Area (mm^2)	129.39 (47.41)	125.60	125.36 – 133.41
Compressive Bone Strength ($BSld/g/cm^4$)	0.25 (0.14)	0.22	0.24 – 0.27
Pericortical Radius (mm)	6.30 (0.05)	6.29	6.21 – 6.40
Trabecular density ($mg.cm^3$)	272.49 (4.06)	264.20	264.51 – 280.46
Control (Griffiths Dataset) (n=173)			
Age (years)[1, 2, 3]	10.86 (0.29)	10.04	10.29 – 11.43
Bone length (mm)[1, 3]	323.23 (4.32)	320.00	314.71 – 331.76
Cortical Density (cm^3) CoD ($mg.cm^3$)[2, 4]	460.07 (6.61)	442.07	447.03 – 473.11
Cortical Area (mm^3)[3, 4]	111.87 (2.66)	102.00	106.62 – 117.13
SSI (mm^3)[1, 3, 4]	136.48 (5.63)	117.50	125.36 – 147.60
Total Area (mm_2)[3]	121.31 (2.71)	113.00	115.96 – 126.66
Compressive Bone Strength ($BSld/g/cm^4$)[3, 4]	0.246 (0.011)	0.19	0.22 – 0.27
Pericortical Radius (mm)[3]	6.13 (0.07)	5.98	6.00 – 6.26
Trabecular density ($mg.cm^3$)[1, 4]	296.39 (6.91)	281.37	282.74 – 310.04
Neuromuscular disorders (n=26)			
Age (years)	11.81 (0.72)	11.72	10.33 – 13.30
Bone length (mm)[5]	298.85 (13.16)	295.00	271.75 – 325.94
Cortical Density (cm^3) CoD ($mg.cm^3$)[4, 5, 6, 7, 8]	350.48 (19.15)	333.41	311.04 – 389.93
Cortical Area (mm^3)[4, 5, 6, 7]	69.48 (8.27)	62.32	52.44 – 86.52
SSI (mm_3)[4, 5, 6, 7]	64.74 (9.25)	66.36	45.69 – 83.80
Total Area (mm^2)[5, 6, 7]	85.91 (10.07)	79.12	65.17 – 106.64
Compressive Bone Strength ($BSld/g/cm^4$)[3, 4, 5, 6, 7, 8]	0.089 (0.012)	0.073	0.063 – 0.11
Pericortical Radius (mm)[5, 6, 7]	4.99 (0.38)	5.21	4.20 – 5.78
Trabecular density ($mg.cm^3$)[4]	233.97 (22.84)	212.35	186.48 – 281.46
Chronic Diseases (n=216)			
Age (years)[1]	12.88 (0.23)	13.49	12.42 – 13.33
Bone length (mm)[1, 9]	340.06 (3.94)	350.00	332.39 – 347.82
Cortical Density (cm^3) CoD ($mg.cm^3$)[6]	477.79 (7.47)	477.35	463.07 – 492.51
Cortical Area (mm_3)[6, 9]	116.40 (3.44)	109.04	109.62 – 123.18
SSI (mm^3)[6]	156.07 (5.56)	146.66	145.11 – 167.03
Total Area (mm^2)[6, 9]	134.80 (3.62)	127.12	127.66 – 141.93
Compressive Bone Strength ($BSld/g/cm^4$)[6]	0.26 (0.01)	0.25	0.24 – 0.28
Pericortical Radius (mm)[6, 9]	6.43 (0.08)	6.34	6.26 – 6.59
Trabecular density ($mg.cm^3$)[1]	256.05 (6.33)	246.94	243.58 – 268.52
Endocrine diseases (n=54)			
Age (years)[2]	13.46 (0.43)	14.31	12.61 – 14.32
Bone length (mm)[10]	347.69 (6.734)	350.00	334.18 – 361.19
Cortical Density (cm^3) CoD ($mg.cm_3$)[2, 7]	498.02 (15.61)	495.84	466.70 – 529.33
Cortical Area (mm^3)[7]	119.12 (5.66)	113.84	107.76 – 130.48
SSI (mm^3)[7]	162.99 (10.20)	152.51	142.54 – 183.26
Total Area (mm_2)[7]	136.59 (6.17)	129.92	124.22 – 148.96
Compressive Bone Strength ($BSld/g/cm_4$)[7]	0.29 (0.018)	0.29	0.25 – 0.33
Pericortical Radius (mm)[7]	6.50 (0.14)	6.41	6.21 – 6.79
Trabecular density ($mg.cm^3$)	273.67 (12.05)	272.65	249.49 – 297.85
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.40	5.70 – 14.86
Bone length (mm)	315.00 (37.55)	310.00	210.74 – 419.26
Cortical Density (cm^3) CoD ($mg.cm_3$)	440.76 (32.24)	461.71	351.25 – 530.27
Cortical Area (mm_3)	82.94 (13.88)	79.84	44.41 – 121.48
SSI (mm^3)	100.93 (27.06)	78.58	25.79 – 176.07
Total Area (mm^2)	102.08 (12.69)	97.28	66.85 – 136.31S
Compressive Bone Strength ($BSld/g/cm^4$)	0.16 (0.045)	0.12	0.036 – 0.28
Pericortical Radius (mm)	5.64 (0.35)	5.56	4.68 – 6.61
Trabecular density ($mg.cm^3$)	200.67 (27.17)	185.77	125.25 – 276.09
Iatrogenic (n=11)			
Age (years)	13.17 (0.97)	14.17	11.00 – 15.34
Bone length (mm)	344.09 (13.75)	335.00	313.46 – 374.72
Cortical Density (cm^3) CoD ($mg.cm^3$)[8]	493.27 (20.20)	515.03	448.26 – 538.29
Cortical Area (mm_3)	107.78 (12.43)	100.32	80.09 – 135.47

SSI (mm^3)	141.98 (21.95)	125.91	93.09 – 190.88
Total Area (mm^2)	126.07 (12.58)	142.56	95.81 – 156.32
Compressive Bone Strength (BSld/g/cm_4)[8]	0.24 (0.029)	0.23	0.17 – 0.31
Pericortical Radius (mm)	6.19 (0.36)	6.73	5.37 – 7.00
Trabecular density ($mg.cm^3$)	268.34 (31.12)	271.97	198.99 – 337.68
Low Motor Competence (AMPitup) Dataset (n=50)			
Age (years)[3]	14.26 (0.21)	13.88	13.84 – 14.67
Bone length (mm)[3, 5, 9, 10]	389.10 (5.235)	390.00	378.58 – 399.62
Cortical Density (cm^3) CoD ($mg.cm^3$)[5]	491.40 (12.72)	490.53	465.83 – 516.97
Cortical Area (mm^3)[3, 5, 9]	136.00 (5.55)	130.50	124.84 – 147.16
SSI (mm^3)[3, 5]	185.46 (9.18)	174.06	167.01 – 203.90
Total Area (mm^2)[3, 5, 9]	152.27 (5.57)	145.04	141.08 – 163.47
Compressive Bone Strength (BSld/g/cm^4)[3, 5]	0.32 (0.018)	0.29	0.28 – 0.35
Pericortical Radius (mm)[3, 5, 9]	6.86 (0.12)	6.78	6.61 – 7.11
Trabecular density ($mg.cm^3$)	283.59 (12.05)	269.50	259.38 – 307.80

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Neuromuscular Disorders and Iatrogenic; 9. Significant difference between Low Motor Competence and Chronic Diseases; 10. Significant difference between Low Motor Competence and Endocrine Diseases.

Supplementary Table 7. pQCT Tibia 4% Descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=615)			
Age (years)	12.28 (0.14)	12.58	12.01 – 12.56
Bone length (mm)	336.82 (2.29)	340.00	332.32 – 341.32
Cortical Density (cm^3) CoD ($mg.cm^3$)	305.94 (1.64)	301.31	302.70 – 309.17
Cortical Area (mm^3)	803.33 (10.56)	811.20	782.59 – 824.07
SSI (mm^3)	1744.18 (30.96)	1724.45	1683.38 – 1804.98
Total Area (mm^2)	908.38 (10.45)	916.32	887.86 – 928.90
Compressive Bone Strength (BSld/g/cm_4)	0.78 (0.01)	0.75	0.75 – 0.81
Pericortical Radius (mm)	16.76 (0.11)	17.08	16.55 – 16.98
Trabecular density ($mg.cm^3$)	232.04 (2.40)	227.76	227.33 – 236.75
Control (Griffiths Dataset) (n=244)			
Age (years)[1, 2, 3]	11.37 (0.24)	10.39	10.89 – 11.84
Bone length (mm)[3]	327.97 (3.31)	325.00	321.44 – 334.50
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3, 4]	318.43 (2.35)	314.71	313.80 – 323.06
Cortical Area (mm_3)[1, 3, 4]	850.36 (14.30)	834.25	822.19 – 878.53
SSI (mm^3)[3, 4]	1844.55 (46.36)	1753.74	1753.22 – 1935.87
Total Area (mm^2)[3, 4]	896.07 (14.33)	865.50	867.83 – 924.30
Compressive Bone Strength (BSld/g/cm^4)[1, 4]	0.88 (0.02)	0.83	0.84 – 0.92
Pericortical Radius (mm)[3, 4]	16.74 (0.13)	16.58	16.48 – 17.00
Trabecular density ($mg.cm^3$)[1, 2, 3, 4]	255.39 (3.40)	249.05	248.70 – 262.08
Neuromuscular disorders (n=19)			
Age (years)	11.77 (0.70)	11.69	10.30 – 13.24
Bone length (mm)[5]	307.11 (13.22)	305.00	279.33 – 334.88
Cortical Density (cm^3) CoD (mg.cm3)[4]	288.51 (10.01)	377.56	267.49 – 309.54
Cortical Area (mm^3)[4, 5, 6, 7, 8]	394.41 (70.32)	373.44	246.68 – 542.14
SSI (mm^3)[4, 5, 6, 7, 8]	715.77 (139.56)	669.13	422.56 – 1008.99
Total Area (mm^2)[4, 5, 6, 7]	576.99 (89.29)	680.96	389.41 – 764.58
Compressive Bone Strength (BSld/g/cm_4)[4, 5, 6, 7]	0.31 (0.06)	0.28	0.19 – 0.43
Pericortical Radius (mm)[4, 5, 6, 7]	12.38 (1.26)	14.72	9.74 – 15.02
Trabecular density ($mg.cm^3$)[4]	174.18 (16.37)	183.71	139.80 – 208.57
Chronic Diseases (n=235)			
Age (years)[1]	12.62 (0.22)	13.08	12.19 – 13.06
Bone length (mm)[9]	335.57 (4.00)	340.00	327.70 – 343.44
Cortical Density (cm^3) CoD ($mg.cm^3$)[1]	297.82 (2.98)	288.30	291.95 – 303.69
Cortical Area (mm^3)[1, 6, 9]	756.05 (16.57)	774.72	723.40 – 788.70
SSI (mm^3)[6, 9]	1629.81 (49.63)	1655.49	1532.03 – 1727.58
Total Area (mm^2)[6, 9]	905.11 (17.58)	925.12	870.47 – 939.75
Compressive Bone Strength (BSld/g/cm^4)[1, 6, 9]	0.71 (0.02)	0.67	0.66 – 0.76
Pericortical Radius (mm)[6, 9]	16.71 (0.18)	17.14	16.35 – 17.08
Trabecular density ($mg.cm^3$)[1]	218.05 (3.89)	207.96	210.38 – 225.72
Endocrine diseases (n=49)			
Age (years)[2]	13.44 (0.43)	14.17	12.57 – 14.31
Bone length (mm)[10]	345.31 (6.48)	350.00	332.28 – 358.33
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	298.94 (4.03)	302.62	290.83 – 307.04
Cortical Area (mm^3)[7]	801.94 (35.15)	871.68	731.27 – 872.62
SSI (mm^3)[7]	1740.76 (94.27)	1752.91	1551.22 – 1930.30
Total Area (mm^2)[7, 10]	927.52 (32.30)	947.04	862.78 – 992.26
Compressive Bone Strength (BSld/g/cm^4)[7]	0.75 (0.04)	0.76	0.67 – 0.83
Pericortical Radius (mm)[7, 10]	16.99 (0.35)	17.34	16.29 – 17.69
Trabecular density ($mg.cm^3$)[2]	219.43 (6.67)	222.91	206.01 – 232.84
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.39	5.70 – 14.86
Bone length (mm)[11]	315.00 (37.55)	310.00	210.74 – 419.26
Cortical Density (cm^3) CoD ($mg.cm^3$)	319.36 (20.21)	318.77	263.25 – 375.47
Cortical Area (mm^3)[11]	539.52 (138.57)	642.72	154.78 – 924.26
SSI (mm^3)	1140.09 (334.47)	1234.13	221.45 – 2068.73
Total Area (mm^2)[11]	674.40 (104.98)	644.00	382.94 – 965.86
Compressive Bone Strength (BSld/g/cm^4)	0.52 (0.14)	0.67	0.14 – 0.91
Pericortical Radius (mm)[11]	14.47 (1.15)	14.32	11.28 – 17.65
Trabecular density ($mg.cm^3$)	195.26 (30.07)	178.51	95.12 – 295.40
Iatrogenic (n=12)			
Age (years)	12.86 (0.91)	13.62	10.85 – 14.87
Bone length (mm)	342.92 (12.61)	332.50	315.17 – 370.66
Cortical Density (cm^3) CoD ($mg.cm^3$)	295.74 (8.59)	291.16	276.83 – 314.66
Cortical Area (mm^3)[8]	821.47 (87.89)	863.04	628.01 – 1014.92
SSI (mm^3)[8]	1834.31 (240.01)	1694.54	1306.04 – 2362.58
Total Area (mm^2)	956.95 (71.13)	958.00	800.40 – 1113.49

Compressive Bone Strength (BSld/g/cm^4)	0.75 (0.11)	0.63	0.51 – 0.99
Pericortical Radius (mm)	17.29 (0.68)	17.44	15.79 – 18.79
Trabecular density (mg.cm^3)	212.84 (16.11)	197.98	177.37 – 248.31
Low Motor Competence (AMPitup) Dataset (n=51)			
Age (years)[3]	14.23 (0.20)	13.95	13.83 – 14.63
Bone length (mm)[3, 5, 9, 10, 11]	318.43 (2.35)	314.71	313.80 – 323.06
Cortical Density (cm^3) CoD (mg.cm^3)[3]	297.83 (4.38)	294.17	289.04 – 306.62
Cortical Area (mm^3)[3, 5, 9, 11]	971.42 (33.43)	971.36	904.28 – 1038.57
SSI (mm^3)[3, 5, 9]	2215.42 (94.54)	2230.30	2025.54 – 2405.30
Total Area (mm^2)[3, 5, 9, 10, 11]	1098.95 (25.72)	1089.92	1047.29 – 1150.60
Compressive Bone Strength (BSld/g/cm^4)[5, 9]	0.89 (0.04)	0.87	0.80 – 0.97
Pericortical Radius (mm)[3, 5, 9, 10, 11]	18.62 (0.22)	18.59	18.17 – 19.06
Trabecular density (mg.cm^3)[3]	226.63 (7.31)	228.53	211.95 – 241.31

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Neuromuscular Disorders and Iatrogenic; 9. Significant difference between Low Motor Competence and Chronic Diseases; 10. Significant difference between Low Motor Competence and Endocrine Diseases; 11. Significant difference between Low Motor Competence and Inborn Errors of Metabolism.

Supplementary Table 8. pQCT Ulna 4% Descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=578)			
Age (years)	12.18 (0.14)	12.50	11.91 – 12.45
Bone length (mm)	230.33 (1.40)	230.00	227.57 – 233.09
Cortical Density (cm^3) CoD ($mg.cm^3$)	307.79 (2.01)	303.06	303.85 – 311.73
Cortical Area (mm^3)	116.15 (1.61)	114.75	113.00 – 119.30
SSI (mm^3)	94.19 (2.00)	85.66	90.26 – 98.13
Total Area (mm^2)	127.97 (1.77)	125.96	124.50 – 131.45
Compressive Bone Strength ($BSld/g/cm^4$)	0.11 (0.00)	0.10	0.11 – 0.12
Pericortical Radius (mm)	6.26 (0.05)	6.30	6.17 – 6.35
Trabecular density ($mg.cm^3$)	246.18 (2.62)	240.46	241.05 – 251.32
Control (Griffiths Dataset) (n=209)			
Age (years)[1, 2, 3]	10.66 (0.23)	10.23	10.20 – 11.12
Bone length (mm)[1, 2, 3]	222.03 (2.21)	220.00	217.68 – 226.39
Cortical Density (cm^3) CoD ($mg.cm^3$)	307.29 (3.01)	305.13	301.35 – 313.23
Cortical Area (mm^3)[3, 4]	112.87 (2.26)	112.50	108.41 – 117.33
SSI (mm^3)[3]	85.89 (2.97)	76.00	80.03 – 91.73
Total Area (mm^2)[1, 2, 3]	118.50 (2.52)	114.25	113.54 – 123.46
Compressive Bone Strength ($BSld/g/cm^4$)[3, 4]	0.11 (0.00)	0.10	0.10 – 0.12
Pericortical Radius (mm)[1, 3]	6.05 (0.07)	6.01	5.92 – 6.18
Trabecular density ($mg.cm^3$)[1, 2]	265.51 (3.82)	256.96	257.97 – 273.05
Neuromuscular disorders (n=18)			
Age (years)	12.04 (0.75)	12.01	10.46 – 13.62
Bone length (mm)[5]	221.11 (9.12)	215.00	201.75 – 240.48
Cortical Density (cm^3) CoD ($mg.cm^3$)	297.23 (9.80)	300.03	276.56 – 317.90
Cortical Area (mm^3)[4, 5, 6, 7]	78.12 (9.71)	77.12	57.64 – 98.61
SSI (mm^3)[5, 6, 7]	59.41 (9.08)	58.46	40.26 – 78.56
Total Area (mm^2)[5]	97.57 (11.03)	103.04	74.30 – 120.85
Compressive Bone Strength ($BSld/g/cm^4$)[4, 5, 6, 7]	0.07 (0.01)	0.07	0.05 – 0.09
Pericortical Radius (mm)[5]	5.31 (0.38)	5.69	4.50 – 6.11
Trabecular density ($mg.cm^3$)	224.56 (20.82)	215.97	180.63 – 268.49
Chronic Diseases (n=235)			
Age (years)[1]	12.79 (0.21)	13.23	12.38 – 13.21
Bone length (mm)[1, 8]	231.67 (2.27)	235.00	227.19 – 236.14
Cortical Density (cm^3) CoD ($mg.cm^3$)	307.80 (3.29)	300.42	301.33 – 314.28
Cortical Area (mm^3)[6, 8]	115.42 (2.77)	113.92	109.96 – 120.88
SSI (mm^3)[6, 8]	97.07 (3.54)	90.14	90.10 – 104.04
Total Area (mm^2)[1, 8]	131.02 (3.10)	129.92	124.91 – 137.13
Compressive Bone Strength ($BSld/g/cm^4$)[6, 8]	0.11 (0.00)	0.10	0.11 – 0.12
Pericortical Radius (mm)[1, 8]	6.31 (0.08)	6.40	6.16 – 6.47
Trabecular density ($mg.cm^3$)[1]	234.82 (4.24)	222.76	226.46 – 243.18
Endocrine diseases (n=51)			
Age (years)[2]	13.59 (0.42)	14.44	12.74 – 14.43
Bone length (mm)[2]	238.14 (3.82)	240.00	230.47 – 245.80
Cortical Density (cm^3) CoD ($mg.cm^3$)	323.57 (9.21)	317.62	305.07 – 342.07
Cortical Area (mm^3)[7, 9]	119.61 (4.45)	117.76	110.68 – 128.54
SSI (mm^3)[7]	103.16 (5.57)	94.47	91.97 – 114.36
Total Area (mm_2)[2]	136.14 (4.86)	138.56	126.37 – 145.91
Compressive Bone Strength ($BSld/g/cm^4$)[7]	0.13 (0.01)	0.11	0.11 – 0.14
Pericortical Radius (mm)	6.50 (0.12)	6.62	6.25 – 6.74
Trabecular density ($mg.cm^3$)[2]	234.00 (8.73)	219.64	216.46 – 251.54
Inborn Errors of metabolism (n=4)			
Age (years)	11.33 (1.64)	11.15	6.10 – 16.56
Bone length (mm)	198.75 (25.85)	205.00	116.48 – 281.02
Cortical Density (cm^3) CoD ($mg.cm^3$)	285.40 (20.23)	281.85	221.01 – 349.78
Cortical Area (mm^3)	118.00 (22.53)	113.76	46.31 – 189.69
SSI (mm^3)	90.18 (22.73)	100.17	17.83 – 162.52
Total Area (mm^2)	126.64 (24.84)	124.08	47.58 – 205.70
Compressive Bone Strength ($BSld/g/cm^4$)	0.10 (0.02)	0.11	0.04 – 0.16
Pericortical Radius (mm)	6.25 (0.63)	6.27	4.24 – 8.26
Trabecular density ($mg.cm^3$)	224.55 (1.90)	225.33	218.49 – 230.61
Iatrogenic (n=11)			
Age (years)	13.02 (0.98)	14.17	10.82 – 15.21
Bone length (mm)	229.09 (8.94)	225.00	209.17 – 249.01
Cortical Density (cm^3) CoD ($mg.cm^3$)	291.14 (13.12)	290.51	261.91 – 320.27
Cortical Area (mm^3)[10]	110.01 (12.25)	116.32	82.71 – 137.30

SSI (mm^3)	88.27 (12.31)	81.80	60.84 – 115.70
Total Area (mm^2)	131.13 (10.96)	129.28	106.70 – 155.56
Compressive Bone Strength (BSld/g/cm^4)	0.10 (0.02)	0.07	0.06 – 0.14
Pericortical Radius (mm)	6.33 (0.31)	6.39	5.64 – 7.03
Trabecular density (mg.cm^3)	221.05 (20.72)	212.83	174.88 – 267.21
Low Motor Competence (AMPitup) Dataset (n=50)			
Age (years)[3]	14.20 (0.19)	13.96	13.81 – 14.59
Bone length (mm)[3, 5, 8]	256.90 (3.10)	260.00	250.66 – 263.14
Cortical Density (cm^3) CoD (mg.cm^3)	302.99 (5.04)	301.14	292.87 – 313.11
Cortical Area (mm^3)[3, 5, 8, 9, 10]	144.67 (4.17)	139.44	136.29 – 153.05
SSI (mm^3)[3, 5, 8]	120.42 (4.98)	116.95	110.40 – 130.43
Total Area (mm^2)[3, 5, 8]	155.26 (4.25)	152.96	146.71 – 163.81
Compressive Bone Strength (BSld/g/cm^4)[3, 5, 8]	0.13 (0.01)	0.12	0.12 – 0.15
Pericortical Radius (mm)[3, 5, 8]	6.97 (0.10)	6.96	6.78 – 7.16
Trabecular density (mg.cm^3)	246.30 (7.81)	237.15	230.62 – 261.99

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$), except for cortical density ($p = 0.552$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Low Motor Competence and Chronic Diseases; 9. Significant difference between Low Motor Competence and Endocrine Diseases; 10. Significant difference between Low Motor Competence and Iatrogenic.

Supplementary Table 9. pQCT Radius 4% Descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=584)			
Age (years)	12.17 (0.14)	12.44	11.89 – 12.44
Bone length (mm)	230.16 (1.41)	230.00	227.39 – 232.93
Cortical Density (cm^3) CoD ($mg.cm^3$)	318.70 (1.93)	308.40	314.92 – 322.48
Cortical Area (mm^3)	219.45 (3.18)	211.28	213.21 – 225.70
SSI (mm^3)	285.07 (5.71)	262.47	273.85 – 296.29
Total Area (mm^2)	277.56 (3.40)	273.00	270.88 – 284.24
Compressive Bone Strength ($BSld/g/cm^4$)	0.22 (0.00)	0.20	0.22 – 0.23
Pericortical Radius (mm)	9.21 (0.06)	9.24	9.09 – 9.32
Trabecular density ($mg.cm^3$)	190.20 (2.02)	184.13	186.23 – 194.17
Control (Griffiths Dataset) (n=212)			
Age (years)[1, 2, 3]	10.65 (0.23)	10.22	10.19 – 11.11
Bone length (mm)[1, 2, 3]	221.94 (2.20)	217.50	217.62 – 226.27
Cortical Density (cm^3) CoD ($mg.cm^3$)	317.93 (3.02)	307..04	311.98 – 323.88
Cortical Area (mm^3)[3]	218.71 (4.73)	209.00	209.38 – 228.03
SSI (mm^3)[3]	269.21 (9.18)	234.65	251.11 – 287.31
Total Area (mm^2)[1, 3]	257.16 (4.94)	246.38	246.42 – 266.90
Compressive Bone Strength ($BSld/g/cm^4$)	0.22 (0.01)	0.20	0.21 – 0.24
Pericortical Radius (mm)[1, 2, 3]	8.89 (0.08)	8.79	8.72 – 9.05
Trabecular density ($mg.cm^3$)[1, 2, 3]	206.29 (3.19)	200.16	200.00 – 212.58
Neuromuscular disorders (n=19)			
Age (years)	12.03 (0.71)	11.76	10.54 – 13.52
Bone length (mm)[4]	219.47 (8.84)	210.00	200.91 – 238.04
Cortical Density (cm^3) CoD ($mg.cm^3$)	320.14 (12.77)	309.39	293.32 – 346.96
Cortical Area (mm^3)[4]	170.28 (22.69)	155.68	122.61 – 217.95
SSI (mm^3)[4, 5]	210.92 (28.97)	207.19	150.06 – 271.78
Total Area (mm^2)[4]	237.98 (20.66)	241.12	194.58 – 281.37
Compressive Bone Strength ($BSld/g/cm^4$)[4]	0.17 (0.02)	0.15	0.12 – 0.21
Pericortical Radius (mm)[4]	8.34 (0.43)	8.70	7.52 – 9.35
Trabecular density ($mg.cm^3$)	178.79 (17.17)	171.20	142.72 – 214.87
Chronic Diseases (n=235)			
Age (years)[1]	12.78 (0.21)	13.23	12.37 – 13.20
Bone length (mm)[1, 6]	231.52 (2.30)	235.00	226.98 – 236.06
Cortical Density (cm^3) CoD ($mg.cm^3$)	318.82 (3.15)	309.04	312.62 – 325.03
Cortical Area (mm^3)[6]	214.91 (5.27)	206.56	204.52 – 225.29
SSI (mm^3)[6]	285.06 (9.50)	268.23	266.35 – 303.77
Total Area (mm^2)[1, 6]	282.05 (5.75)	282.40	270.72 – 293.38
Compressive Bone Strength ($BSld/g/cm^4$)	0.22 (0.01)	0.22	0.21 – 0.23
Pericortical Radius (mm)[1, 6]	9.26 (0.10)	9.35	9.07 – 9.45
Trabecular density ($mg.cm^3$)[1]	183.53 (3.25)	178.37	177.12 – 189.93
Endocrine diseases (n=52)			
Age (years)[2]	13.47 (0.43)	14.31	12.62 – 14.33
Bone length (mm)[2, 7]	237.02 (3.91)	240.00	229.18 – 244.86
Cortical Density (cm^3) CoD ($mg.cm^3$)	321.16 (7.10)	310.62	306.91 – 335.41
Cortical Area (mm^3)	230.42 (9.94)	230.64	210.47 – 250.37
SSI (mm^3)[5]	313.06 (17.68)	294.46	277.56 – 348.56
Total Area (mm^2)	302.56 (10.89)	297.04	280.69 – 324.43
Compressive Bone Strength ($BSld/g/cm^4$)	0.24 (0.01)	0.21	0.21 – 0.27
Pericortical Radius (mm)[2]	9.63 (0.18)	9.59	9.28 – 9.99
Trabecular density ($mg.cm^3$)[2]	179.29 (5.37)	179.64	168.51 – 190.07
Inborn Errors of metabolism (n=4)			
Age (years)	11.33 (1.64)	11.15	6.10 – 16.56
Bone length (mm)	198.75 (25.85)	205.00	116.48 – 281.02
Cortical Density (cm^3) CoD ($mg.cm^3$)	334.50 (58.60)	300.91	148.03 – 520.98
Cortical Area (mm^3)	175.96 (48.81)	144.00	20.61 – 331.31
SSI (mm^3)	227.98 (81.55)	184.05	-31.56 – 487.51
Total Area (mm^2)	237.20 (59.59)	187.84	47.57 – 426.83
Compressive Bone Strength ($BSld/g/cm^4$)	0.18 (0.04)	0.18	0.04 – 0.31
Pericortical Radius (mm)	8.45 (0.99)	7.66	5.30 – 11.59
Trabecular density ($mg.cm^3$)	166.20 (12.42)	173.86	126.68 – 205.72
Iatrogenic (n=11)			
Age (years)	13.02 (0.98)	14.17	10.82 – 15.21
Bone length (mm)	229.09 (8.94)	225.00	209.17 – 249.01
Cortical Density (cm^3) CoD ($mg.cm^3$)	320.86 (13.45)	305.48	290.88 – 350.83
Cortical Area (mm^3)	222.75 (27.16)	190.88	162.22 – 283.27

SSI (mm^3)	293.00 (39.78)	233.34	204.36 – 282.27
Total Area (mm^2)	298.05 (18.99)	286.56	255.73 – 340.37
Compressive Bone Strength (BSld/g/cm^4)	0.22 (0.03)	0.18	0.16 – 0.29
Pericortical Radius (mm)	9.59 (0.30)	9.43	8.93 – 10.25
Trabecular density (mg.cm^3)	175.06 (16.52)	185.00	138.26 – 211.86
Low Motor Competence (AMPitup) Dataset (n=51)			
Age (years)[3]	14.25 (0.20)	13.97	13.86 – 14.64
Bone length (mm)[3, 4, 6, 7]	257.75 (3.16)	260.00	251.40 – 264.09
Cortical Density (cm^3) CoD (mg.cm^3)	316.97 (4.79)	308.77	306.97 – 326.19
Cortical Area (mm^3)[3, 4, 6]	253.36 (9.67)	245.44	233.93 – 272.79
SSI (mm^3)[3, 4, 6]	352.86 (14.91)	330.38	322.91 – 382.82
Total Area (mm^2)[3, 4, 6]	329.73 (8.37)	328.16	312.92 – 346.54
Compressive Bone Strength (BSld/g/cm^4)[4]	0.25 (0.01)	0.25	0.23 – 0.27
Pericortical Radius (mm)[3, 4, 6]	10.10 (0.13)	10.11	9.85 – 10.36
Trabecular density (mg.cm^3)[3]	174.56 (4.54)	174.22	165.44 – 183.69

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$); BSI ($p = 0.006$), except for cortical density ($p = 1.000$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Neuromuscular Disorders and Low Motor Competence; 5. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 6. Significant difference between Low Motor Competence and Chronic Diseases; 7. Significant difference between Low Motor Competence and Endocrine Diseases;

Supplementary Table 10. pQCT Radius 66%. Characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=424)			
Age (years)	12.55 (0.16)	13.04	12.23 – 12.87
Bone length (mm)	233.70 (1.59)	235.00	230.57 – 236.82
Cortical Density (cm^3) CoD ($mg.cm^3$)	823.08 (4.93)	821.84	813.39 – 832.77
Cortical Area (mm^3)	84.55 (1.03)	82.88	82.52 – 86.57
SSI (mm^3)	194.54 (4.10)	179.40	186.48 – 202.59
Total Area (mm^2)	115.46 (1.45)	112.37	112.62 – 118.31
Compressive Bone Strength ($BSld/g/cm^4$)	0.47 (0.01)	0.44	0.45 – 0.49
Muscle Density (mg/cm^3)	79.25 (0.12)	79.35	79.02 – 79.48
Muscle cross-sectional area (mg/cm^2)	21.14 (0.34)	19.78	20.47 – 21.82
Subcutaneous fat area (cm^2)	9.15 (0.31)	7.83	8.55 – 9.75
Fat percentage (%)	31.26 (0.49)	31.98	30.30 – 32.23
Mid-cortical ring density ($mg.cm^3$)	914.87 (4.98)	912.99	905.07 – 924.67
Endocortical radius (mm)	3.17 (0.03)	3.09	3.11 – 3.22
Pericortical radius (mm)	6.00 (0.04)	5.96	5.93 – 6.08
Control (Griffiths Dataset) (n=187)			
Age (years)[1, 2, 3]	10.82 (0.25)	10.14	10.32 – 11.32
Bone length (mm)[1, 2, 3]	222.58 (2.33)	215.00	217.98 – 227.18
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3]	781.08 (7.13)	778.79	767.02 – 795.14
Cortical Area (mm^3)[1, 2, 3]	80.39 (1.63)	75.25	77.17 – 83.61
SSI (mm^3)[1, 2, 3]	179.10 (6.62)	155.13	166.05 – 192.16
Total Area (mm^2)[2, 3]	111.15 (2.25)	104.75	106.71 – 115.59
Compressive Bone Strength ($BSld/g/cm^4$)[1, 2, 3]	0.40 (0.01)	0.33	0.37 – 0.43
Muscle Density (mg/cm^3)[4]	79.51 (0.11)	79.40	79.29 – 79.74
Muscle cross-sectional area (mg/cm^2)[1, 3]	19.86 (0.52)	17.59	18.84 – 20.89
Subcutaneous fat area (cm^2)[3, 4]	7.76 (0.29)	7.01	7.19 – 8.33
Fat percentage (%)[a]	30.88 (0.63)	31.59	29.64 – 32.11
Mid-cortical ring density ($mg.cm^3$)[1, 2]	889.01 (7.11)	883.42	874.97 – 903.04
Endocortical radius (mm)	3.14 (0.04)	3.10	3.06 – 3.22
Pericortical radius (mm)[2, 3]	5.89 (0.06)	5.78	5.78 – 6.00
Neuromuscular disorders (n=10)			
Age (years)	12.31 (0.98)	12.23	10.10 – 14.53
Bone length (mm)	225.00 (14.08)	220.00	193.14 – 256.86
Cortical Density (cm^3) CoD ($mg.cm^3$)	786.65 (30.32)	792.64	718.07 – 855.23
Cortical Area (mm^3)	74.88 (5.76)	74.96	61.85 – 87.91
SSI (mm^3)[6]	143.23 (15.16)	139.43	108.95 – 177.52
Total Area (mm^2)	103.20 (7.26)	108.64	86.79 – 119.61
Compressive Bone Strength ($BSld/g/cm^4$)	0.37 (0.05)	0.34	0.25 – 0.48
Muscle Density (mg/cm^3)[4, 5, 6]	76.01 (1.00)	76.37	73.75 – 78.28
Muscle cross-sectional area (mg/cm^2)	20.32 (1.36)	18.63	17.25 – 23.39
Subcutaneous fat area (cm^2)[4]	15.82 (3.37)	13.06	8.19 – 23.45
Fat percentage (%)[a, b, c]	42.30 (2.56)	42.20	36.49 – 48.10
Mid-cortical ring density ($mg.cm^3$)	875.49 (33.37)	870.65	800.01 – 950.98
Endocortical radius (mm)	3.04 (0.15)	3.08	2.69 – 3.38
Pericortical radius (mm)	5.68 (0.21)	5.87	5.20 – 6.17
Chronic Diseases (n=143)			
Age (years)[1]	13.84 (0.23)	14.64	13.38 – 14.29
Bone length (mm)[1, 7]	239.24 (2.64)	240.00	234.02 – 244.45
Cortical Density (cm^3) CoD ($mg.cm^3$)[1]	858.93 (7.94)	857.01	843.24 – 874.62
Cortical Area (mm^3)[1]	86.89 (1.78)	87.68	83.36 – 90.41
SSI (mm^3)[1]	207.12 (6.95)	197.57	193.37 – 220.87
Total Area (mm^2)	117.77 (2.51)	114.88	112.82 – 122.72
Compressive Bone Strength ($BSld/g/cm^4$)[1]	0.52 (0.02)	0.51	0.49 – 0.55
Muscle Density (mg/cm^3)[5]	79.27 (0.17)	79.35	78.94 – 79.60
Muscle cross-sectional area (mg/cm^2)[1, 7]	21.88 (0.57)	20.47	20.75 – 23.01
Subcutaneous fat area (cm^2)[7]	9.53 (0.61)	8.03	8.33 – 10.74
Fat percentage (%)[b]	30.89 (0.91)	31.71	29.09 – 32.69
Mid-cortical ring density ($mg.cm^3$)[1]	943.72 (8.76)	949.62	926.41 – 961.03
Endocortical radius (mm)	3.18 (0.05)	3.09	3.08 – 3.27
Pericortical radius (mm)	6.06 (0.07)	6.01	5.93 – 6.19
Endocrine diseases (n=31)			
Age (years)[2]	14.51 (0.42)	14.80	13.65 – 15.36
Bone length (mm)[2]	245.48 (4.25)	250.00	236.81 – 254.16
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	874.25 (17.29)	893.41	838.93 – 909.57
Cortical Area (mm^3)[2]	92.77 (3.15)	90.72	86.33 – 99.21
SSI (mm^3)[2, 6]	229.59 (12.47)	220.64	204.12 – 255.05
Total Area (mm^2)[2]	126.06 (4.74)	121.12	116.37 – 135.74

Compressive Bone Strength (BSld/g/cm^4)[2]	0.57 (0.03)	0.54	0.50 – 0.64
Muscle Density (mg/cm^3)[6]	79.69 (0.53)	79.83	78.61 – 80.77
Muscle cross-sectional area (mg/cm^2)	21.17 (1.20)	20.97	18.71 – 23.63
Subcutaneous fat area (cm^2)[8]	9.31 (1.57)	6.42	6.10 – 12.52
Fat percentage (%)[c]	28.75 (2.38)	24.41	23.89 – 33.60
Mid-cortical ring density (mg.cm^3)[2]	950.05 (19.16)	962.64	910.92 – 989.19
Endocortical radius (mm)	3.31 (0.11)	3.25	3.08 – 3.54
Pericortical radius (mm)[2]	6.19 (0.12)	6.19	6.05 – 6.53
Inborn Errors of metabolism (n=2)			
Age (years)	11.16 (0.76)	11.16	1.56 – 20.75
Bone length (mm)	205.00 (25.00)	205.00	-112.66 – 522.66
Cortical Density (cm^3) CoD (mg.cm^3)	767.50 (48.13)	767.50	155.90 – 1379.11
Cortical Area (mm^3)	61.76 (24.96)	61.76	-255.39 – 378.91
SSI (mm^3)	106.75 (59.54)	106.75	-649.83 – 863.33
Total Area (mm^2)	82.72 (37.12)	82.72	-388.93 – 554.37
Compressive Bone Strength (BSld/g/cm^4)	0.27 (0.07)	0.27	-0.56 – 1.11
Muscle Density (mg/cm^3)	79.36 (2.34)	79.36	49.60 – 109.11
Muscle cross-sectional area (mg/cm^2)	15.51 (4.85)	15.51	-46.12 – 77.14
Subcutaneous fat area (cm^2)	3.45 (0.03)	3.45	3.03 – 3.87
Fat percentage (%)	24.42 (4.39)	24.42	-31.40 – 80.24
Mid-cortical ring density (mg.cm^3)	845.05 (103.13)	845.05	-465.28 – 2155.39
Endocortical radius (mm)	2.53 (0.75)	2.53	-7.06 – 12.12
Pericortical radius (mm)	4.99 (1.18)	4.99	-10.00 – 19.99
Iatrogenic (n=6)			
Age (years)	13.57 (1.62)	15.29	9.41 – 17.74
Bone length (mm)	224.17 (10.36)	225.00	197.53 – 250.80
Cortical Density (cm^3) CoD (mg.cm^3)	866.62 (50.25)	858.91	737.46 – 995.78
Cortical Area (mm^3)	82.37 (4.93)	80.24	69.70 – 95.04
SSI (mm^3)	172.15 (19.94)	172.73	120.89 – 223.42
Total Area (mm^2)	104.67 (5.70)	104.88	90.01 – 119.33
Compressive Bone Strength (BSld/g/cm^4)	0.53 (0.09)	0.52	0.31 – 0.75
Muscle Density (mg/cm^3)	79.19 (1.01)	79.57	76.59 – 81.79
Muscle cross-sectional area (mg/cm^2)	18.76 (2.11)	16.73	13.34 – 24.18
Subcutaneous fat area (cm^2)	8.43 (2.83)	5.70	1.16 – 15.71
Fat percentage (%)	31.74 (4.30)	30.27	20.70 – 42.78
Mid-cortical ring density (mg.cm$_3$)	958.36 (52.04)	945.73	824.58 – 1092.13
Endocortical radius (mm)	2.84 (0.13)	2.91	2.51 – 3.16
Pericortical radius (mm)	5.74 (0.16)	5.77	5.33 – 6.15
Low Motor Competence (AMPitup Dataset) (n=45)			
Age (years)[3]	14.31 (0.20)	14.07	13.91 – 14.71
Bone length (mm)[3, 7]	258.67 (3.29)	260.00	252.03 – 265.30
Cortical Density (cm^3) CoD (mg.cm^3)[3]	853.20 (10.27)	851.45	832.50 – 873.89
Cortical Area (mm^3)[3]	92.18 (2.25)	90.72	87.66 – 96.71
SSI (mm^3)[3]	212.81 (8.91)	207.39	194.84 – 230.77
Total Area (mm^2)[3]	124.39 (3.73)	124.00	116.88 – 131.90
Compressive Bone Strength (BSld/g/cm^4)[3]	0.53 (0.02)	0.54	0.49 – 0.57
Muscle Density (mg/cm^3)	78.50 (0.68)	78.75	77.12 – 79.88
Muscle cross-sectional area (mg/cm^2)[3, 7]	24.87 (1.08)	23.51	22.68 – 27.05
Subcutaneous fat area (cm^2)[3, 7, 8]	12.46 (0.83)	12.66	10.79 – 14.14
Fat percentage (%)	33.59 (1.50)	35.24	30.56 – 36.63
Mid-cortical ring density (mg.cm^3)	912.49 (11.80)	907.13	888.71 – 936.28
Endocortical radius (mm)	3.27 (0.09)	3.06	3.09 – 3.45
Pericortical radius (mm)[3]	6.25 (0.09)	6.27	6.07 – 6.44

All variables are not normally distributed, except for fat percentage ($p = 0.307$). A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$); total area ($p = 0.001$); muscle density ($p = 0.006$); pericortical radius ($p = 0.001$), except for endocortical radius ($p = 0.482$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Chronic Diseases; 6. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 7. Significant difference between Low Motor Competence and Chronic Diseases; 8. Significant difference between Low Motor Competence and Endocrine Diseases. A Bonferroni test reported significant disease group differences for fat percentage ($p = 0.007$). **Normally distributed: Fat Percentage:** a. Significant difference between Control and Neuromuscular Disorders; b. Significant difference between Neuromuscular Disorders and Chronic Diseases; c. Significant difference between Neuromuscular Disorders and Endocrine Diseases.

Supplementary Table 11. pQCT Tibia 66% Characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=591)			
Age (years)	12.36 (0.14)	12.67	12.08 – 12.64
Bone length (mm)	337.95 (2.21)	340.00	333.61 – 342.29
Cortical Density (cm^3) CoD ($mg.cm^3$)	856.67 (3.35)	856.93	850.10 – 863.25
Cortical Area (mm^3)	295.59 (3.97)	290.24	287.78 – 303.40
SSI (mm^3)	1598.87 (31.99)	1492.04	1536.04 – 1661.70
Total Area (mm^2)	472.77 (6.36)	468.32	460.28 – 485.25
Compressive Bone Strength ($BSld/g/cm^4$)	1.54 (0.03)	1.43	1.48 – 1.59
Muscle Density (mg/cm^3)	78.09 (0.13)	78.70	77.82 – 78.35
Muscle cross-sectional area (mg/cm^2)	45.37 (0.66)	42.77	44.07 – 46.67
Subcutaneous fat area (cm^2)	20.36 (0.55)	16.73	19.28 – 21.44
Fat percentage (%)	29.63 (0.40)	95.58	28.84 – 30.42
Mid-cortical ring density ($mg.cm^3$)	999.48 (3.58)	1001.91	992.45 – 1006.51
Endocortical radius (mm)	7.37 (0.06)	7.28	7.25 – 7.49
Pericortical radius (mm)	11.99 (0.08)	12.08	11.83 – 12.15
Control (Griffiths Dataset) (n=231)			
Age (years)[1, 2, 3]	11.32 (0.25)	10.35	10.84 – 11.81
Bone length (mm)[1, 3]	326.38 (3.38)	320.00	319.72 – 333.04
Cortical Density (cm^3) CoD ($mg.cm^3$)[a, b]	835.82 (4.32)	827.87	827.30 – 844.33
Cortical Area (mm^3)[3, 4]	292.87 (6.13)	279.50	280.80 – 304.94
SSI (mm^3)[3, 4]	1525.81 (50.71)	1299.05	1425.89 – 1625.73
Total Area (mm^2)[3, 4]	455.27 (9.11)	432.00	437.32 – 473.23
Compressive Bone Strength ($BSld/g/cm^4$)[3, 4]	1.48 (0.04)	1.30	1.40 – 1.57
Muscle Density (mg/cm^3)[1, 4]	23.17 (0.56)	21.89	22.08 – 24.26
Muscle cross-sectional area (mg/cm^2)[3]	113.54 (2.79)	107.50	108.04 – 119.03
Subcutaneous fat area (cm^2)[1, 2, 3, 4]	16.22 (0.48)	14.16	15.27 – 17.16
Fat percentage (%)[3, 4]	27.23 (0.40)	27.34	26.45 – 28.01
Mid-cortical ring density ($mg.cm_3$)	991.91 (4.73)	984.00	982.60 – 1001.22
Endocortical radius (mm)[3]	7.13 (0.08)	7.04	6.98 – 7.28
Pericortical radius (mm)[c, d]	11.81 (0.11)	11.63	11.58 – 12.03
Neuromuscular disorders (n=17)			
Age (years)	11.80 (0.70)	11.76	10.31 – 13.30
Bone length (mm)[5]	300.29 (14.02)	305.00	270.58 – 330.00
Cortical Density (cm^3) CoD ($mg.cm^3$)	887.07 (23.29)	891.71	837.70 – 936.44
Cortical Area (mm^3)[4, 5, 6, 7, 8]	172.32 (17.01)	148.63	136.27 – 208.37
SSI (mm^3)[4, 5, 6, 7, 8]	782.71 (116.49)	580.11	535.77 – 1029.65
Total Area (mm^2)[4, 5, 6, 7, 8]	297.31 (33.32)	238.72	226.67 – 367.95
Compressive Bone Strength ($BSld/g/cm^4$)[4, 5, 6, 7, 8]	0.88 (0.09)	0.81	0.69 – 1.07
Muscle Density (mg/cm^3)[4, 8]	14.29 (2.70)	12.10	8.56 – 20.01
Muscle cross-sectional area (mg/cm^2)[5]	92.24 (14.11)	72.48	62.34 – 122.15
Subcutaneous fat area (cm^2)[4]	31.20 (6.10)	26.11	18.17 – 44.13
Fat percentage (%)[4, 6]	46.46 (5.10)	36.89	35.64 – 57.28
Mid-cortical ring density ($mg.cm^3$)	1016.60 (21.39)	1037.20	971.25 – 1061.94
Endocortical radius (mm)[5, 7]	6.01 (0.45)	5.36	5.06 – 6.95
Pericortical radius (mm)[d, e, f, g, h]	9.40 (0.55)	8.71	8.24 – 10.56
Chronic Diseases (n=228)			
Age (years)[1]	12.83 (0.22)	13.34	12.40 – 13.26
Bone length (mm)[1, 9]	340.73 (3.52)	350.00	333.79 – 347.66
Cortical Density (cm^3) CoD ($mg.cm^3$)[a]	870.17 (5.65)	883.24	859.05 – 881.29
Cortical Area (mm^3)[6, 9]	293.12 (6.58)	288.64	280.16 – 306.08
SSI (mm^3)[6, 9]	1614.54 (52.44)	1549.92	1511.21 – 1717.87
Total Area (mm^2)[6, 9]	475.51 (10.90)	472.00	454.03 – 496.99
Compressive Bone Strength ($BSld/g/cm^4$)[6]	1.56 (0.05)	1.54	1.47 – 1.65
Muscle Density (mg/cm^3)[1]	19.79 (0.70)	17.66	18.40 – 21.18
Muscle cross-sectional area (mg/cm^2)[9]	124.06 (3.75)	116.48	116.68 – 131.45
Subcutaneous fat area (cm^2)[1, 9]	21.71 (1.05)	16.96	19.64 – 23.78
Fat percentage (%)[6]	30.26 (0.10)	28.62	28.88 – 31.65
Mid-cortical ring density ($mg.cm^3$)	1003.88 (6.37)	1015.33	991.34 – 1016.43
Endocortical radius (mm)[9]	7.43 (0.11)	7.33	7.22 – 7.64
Pericortical radius (mm)[f, i]	12.01 (0.14)	12.15	11.73 – 12.28
Endocrine diseases (n=48)			
Age (years)[2]	13.36 (0.46)	14.50	12.42 – 14.29
Bone length (mm)[10]	343.96 (7.01)	350.00	329.86 – 358.06
Cortical Density (cm^3) CoD ($mg.cm^3$)[b]	880.71 (14.24)	894.25	852.06 – 909.36
Cortical Area (mm^3)[7]	300.83 (11.86)	307.84	276.98 – 324.68
SSI (mm^3)[7]	1664.20 (97.64)	1671.29	1467.77 – 1860.63
Total Area (mm^2)[7]	489.66 (19.76)	488.88	449.91 – 529.41

Compressive Bone Strength (BSld/g/cm^4)[7]	1.65 (0.10)	1.70	1.45 – 1.85
Muscle Density (mg/cm^3)	20.53 (1.68)	18.15	17.16 – 23.91
Muscle cross-sectional area (mg/cm^2)	131.82 (9.62)	123.52	112.48 – 151.16
Subcutaneous fat area (cm^2)[2, 10]	22.19 (1.88)	20.47	18.41 – 25.97
Fat percentage (%)	30.93 (1.57)	31.20	27.78 – 34.09
Mid-cortical ring density (mg.cm^3)	1016.37 (14.14)	1037.01	987.92 – 1044.81
Endocortical radius (mm)[7]	7.60 (0.23)	7.49	7.14 – 8.06
Pericortical radius (mm)[g, j]	12.25 (0.25)	12.37	11.73 – 12.76
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.40	5.70 – 14.86
Bone length (mm)[11]	315.00 (37.55)	310.00	210.74 – 419.26
Cortical Density (cm^3) CoD (mg.cm^3)	784.20 (40.52)	815.58	671.71 – 896.70
Cortical Area (mm^3)	228.80 (43.94)	177.12	107.64 – 349.95
SSI (mm^3)	1198.86 (406.53)	681.16	70.15 – 2327.57
Total Area (mm^2)	416.35 (82.78)	339.36	186.51 – 646.19
Compressive Bone Strength (BSld/g/cm^4)	0.94 (0.23)	0.80	0.30 – 1.59
Muscle Density (mg/cm^3)	24.15 (2.90)	22.68	16.09 – 32.31
Muscle cross-sectional area (mg/cm^2)	128.86 (28.24)	100.48	50.45 – 207.28
Subcutaneous fat area (cm^2)[11]	12.04 (2.90)	10.13	3.98 – 20.10
Fat percentage (%)	26.96 (1.90)	28.56	21.68 – 32.25
Mid-cortical ring density (mg.cm^3)	916.45 (47.76)	916.40	783.84 – 1049.05
Endocortical radius (mm)	7.51 (0.79)	7.11	5.31 – 9.71
Pericortical radius (mm)	11.24 (1.04)	10.36	8.34 – 14.13
Iatrogenic (n=12)			
Age (years)	13.35 (0.96)	14.47	11.24 – 15.46
Bone length (mm)	343.75 (12.56)	337.50	316.12 – 371.38
Cortical Density (cm^3) CoD (mg.cm^3)	864.47 (30.35)	853.39	797.67 – 931.27
Cortical Area (mm^3)[8]	320.16 (26.13)	317.92	262.65 – 377.67
SSI (mm^3)[8]	1718.33 (179.64)	1745.00	1322.95 – 2113.71
Total Area (mm^2)[8]	501.39 (35.94)	482.96	422.29 – 580.48
Compressive Bone Strength (BSld/g/cm^4)[8]	1.73 (0.19)	1.45	1.31 – 2.16
Muscle Density (mg/cm^3)[8]	26.57 (4.43)	27.32	16.82 – 26.29
Muscle cross-sectional area (mg/cm^2)	103.68 (16.56)	97.04	67.22 – 140.13
Subcutaneous fat area (cm^2)	19.51 (2.85)	19.58	13.23 – 25.79
Fat percentage (%)	29.29 (2.34)	31.44	24.13 – 34.45
Mid-cortical ring density (mg.cm^3)	1015.00 (34.30)	1051.35	939.50 – 1090.49
Endocortical radius (mm)	7.48 (0.38)	7.43	6.65 – 8.31
Pericortical radius (mm)[h]	12.45 (0.45)	12.23	11.45 – 13.45
Low Motor Competence (AMPitup Dataset) (n=50)			
Age (years)[3]	14.27 (0.19)	13.96	13.88 – 14.66
Bone length (mm)[3, 5, 9, 10, 11]	387.90 (4.88)	390.00	378.09 – 397.71
Cortical Density (cm^3) CoD (mg.cm^3)	863.88 (11.19)	868.76	841.38 – 886.37
Cortical Area (mm^3)[3, 5, 9]	356.71 (10.90)	341.44	334.80 – 378.62
SSI (mm^3)[3, 5, 9]	2101.36 (89.71)	2044.44	1921.09 – 2281.63
Total Area (mm^2)[3, 5, 9]	586.44 (18.04)	568.56	550.19 – 622.69
Compressive Bone Strength (BSld/g/cm^4)[3, 5]	1.81 (0.08)	1.75	1.66 – 1.97
Muscle Density (mg/cm^3)	19.39 (15.0)	19.09	16.37 – 22.40
Muscle cross-sectional area (mg/cm^2)[3, 5, 9]	158.24 (9.46)	140.72	139.24 – 177.25
Subcutaneous fat area (cm^2)[3, 9, 10, 11]	29.23 (1.65)	27.68	25.92 – 32.55
Fat percentage (%)[3]	31.46 (1.08)	31.72	29.30 – 33.63
Mid-cortical ring density (mg.cm$_3$)	995.50 (11.80)	1009.37	971.80 – 1019.21
Endocortical radius (mm)[3, 5, 9]	8.42 (0.20)	8.33	8.02 – 8.82
Pericortical radius (mm)[c, e, i, j]	13.44 (0.20)	13.31	13.03 – 13.85

All variables are not normally distributed, except for cortical density ($p = 0.164$) and pericortical radius ($p = 0.681$). A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$); mid-cortical density ($p = 0.008$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Control and Neuromuscular Disorders; 5. Significant difference between Neuromuscular Disorders and Low Motor Competence; 6. Significant difference between Neuromuscular Disorders and Chronic Diseases; 7. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 8. Significant difference between Neuromuscular Disorders and Iatrogenic; 9. Significant difference between Low Motor Competence and Chronic Diseases; 10. Significant difference between Low Motor Competence and Endocrine Diseases; 11. Significant difference between Low Motor Competence and Inborn Errors of Metabolism. A Bonferroni test reported significant disease group differences for cortical density ($p < 0.001$) and pericortical radius ($p < 0.001$). **Normally distributed: Cortical Density:** a. Significant difference between Control and Chronic Diseases; b. Significant difference between Control and Endocrine Diseases. **Pericortical Density:** c. Significant difference between Control and Low Motor

Competence; d. Significant difference between Control and Neuromuscular Disorders; e. Significant difference between Neuromuscular Disorders and Low Motor Competence; f. Significant difference between Neuromuscular Disorders and Chronic Diseases; g. Significant difference between Neuromuscular Disorders and Endocrine Diseases; h. Significant difference between Neuromuscular Disorders and Iatrogenic; i. Significant difference between Low Motor Competence and Chronic Diseases; j. Significant difference between Low Motor Competence and Endocrine Diseases.

Supplementary Table 12. pQCT Ulna 66% Descriptive characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=421)			
Age (years)	12.40 (0.17)	12.86	12.07 – 12.72
Bone length (mm)	232.35 (1.59)	232.62	229.23 – 235.47
Cortical Density (cm^3) CoD ($mg.cm^3$)	832.07 (5.01)	823.80	822.22 – 841.93
Cortical Area (mm^3)	110.32 (1.38)	106.40	107.62 – 113.03
SSI (mm^3)	262.11 (5.11)	239.73	252.06 – 272.16
Total Area (mm^2)	139.90 (1.65)	135.20	136.66 – 143.13
Compressive Bone Strength ($BSld/g/cm^4$)	0.66 (0.01)	0.65	0.63 – 0.69
Mid-cortical ring density ($mg.cm^3$)	941.75 (5.15)	938.46	931.62 – 952.88
Endocortical radius (mm)	3.30 (0.02)	3.25	3.25 – 3.34
Pericortical radius (mm)	6.61 (0.04)	6.56	6.53 – 6.68
Control (Griffiths Dataset) (n=188)			
Age (years)[1, 2, 3]	10.69 (0.25)	10.21	10.20 – 11.19
Bone length (mm)[1, 2, 3]	221.59 (2.27)	217.50	217.11 – 226.06
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3, a]	793.12 (6.95)	777.78	779.41 – 806.83
Cortical Area (mm^3)[2, 3]	106.20 (1.99)	100.38	102.28 – 110.11
SSI (mm^3)[1, 2, 3]	245.43 (7.59)	222.12	230.46 – 260.40
Total Area (mm^2)	136.04 (2.33)	131.75	131.45 – 140.64
Compressive Bone Strength ($BSld/g/cm^4$)[1, 2, 3]	0.58 (0.02)	0.49	0.54 – 0.62
Mid-cortical ring density ($mg.cm^3$)	921.45 (6.87)	912.60	907.91 – 935.00
Endocortical radius (mm)	3.27 (0.03)	3.27	3.21 – 3.34
Pericortical radius (mm)	6.52 (0.05)	6.44	6.42 – 6.63
Neuromuscular disorders (n=11)			
Age (years)	12.42 (0.86)	12.76	10.50 – 14.35
Bone length (mm)	227.27 (12.73)	230.00	198.91 – 255.63
Cortical Density (cm^3) CoD ($mg.cm^3$)	803.32 (28.86)	807.89	739.02 – 867.61
Cortical Area (mm^3)	96.00 (5.79)	101.28	83.11 – 108.89
SSI (mm^3)	211.73 (18.00)	209.08	171.63 – 251.83
Total Area (mm^2)	128.23 (7.72)	133.44	111.03 – 145.44
Compressive Bone Strength ($BSld/g/cm^4$)[4, 5]	0.50 (0.06)	0.46	0.38 – 0.63
Mid-cortical ring density ($mg.cm^3$)	895.04 (37.85)	935.53	810.71 – 979.36
Endocortical radius (mm)	3.27 (0.15)	3.31	2.95 – 3.60
Pericortical radius (mm)	6.33 (0.20)	6.52	5.88 – 6.77
Chronic Diseases (n=144)			
Age (years)[1]	13.64 (0.23)	14.52	13.18 – 14.10
Bone length (mm)[1, 6]	237.16 (2.65)	240.00	231.92 – 242.40
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, a]	864.11 (8.48)	874.33	847.34 – 880.88
Cortical Area (mm^3)	112.69 (2.52)	111.76	107.70 – 117.68
SSI (mm^3)[1]	276.52 (9.39)	257.46	257.94 – 295.08
Total Area (mm^2)	142.68 (3.11)	137.68	136.53 – 148.83
Compressive Bone Strength ($BSld/g/cm^4$)[1]	0.72 (0.02)	0.74	0.68 – 0.77
Mid-cortical ring density ($mg.cm^3$)	966.65 (9.22)	976.76	948.43 – 984.88
Endocortical radius (mm)	3.34 (0.05)	3.24	3.24 – 3.43
Pericortical radius (mm)	6.66 (0.07)	6.62	6.52 – 6.80
Endocrine diseases (n=30)			
Age (years)[2]	14.32 (0.48)	14.73	13.34 – 15.29
Bone length (mm)[2]	244.33 (4.33)	250.00	235.47 – 253.20
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	881.21 (18.46)	887.27	843.45 – 918.97
Cortical Area (mm^3)[2]	119.17 (3.93)	117.36	111.13 – 127.21
SSI (mm^3)[2]	291.94 (15.13)	281.89	261.00 – 322.88
Total Area (mm^2)	146.17 (4.43)	143.92	137.10 – 155.23
Compressive Bone Strength ($BSld/g/cm^4$)[2, 5]	0.80 (0.04)	0.81	0.71 – 0.89
Mid-cortical ring density ($mg.cm^3$)	980.02 (22.42)	984.53	934.16 – 1025.88
Endocortical radius (mm)	3.32 (0.07)	3.27	3.18 – 3.47
Pericortical radius (mm)	6.78 (0.10)	6.74	6.57 – 6.99
Inborn Errors of metabolism (n=2)			
Age (years)	11.15 (0.76)	11.15	1.55 – 20.75
Bone length (mm)	205.00 (25.00)	205.00	-112.66 – 522.66
Cortical Density (cm^3) CoD ($mg.cm^3$)	802.51 (1.17)	802.51	787.66 – 817.36
Cortical Area (mm^3)	74.40 (37.28)	74.40	-399.29 – 548.09
SSI (mm^3)	138.33 (83.50)	138.33	-922.66 – 1199.31
Total Area (mm^2)	90.32 (40.88)	90.32	-429.11 – 609.75
Compressive Bone Strength ($BSld/g/cm^4$)	0.41 (0.22)	0.41	-2.42 – 3.24
Mid-cortical ring density ($mg.cm^3$)	851.46 (62.01)	851.46	63.50 – 1639.42
Endocortical radius (mm)	2.51 (0.51)	2.51	-3.97 – 8.99
Pericortical radius (mm)	5.21 (1.23)	5.21	-10.48 – 20.89
Iatrogenic (n=5)			
Age (years)	13.98 (1.89)	15.15	8.74 – 19.22
Bone length (mm)	228.00 (13.00)	225.00	191.91 – 264.09
Cortical Density (cm^3) CoD ($mg.cm^3$)	926.73 (46.66)	924.50	797.18 – 1056.29
Cortical Area (mm^3)	96.42 (6.35)	95.68	78.79 – 114.04

SSI (mm^3)	231.85 (30.54)	219.04	147.06 – 316.64
Total Area (mm^2)	123.14 (8.51)	120.96	99.51 – 146.77
Compressive Bone Strength (BSld/g/cm^4)	0.68 (0.07)	0.61	0.48 – 0.89
Mid-cortical ring density (mg.cm^3)	1050.40 (52.52)	1078.31	904.59 – 1196.29
Endocortical radius (mm)	3.09 (0.16)	2.99	2.66 – 3.52
Pericortical radius (mm)	6.21 (0.22)	6.19	5.60 – 6.82
Low Motor Competence (AMPitup Dataset) (n=41)			
Age (years)[3]	14.30 (0.21)	14.02	13.88 – 14.72
Bone length (mm)[3, 6]	259.27 (3.46)	260.00	252.28 – 266.26
Cortical Density (cm^3) CoD (mg.cm^3)[3]	859.82 (12.14)	863.02	835.28 – 884.36
Cortical Area (mm^3)[3]	121.74 (4.01)	115.68	113.63 – 129.85
SSI (mm_3)[3]	289.42 (13.77)	263.94	261.59 – 317.25
Total Area (mm_2)	150.81 (5.12)	141.76	140.46 – 161.16
Compressive Bone Strength (BSld/g/cm^4)[3, 4]	0.76 (0.03)	0.71	0.70 – 8.22
Mid-cortical ring density (mg.cm^3)	923.00 (13.64)	951.67	895.43 – 950.57
Endocortical radius (mm)	3.35 (0.07)	3.35	3.21 – 3.48
Pericortical radius (mm)	6.88 (0.11)	6.72	6.65 – 7.11

All variables are not normally distributed, except for mid-cortical density ($p = 0.167$). A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$); total area ($p = 0.015$); pericortical radius ($p = 0.016$), except for endocortical radius ($p = 0.531$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4. Significant difference between Neuromuscular Disorders and Low Motor Competence; 5. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 6. Significant difference between Low Motor Competence and Chronic Diseases. A Bonferroni test reported significant disease group differences for mid-cortical density ($p < 0.001$). **Normally distributed: Cortical Density:** a. Significant difference between Control and Chronic Diseases.

Supplementary Table 13. pQCT Fibula 66% Characteristics for total sample and disease groups.

	Mean (SD)	Median	95% CI
Total (n=587)			
Age (years)	12.41 (0.14)	12.75	12.13 – 12.69
Bone length (mm)	339.02 (2.21)	340.00	334.69 – 343.35
Cortical Density (cm^3) CoD ($mg.cm^3$)	830.85 (3.85)	827.42	823.28 – 838.42
Cortical Area (mm^3)	63.42 (0.89)	61.76	61.66 – 65.18
SSI (mm^3)	97.80 (2.34)	83.96	93.20 – 102.39
Total Area (mm^2)	71.41 (1.08)	68.00	69.28 – 73.53
Compressive Bone Strength ($BSld/g/cm^4$)	0.42 (0.01)	0.38	0.41 – 0.44
Pericortical radius (mm)	4.61 (0.03)	4.56	4.54 – 4.68
Mid-cortical density ($mg.cm^3$)	948.51 (4.94)	951.29	938.81 – 958.20
Control (Griffiths Dataset) (n=232)			
Age (years)[1, 2, 3]	11.32 (0.25)	10.35	10.83 – 11.80
Bone length (mm)[1, 3]	326.50 (3.37)	322.50	319.87 – 333.14
Cortical Density (cm^3) CoD ($mg.cm^3$)[1, 2, 3]	808.84 (5.03)	803.13	798.94 – 818.74
Cortical Area (mm^3)[3]	62.01 (1.44)	56.13	59.17 – 64.86
SSI (mm^3)[3]	91.87 (3.95)	72.46	84.08 – 99.66
Total Area (mm^2)[3]	68.59 (1.69)	62.25	65.26 – 71.92
Compressive Bone Strength ($BSld/g/cm^4$)[3]	0.40 (0.01)	0.33	0.37 – 0.42
Pericortical radius (mm)[3]	4.52 (0.05)	4.37	4.42 – 4.63
Mid-cortical density ($mg.cm^3$)[1, 2, 3]	919.00 (6.38)	908.04	906.44 – 931.57
Neuromuscular disorders (n=17)			
Age (years)	11.94 (0.75)	11.76	10.35 – 13.53
Bone length (mm)[4]	300.29 (14.02)	305.00	270.58 – 330.00
Cortical Density (cm^3) CoD ($mg.cm^3$)	833.47 (22.11)	825.15	786.61 – 838.82
Cortical Area (mm^3)[4, 5, 6]	45.69 (5.00)	48.32	35.08 – 56.29
SSI (mm^3)[4, 6]	62.08 (9.65)	61.39	41.62 – 82.55
Total Area (mm^2)[4, 6]	51.60 (5.70)	54.56	39.52 – 63.69
Compressive Bone Strength ($BSld/g/cm^4$)[4, 6]	0.31 (0.04)	0.28	0.21 – 0.40
Pericortical radius (mm)[5, 6]	3.83 (0.23)	3.90	3.33 – 4.32
Mid-cortical density ($mg.cm^3$)	922.58 (28.79)	939.63	861.55 – 983.62
Chronic Diseases (n=225)			
Age (years)[1]	12.96 (0.21)	13.47	12.54 – 13.38
Bone length (mm)[1, 7]	342.82 (3.48)	350.00	335.97 – 349.67
Cortical Density (cm^3) CoD ($mg.cm^3$)[1]	846.72 (6.64)	855.19	833.63 – 859.81
Cortical Area (mm^3)[5, 7]	63.34 (1.44)	62.88	60.49 – 66.18
SSI (mm^3)[7]	100.08 (3.68)	92.80	92.84 – 107.32
Total Area (mm^2)[7]	72.22 (1.81)	69.44	68.64 – 75.79
Compressive Bone Strength ($BSld/g/cm_4$)	0.44 (0.01)	0.42	0.41 – 0.46
Pericortical radius (mm)[5, 7]	4.63 (0.06)	4.62	4.51 – 4.74
Mid-cortical density ($mg.cm^3$)[1]	971.03 (8.78)	990.97	953.72 – 988.34
Endocrine diseases (n=47)			
Age (years)[2]	13.44 (0.46)	14.56	12.53 – 14.36
Bone length (mm)[8]	345.32 (6.94)	350.00	331.34 – 359.29
Cortical Density (cm^3) CoD ($mg.cm^3$)[2]	857.47 (15.96)	886.17	825.35 – 889.59
Cortical Area (mm^3)[6]	66.23 (2.74)	68.32	60.71 – 71.75
SSI (mm^3)[6]	105.68 (7.07)	101.16	91.44 – 119.92
Total Area (mm^2)[6]	75.01 (3.20)	77.12	68.56 – 81.46
Compressive Bone Strength ($BSld/g/cm^4$)[6]	0.47 (0.03)	0.45	0.41 – 0.52
Pericortical radius (mm)[6]	4.74 (0.11)	4.83	4.52 – 4.95
Mid-cortical density ($mg.cm^3$)[2]	978.76 (19.49)	1023.03	939.52 – 1018.00
Inborn Errors of metabolism (n=5)			
Age (years)	10.28 (1.65)	10.40	5.70 – 14.86
Bone length (mm)[9]	315.00 (37.55)	310.00	210.74 – 419.26
Cortical Density (cm^3) CoD ($mg.cm^3$)	721.62 (65.88)	716.47	538.71 – 904.53
Cortical Area (mm_3)[9]	40.74 (5.53)	38.72	25.38 – 56.09
SSI (mm^3)[9]	46.75 (12.34)	38.87	12.48 – 81.03
Total Area (mm^2)[9]	47.39 (5.74)	48.96	31.45 – 63.33
Compressive Bone Strength ($BSld/g/cm^4$)[9]	0.22 (0.07)	0.19	0.03 – 0.41
Pericortical radius (mm)[9]	3.83 (0.24)	3.94	3.16 – 4.50
Mid-cortical density ($mg.cm^3$)	809.79 (81.57)	771.41	583.33 – 1036.25
Iatrogenic (n=11)			
Age (years)	13.17 (0.98)	14.17	11.00 – 15.34
Bone length (mm)	344.09 (13.75)	335.00	313.46 – 374.72
Cortical Density (cm^3) CoD ($mg.cm^3$)	827.69 (36.27)	827.00	746.86 – 908.51
Cortical Area (mm^3)	64.10 (4.62)	67.36	53.80 – 74.40
SSI (mm^3)	89.07 (10.92)	91.62	64.75 – 113.39
Total Area (mm^2)	70.59 (5.66)	70.24	57.97 – 83.21

Compressive Bone Strength (BSld/g/cm^4)	0.42 (0.05)	0.37	0.32 – 0.52
Pericortical radius (mm)	4.60 (0.21)	4.64	4.13 – 5.07
Mid-cortical density (mg.cm^3)	957.38 (43.02)	972.91	861.53 – 1053.23
Low Motor Competence (AMPitup Dataset) (n=50)			
Age (years)[3]	14.28 (0.19)	13.96	13.89 – 14.67
Bone length (mm)[3, 4, 7, 8, 9]	388.50 (4.87)	390.00	378.71 – 398.29
Cortical Density (cm^3) CoD (mg.cm^3)[3]	847.27 (11.78)	859.43	823.60 – 870.94
Cortical Area (mm^3)[3, 4, 7, 9]	75.81 (2.60)	73.52	70.59 – 81.04
SSI (mm$_3$)[3, 4, 7, 9]	126.76 (7.23)	119.87	112.24 – 141.28
Total Area (mm^2)[3, 4, 7, 9]	86.74 (3.11)	83.60	80.49 – 92.99
Compressive Bone Strength (BSld/g/cm^4)[3, 4, 9]	0.50 (0.02)	0.48	0.46 – 0.55
Pericortical radius (mm)[3, 4, 7, 9]	5.11 (0.09)	5.12	4.92 – 5.30
Mid-cortical density (mg.cm^3)[3]	976.36 (13.17)	993.84	949.89 – 1002.83

All variables are not normally distributed. A Kruskal Wallis test reported significant disease group differences for all pQCT bone measures, age and bone length ($p < 0.001$). **Not normally distributed:** 1. Significant difference between Control and Chronic Diseases; 2. Significant difference between Control and Endocrine Diseases; 3. Significant difference between Control and Low Motor Competence; 4.Significant difference between Neuromuscular Disorders and Low Motor Competence; 5. Significant difference between Neuromuscular Disorders and Chronic Diseases; 6. Significant difference between Neuromuscular Disorders and Endocrine Diseases; 7. Significant difference between Low Motor Competence and Chronic Diseases; 8. Significant difference between Low Motor Competence and Endocrine Diseases; 9. Significant difference between Low Motor Competence and Inborn Errors of Metabolism.

Supplementary Table 14. Number of significant differences for each variable and bone site compared to the control group.

	Fibula 4%	**Tibia 4%**	**Ulna 4%**	**Radius 4%**	**Radius 66%**	**Tibia 66%**	**Ulna 66%**	**Fibula 66%**	**Total**	**Highest Possible Total**	**Percent**
Neuromuscular disorders	5	7	2	0	3	8	0	0	25	83	30.12
Chronic Diseases	4	5	5	5	8	5	6	4	42	83	50.60
Endocrine diseases	2	3	4	4	9	3	6	3	34	83	40.96
Inborn Errors of metabolism	0	0	0	0	0	0	0	0	0	83	0.00
Iatrogenic	0	0	0	0	0	0	0	0	0	83	0.00
Low Motor Competence (AMPitup) Dataset	7	8	7	7	10	11	6	9	65	83	78.31
Total	18	23	18	16	30	27	18	16	166		
Highest Possible Total	54	54	54	54	84	84	60	54		498	
Percent	33.33	42.59	33.33	29.63	35.71	32.14	30.00	29.63			33.33

Supplementary Table 15. Number of significant differences for each variable and bone site.

	Fibula 4%	**Tibia 4%**	**Ulna 4%**	**Radius 4%**	**Radius 66%**	**Tibia 66%**	**Ulna 66%**	**Fibula 66%**	**Total**	**Highest Possible Total**	**Percent**
Control (Griffiths Dataset)	18	23	18	16	30	27	18	16	166	498	33.33
Neuromuscular disorders	27	25	14	7	8	34	2	12	129	498	25.90
Chronic Diseases	13	16	14	10	13	19	7	11	103	498	20.68
Endocrine diseases	9	11	8	9	13	12	7	9	78	498	15.66
Inborn Errors of metabolism	0	4	0	0	0	2	0	6	12	498	2.41
Iatrogenic	2	2	1	0	0	6	0	0	11	498	2.21
Low Motor Competence (AMPitup) Dataset	19	27	21	19	14	32	8	27	167	498	33.53
Total	88	108	76	61	78	132	42	81	666		
Highest Possible Total	378	378	378	378	588	588	420	378		3486	
Percent	23.28	28.57	20.11	16.14	13.27	22.45	10.00	21.43			19.10

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ORIGINAL ARTICLE

Appendicular fracture epidemiology of children and adolescents: a 10-year case review in Western Australia (2005 to 2015)

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Abstract

Summary Fracture incidence data of Australian children and adolescents have not been reported in the literature. A 10-year case review of fracture presentations in Western Australia is provided. Between 2005 and 2015, fracture incidence increased relative to population growth. This is concerning, and interventions are required to reverse this trend.

Purpose Fracture incidence in 0–16-year-olds is high and varies between countries. Boys have a 1.5:1 ratio of fracture incidence compared to girls. There are no specific data for Australia. Western Australia is a state with unique geography and population distribution having only a single tertiary paediatric hospital (Princess Margaret Hospital, PMH, in Perth) managing the majority of children and adolescents with fractures in the Emergency Department (ED). The aims of this study were to characterise fracture presentations to PMH-ED and compare the incidence to population data.

Methods A database audit of fracture presentations between 2005 and 2015 for fracture rates with a sub-analysis for gender, fracture site and age and a comparison to Perth Metropolitan and Western Australian population data was performed.

Results Analysis included 31,340 presentations. Fracture incidence, adjusted for the annual population size, increased from 0.63% in 2005 to 0.85% in 2015 ($p < 0.001$). The month of May reported the highest fracture rate ($p < 0.001$) corresponding with the start of the winter sports season. Males had a 1.5 times higher fracture incidence than females ($p < 0.001$), with upper limb fractures three times more common than lower limb fractures ($p < 0.001$). Fracture incidence increased with age until the early teenage years (15 years for males; 12 years for females) when a decline occurred.

Conclusions Increased fracture incidence in Western Australia between 2005 and 2015 identifies a concerning trend for bone health in children and adolescents. Further research is needed to identify potential lifestyle factors that impact fracture incidence translating into evidence-based strategies to reverse these trends and improve bone health.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11657-018-0478-9) contains supplementary material, which is available to authorized users.

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Original Article

Reliability of upper-limb diaphyseal mineral and soft-tissue measurements using peripheral Quantitative Computed Tomography (pQCT)

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Abstract

Objectives: To quantify between-day reliability of upper-body diaphyseal measurements (radius, ulna, humerus) using peripheral Quantitative Computed Tomography (pQCT). **Methods:** Fourteen males (age: 25.8±2.3 years,) underwent repeat pQCT scans (one to two days apart) at mid-shaft ulna (60%), mid-shaft radius (60%) and mid-shaft humerus (50%) cross-sections of the non-dominant limb. Intraclass correlation coefficients (ICC) and coefficients of variation (CV) were determined for musculoskeletal morphology variables. **Results:** Reliability was excellent (ICC: 0.76–0.99; CV: 1.3–7.3) at all sites for bone mass, stress-strain index, endocortical and pericortical radius, endocortical volumetric bone mineral density (vBMD), muscle area, total area, non-cortical area, and cortical area. Reliability was good to excellent (ICC: 0.58–0.80; CV: 0.6–3.7) for polar vBMD and mid-cortical vBMD; fair to excellent (ICC: 0.30–0.88; CV: 0.5–8.0) for muscle density and cortical density; and fair to good (ICC: 0.25–0.60; CV: 3.4–7.6) for pericortical vBMD. Average reliability across the three sites was excellent (ICC ≥0.77; CV ≤8.0). **Conclusions:** Overall between-day reliability of pQCT was excellent for the mid-shaft ulna, radius and humerus. pQCT provides a reliable and feasible body composition and skeletal morphology assessment tool for upper limb longitudinal investigations in scientific and clinic settings.

Keywords: Bone, Ulna, Humerus, Radius, Reliability

Introduction

Peripheral Quantitative Computed Tomography (pQCT) produces a series of two-dimensional scans reconstructed to provide a three-dimensional image at specific cross-sections to determine volumetric measures of bone material, structure and strength, along with muscle and fat morphology of the upper and lower limbs[1-3]. The clinical utility of pQCT to assess segmental tissue composition, the effects of bone disease(s), and osteogenic adaptations due to exercise and growth is increasing[2], thus it is important to quantify the reliability of pQCT at various sites and across commonly assessed variables in order to determine which measures provide consistent and dependable results[4]. If pQCT results are unreliable, incorrect measurements may lead to misdiagnoses, false-positive or false-negative outcomes due to scan variability, and may compromise the ability of clinicians and researchers to accurately assess the efficacy of interventions.

Few studies have described the reliability of pQCT measures[5,6], principally focusing on isolated lower limb sites. Specifically, excellent reliability for cortical and trabecular bone mineral density and stress strain index (SSI) was observed when scanning the second metatarsal of cadavers[5]; and for bone mineral density in the subchondral

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The bone health of Western Australian adolescents with neuromuscular disorders, chronic diseases and low motor competence are different to healthy controls.

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Aim

To determine differences in bone health between Western Australian adolescents with neuromuscular disorders, chronic diseases, endocrine diseases, inborn errors of metabolism, iatrogenic disease, and low motor competence, compared to healthy controls.

Participants[a]

Griffith data set (healthy controls)

- Healthy age matched controls.
- n = 244; age = 11.4 ± 0.2 years; 54% boys.

AMPitup data set (low motor competence)

- Motor competence - McCarron Assessment of Neuromuscular Development (MAND)[2].
- Mild motor disability and/or history of movement difficulties [1].
- n = 51; age = 14.2 ± 0.2 years; 67 % boys.

Disease groups[3]

- Neuromuscular Disorders: Cerebral Palsy, Duchenne Muscular Dystrophy
  n = 26; age = 11.8 ± 0.76 years; 50% boys.
- Chronic Diseases: Leukemia, Cystic Fibrosis
  n = 235; age = 12.6 ± 0.2 years; 36% boys.
- Endocrine Diseases Hyperthyroidism, Delayed Puberty
  n = 54; age = 13.5 ± 0.4 years; 28% boys.
- Inborn errors of metabolism: Protein Intolerance, Galactosaemia
  n = 5; age = 10.3 ± 1.7 years; 60% boys.
- Iatrogenic: Glucocorticoids, Radiotherapy
  n = 12; age = 12.9 ± 0.9 years; 42% boys.

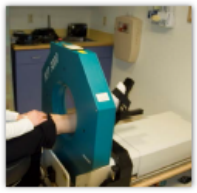
Results

Overall group differences were **significant for:**

- Cortical area, muscle density, subcutaneous fat area, fat percentage and mid-cortical density for all sites.
- Cortical density only at Tibia 4% and Fibula 4%.

Not significant for muscle area, mid-cortical ring density and endocortical radius in all sites where variables were measured[b].

Method



- Peripheral Quantitative Computed Tomography (pQCT).
- Volumetric scans on dominant limbs.
- Bone sites: 4% and 66%:
  - forearm (ulna and radius)
  - lower leg (tibia and fibula).
- 67 muscle-bone measurements computed.

Statistical analysis

General Linear Models (GLM) controlling for age, gender and bone length with Bonferroni adjustment.

GLMs across muscle and bone measures

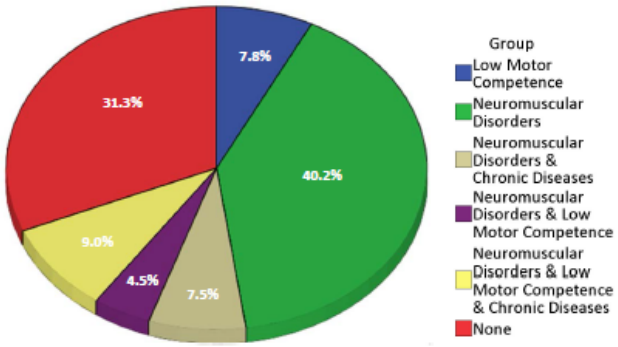


Figure 1. Percentage of significant GLM group differences.

- GLM analysis reported **significant group differences for 68.7%** of all muscle and bone measures (Figure 1).
  - Neuromuscular disorders represented 61% overall.
  - Chronic diseases and low motor competence the only other significant group difference to healthy controls.
- **No group differences** were reported for endocrine diseases, inborn errors of metabolism and iatrogenic groups.
- **Tibia 4% and Fibula 4% sites** had significant group differences across all available muscle and bone measurements.

Discussion

- Neuromuscular disorders, multiple chronic diseases and low motor competence effect the tibia greatly by decreasing the amount of weight bearing to the lower body.
- A lack of significant differences suggest that Fibula 66% bone loading is not as integral for bone adaptation as with the Tibia 66%.
- Lower scores for the Tibia for neuromuscular disorders, chronic diseases and low motor competence groups suggest that the decreased loading to the lower limbs explain the decreased bone adaptation evident in the data.
- Neuromuscular disorders can also limit healthy rates of upper body movement, which may also account for the poorer forearm bone characteristics in this group.

Conclusion

These findings demonstrate a strong positive correlation between neuromuscular competence and bone health. Detailed characterisation of peripheral bone health reveals potential areas for targeted exercise intervention.

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Footnote:
a Sample size drawn varied across groups for muscle and bone measures.
b These measurements were not made for Tibia 4% or Fibula 4%

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Science, Health and Community

MEDIA – The West Australian Newspaper – 4th February 2018. :

Osteoprosis shock for WA children

The image of this newspaper story is not included in this version of the thesis

MEDIA – PerthNow (Sunday Times) and News.com.au

Lifestyle blamed for kids fracture rise

The image of this news story is not included in this version of the thesis