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Nicolas H. Hart
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BONE STRENGTH, LOAD TOLERANCE AND INJURY RISK IN ELITE AUSTRALIAN FOOTBALL

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MSc, CSCS, ESSAM

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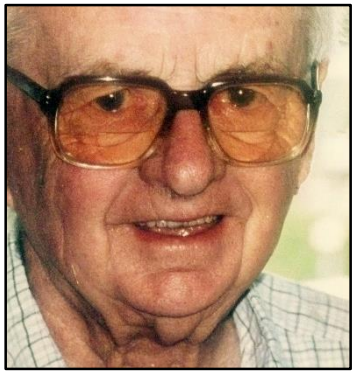
THESIS DEDICATION

I wish to dedicate this work to my beloved Grandmother, ***Jeanne-Marie Rawlings***. Her intellect, ambition, strength and inquisitive nature were qualities I greatly respected and admired. Her love, support and encouragement was unconditional. She tragically passed away during the final stages of this Doctoral work. I greatly wish she was alive today to share this milestone; however I dedicate this to her now as a monument to her life and her remarkable achievements.

In loving memory…

Jeanne-Marie Rawlings



Keith Rawlings

Anne Rawlings

USE OF THESIS

The Use of Thesis statement is not included in this version of the thesis.

The declaration page
is not included in this version of the thesis

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There are many people I wish to thank and acknowledge, for I would not have survived this intense and prolonged journey without their encouragement, advice, support and friendship.

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ABSTRACT

A paucity of research exists to characterise and investigate lower-body musculoskeletal characteristics and morphological adaptations in elite Australian Footballers with the aim to improve screening, monitoring and load management practices. Given the high prevalence of lower-body skeletal injuries in Australian Football; and the ability to measure, modify and train muscle and bone strength and their derivatives; this project served to extend scientific understanding of musculoskeletal morphology and bone strength characteristics in elite level field-based team sport athletes through a series of research studies using Dual-energy X-ray Absorptiometry (DXA) and peripheral Quantitative Computed Tomography (pQCT). In particular, studies one and two provided normative and comparative lower-body musculoskeletal profiles of elite Australian Footballers, stratified by training age (exposure), limb function (asymmetry) and injury incidence (stress fracture), while study three quantified the morphological changes and magnitude of adaptation and maladaptation experienced by Australian Footballers following an in-season and off-season annual phase. The general conclusion provided by the collective studies of this thesis promotes the importance of bone structure and geometry as potent contributors to skeletal robustness, and bone strength. Athletes with higher levels of training exposure and greater physical resilience exhibited higher tibial mass and cortical density with thicker cortical walls and larger muscle and bone cross-sectional areas. Asymmetrical adaptations from differential loading patterns between limbs through-out an in-season and off-season generate vastly different unilateral load tolerance capabilities when extrapolated overtime. The high-impact gravitational loads experienced by the support limb appear to optimise the development of robust skeletal properties specific to bone structure and geometry which may serve as a loading model to prophylactically enhance bilateral musculoskeletal strength and resilience.

Study one provided a set of normative and comparative lower-body musculoskeletal values to describe and compare muscle and bone morphology between less experienced and more experienced athletes (training age); and differential loading patterns between the kicking and support limbs (limb function). Fifty-five athletes were stratified into less experienced (≤ 3 years; n = 27) and more experienced (> 3 years; n = 28) groups in accordance with their training age. All athletes underwent whole-body DXA scans and lower-body pQCT tibial scans on the kicking and support limbs respectively. More experienced players exhibited greater tibial mass, trabecular vBMD, cortical vBMD and total vBMD ($p < 0.009$; $d \geq 0.79$); greater cortical thickness and cortical area ($p < 0.001$; $d \geq 0.92$), and larger stress-strain indices and absolute fracture loads ($p \leq 0.018$; $d \geq 0.57$) than less experienced players. More experienced players also exhibited greater muscle mass and muscle cross-sectional area ($p \leq 0.016$; $d \geq 0.68$). Differences were also observed between limbs, with greater material (tibial mass and cortical vBMD), structural (trabecular area, cortical area, total area, periosteal area and cortical thickness) and strength (stress-strain index and absolute fracture load) characteristics evident in the support leg comparative to the kicking leg of more experienced players ($d \geq 0.20$); with significantly higher asymmetries in tibial mass and cross-sectional area evident in more experienced players than less experienced players as a product of limb function over time. The findings of this study illustrate that training exposure and continued participation in Australian Football produced greater lower-body material, structural and strength adaptations; with chronic exposure to asymmetrical loading patterns developing differential morphological changes between the kicking and support limbs. Indeed, routine high-impact, gravitational load afforded to the support limb preferentially improves bone structure and geometry (cross sectional area and thickness) as potent contributors to bone strength and skeletal fatigue resistance.

Study two provided a retrospective and comparative set of lower-body musculoskeletal data to describe and compare muscle and bone morphology between injured and non-injured Australian Football athletes, in addition to injured and non-injured limbs within injured players, in order to identify musculoskeletal characteristics which may predispose athletes to stress fractures or highlight skeletal fragility. Fifty-five athletes were stratified into injured (n = 13) and non-injured (n = 42) groups. All athletes underwent whole-body DXA scans and lower-body pQCT tibial scans across both limbs. Injured players exhibited lower tibial mass ($p \leq 0.019$; $d \geq 0.68$), cortical vBMD ($d \geq 0.38$) and marrow vBMD ($d \geq 0.21$); smaller cortical area and periosteal area ($p \leq 0.039$; $d \geq 0.63$); smaller trabecular area, marrow area, total area, endocortical area and cortical thickness ($d \geq 0.22$); lower stress-strain indices, absolute fracture loads and relative fracture loads (support leg: $p \leq 0.043$; $d \geq 0.70$, kicking leg: $d \geq 0.48$) than non-injured players. Injured players also exhibited lower muscle cross-sectional area and muscle mass ($p \leq 0.034$; $d \geq 0.79$), yet higher muscle density ($d \geq 0.28$) than non-injured players. Differences between injured and non-injured limbs internal to injured players were also observed, with lower material (tibial mass and total vBMD), structural (cortical area and cortical thickness) and strength (stress-strain index and relative fracture load) in the injured limb comparative to the non-injured limb ($d = 0.20 – 0.70$). Muscle density was lower in the injured limb ($d = 0.54$). The findings of this study illustrate a general inferiority and global musculoskeletal weakness in injured players, with non-injured players ~10-12% stronger across both limbs. Injured players were skeletally slender with smaller muscle and bone cross-sectional areas and thinner cortices. Similarly, injured limbs of injured players also exhibited smaller structural proportions, highlighting the importance of cortical area and cortical thickness as key structural and geometric skeletal properties with potent contributions to bone strength and resilience.

Study three provided a seasonal investigation into lower-body musculoskeletal adaptations over the course of a ~26 week in-season and ~10 week off-season period in Australian Football. Forty athletes (n = 40) and twenty-two athletes (n = 22) were recruited to quantify morphological changes in muscle and bone following the in-season and off-season periods respectively. All athletes underwent whole-body DXA scans and lower-body pQCT tibial scans for the kicking and support limbs at the commencement and conclusion of each season. Australian Football athletes exhibited increases in trabecular vBMD, total vBMD and cortical thickness in the kicking leg; with increased cortical vBMD, total vBMD, trabecular area, total area, periosteal area, cortical thickness and reduced endocortical area in the support leg following the in-season period. Percent changes between limbs were significantly different for trabecular vBMD, cortical vBMD, total vBMD and trabecular area ($p \leq 0.049$; $d \geq 0.46$), despite similar increments in bone strength (~44 – 50 N), demonstrating asymmetrical morphological responses to differential loading patterns in-season. Conversely, Australian Football athletes exhibited material decreases in tibial mass, trabecular vBMD, cortical vBMD and total vBMD in both limbs over the off-season by similar yet opposite magnitudes to the benefits accrued during the in-season, in addition to reduced muscle area, highlighting a general musculoskeletal de-training effect. Structural adaptations were mostly maintained or increased for both limbs over the off-season, with bone strength completely reversed in the kicking leg, yet wholly preserved in the support leg; a lasting adaptation from regular high-impact, gravitational loading specific to the support leg. The findings of this study illustrate the osteogenic potential of a ~26 week in-season, and the de-training potential of a ~10 week off-season. Specifically, the kicking and support limbs continued to show asymmetrical morphological adaptations to differential in-season and off-season loading and de-loading patterns.

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LIST OF ABBREVIATIONS

aBMC	-	Areal Bone Mineral Content
aBMD	-	Areal Bone Mineral Density
ACTH	-	Adrenocorticotropic Hormone
AFL	-	Australian Football League
AFLPA	-	AFL Players Association
ASCA	-	Australian Strength & Conditioning Association
ATP	-	Adenosine Triphosphate
BA	-	Bone Area
BAP / BALP	-	Bone Alkaline Phosphate
BMC	-	Bone Mineral Content
BMD	-	Bone Mineral Density
BMI	-	Body Mass Index
BMP	-	Bone Morphogenic Protein
BMU	-	Basic Multicellular Unit
BSI	-	Bone Strength Index
CBA	-	Collective Bargaining Agreement
cm	-	Centimetre
CSA	-	Cross-sectional Area
CSMI	-	Cross-sectional Moment of Inertia
Ct	-	Cortical

CTx	-	Carboxyterminal Crosslink
CV	-	Coefficient of Variation
DNA	-	Deoxyribonucleic Acid
DPD / D-PYR	-	Deoxypiridoline
DXA	-	Dual-energy X-ray Absorptiometry
Ec	-	Endocortical
ERT	-	Estrogen Replacement Therapy
FGF	-	Fibroblast Growth Factor
FL	-	Fracture Load
GDF	-	Myostatin
HGH	-	Human Growth Hormone
HR-pQCT	-	High Resolution pQCT
HRT	-	Hormone Replacement Therapy
ICC	-	Intraclass Correlation Coefficient
ICST	-	International Conference of Strength Training
IGF	-	Insulin Growth-like Factor
IL	-	Interleukin
IV	-	Intravenous
kg	-	Kilogram
LE	-	Less Experienced
ME	-	More Experienced

MES	**-**	Minimum Effective Strain
m	**-**	Metre
Ma	**-**	Marrow
mm	**-**	Millimetre
MMP	**-**	Matrix Metalloproteinase
MPa	**-**	Megapascals
MRI	**-**	Magnetic Resonance Imaging
N	**-**	Newtons
N/m^2	-	Newton Metres Squared
NTx	**-**	Aminoterminal Crosslink
OC / BGP	-	Osteocalcin
OI	**-**	Osteogenic Index
Pa	**-**	Pascals
PGE2	**-**	Prostaglandin E2
PICP	**-**	Carboxyterminal Type 1 Collagen
PINP	**-**	Aminoterminal Type 1 Collagen
PMI	**-**	Polar Moment of Inertia
pQCT	-	Peripheral Quantitative Computed Tomography
Ps	**-**	Periosteal
PTH	**-**	Parathyroid Hormone
PYR	**-**	Pyridinoline
QCT	**-**	Quantitative Computed Tomography

RANKL	-	Receptor Activator of Nuclear Factor Kappa B Ligand
rBFR/BS	-	Relative Bone Formation Rate
SC	-	Subcutaneous
SERMs	-	Selective Estrogen Receptor Modulators
SI	-	Symmetry Index
SMA	-	Second Moment Area
SPARC	-	Osteonectin
SPRINZ	-	Sports Performance Research Institute, New Zealand
SSI	-	Stress-Strain Index
SSIPOL	-	Stress-Strain Index Polar
SWC	-	Smallest Worthwhile Change
Tb	-	Trabecular
TGF	-	Transforming Growth Factor
TRAP5	-	Tartrate-Resistance Acid Phosphate
TSH	-	Thyroid Stimulation Hormone
Tt	-	Total
ucOC	-	Undercarboxylated Osteocalcin
vBMC	-	Volumetric Bone Mineral Content
vBMD	-	Volumetric Bone Mineral Density
WHO	-	World Health Organisation
Yrs	-	Years

CHAPTER ONE - INTRODUCTION

1.0. Background

Australian Football is a unique, dynamic, fast-paced and multidimensional field-based sport performed over four 20-minute periods (Johnston et al, 2012; Pruyn et al, 2012; Gray & Jenkins, 2010; Young & Pryor, 2007; Pyne, Gardner, Sheehan & Hopkins, 2005). At the elite level, players compete in a national competition known as the Australian Football League (AFL) which places high physical demands on athletes in order to be successful. In particular, AFL athletes require a unique combination of physical, technical, mental and tactical attributes (Kempton, Sullivan, Bilsborough, Cordy & Coutts, 2015; Bilsborough et al, 2014a; Coutts et al, 2014; Gastin, McLean, Breed & Spittle, 2014; Hart, Nimphius, Spiteri & Newton, 2014a; Hart, Spiteri, Lockie, Nimphius & Newton, 2014b; Hart, Nimphius, Weber, Dobbin & Newton, 2013a; Hart, Nimphius, Cochrane & Newton, 2013b; Young & Pryor, 2007; Young et al, 2005), which are carefully and precisely developed, monitored and managed by a multidisciplinary team of strength and conditioning specialists, sport scientists, medical doctors and physiotherapists. Given the substantive financial investment, time and resources devoted to preparing and developing individual athletes in Australian Football (Hickey, Shield, Williams & Opar, 2014; Moriera et al, 2014; Cardinale, Newton & Nosaka, 2011; Orchard, Seward, McGivern & Hood, 1999); the significance and importance of performance enhancement and injury reduction strategies are clearly evident (Fortington et al, 2015; Buchheit et al, 2013; Rogalski, Dawson, Heasman & Gabbett, 2013; Orchard & Seward, 2009; Orchard et al, 1999).

Modern-day elite athletes, in particular, are required to engage in full-time preparation, training and competition workloads (Moriera et al, 2014; Cardinale, Newton & Nosaka, 2011; Kelly, 2007; Gamble, 2006) in order to maximise their physical potential whilst providing greater resilience to injury, illness or fatigue (Ratamess, 2012; Morton, 1997). Due to the superior athletic conditioning present in high performance athletes, there is often a need for high intensity, high volume training loads in order to elicit adequate physiological adaptation (Coutts et al, 2014; Gabbett & Ullah, 2012; Ratamess, 2012; Turner, 2011; Kelly, 2007; Gamble, 2006). However, this training-performance (dose-response) relationship is complex. While athletic performance and training gains generally improve with increases in training loads, so too does the incidence of injury and illness, which are most commonly linked with the highest training loads (Gabbet & Ullah, 2012; Piggott, Newton & McGuigan, 2009; Stewart & Hopkins, 2000; Foster, 1998). As such, strength and conditioning professionals are required to design and develop well-structured and periodised training programs, which manipulate training volume and intensity in conjunction with short-term unloading periods in order to maintain the precarious position between under-training (minimal adaptation) and over-training (illness, fatigue or injury) (Ratamess, 2012; Turner, 2011; Piggott et al, 2009; Stone et al, 1999a; Stone et al, 1999b).

Despite concerted time and effort placed toward managing athletic workloads in Australian Football, injury rates and severity are still significant and continue to rise (Rogalski et al, 2013; Orchard, Seward & Orchard, 2012; Orchard & Seward, 2009; Finch, Valuri, Ozanne-Smith, 1998). While the occurrence of injury can never truly be eliminated, the frequency and severity of injuries can be considerably reduced through adequate strength and conditioning intervention and appropriate load management practices (Lauersen, Bertelsen & Andersen, 2014; Moriera et al, 2014; Rogalski et al, 2013; Petersen, Thorborg, Nielsen,

Budtz-Jørgensen & Hölmich, 2011). Unfortunately the sustained evolution and game-based volatility of Australian Football continually modifies the physiological demands of the sport, subsequently complicating current athletic monitoring and injury reduction endeavors (Rogalski et al, 2013; Orchard, Seward & Orchard, 2012; Norton, Craig & Olds, 1999). As a result, more sophisticated, integrated and targeted screening, monitoring and assessment procedures need to be established in order to promptly and accurately identify athletes at risk of injury (Dallinga, Benjaminse & Lemmink, 2012); effectively preventing and managing the likelihood of injury occurrence through improving athlete resilience.

Injuries sustained in Australian Football are broadly categorised as traumatic (acute onset) and overuse (gradual onset) injuries (Merkel & Molony, 2012; Smoljanovic et al, 2009; Ekstrand, Karlsson & Hodson, 2003) affecting both soft-tissue (muscle, tendon, ligament) and hard-tissue (bone) structures (Orchard, Seward Orchard, 2012; Finch, Valuri, Ozanne-Smith, 1998; Orchard, Wood, Seward & Broad, 1998). Traumatic injuries result from an applied external force which exceeds the maximum durability of the bone, muscle-tendon or ligament on a single occasion (tackling, collision, change of direction, rapid acceleration or deceleration); whereas overuse injuries are a product of repetitive low-grade forces (walking, running, kicking, jumping) which exceed the tolerance of such tissues over time (Gabbett & Ullah, 2012; Ekstrand & Torstveit, 2010). Presently, injury prevention research in Australian Football has exclusively directed attention towards soft-tissue injuries (Duhig, 2014; Hickey, Shield, Williams & Opar, 2014; Freckleton, Cook & Pizzari, 2014; Opar et al, 2014a; Opar et al, 2014b; Opar et al, 2014c; Serpell et al, 2014; Verrall, Estermann & Hewett, 2014; Pizzari, Taylor & Coburn, 2013; Orchard, Driscoll, Seward & Orchard, 2012; Schache et al, 2011; Taylor et al, 2011; Warren, Gabbe, Schneider-Kolsky &

Bennell, 2010; Watsford et al, 2010; Cochrane, Lloyd, Buttfield, Seward & McGivern, 2007; Hrysomallis, McLaughlin & Goodman, 2007; Hoskins & Pollard, 2005; Verrall, Slavotinek & Barnes, 2005; Gabbe, Bennell & Finch, 2006a; Gabbe, Bennell, Finch, Wajswelner & Orchard, 2006b; Orchard, Farhart & Leopold, 2004; Cameron, Adams & Maher, 2003; Orchard, 2002; Orchard, 2001; Orchard, Seward & McGivern, 2001; Verrall et al, 2001; Orchard et al, 1999; Bennell et al, 1998). This central theme in Australian Football literature appears symptomatic of an evident bias within AFL injury surveillance reports, possibly owing to the high incidence rates of soft-tissue injury over the past decade (Orchard, Seward & Orchard, 2013; Orchard, Seward & Orchard, 2012; Orchard & Seward, 2003). However, hard-tissue injuries have continually increased over the past ten years (Orchard, Seward & Orchard, 2013; Orchard, Seward & Orchard, 2012; Orchard & Seward, 2003), with no known studies designed to examine lower-body hard-tissue pathology, highlighting an obvious inadequacy within the current research landscape.

Injury surveillance reports are generated annually by the AFL, providing a competition-wide categorical index of 34 different injury classifications (Orchard, Seward & Orchard, 2012; Orchard & Seward, 2009). In particular, these reports document the number of new injuries per club, per season (incidence); the number of repeat injuries per club, per season (recurrence); and the number of games missed per club, per season (prevalence) for each injury classification (Orchard, Seward & Orchard, 2013; Orchard & Seward, 2009; Orchard & Seward, 2002). In a ten-year special injury surveillance report (Orchard, Seward & Orchard, 2012), lower-limb fractures were identified as the 2nd highest cause of missed games in the competition (14.8 games per club, per season), ranked marginally behind hamstring strains as the leading injury concern (16.5 games per club, per season). However,

rather successfully, the incidence, recurrence and prevalence of hamstring strains have steadily declined over the past 5 years in response to heightened injury-specific research and new management techniques (Opar et al, 2014a; Opar et al, 2014b; Opar et al, 2014c; Orchard et al, 2012; Warren et al , 2010; Watsford et al, 2010; Brughelli, Nosaka & Cronin, 2009; Gabbe, Bennell & Finch, 2006a; Gabbe et al 2006b; Hoskins & Pollard, 2005; Verrall, Slavotinek & Barnes, 2005; Cameron, Adams & Maher, 2003; Croisier, Forthomme, Namurois, Vanderthommen & Crielaard, 2002; Orchard, 2002; Verrall, Slavotinek, Barnes, Fonm & Spriggins, 2001); whereas lower limb fractures have, in contrast, continued to rise (Orchard et al, 2012; Ekstrand, Hagglund & Walden, 2011) in the absence of any research outcomes or appropriate industry recognition. Given that lower limb hard-tissue injuries generate an approximate competition-wide expense of $1.5 million in lost player wages every year ([$300,000 annual salary ÷ 52 weeks] x [14.8 games x 18 clubs] = $1,536,923.00); this paucity of research is surprising, and provides a clear rationale for injury-specific research into lower-body bone health, strength and adaptation.

Skeletal fragility is directly related to injury risk in football sports (Warden et al, 2005; Murphy, Connolly & Beynnon, 2003; Melton, Atkinson, O'Connor, O'Fallon & Riggs, 1998). Athletes with lower bone mass and slender bones are more vulnerable to impact fracture and stress fracture than athletes with greater bone mass and more robust bones (Wallace et al, 2012; Burr, 2011; Darelid et al, 2010; Tommasini, Nasser, Hu & Jepsen, 2008; Tommasini, Nasser, Schaffler & Jepsen, 2005; Murphy et al, 2003; Beck et al, 2000). While bone mass accrual occurs most rapidly in teenage years, peak bone mass is not fully achieved until the mid-to-late twenties (Laudermilk et al, 2012; Baird et al, 2011; Manske, Lorincz & Zernicke, 2009; Weaver, 2008; Fredericson et al, 2007; Pitukcheewanont &

Safani, 2006; Heaney et al, 2000; Jarvinen, Sievanen, Johikaara & Einhorn, 2005; Kohrt, Bloomfield, Little, Nelson & Yingling, 2004; Bradney et al, 1998), providing practitioners with a considerable opportunity (window of adaptation) to improve resilience to hard-tissue injury by heightening bone mass and skeletal robustness during early-stage development (Ireland, Rittweger, Schonu, Lamberg-Allardt & Vijakainen, 2014; Warden & Roosa, 2014; Gustavsson, Thorsen & Nordstrom, 2003; Modelsky & Lewis, 2002). Despite the apparent age-related ceiling of bone mass proliferation, bone strength is still able to continue to increase through other forms of spatially relevant mechanisms and adaptations specific to geometrical rearrangement and bone health homeostasis (Seeman, 2013; Horcajada & Offord, 2012; Nordin & Frankel, 2012; Cardinale, Newton & Nosaka, 2011; Martin & Correa, 2010; Rantalainen, Nikander, Heinonen, Suominen & Sievanen, 2010b; Bouxsein & Karasik, 2006; Ural & Vashishth, 2006). The regular and comprehensive examination of bone material, structure and strength in athletes can therefore provide practitioners with an insight into bone health and injury risk stratification through-out their athletic life-span.

Bone is a highly adaptive, structurally dynamic and metabolically active organ that is superior to all other materials within the human body in terms of elasticity, strength and toughness (Fonseca, Moriera-Goncalves, Coriolano & Duarte, 2014; Cardinale, Newton & Nosaka, 2011; Manske, Lorincz & Zernicke, 2009; Ritchie, Beuhler & Hansma, 2009). In particular, bone structure, size and strength is reliant upon and responsive to the routine physiological and mechanical demands placed upon it (Korhonen et al, 2012; Greene, Naughton, Bradshaw, Moresi & Ducher, 2012; Gong, Dong, Gao, Lv & Zhang, 2010; Turner, 2007; Greene, Naughton, Briody, Kemp & Woodhead, 2006; Lorentzon, Mellstrom & Ohlsson, 2005; Frost, 2004). Mechanical stimuli thus initiate or inhibit bone modeling

and remodeling processes in response to variations in external load or as a consequence of immobilisation (Nguyen, Tang, Nguyen & Alliston, 2013; Belavy et al, 2011; Bloomfield, 2010; Chen, Liu, You & Simmons, 2010; Korht, Barry & Schwartz, 2009; Robling, Castillo & Turner, 2006). More specifically, bone continuously modifies and regenerates itself in the presence or absence of mechanical loading, which subsequently leads to the accrual (formation), maintenance (homeostasis) or degradation (resorption) of bone mass (Nordin & Frankel, 2012; Crockett et al, 2011; Eriksen, 2010; Raggatt & Patridge, 2010; Clarke, 2008; Hadjdakis & Androulakis, 2006; Seeman & Delmas, 2006). However, for hard-tissue to routinely withstand and adapt to any form of mechanical load, bone health must be maintained. This is achieved through a sophisticated process involving the careful cellular regulation and co-ordination of osteoblasts (bone matrix deposit) and osteoclasts (bone matrix resorption) in order to remove damaged bone material and subsequently replace it with new, robust material (Singh et al, 2012; Crockett et al, 2011; Feng & McDonald, 2011; Eriksen, 2010; Hill & Tumber, 2010; Raggatt & Patridge, 2010; Seeman, 2009; Filvaroff & Derynck, 1998; Erlebacher, Filvaroff, Gitelman & Derynck, 1995). As bone remodeling is a continuous regenerative process, even a slight perturbation or imbalance in either of these regulatory cells can lead to osteopenia or osteoporosis; such is the importance of bone health to subsequent load tolerance capabilities of hard-tissue structures (Giusti & Bianchi, 2015; Body et al, 2011; Martin & Correa, 2010; Khosla, Amin, Orwoll, 2008; Filvaroff & Derynck, 1998; Erlebacher et al, 1995; Orwoll & Klein, 1995). In particular, the mechanical integrity and performance of bone under various loading conditions is directly affected by its mechanical properties and geometric characteristics (Fonseca et al, 2014; Nguyen et al, 2013; Nordin & Frankel, 2012; Gong et al, 2010; Jarvinen et al, 2005) which are both sensitive to bone health and underpin bone strength.

The ability of bone to manage and withstand forces and moments (mechanical behaviour) differs substantially across the loading spectrum under various loading conditions; specific to the mode, magnitude, direction, rate and frequency of load applied (Kemmler & von Stengel, 2011; Edwards, Taylor, Rudolph, Gillette & Derrick, 2009; Kohrt, Barry & Schwartz, 2009; Manske, Lorincz & Zernicke, 2009; Robling, Castillo & Turner, 2006; Kohrt et al, 2004). As bone is anisotropic in nature, it has different thresholds of load tolerability across different planes of action (Nordin & Frankel, 2012; Cardinale, Newton & Nosaka, 2011; Shahar et al, 2007; Iyo, Maki, Sasaki & Nakata, 2004; Doblare & Garcia, 2002). In Australian Football, athletes are routinely exposed to various, unpredictable and volatile lower-body loading patterns spanning from cyclical low-grade forces when walking or running, to sudden high-grade forces when jumping, landing, kicking or changing direction. As a result; compressive, torsional, transverse and tensile loads in combination and in isolation are routinely applied to hard-tissue structures of footballers, exposing the skeleton to stimuli that can lead to positive bone-specific and site-specific adaptations (Rantalainen, Nikander, Daly, Heinonen, & Sievanen, 2011b; Nikander et al, 2010a; Rantalainen et al, 2010b; Ducher, Hill, Angeli, Bass & Eser, 2009; Kohrt, Barry & Schwartz, 2009); or in the absence of suitable conditioning, recovery and nutrition, an increased likelihood of lower limb injury (Corrarino, 2012; Moran, Finestone, Arbel, Shabsin & Laor, 2012a; Harrast & Colonno, 2010; Twomey, Finch, Roediger & Lloyd, 2009; Gabbe et al, 2004; Murphy, Connolly & Beynnon, 2003; Taylor & Lee, 2003; Burr et al, 1997). Bone strength should therefore be an essential focus of athlete preparation and injury prevention programs for athletes.

Despite the complex and multidimensional relationship between various loading schemes and hard-tissue mechanical properties; bone strength and stiffness are greatest in the direction by which loads are most commonly expressed (Nguyen et al, 2013; Rantalainen et al, 2010b; Vainionpaa et al, 2009). This adaptive response to mechanical loading highlights a specificity of adaptation (site-specific) as force transmission regulates osteogenic (anabolic) bone formation outcomes concomitantly with other stochastic (spatially non-specific) adaptations (Cardinale, Newton & Nosaka, 2011; Eriksen, 2010; Raggatt & Patridge, 2010; Kohrt, Barry & Schwartz, 2009; Tanaka, Alam & Turner, 2003). In particular, the regulation and co-ordination of bone to physically adapt to loading demands is initiated and managed at the cellular level by osteocytes through mechanotransduction (Reis, Silva, Queiroga, Lucena & Potes, 2011; Bonewald, 2006; Klein-Nulend, Bacabac & Mullender, 2005; Robling & Turner, 2002). Proportionate to mechanical stimulation, osteocytes biochemically promote osteogenesis by coordinating osteoblast and osteoclast activity so that deposition exceeds resorption (Humphrey, Dufresne & Schwartz, 2014; Thompson, Rubin & Rubin, 2012; Ozcivici et al, 2010); in this regard, older osteoblasts make way for new osteoblasts by transforming into osteocytes which become embedded into the bone-matrix. As osteocytes form 95% of bone-matrix composition, this increase in osteocyte concentration leads to an increase in bone mass while maintaining regulatory osteoblast-to-osteoclast homeostasis (Bonewald, 2011; Crockett et al 2010; Eriksen, 2010; Gong et al, 2010; Raggatt & Patridge, 2010; Bonewald, 2007).

Bone strength adaptability provides strength and conditioning practitioners with an important modifiable characteristic to screen, monitor, and target with exercise interventions. Although mechanical loading induced by weight-bearing exercise and

resistance training programs provide direct osteogenic effects to the skeleton at site-specific load-bearing regions, there is a lack of consensus with regards to the precise programming variables required to optimally enhance bone strength. Complexity arises as the mechanical load needed to stimulate osteogenesis decreases as strain magnitude and frequency increases; and furthermore, mechanosensitivity of osteocytes can become saturated beyond a certain threshold of loading cycles, limiting additional benefits beyond such a point (Robling, Turner & Castillo, 2006; Saxon, Robling, Alam & Turner, 2005; Gross et al, 2004; Srinivasan, Weimer, Agans, Bain & Gross, 2002; Robling, Burr & Turner, 2001a). Recent evidence, however, promotes the use of dynamic, explosive, multi-planar activities involving impact loads, due to the co-contribution of large muscular contraction forces, large ground reaction forces and rapid rates of change in forces exerted onto the skeleton providing a greater stimulus to the cells responsible for bone remodeling, therefore heightening osteogenic outcomes (Ireland, Rittweger & Degens, 2014; Weidauer et al, 2014; Gong et al, 2010; Kohrt, Barry & Schwartz, 2009; Robling, 2009; Vainionpaa et al, 2009; Fredericson et al, 2007; Warden, Fuchs & Turner, 2004; Duda et al, 1998).

Investigations into bone strength for field-based team-sports remain scarce. Consequently, the association between bone strength and bone adaptation to injury incidence remains unclear. As bone strength is a measureable and trainable athletic characteristic, research is required in order to characterise lower-body bone mass, geometry, density and strength in field-based team sports to ascertain whether common factors exist between athletes who are susceptible to injury versus those who are injury resilient. Further, the dose-response relationship between seasonal bone strength adaptations, seasonal game-based and training-based loading schemes, and subsequent injury incidence require scientific investigation.

1.1. Purpose of Research

This project aimed to examine the association between lower-body musculoskeletal properties with training exposure and skeletal injury incidence in a team-based field-sport. Specifically, this project provides a normative and developmental examination of muscle and bone morphology in Australian Football (less experienced vs. more experienced; injured vs. non-injured); whilst also reporting seasonal musculoskeletal changes following a competitive in-season and off-season period. The project aspired to establish a benchmark of measures obtainable by numerous available imaging techniques (DXA or pQCT) as a team-based screening tool for bone-injury risk stratification in team-based field-sports.

1.2. Significance of Research

Limited research presently exists to investigate injury prevention strategies for lower-body skeletal injuries in elite Australian Football. Given that bone strength is a measureable, modifiable and trainable athletic characteristic which has relevance to injury risk and load tolerance capabilities in general populations (Fonseca et al, 2014; Davison et al, 2006; Jarvinen et al, 2005; Ammann & Rizzoli, 2003; Einhorn, 1992), this project serves to extend scientific understanding of bone health and strength in a team-based, field-based athletic population in order to establish the relationship between lower-body loading demands and skeletal injury risk. Specifically, this project produced a series of studies to comprehensively examine and compare lower-body musculoskeletal morphology in elite Australian Football players when stratified by training age, limb function, and injury history; and quantified seasonal adaptation outcomes in lower-body musculoskeletal characteristics through-out an in-season and off-season period.

1.3. Research Questions

<u>Study 1:</u> Normative and comparative quantification of lower-body musculoskeletal characteristics in elite Australian Footballers.

1) Are there different muscle and bone material, structural and strength characteristics between less experienced and more experienced elite Australian Football athletes?

2) Are there asymmetrical adaptations in muscle and bone material, structure and strength characteristics between the kicking and support limbs of Australian Football players?

<u>Study 2:</u> Injured and non-injured comparisons of lower-body musculoskeletal characteristics in elite Australian Footballers.

1) Are there differences in muscle and bone material, structure and strength characteristics between non-injured and previously injured elite Australian Football players with recent stress fracture history?

2) Are there morphological differences in muscle and bone characteristics between injured and non-injured limbs within previously injured elite Australian Football players with recent stress fracture history?

3) Which lower-body musculoskeletal variables appear to associate with skeletal fragility and previous stress fracture incidence in elite Australian Football?

Study 3: **In-season and off-season lower-body musculoskeletal adaptations in elite Australian Footballers**

1) What musculoskeletal material, structural and strength changes occur in elite Australian Footballers following the ~26 week AFL in-season competition phase?

2) Is there a morphological detraining (muscle and bone loss) effect in elite Australian Footballers following a self-guided training program over the course of a ~10 week AFL off-season phase?

3) Are there asymmetrical muscle and bone material, structural and strength adaptations between the kicking and support limbs of elite Australian Football players over one in-season and off-season phase?

1.4. Research Studies

A series of three experimental studies with multiple comparisons have been developed to comprehensively quantify and examine the lower-body musculoskeletal characteristics of elite Australian Football athletes including anthropometry, whole-body composition, and lower-body muscle and bone material, structure and strength measures. The first study compares the effects of training age (load exposure) and limb function (load asymmetry) on musculoskeletal development; the second study determines the main musculoskeletal differences between non-injured and previously injured players as well as non-injured and injured limbs within previously injured players; and the final study reports the differential morphological adaptations and maladaptations of the kicking and support limbs in Australian Footballers following a ~26 week in-season and ~10 week off-season phase.

1.5. Limitations and Delimitations

1) The outcomes of this thesis are delimited to the cohort of subjects used; specifically male athletes participating in the Australian Football League. The applications of these findings are therefore limited to this population and might not transfer to other types of sporting competitions or athlete cohorts.

2) Musculoskeletal differences identified between loading exposure at the elite level were inferred using training age stratifications. However, differences in biological age may act as a confounding factor due to morphological variance with aging. Although the effects of mechanical loading are distinguishable prior to the establishment of peak bone mass; some variation in musculoskeletal values between groups may be due to the biological ageing process.

3) Retrospective inclusion of athletes with recent stress fracture history (~6 to 12 months) prior to measurement formed the injured group in this thesis. While all players were fully rehabilitated and provided with additional prophylactic intervention, some evident differences between non-injured and injured players could be a residual product of post-injury immobilisation and recovery procedures.

4) Although in-season and off-season musculoskeletal changes were measured, the precise volume-load of mechanical stimulus experienced by each athlete would have differed amongst the team during each seasonal phase. While these athletes were recruited from the same team and managed by the same practitioners, their differences in individual load management and training requirements might have held an undetermined influence on the established and reported outcomes.

CHAPTER TWO - LITERATURE REVIEW

2.0. Overview

This literature review examines two main themes pertaining to bone strength in athletes. Specifically, this chapter describes: 1) the anatomical, physiological and biomechanical basis of bone strength; and 2) the influence of physical activity, pharmacology and nutrition on bone strength. While bone theory is broadly discussed in relation to the entire skeleton; the central focus of this review refers to the lower-body in accordance with the purpose of this Thesis.

2.1. Bone Anatomy

2.1.1. Skeletal Function

The human skeleton is responsible for several important mechanical and non-mechanical functions (Banfi, Lombardi, Colombini & Lippi, 2010; Clarke, 2008; Jarvinen et al, 2005). Mechanically, it provides a structural framework and stable foundation for human movement and locomotion to occur by generating mechanical rigidity and kinematic connectivity within the body (Clarke, 2008; Jarvinen et al, 2005; Taichman, 2005; Frost, 2003; Burr, 1997). It specifically achieves this by providing skeletal muscle with attachment sites to use as leverage points and platforms with which to act, contract and produce force (Nordin & Frankel, 2012; Feng & McDonald, 2011; Cardinale, Newton & Nosaka, 2011; Jarvinen et al, 2005; Harada & Rodan, 2003; Turner & Pavalko, 1998). Bone also mechanically serves to protect the brain, spinal cord and internal organs; and non-mechanically provides a reservoir for mineral deposition and blood regulation of

calcium and phosphorous; supports haematopoiesis; defends against acidosis; and absorbs or captures potentially toxic minerals (Feng & McDonald, 2011; Schwab & Scalapino, 2011; Clarke, 2008; Jarvinen et al, 2005; Harada & Rodan, 2003). In order to fulfil these many functions simultaneously, bone has unique structural, morphological and mechanical properties which are highly dynamic, metabolically active and physiologically adaptive to the environment in which they're exposed (Karlsson & Rosengren, 2012; Raggatt & Patridge, 2010; Hadjidakis & Androulakis, 2006; Taichman, 2005). Bone is also highly vascular, and therefore able to constantly model (form new bone) and remodel (recycle damaged bone) in response to routinely imposed mechanical demands, subsequently altering its configuration and material properties to preserve or increase bone strength in order to meet its functional requirements (Seeman, 2013; Nordin & Frankel, 2012; Crockett et al, 2011; Seeman & Delmas, 2006; Frost, 2003).

In its adult form, the human skeleton consists of approximately 200 distinguishable bones, with 74 located in the axial skeleton, and 126 located in the appendicular skeleton (Brandi, 2009; Clarke, 2008). Long bones, however, are the most commonly loaded structures and therefore strongest load-bearing bones in the body, predominantly located in the appendicular skeleton. They comprise of a hollow cylindrical shaft known as the diaphysis; a cone-shaped proximal and distal metaphysis; and a rounded proximal and distal epiphysis (Marieb & Hoehn, 2013; White, Black & Folkins, 2012; Clarke, 2008; Orwoll, 2003; Sikavitsas, Temenoff & Mikos, 2001), each portion with different architectural features which are organised and configured to withstand and manage different physical loads during regular activities of daily living (Seeman, 2013; Brandi, 2009; Beaupied, Lespessailles & Benhamou, 2007; Taichman, 2005; Bayraktar et al, 2004).

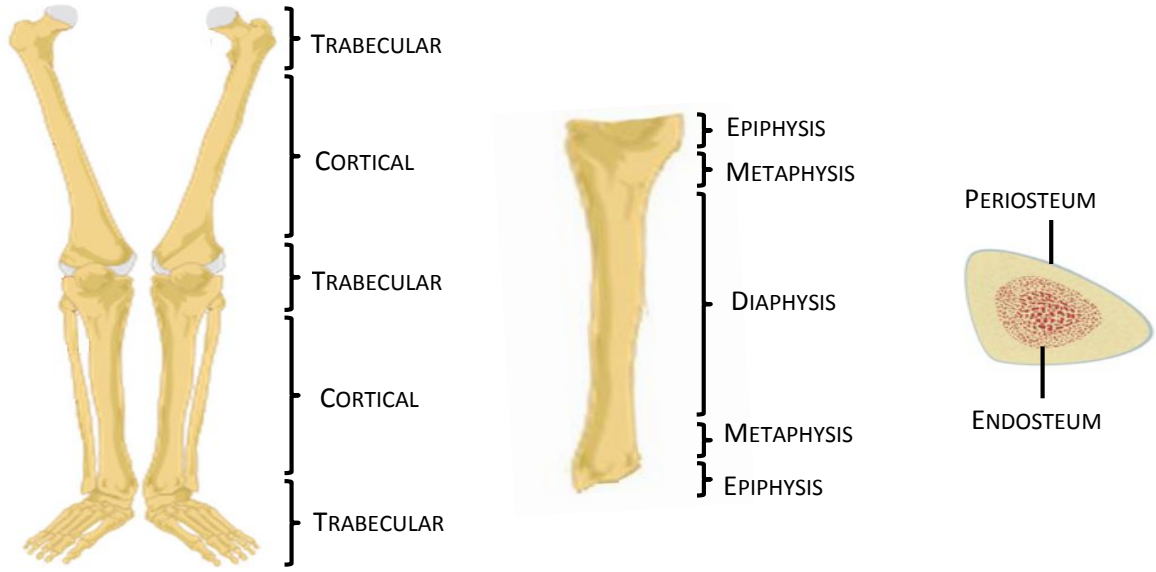


Figure 1. Illustrations of the lower appendicular skeleton with trabecular and cortical dominant regions outlined (left); the isolated Tibia with structural regions identified (middle); and a cross-sectional view of the Tibial diaphysis showing the periosteum and endosteum (right).

2.1.2. Macroscopic Architecture

Bone is a structurally complex and sophisticated biomaterial, superior to all others in terms of elasticity, strength and toughness (Fonseca et al, 2014; Cardinale, Newton & Nosaka, 2011; Martin & Correa, 2010; Ritchie, Beuhler & Hansma, 2009). It must be rigid and stiff to withstand forces and accommodate loading, yet be flexible and elastic to deform and absorb energy (Brandi, 2009; Seeman & Delmas, 2006; Currey, 2003). It must shorten and widen under compression, yet lengthen and narrow under tension; whilst also withstand torsional and sheer forces in isolation and combination without experiencing catastrophic failure (Seeman, 2013; Seeman & Delmas, 2006). In order to concomitantly manage these contradictory and paradoxical requirements, the skeleton contains two key macroscopic osseous tissues (trabecular and cortical bone) which are architecturally, microscopically and functionally different (Martin & Correa, 2010; Zebaze et al, 2010; Mosekilde, Ebbesen,

Tornvig & Thomsen, 2000; Weiner & Wagner, 1998; Rho, Kuhn-Spearing & Zioupos. 1998; Keaveny & Hayes, 1993). In its entirety, skeletal mass is comprised of approximately 20% trabecular tissue and 80% cortical tissue, which co-exists at various rates in all bones through-out the body in accordance with the functional and regional demands of each individual bone (Seeman, 2013; Nordin & Frankel, 2012; Brandi, 2009; Clarke, 2008; Huiskes, 2000; Keaveny & Hayes, 1993). The structural intricacies and interactions between these two osseous tissues, in particular, enable long bones to be remarkably light yet durable and strong in order to facilitate locomotion (Seeman, 2013; Seeman 2008; Seeman & Delmas, 2006; Yeni, Brown, Wang & Norman, 1997).

2.1.2.1. Trabecular Bone

Trabecular bone, also known as cancellous bone, is encapsulated beneath cortical bone. It is most prominently found in weight-bearing skeletal structures, specifically the proximal and distal ends of long-bones (epiphyseal and metaphyseal regions); the carpals and tarsals of the extremities; and vertebrae (Seeman, 2013; Clarke, 2008; Huiskes, Ruimerman, van Lenthe & Janssen, 2000; Rho, Kuhn-Spearing & Zioupos. 1998; Parfitt, 1994a). Texturally, trabecular tissue presents as a meshwork of bone (trabeculae) with many interconnecting spaces through-out which contain red bone marrow (Zebaze et al, 2010; Szulc, Seeman, Duboeuf, Sornay-Rendu & Delmas, 2006; Travlos, 2006; Ruimerman, Hilbers, van Reitbergen & Huiskes, 2005; Taichman, 2005; Jacobs, 2000). The three-dimensional lattice-like structure of trabecular bone is primarily organised in the direction from which the greatest stresses are most commonly experienced; a functionally adaptive and dynamic response to mechanical loading (Gong, Zhu, Gao, Lv & Zhang, 2010; Ruimerman, van Rietbergen, Hilbers & Huiskes, 2005; Currey, 2003b; Frost, 2003; Ruimerman, Huiskes,

van Lenthe & Janssen, 2001; Jacobs, 2000; Huiskes et al, 2000). The spongy and porous architecture of trabecular bone enables it to store large amounts of energy prior to yielding (Nordin & Frankel, 2012; Hadjidakis & Androulakis, 2006; Kopperdahl & Keaveny, 1998; Ding et al, 1997; Keaveny & Hayes, 1993), thus allowing it to routinely tolerate cyclical low-grade forces.

2.1.2.2. Cortical Bone

Cortical bone, also known as compact bone, forms the thin superficial layer of all bones; though is most prominently found in the thick central cortex (diaphysis) of long bones through-out the appendicular skeleton (Marieb & Hoehn, 2013; Cardinale, Newton & Nosaka, 2011; Clarke, 2008; Augat & Schorlemmer, 2006). Cortical bone always encapsulates trabecular bone, however the relative co-existence and composition of each tissue varies between bones through-out the skeleton (Fonseca et al, 2013; Nordin & Frankel, 2012; Zebaze et al, 2010; Beaupied, Lespessailles & Benhamou, 2007). In long bones, cortical tissue is arranged in a cylindrical fashion with concentric layers across two primary surfaces; the periosteum (a dense fibrous membrane forming the outside layer) and endosteum (a thin membrane forming the inner layer) of the diaphyseal shaft (Carnelli, Vena, Dao, Ortiz & Contro, 2013; Marieb & Hoehn, 2013; Seeman 2013; Techawinboonwong, Song, Leonard & Wehrli, 2008; Seeman, 2007; Augat & Schorlemmer, 2006; Szulc et al, 2006; Orwoll, 2003). Both surfaces contain important cells (osteoclasts, osteoblasts and osteocytes) responsible for modelling and remodelling processes essential to bone adaptation and osteogenesis (Singh et al, 2012; Robling, Castillo & Turner, 2006; Seeman & Delmas, 2006; Orwoll 2003; Manolagas, 2000). The endosteum additionally lines the central cavity with yellow marrow (Marieb & Hoehn, 2013; Seeman, 2007; Szulc et al, 2006; Travlos, 2006; Taichman, 2005). Structurally,

cortical bone is highly organised, densely packed, rigid, and texturally smooth (Carnelli et al, 2013; Nordin & Frankel, 2012; Hadjidakis & Androulakis, 2006; Szulc et al, 2006), with mineralized lamellar bone and collagen fibre matrix most prominently arranged in the direction of routine mechanical stress (Carnelli et al 2013; Augat & Schorlemmer, 2006; Pearson & Lieberman, 2004; Currey, 2003b; Burr, 2002; Sevostianov & Kachanov, 2000). This provides cortical bone with an increased capability to tolerate sudden, high impact forces; ~25% stronger than trabecular bone (Fonseca et al, 2014; Nordin & Frankel, 2012; Augat & Schorlemmer, 2006; Hadjidakis & Androulakis, 2006; Bayraktar et al., 2004).

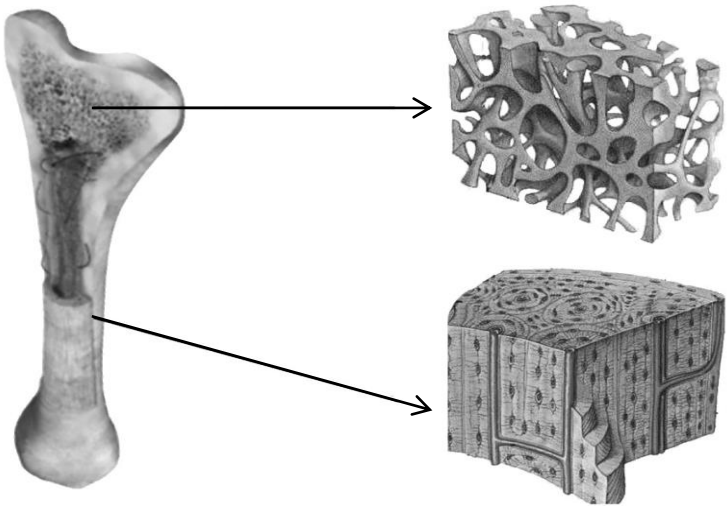


Figure 2. Illustrations of a longitudinal cross-section of the human tibia (left, adapted from Favaro, Powell & Ammann, 2007); with structural magnifications of trabecular bone (top) and cortical bone (bottom).

2.1.3. Microscopic Architecture

Bone also has microscopic and sub-microscopic levels which, together with the previously described macroscopic level, form a multidimensional architectural biomaterial with a deliberate mass (size, geometry and density) aimed at achieving optimal structural strength (Fonseca et al, 2014; Martin & Correa, 2010; Brandi, 2009; Davison et al, 2006; Bouxsien,

2003). Microscopically, bone presents in the form of woven and lamellar bone at the tissue level (Liu et al, 2010; Su, Sun, Cui & Landis, 2003; Sikavitsas, Temenoff & Mikos, 2001; Rho, Kuhn-Spearing & Zioupos. 1998; Turner, Forwood, Rho & Yoshikawa, 1994); and consists of organic and inorganic components at the material level (Bala, Farlay & Boivin, 2013; Feng & McDonald, 2011; Reis et al, 2011; Martin & Correa, 2010; Yeni, Brown & Norman, 1998; Hangartner & Gilsanz, 1996).

2.1.3.1. Tissue Level

Bone presents in the form of immature (woven) and mature (lamellar) tissue at different stages of the modelling and re-modelling processes at the microscopic level (Liu et al, 2010; Clarke, 2008; Shapiro, 2008; Currey, 2003a; Weiner, Traub & Wagner, 1999; Forwood & Turner, 1995; Turner, Forwood, Rho & Yoshikawa, 1994). Woven tissue is an immature form of bone characterised by a random and spontaneous collagen arrangement; a large volume of cells; and relatively low tissue density (Currey, 2003a; Weiner & Wagner, 1998). It is formed rapidly, producing a highly unorganised and porous structure (Liu et al, 2010; Clarke, 2008; Su, Sun, Cui & Landis, 2003). Woven bone features primarily through-out development, exclusively forming the entire skeleton at birth prior to a graduated transformation into mature lamellar bone during growth and physical maturation (Clarke, 2008; Currey, 2003a; Sikavitsas, Temenoff & Mikos, 2001; Kusuzaki et al, 2000). At any other time, woven bone formation occurs only following an injury or extreme structural overload which is thought to be a rapid, protective and restorative response to significantly damaged or weakened hard tissue structures (Cardinale, Newton & Nosaka, 2012; McBride & Silva, 2012; Marsell & Einhorn, 2011; Fazzalari, 2011; Liu et al, 2010). It is therefore considered a premature and provisional material. Lamellar tissue, however, is a mature form of bone, which eventually replaces woven tissue in the form of trabecular or cortical

bone formations (described earlier in section 2.1.2.). Lamellar tissue is characterised by a precise and deliberate parallel and concentric arrangement of lamellae sheets produced slowly due to a low turnover rate (Cardinale, Newton & Nosaka, 2012; Sikavitsas, Temenoff & Mikos, 2001; Weiner, Traub & Wagner, 1999; Rho, Kuhn-Spearing & Zioupos. 1998). Lamellae sheets are formed in alternating directions that vary in rotational position and thickness in order to optimally withstand mechanical loads; in particular torsional stress (Fonseca et al, 2014; Marieb & Hoehn, 2013; Su et al, 2003; Weiner, Traub & Wagner, 1999; Rho, Kuhn-Spearing & Zioupos, 1998). Lamellar bone is therefore denser and stronger than woven bone (Clarke, 2008; Currey, 2003a; Zioupos & Currey, 1994).

2.1.3.2. Material Level

Bone is a specialised, bi-phasic connective tissue consisting of extracellular organic material coupled with a uniquely high content of mineralised inorganic material (Fonseca et al, 2014; Bala, Farlay & Boivin, 2013; Nordin & Frankel, 2012; Martin & Correa, 2010; Burr, 2002; Burger & Klein-Nulend, 1999). The organic portion provides bone with one-third of its mass and two-thirds of its volume; whereas the inorganic portion provides bone with the remaining two-thirds of its mass and one-third of its volume (Reis et al, 2011; Davison et al, 2006; Hangartner & Gilsanz, 1996). The extracellular organic component is primarily collagenous, conferring flexibility and resilience to bone by solidifying in tension as a protection against stretching, twisting and torsion (Martin & Shapiro, 2007; Viguet-Carrin, Garnero & Delmas, 2006; Fratzl et al, 2004; Wang & Puram, 2004; Yamashita et al, 2001). Conversely, the mineralised inorganic component is primarily calcium and phosphate in the form of an insoluble salt known as hydroxyapatite (Bala, Farlay & Boivin, 2013; Golub, 2011; Farlay, Panczer, Rey, Delmas & Boivin, 2010; Golub, 2009; Bouxsein, 2003; Boivin & Meunier, 2002), giving bone its hardness and rigidity, particularly in

compression (Boivin et al, 2008; Allen & Burr, 2007; Follet, Boivin, Rumelhart & Meunier, 2004). As a result, the overall structural strength of bone relies upon the joint contribution and inter-play of these organic and inorganic material properties (Fonseca et al, 2014; Cardinale, Newton & Nosaka, 2012; Farlay et al 2010; Boivin et al, 2008; Seeman & Delmas, 2006), such that variations of inorganic mineral density will potentially adjust stiffness and flexibility arrangements in bone (Bala, Farlay & Boivin, 2013; Bala, Farlay, Delmas, Meunier & Boivin, 2010; Seeman & Delmas, 2006); the optimal balance of which remains largely unknown. Fortunately, this can be somewhat examined as elements held within the mineralised (inorganic) portion of bone provide considerable resistance to X-ray beams, forming the theoretical basis underpinning the use of bone densitometry devices (described in detail in section 2.4.1.).

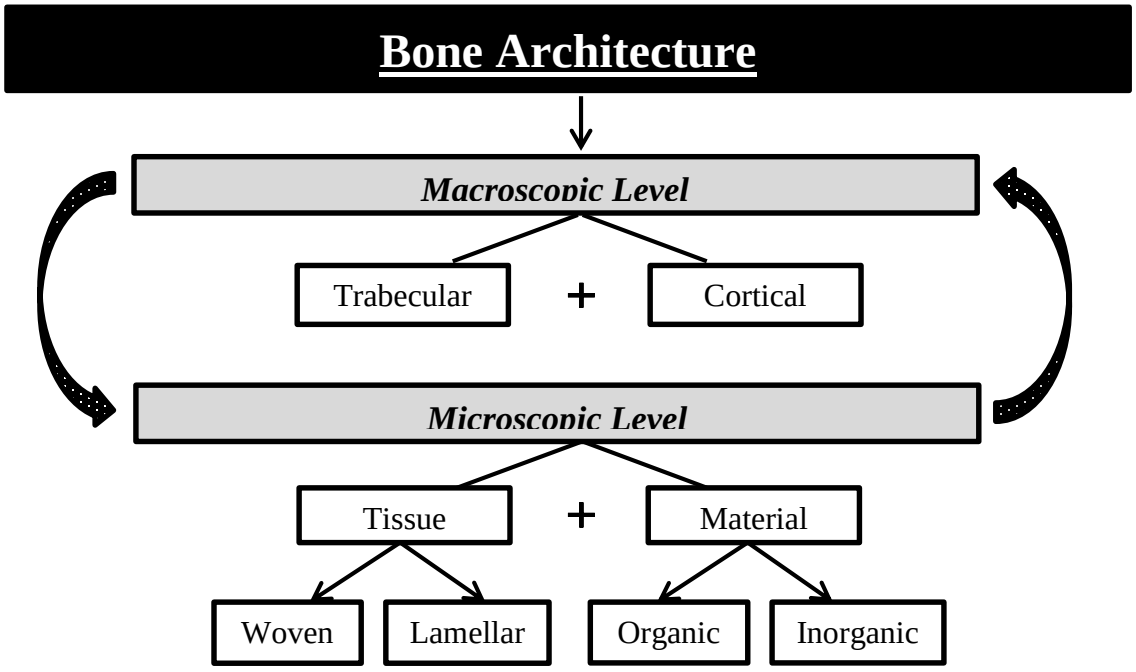


Figure 3. A schematic overview of the hierarchical and multidimensional architectural structures present within human bone; excluding the nanoscopic level (Brandi, 2009; Seeman 2008; Rho, Kuhn-Spearing & Zioupos, 1998; Weiner & Wagner, 1998).

2.2. Bone Physiology

Historically, bone has been regarded as the domain of anatomical study. However mechanically receptive, biologically adaptive and metabolically active components of bone have since solidified it as a biomaterial well-suited for physiological and biomechanical investigation (Cardinale, Newton & Nosaka, 2012; Taylor, Hazenberg & Lee, 2007; Pearson & Lieberman, 2004; Frost, 2003). In particular, the skeleton is able to construct (model) and reconstruct (remodel) itself through cellular processes in response to developmental and mechanical loading demands through tightly controlled cellular activities (Stern & Nicolella, 2013; Singh et al, 2012; Schwab & Scalapino, 2011; Eriksen, 2010; Raggatt & Partidge, 2010; Seeman & Demas, 2006; Harada & Rodan, 2003).

2.2.1. Cellular Mechanisms

Bone is generated, regulated and maintained by an interaction of four key cells: osteoblasts, osteoclasts, osteocytes and extra-cellular lining cells (Nguyen, Tang, Nguyen & Alliston, 2013; Feng & McDonald, 2011; Crockett et al, 2011; Hill & Tumber, 2010; Seeman, 2009; Parfitt, 1994b). Osteoblasts are anabolic in nature, producing new bone material by synthesizing and calcifying newly generated collagen (Cardinale, Newton & Nosaka, 2012; Raggatt & Patridge, 2010; Hadjidakis & Androulakis, 2006; Burger & Klein-Nulend, 1999). Osteoblasts are uniquely adaptable and compatible, transforming into bone lining cells (surrounding the extra-cellular matrix) and osteocytes (embedded within the bone matrix) during the osteogenic process (Singh et al, 2012; Karsenty, Kronenburg & Settembre, 2009; Karsenty, 2008; Franz-Odendaal, Hall & Witten, 2006). Conversely, osteoclasts are antagonists to osteoblasts; a catabolic cell which degrades, dissolves and resorbs bone material, often as a response to material damage or disuse (Raggatt &

Partridge, 2010; Mizoguchi et al, 2009; Manolagas, 2000; Filvaroff & Derynck, 1998). Osteoclasts have a limited lifespan, undergoing apoptosis (programmed cell death) within 2 to 4 weeks of osteoclastogenesis (Singh et al, 2012; Yavropoulou & Yovos, 2008; Manolagas, 2000). Osteoblasts and osteoclasts work independently during bone creation and formation (modelling); and co-operatively via a basic multi-cellular unit (BMU) during bone maintenance and homeostasis (remodelling), described further in Section 2.2.2.

Osteocytes are central to bone development and renewal due to their status as the most abundant residential cell in bone, accounting for approximately 90% to 95% of all bone cells (Lu, Huo, Chiang & Guo, 2012; Bonewald, 2011; Franz-Odendaal, Hall & Witten, 2006; Burger & Klein-Nulend, 1999; Marotti, 1996). Specifically, osteocytes are descendants of osteoblasts produced during osteogenesis, which subsequently become entombed within the mineralised collagen matrix (Singh et al, 2012; Bonewald, 2011; Hill & Tumber, 2010; Franz-Odendaal, Hall & Witten, 2006; Huiskes et al, 2000). Osteocytes form a well-connected network of sensory channels to detect environmental alterations and communicate reactionary processes to osteoblasts, bone lining cells and fellow osteocytes (Nguyen et al, 2013; Lu et al, 2012; Bonewald, 2005; Kusuzaki et al, 2000; Aarden, Burger & Nijweide, 1994). This network is explicitly formed by dendritic connections (~60 to 80 per osteocyte) which proliferate through canaliculated passages to provide a functional and mechanosensitive platform integral to the detection of mechanical load and associated microdamage (Nguyen et al, 2013; Stern & Nicolella, 2013; Lu et al, 2012; Bonewald, 2011; Bonewald, 2005). This function, known as mechanotransduction (described in section 2.2.3.) enables bone to detect and convert mechanical energy into proportionate biochemical signals in order to promote growth and repair processes (Stern & Nicolella, 2013; Reis et al, 2011; Ozcivici et al, 2010; Bonewald, 2006; Aarden et al, 1994).

2.2.2. Hormonal Mechanisms

Bone growth, development and preservation largely relies on hormonal regulation; stochastically controlling skeletal homeostasis through-out the lifespan in order to facilitate non-mechanical functions of bone (Sapir-Koren & Livshits, 2011; Leppanen et al, 2010; Martin & Correa, 2010; Venken, Callewaert, Boonen & Vanderschueren, 2008; Lindsay, 2004; Rizzoli, Bonjour & Ferrari, 2001). Specifically, the endocrine system serves to maintain bone mineral deposition and homeostatic balance through continual, non-mechanically induced generation and regeneration of bone during biological growth and maturation (Imai et al, 2013; Manolagas, O'Brien & Almeida, 2013; Karsenty & Yadav, 2011; Fukumoto & Martin, 2009; Seeman & Delmas, 2006). While the endocrine system does not explicitly strive to optimise bone strength, endocrine status can have a profound, indirect and negative impact on structural integrity and mechanical competency when irregular hormonal environments arise (Khosla, Oursler & Monroe, 2012; Ducy, 2011; Hamilton et al, 2010; Lindsay, 2004; Rizzoli et al, 2001; Ribot & Tremollieres, 1997; Lanyon, 1996; Britto, Fenton, Holloway & Nicholson, 1994). Endocrine activity therefore forms a central component of a complex biological system which mediates calcium-phosphate balance, energy metabolism and bone mineralisation in response to dynamic and volatile physiological requirements (Fuqua & Rogol, 2013; Sinnesael, Claessens, Boonen & Vanderschueren, 2013; Colaianni et al, 2012; Ducy, 2011; Karsenty, 2011; Karsenty, 2006; Godfrey, Madgwick & Whyte, 2003; Ohlsson, Bengtsson, Issakson, Andreassen & Slootweg, 1998). In this regard, endocrine function majorly influences bone health and metabolism, ascending into domination through adulthood and advanced ageing (Agas, Sabbieti & Marchetti. 2013; Manolagas et al, 2013; Esbrit & Alcaraz, 2013; Khosla, Oursler & Monroe, 2012; Sapir-Koren & Livshits, 2011; Lanyon, 1996; Britto et al, 1994).

Table 1. *Endocrine regulation of bone metabolism.*

Hormones	General Description	Bone Metabolism
Growth Regulators		
hGH	Peptide hormone secreted from the anterior pituitary; influences muscle, liver, kidney and bone; promotes longitudinal growth of bone.	Stimulates Formation
IGF-1	Polypeptide with an essential role in growth and development; primarily circulated by liver; also paracrine delivered by non-hepatic tissues.	Stimulates Formation
Glucocorticoids	Produced by adrenal glands, inhibits synthesis of IGF-1, supresses BMP-2 and calcium absorption.	Inhibits Formation Stimulates Resorption
Ghrelin	Gut-derived peptide hormone; secretagogue of growth hormone; modulates energy homeostasis.	Stimulates Formation Inhibits Resorption
Leptin	Adipocyte peptide hormone; proportional to fat stores; modulates energy homeostasis.	Inhibits Formation Stimulates Resorption
Thyroxin (T_3 and $T_{4)}$	Tyrosine-based hormones produced by thyroid gland; regulates energy metabolism through thyroid stimulation hormone (TSH) activity.	Stimulates Formation Stimulates Resorption Net Effect: Homeostatic
ACTH	Peptide hormone secreted from the anterior pituitary; stimulates cortisol production; dose-dependent proliferation of osteoblast activity.	Stimulates Formation Stimulates Resorption Net Effect: Homeostatic
Oxytocin	Peptide hormone secreted from the posterior pituitary; modulated by estrogen; autocrine-paracrine osteoblast regulator of formation.	Stimulates Formation Stimulates Resorption Net Effect: Homeostatic
Gonadal Regulators		
Androgens	Sex steroid secreted from testes (men) and adrenals (men and women); also converts to estrogen; acts in presence of hGH.	Stimulates Formation
Estrogen	Synthesised from androgens in ovaries (women) and extra-glandular tissue (men and women); dominant role in bone metabolism.	Permits Formation Inhibits Resorption
Calcitropic Regulators		
PTH	Polypeptide secreted by parathyroid gland, tightly controls calcium and phosphate; acts to maintain bone mineral homeostasis.	Stimulates Formation Stimulates Resorption Net Effect: Formation
Calcitonin	Secreted by thyroid gland when plasma calcium is elevated; lowers plasma calcium; deposits into bone; relatively weak in comparison to PTH.	Stimulates Formation Inhibits Resorption
Vitamin D_3	Activated in the liver and kidney; essential for intestinal absorption of calcium and phosphate; deficiency results in bone demineralisation.	Permits Formation Stimulates Resorption

Endocrinological regulation of bone metabolism is highly influenced and tightly controlled by sub-categories of growth, gonadal and calcitropic hormones (summarised in Table 1), with varying levels of contribution and relative dominance through-out life (Colaianni et al, 2014; Agas et al, 2013; Csakvary et al, 2013; Imai et al, 2013; Manolagas et al, 2013; Khosla, 2012; Dhanwal, 2011; Karsenty, 2011; Isales, Zaidi & Blair, 2010; Leppanen et al, 2010; Quarles, 2008; Fukushima et al, 2005; Elmquist & Strewler, 2005; Misra et al, 2003; Olney, 2003; Pfeifer, Begerow & Minne, 2002; Neer et al, 2001; Langdahl & Eriksen, 1998; Ohlsson et al, 1998; Gallagher et al, 1998; Uzzan et al, 1996). Specifically, growth hormones exert formative effects; gonadal hormones exert formative and anti-resorptive effects; and calcitropic hormones exert homeostatic effects; co-operatively acting to promote bone mass accrual during growth and maturation (Delhanty, van der Eerden & van Leeuwen, 2014; Esbrit & Alcaraz, 2013; Fuqua & Rogol, 2013; Sinnesael et al, 2013; Colaianni et al, 2012; Khosla, Oursler & Monroe, 2012; Legiran & Brandi, 2012; Ducy 2011; Williams, 2009; Venken et al, 2008; Grote et al, 2005; Godfrey et al, 2003; Yakar et al, 2002; Kroll, 2000; MacDonald, Gallagher & Russell, 1986; Britto et al, 1994). However, hormonal activity begins to decline following the establishment of peak bone mass, as bone formation and resorption shifts from net formation during ontogeny; to equilibrium during early-to-middle adulthood; and net resorption during advanced and older age (Khosla, Amin & Orwell, 2008; Seeman & Delmas, 2006; Bone et al, 2004; Seeman, 2002; Rizzoli et al, 2001). This imbalance in bone metabolism is primarily driven by altered endocrine-paracrine activity, and confounded by multi-dimensional, synergistic and antagonistic hormonal interactions necessary to achieve and maintain metabolic homeostasis (Agas et al, 2013; Raggatt & Patridge, 2010; Hadjidakis & Androulakis, 2006; Takeda & Karsenty, 2001; Manolagas, 2000). As a result, hormonal imbalances and

environmental irregularities underpinning deficient endocrine function form the nutritional and pharmacological basis of bone preservation strategies (Khosla, Amin & Orwell, 2008; Weaver, 2008; Palacios, 2006; Bone et al, 2004; Levy 2002), utilising natural and artificial suppression and stimulation of bone resorption and formation to prevent and manage pathogenic conditions through-out the life-span (described in sections 2.4.3 and 2.4.4)

2.2.3. Bone Adaptation

2.2.3.1. Mechanotransduction

Bone modelling and remodelling paradigms pioneered by Julius Wolff, improved by Wilhelm Roux (Wolff's Law), and expanded upon by Harold Frost (Mechanostat Theory), remain the central focus of emerging research (Frost, 2004; Frost, 2003; Frost, 2001; Frost, 1999; Frost, 1998; Frost, 1996; Frost, 1994; Frost, 1990a; Frost, 1990b; Wolff, Maquet & Furlong, 1986; Frost, 1983; Frost, 1969; Roux, 1885; Wolff, 1892; Roux, 1881; Wolff, 1870; Wolff, 1869). Their meritorious work collectively describes the ability of bone to alter its mass and structure in response to routine mechanical loads (Hammer, 2014; Stoltz, 2012; Chen et al, 2010; Ruff, Holt & Trinkaus, 2006; Skerry, 2006; Pearson & Leiberman, 2004; Huiskes, 2000; Lee & Taylor, 1999; Turner & Pavalko, 1998). However, scientific understanding of this mechanobiological relationship remains poorly understood. The conceptual basis of mechanical events stimulating and mediating bone formation, adaptation, maintenance and repair is widely accepted (Cardinale, Newton & Nosaka, 2012; Chen et al 2010; Klein-Nulend, Bacabac & Mullender, 2005; Burger & Klein-Nulend, 1999; Turner, 1998). However, the cellular mechanisms and structural framework which underpins this observed phenomenon is not yet fully understood and forms the basis of current-day research (Reis et al, 2011; Chen et al, 2010; Wu et al, 2009; Bonewald, 2007; Robling & Turner, 2002; Turner, 1999).

In principle, mechanotransduction refers to the conversion of biophysical forces (mechanical load) into cellular responses which drive morphological change at the tissue level; a functional adaptation of bone which purposely improves structural integrity and strength (Humphrey, Dufresne & Schwartz, 2014; Nguyen et al, 2013; Stern & Nicolella, 2013; Thompson, Rubin & Rubin, 2012; Ozcivici et al, 2010; van Oers et al, 2008; Jarvinen et al, 2003). This epigenetic detection of mechanical force and their conferred cellular responses primarily involve four key activities: 1) mechanical coupling, 2) biochemical coupling, 3) signal transmission, and 4) effector response (Humphrey, Dufresne & Schwartz, 2014; Shapiro, 2008; Bonewald, 2006; Sikavitsas, Temenoff & Mikos, 2001; Duncan & Turner, 1995). Specifically, forces which lead to bone deformation create interstitial fluid movement within canaliculi, stimulating biochemical activity via mechanosensory cells (Thompson, Rubin & Rubin, 2012; Bacabac, Smit, Mullender, Van Loon & Nulend, 2005; Ciani, Doty & Fritton, 2005; Bacabac et al, 2004; Han, Cowin, Schaffler & Weinbaum, 2004; Knothe Tate, Adamson, Tami & Bauer, 2004; Bacabac et al, 2003; Knothe Tate, 2003). Piezoelectric signals are subsequently transmitted through comprehensive lacuno-canalicular networks of osteocytes, lining cells and osteoblasts to determine the format and magnitude of cellular response to the perceived dose of mechanical load (Reis et al, 2011; Ozcivici et al, 2010; Ruimerman et al, 2005; Nicolella & Lankford, 2002; Sikavitsas, Temenoff & Mikos, 2001; Martin, 2000; Burger & Klein-Nulend, 1999; Klein-Nulend, et al, 1995; Cowin, Moss-Salentijn & Moss, 1991). This fundamental dose-response relationship between mechanical load and structural adaptation provides the foundation of bone modelling and re-modelling theory (Humphrey, Dufresne & Schwartz, 2014; Stern & Nicolella, 2013; Thompson, Rubin & Rubin, 2012; Ozcivici et al, 2010; Judex, Gupta & Rubin, 2009; Wu et al, 2009; Jarvinen et al, 2003).

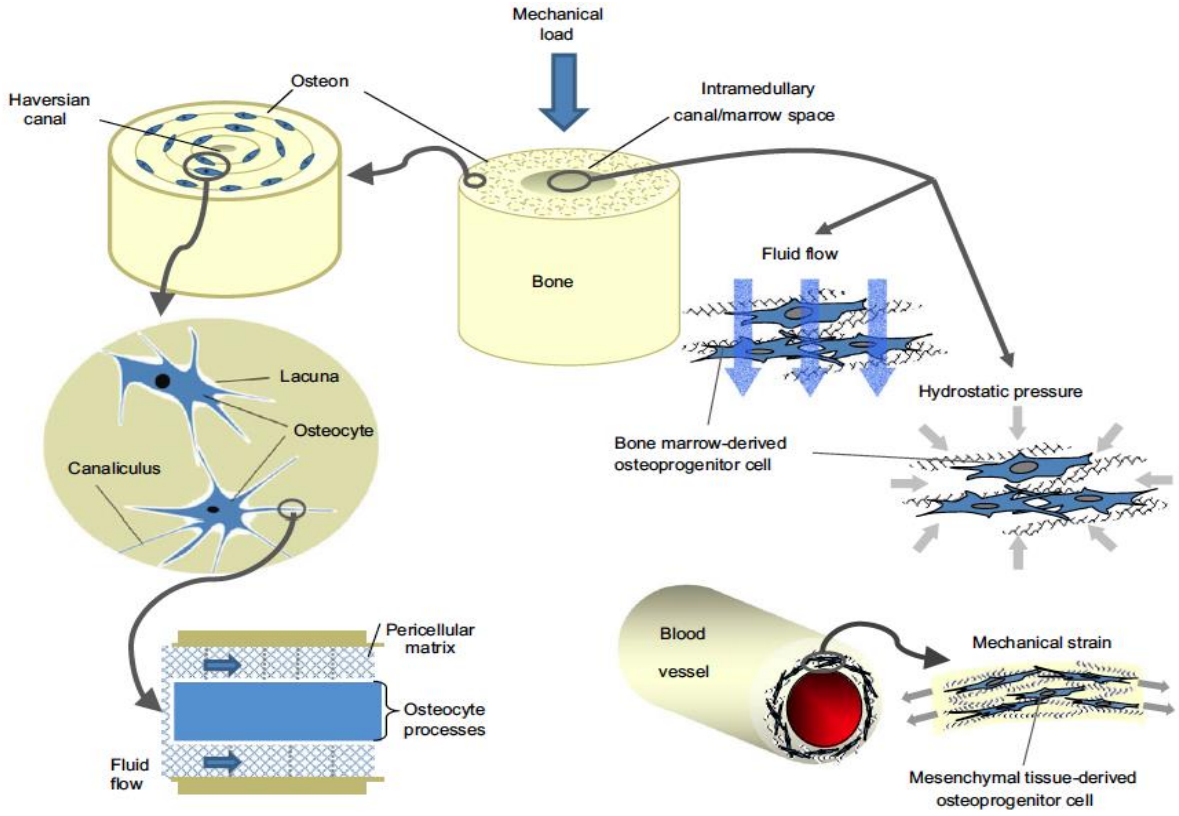


Figure 4. The process of mechanotransduction (adapted from Chen et al, 2010): illustrating the hierarchical structure of bone and the organisational structure of osteocytes within (left); and the mechanically induced fluid flow from hydrostatic pressure and osteoprogenitors through which biochemical signals proliferate (right).

2.2.3.2. Modelling

Modelling is a dynamic and constructive process which adjusts the size, shape and strength of bone in order to achieve its structural potential during ontogeny, specifically in response to physiological and mechanical influences through-out physical maturation (Seeman, 2013; Clarke 2008; Seeman, 2007; Szulc et al, 2006; Heino, Hentunen & Vaananen, 2004; Prendergast, 2002). It comprises of a complex and multifarious array of cellular and material activity which interact to position and configure cells and matrices uniformly during growth and development (Gong et al, 2010; Pearson & Lieberman, 2004; Turner,

1998). At the cellular level, osteoblasts work independently from osteoclasts to create an environment where matrix deposition exceeds matrix resorption (Chen et al, 2010; Clarke, 2008; Szulc et al, 2006; Martin & Sims, 2005; Frost, 2004; Seeman, 2004). At the tissue level, this is expressed through periosteal apposition and simultaneous yet slower endocortical resorption (Clarke, 2008; Seeman, 2008b; Seeman, 2007; Bouxsein & Karasik, 2006; Szulc et al, 2006; Orwoll, 2003; Seeman, 1998), leading to the formation of new bone material and partial preservation of old bone material to deliver a net increase in bone mass (Seeman, 2013; Kukuljan et al, 2011; Chen et al, 2010; Seeman & Delmas, 2006; Jarvinen et al, 2003; Uusi-Rasi et al, 2003).

Longitudinal and radial growth are developmental features of depositional modelling during ontogeny. In particular, collagen is synthesised and deposited onto the extracellular matrix in order to elongate, thicken and widen the periosteum; while endocortical resorption expands the marrow cavity to concurrently increase the diameter of the endosteum together with the periosteum (Seeman, 2013; Clarke, 2008; Seeman, 2008a; Seeman, 2008b; Seeman, 2007; Pearson & Leiberman, 2004; Orwoll, 2003; Raab-Cullen, Thiede, Petersen, Kimmel & Recker, 1994a). These morphological alterations structurally enhance bone strength through two key mechanisms: 1) increasing the cross-sectional area, and 2) increasing the polar moment of inertia (Fonseca et al, 2014; Clarke, 2008; Seeman, 2008a; Bouxsein & Karasik, 2006; Pearson & Leiberman, 2004; Prendergast, 2002). This keeps stresses and strains of applied mechanical loads within a desired range by distributing compressive forces over a larger area, while also resisting bending and twisting forces at the mid-shaft (Seeman, 2008b; Bouxsein & Karasik, 2006; Friedman, 2006; Pearson & Leiberman, 2004; Beck. 2003; Cullen, Smith & Akhter, 2000; Turner & Burr, 1993).

Bone formation is presently thought to be limited to the first three-decades of human life; achieving maturity at this time to establish peak bone mass (Horcajada & Offord, 2012; Nilsson, Ohlsson, Oden, Mellstrom & Lorentzon, 2012; Huuskonen et al, 2001). The potential of bone to develop during growth is influenced by a range of non-modifiable (gender, ethnicity, genetics) and modifiable (nutrition, hormones, lifestyle, physical activity) factors which ultimately determine skeletal maturity (Seeman, 2008a; Bouxsein & Karasik, 2006; Duan, Wang, Evans & Seeman, 2005; Wang, Duan, Beck & Seeman, 2005; Heino, Hentunen & Vaananen, 2004; Orwoll, 2003; Cullen, Smith & Akhter, 2000; Seeman, 1998). However, the accrual of bone is not a linear process, with bone developing most rapidly in adolescent years; acquiring ~50 to 60% of total adult bone mass within this short and critical period of time (Laudermilk et al, 2012; Weaver, 2008; Pitukcheewanont & Safani, 2006; Hartman, Hochberg & Shamir, 2003; Ilich & Kerstetter, 2000; Bonjour et al, 1991). Given the heightened sensitivity and responsiveness of bone during its premature stage of life; a considerable opportunity (window of adaptation) is provided to improve skeletal robustness and resilience through maximising bone mass during early-stage development (Ireland et al, 2014; Warden & Roosa, 2014; Nikander et al, 2010b; Pettersson, Nilsson, Sundh, Mellstrom & Lorentzon, 2010; Janz et al, 2006; Ruff, 2003; MacKelvie, Khan & McKay, 2002; Modlesky & Lewis, 2002; McKelvie, McKay, Khan & Crocker, 2001; Cullen, Smith & Akhter, 2000). Despite this apparent ceiling of bone mass augmentation, bone strength is able to increase through other spatially relevant mechanisms in maturity using a regulatory process known as re-modelling (Seeman, 2013; Horcajada & Offord, 2012; Martin & Correa, 2010; Bouxsein & Karasik, 2006; Ural & Vashishth, 2006; Harada & Rodan, 2003; Neu, Rauch, Manz & Schoenau, 2001).

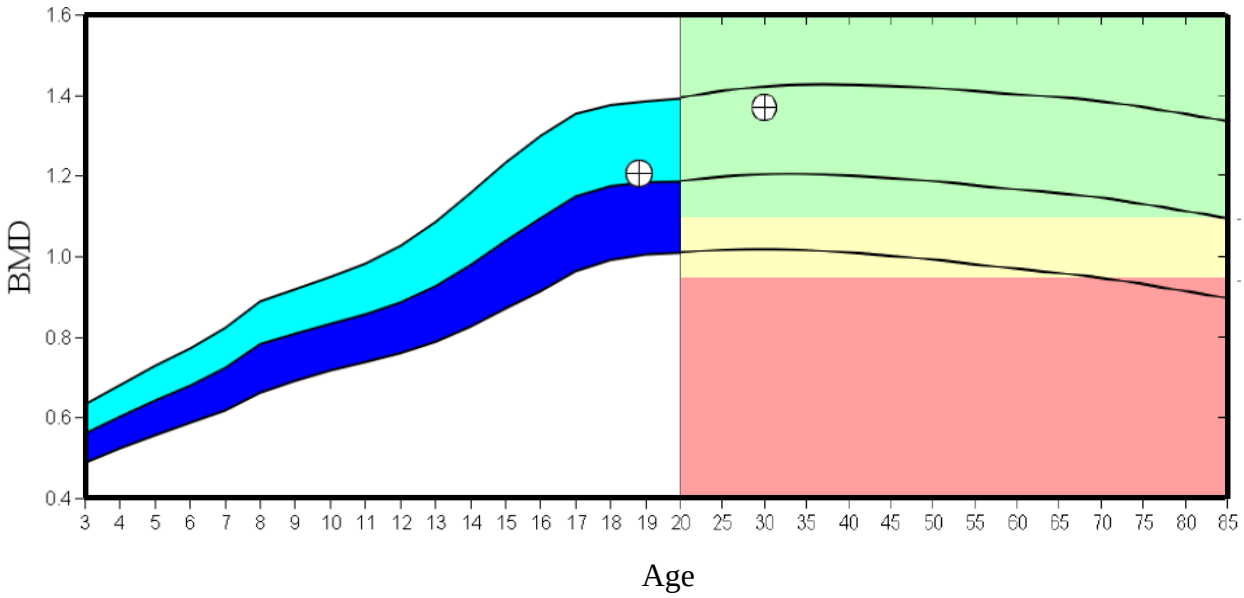


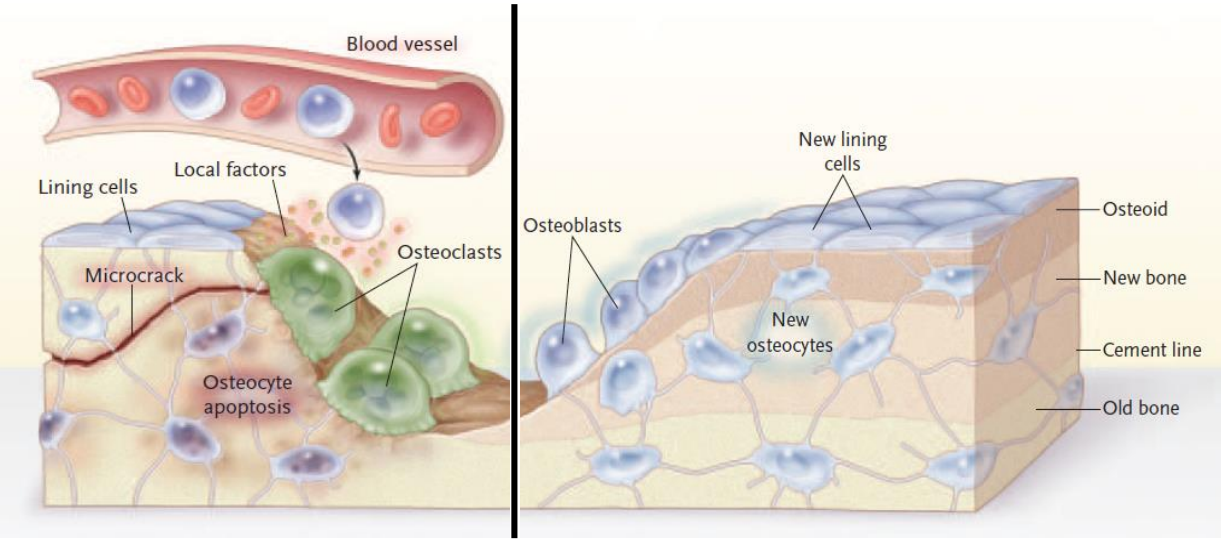
Figure 5. Bone mineral density accrual, maintenance and loss through-out the life-span as as indication of bone mass alterations; with approximately 50 – 60% of total adult bone mass gained during adolescent years preceding peak bone mass and skeletal maturity at ~30 years of age. Bone mass deteriorates gradually following peak bone mass into older age to within normal (green), osteopenic (yellow) or osteoporotic (red) bone density ranges.

2.2.3.3. Remodelling

Remodelling is an on-going, homeostatic and restorative process which replaces old and damaged bone with new and healthy material in order to maintain and improve structural integrity and mechanical competency (Burr, 2011; Crockett, Rogers, Coxon, Hocking & Helfrich, 2011; Feng & McDonald, 2011; Eriksen, 2010; Raggatt & Partridge, 2010; Seeman, 2008a; Seeman 2008b; Hadjidakis & Androulakis, 2006; Filvaroff & Derynck, 1998; Parfitt, 1994b). The regulatory nature of re-modelling relies upon integrated environmental and sensory signals in order to provide a feedback-controlled modulation of skeletal structure; a mechanism designed to sustain current and future functional requirements (Seeman, 2013; Eriksen, 2010; Brandi, 2009; Clarke, 2008; Seeman & Delmas, 2006; Szulc et al, 2006; Harada & Rodan, 2003). This complex and multidimensional process is essential to ensure bone structure remains precariously

balanced between excessive bone mass and excessive bone fragility (a continuum of robustness to slenderness) in order to optimise bone strength without sacrificing mobility; one of many paradoxical expressions of bone adaptation (Singh et al, 2012; Seeman 2008; Robling, Castillo & Turner, 2006; Manolagas, 2000; Filvaroff & Derynck, 1998).

Remodelling occurs through stochastic and deterministic mechanisms (Crockett et al, 2011; Reis et al, 2011; Eriksen, 2010; Brandi, 2009; Harada & Rodan, 2003; Heaney, 1994). Stochastic remodelling describes randomly delivered and spatially non-specific forms of regeneration via the endocrine system (outlined in section 2.2.2.), whereas deterministic remodelling forms the morphological and mechanosensitive basis of bone strength adaptation through-out the lifespan (Burr, 2011; Chen et al, 2010; Robling, Castillo & Turner, 2006; Manolagas, 2000; Hillam & Skerry, 1995). Specifically, deterministic remodelling represents a precisely assigned, targeted and site-specific form of remediation to repair damaged bone as a consequence of mechanical behaviour (Nosaka, Newton & Cardinale, 2012; Burr, 2011; Crockett et al, 2011; Herman, Cardoso, Majeska, Jepsen & Schaffler, 2010; Skerry, 2006; Li, Mashiba & Burr, 2001; Neu et al, 2001). In particular, bone acutely and accumulatively incurs microdamage in response to mechanical loading (gravitational and muscular forces), requiring coordinated cellular-level and tissue-level activity in order to manage and prevent structural failure and bone fracture (Seeman, 2013; Reis et al, 2011; Raggatt & Partridge, 2010; Brandi, 2009; Li, Mashiba & Burr, 2001). As a result, bone is resorbed in regionally and temporally distinct locations, detected and driven at the cellular level by osteocytes through mechanotransduction (outlined in section 2.2.3.1) in order to target, repair and replace damaged material at the tissue-level (Seeman, 2013; Burr, 2011; Crockett et al, 2011; Eriksen, 2010; Herman et al, 2010; Seeman & Delmas, 2006; Filvaroff & Derynck, 1998).



RESORPTION **FORMATION**

Figure 6. A graphical representation of the remodelling cycle (adapted from Seeman & Delmas, 2006). Bone resorption (left) is stimulated by a micro-crack which severs canaliculi channels between osteocytes leading to osteocytic apoptosis. Lining cells and osteocytes release signals attracting cells from blood and marrow reservoirs into the damaged area leading to osteoclastogenesis. Bone formation (right) commences with successive streams of osteoblastic activity depositing new lamellar bone. Osteoblasts then transform into new lining cells (extra-cellular layer) or osteocytes (embedded in osteoid and bone matrix).

Unlike modelling; remodelling requires a coordinated, tightly coupled and sequentially activated cellular response between osteoclasts and osteoblasts in order to resorb damaged bone and deposit healthy bone without sacrificing mechanical competency (Crockett et al, 2011; Martin & Correa, 2010; van Oers, Ruimerman, Tanck, Hilbers & Huiskes, 2008; Szulc et al, 2006; Filvaroff & Derynck, 1998; Parfitt, 1994b). This response is effectuated by basic multicellular units (BMU's); temporary structures composed of grouped osteoclasts and osteoblasts in the presence of blood supply and connective tissue (Feng & McDonald, 2011; Raggatt & Partridge, 2010; Seeman, 2008a; Frost, 2004; Jilka, 2003; Frost, 2001; Parfitt, 1994a). Biologically, these multicellular units are similar between

cortical and trabecular bone, following a standard activation-resorption-formation sequence via osteocyte-osteoclast-osteoblast integration (Singh et al, 2012; van Oers et al, 2008; Hadjidakis & Androulakis, 2006; Manolagas, 2000; Heaney, 1994). However, owing to their differences in organisation, morphology and vascular supply; cortical bone remodels using a tunnel-like resorptive cavity (2000 µm long; 200 µm wide), with a low surface-to-volume ratio and slow turnover rate; whereas trabecular bone remodels using a superficial trench-like resorptive cavity (60 µm deep), with a high surface-to-volume ratio and faster turnover rate (Eriksen, 2010; Gong et al, 2010; van Oers et al, 2008; Hadjidakis & Androulakis, 2006; Robling, Castillo & Turner, 2006). As a proportion of total skeletal mass, approximately 3 to 5% of cortical bone and 25 to 28% of trabecular bone is remodeled each year; completely regenerating the adult skeleton approximately every 10 years (Hill & Tumber, 2010; Hadjidakis & Androulakis, 2006; Manolagas, 2000; Parfitt, 1994a).

Table 2. *Adult bone remodelling (adapted from Manolagas, 2000; Parfitt, 1994a)*

- Lifespan of BMU: **~6-9 months**
- Duration of remodelling: **~4-6 months**
- Speed of remodelling: **~25 µm/day**
- Bone volume replaced by a single BMU: **~0.025 mm^3**
- Lifespan of osteoclasts: **~2 weeks**
- Lifespan of osteoblasts (active): **~3 months**
- Interval between successive remodelling events at the same location: **~2-5 years.**
- Rate of turnover of whole skeleton: **~10% per year** [a]

[a] 10% per year approximation assumes 4% turnover per year of cortical bone (75% of the skeleton), and 28% turnover per year of trabecular bone (25% of the skeleton): Calculated as [0.75 x 4] + [0.25 x 28] = 10%; BMU = basic multicellular unit.

2.2.3.4. **Degradation**

Degradation is a gradual deconstructive process whereby bone material and structure begin to decline and decay through catabolic cellular activity such that resorption exceeds deposition overtime, subsequently compromising the mechanical competency and ultimate strength of bone (Clansey, Hanlon, Wallace & Lake, 2012; Bloomfield, 2010; Herman, Cardoso, Majeksa, Jepsen & Schaffler, 2010; Sievanen, 2010; Robling, Castillo & Turner, 2006; Bennell, Matheson, Meeuwisse & Brukner, 1999). This occurs through non-mechanical and mechanical mechanisms in isolation and combination. Non-mechanical degradation represents the presently irreversible bone loss during advanced biological ageing and associated pathological conditions such as osteopenia, osteoporosis and other disease-states (Khosla, 2013; Seeman, 2013; Bergmann et al, 2011; Feng & McDonald, 2011; Lau & Guo, 2011; Sandhu & Hampson, 2011; Martin & Corea, 2010; Khosla, Amin & Orwoll, 2008; Riggs et al, 2008); whereas mechanical degradation refers to environments of disuse (immobilisation and microgravity) or overuse (repetitive loading) which are preventable and reversible (Cervinka, Rittweger, Hyttinen, Felsenberg & Sievanen, 2011; Landrigan et al, 2011; Macione et al, 2011; Berg, Eiken, Miklavcic & Mekjavic, 2007; Robling, Castillo & Turner, 2006; Danova et al, 2003; Ehrlich & Lanyon, 2002; LeBlanc, Schneider, Evans, Engelbreston & Krebs, 1990). As the cellular governance of bone generation, regeneration and repair is mainly responsive to mechanical load (Bergmann et al, 2011; Herman et al, 2010; Taylor, Hazenberg & Lee, 2007; Robling, Castillo & Turner, 2006; Seeman & Delmas, 2006; Frost, 2004; Bauer & Snow, 2003; Bennell et al, 1999), the absence or overload stimulus can lead to net-resorptive activity and subsequent bone degradation (Ellman et al, 2013; Feng & McDonald, 2011; Lau & Guo, 2011; Gaudio et al, 2010; Sievanen, 2010; Berg et al, 2007; Giangregorio & Blimkie, 2002).

Removal of mechanical loads through microgravity (space travel), disuse (immobilisation) or spinal cord injury (partial or complete paralysis) results in rapid loss of bone mass (Gislason et al, 2014; Lloyd et al, 2014; Torcasio et al, 2014; Wall et al, 2014; Armbrecht et al, 2011; Cervinka et al, 2011; Rittweger et al, 2010; Sievanen, 2010; Rittweger & Felsenberg, 2009; Rittweger et al, 2009; Berg et al, 2007; Rittweger et al, 2005; Baecker et al, 2003; Klein-Nulend, Bacabac, Veldhuijzen & Van Loon, 2003; Leblanc, Schneider, Evans, Engelbretson & Krebs, 1990). Specifically, bone density decreases by ~2% each month through microgravity, partial paralysis or immobilisation without injury; and ~7% each month following complete paralysis or immobilisation with associated musculo-skeletal injury (Lloyd et al, 2014; Torcasio et al, 2014; Feng & McDonald, 2011; Sievanen, 2010; Robling, Castillo & Turner, 2006; Shields et al, 2006; Lang et al, 2004; Giangregorio & Blimkie, 2002; Vico et al, 2000; Collet et al, 1997; del Puente et al, 1996). However, actual strength loss is likely greater, as concurrent reductions in cross-sectional area and mineral content are concealed by bone density measures, yet have dramatic consequences on bone strength (Fonseca et al, 2014; Brandi, 2009; Bouxsein & Karasik, 2006; Davison et al, 2006; Jarvinen et al, 2005; Bauer & Snow, 2003; Mosekilde et al, 2000). Nevertheless, bone loss is incremental and progressive with time and occurs more rapidly in trabecular bone than cortical bone, owing to their different rates of responsiveness to muscular and gravitational osteogenic stimuli (Feng & McDonald, 2011; Lau & Guo, 2011; Riggs et al, 2008; Robling, Castillo & Turner, 2006; Ruimerman et al, 2005; Mosekilde et al, 2000). In reversible situations, the time-course and magnitude of recovery is markedly slower and more gradual than loss (Nagaraja & Jo, 2014; Cervinka et al, 2011; Rittweger et al, 2010; Rittweger & Felsenberg, 2009; Ju, Sone, Okamoto & Fukunaga, 2008; Robling, Castillo & Turner, 2006; Giangregorio & Blimkie, 2002; Leblanc et al, 1990).

Excessive mechanical loads supplied through repetitive and cyclical activity may also yield net-resorptive and degradative effects on bone (Harrast & Colonno, 2010; Edwards, Taylor, Rudolphi, Gillette & Derrick, 2009; Popp et al, 2009; Warden et al, 2005; Beck et al, 1996). In the absence of appropriate recovery, bone fatigue leads to the accumulation of microdamage and coalescence of microcracks, subsequently increasing the total magnitude and rate of remodelling activity at any given time (McCormick, Nwachukwu & Provencher, 2012; Moran et al, 2012a; Herman et al, 2010; Warden, Burr & Brukner, 2006; Warden et al, 2005; Jones, Thacker, Gilchrist, Kimsey & Sosin, 2002). Given that bone reparation requires damaged tissue to be removed (~1 month) and then replaced (~3 months) at various bone sites simultaneously; excessive magnitudes and rates of remodelling have considerable microstructural consequences, progressively weakening bone through loss of stiffness and strength until eventual failure in the form of stress reactions, stress fractures, or heightened susceptibility to traumatic fracture (Moran et al, 2012a; Harrast & Colonno, 2010; Edward et al, 2009; Popp et al, 2009; Warden, Burr & Brukner, 2006; Harada & Rodan, 2003; Beck et al, 1996). In this regard, weakened bone acquires damage at lower relative strain magnitudes; thus fatigued bone creates a progressive and positive feed-back loop between mechanical load and damage accumulation (Ellman et al, 2013; Clansey et al, 2012; Tommasini et al, 2008; Taylor, Hazenberg & Lee, 2007; Warden, Burr & Brukner, 2006; Tommasini et al, 2005; Bennell et al, 1999; Burr et al, 1997). Increasing bone strength reduces fatigability to customary loads, providing greater protection against exercise-induced degeneration; however, more importantly, rest and recovery periods are imperative to ensure structural integrity and mechanical competency remain (Fonseca et al, 2014; Bergmann et al, 2011; Taylor, Hazenberg & Lee, 2007; Davison et al, 2006; Robling, Castillo & Turner, 2006; Milgrom, Simkin, Eldad, Nyska & Finestone, 2000).

2.3. Bone Biomechanics

2.3.1. Mechanical Loading

Bone formation, regeneration and degradation processes are stimulated by mechanical strain as a result of applied mechanical stress in the form of muscular contraction and gravitational forces (Bergmann et al, 2011; Ozcivici et al, 2010; Judex, Gupta & Rubin, 2009; Kohrt, Barry & Schwartz, 2009; Skerry, 2006; Frost, 2004; Ehrlich & Lanyon, 2002; Sikavitsas, Temenoff & Mikos, 2001; Turner, 1998). In particular, bone cells are responsive to local strains expressed in their precise vicinity by routine stresses supplied by activities of daily living (Ellman et al, 2013; Reis et al, 2011; Yang, Bruggemann & Rittweger, 2011; Chen et al, 2010; Ruff, Holt & Trinkaus, 2006; Ehrlich & Lanyon, 2002; Hsieh, Robling, Ambrosius, Burr & Turner, 2001; Fritton, McLeod & Rubin, 2000; Turner & Pavalko, 1998; Rubin, McLeod & Bain, 1990); therefore, the determinants of bone adaptation in response to mechanical load involve all aspects of the strain environment, including strain magnitude, strain rate, strain frequency, strain distribution, number of loading cycles, and rest-recovery periods (Reis et al, 2011; Ozcivici et al, 2010; Judex, Gupta & Rubin, 2009; Kohrt, Barry & Schwartz, 2009; Robling, Castillo & Turner, 2006; Skerry, 2006; Amidzic, Riehli, Fehr, Weinbruch & Elbert, 2001; Turner, 1998; Gross, Edwards, McLeod & Rubin, 1997; Mosley, March, Lynch, & Lanyon, 1997). Specifically, all components of the strain environment are interlinked and interdependent, such that they collectively contribute to the osteogenic effect and potency of mechanical loading.

2.3.1.1. **Stress-Strain**

Bone receives stress (external force) which produces strain (structural deformation). In particular, applied forces generate stresses of varying intensities that produce strains of

varying magnitudes and modes (Burr, 2011; Yang, Bruggemann & Rittweger, 2011; Friedman, 2006; Turner & Robling, 2005b; Currey, 2003a; Huiskes, 2000; Duncan & Turner, 1995; Forwood & Turner, 1995; Turner & Burr, 1993; Turner, 1991). Stress is a measure of load per unit of area, expressed in Newtons per square metre (N/m^2) or Pascals (Pa); whereas strain is a measure of linear or shear deformation expressed as microstrain (με), or as a percentage (%) of change in dimension (Nordin & Frankel, 2012; Wang & Puram, 2004; Ammann & Rizzoli, 2003; Weiner & Wagner, 1998; Turner & Burr, 1993). The interaction of stress and strain provides insight into the mechanical behaviour of material properties in bone when deforming under load (Fonseca et al, 2014; Burr, 2011; Yang, Bruggemann & Rittweger, 2011; Friedman, 2006; Pearson & Leiberman, 2004; Wang & Puram, 2004; Ammann & Rizzoli, 2003; Currey, 2003a; Hayes & Gerhart, 1995).

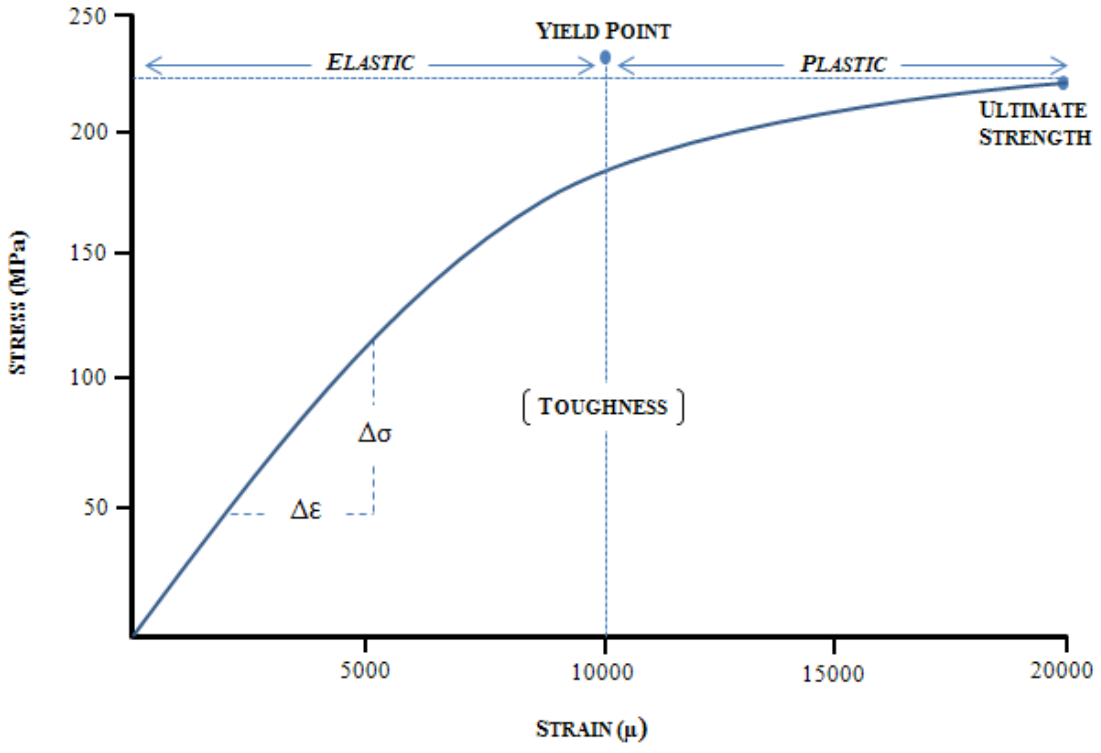


Figure 7. Stress-strain curve (adapted from Nordin & Frankel, 2012; Beaupied, Lespessailles & Benhamou, 2007; Friedman, 2006; Einhorn, 1992), demonstrating elastic and plastic regions; toughness, resilience and ultimate strength.

Bones under strain exhibit two distinct behavioural characteristics either side of their yield point, noted as elastic and plastic regions on the stress-strain curve (Cardinale, Newton & Nosaka, 2011; Beaupied, Lespessailles & Benhamou, 2007; Friedman, 2006; Turner & Burr, 1993; Einhorn, 1992). In the elastic region, lower level strains beneath the yield point allow bone material to elastically store and return applied stress, subsequently escaping microdamage in the process (Bayraktar et al, 2004; Pearson & Leiberman, 2004; Einhorn, 1992; Burstein, Zika, Heiple & Klein, 1975; Burstein, Currey, Frankel & Reilly, 1972). Conversely, in the plastic region, higher level strains above the yield point deform bone material beyond its point of resilience, consequently generating material damage, usually in the form of micro-cracks (Burr, 2011; Kulin, Jiang & Vecchio, 2011; Ammann & Rizzoli, 2003; Schaffler, 2003; Currey, 1984; Carter & Spengler, 1978). Resilience explicitly refers to the capacity of bone to elastically store energy and thus resist microdamage, and is represented by the area under the elastic portion of the stress-strain curve (Nordin & Frankel, 2012; Cardinale, Newton & Nosaka, 2011; Russo, 2009; Schaffler, 2003; Hayes & Gerhart, 1995; Einhorn, 1992; Currey, 1984). Elasticity or stiffness of biomaterial (Young's modulus; $E = \Delta\varepsilon / \Delta\sigma$) can considerably modify skeletal resilience in response to changes in the gradient of the stress-strain curve (Beaupied, Lespessailles & Benhamou, 2007; Bayraktar et al, 2004; Pearson & Leiberman, 2004; Currey, 2003a; Dong & Guo, 2004; Zysset, 2003; Weiner & Wagner, 1998; Keller, Mao & Spengler, 1990). Similarly, an adjustment in resilience can subsequently alter skeletal toughness, represented by the whole area (elastic and plastic regions) under the stress-strain curve (Cardinale, Newton & Nosaka, 2011; Russo, 2009; Wang & Puram, 2004; Ammann & Rizzoli, 2003; Yeni & Fyhrie, 2003; Weiner & Wagner, 1998; Hayes & Gerhart, 1995; Einhorn, 1992; Burstein et al, 1972), thus altering the total amount of energy absorbed by bone prior to failure.

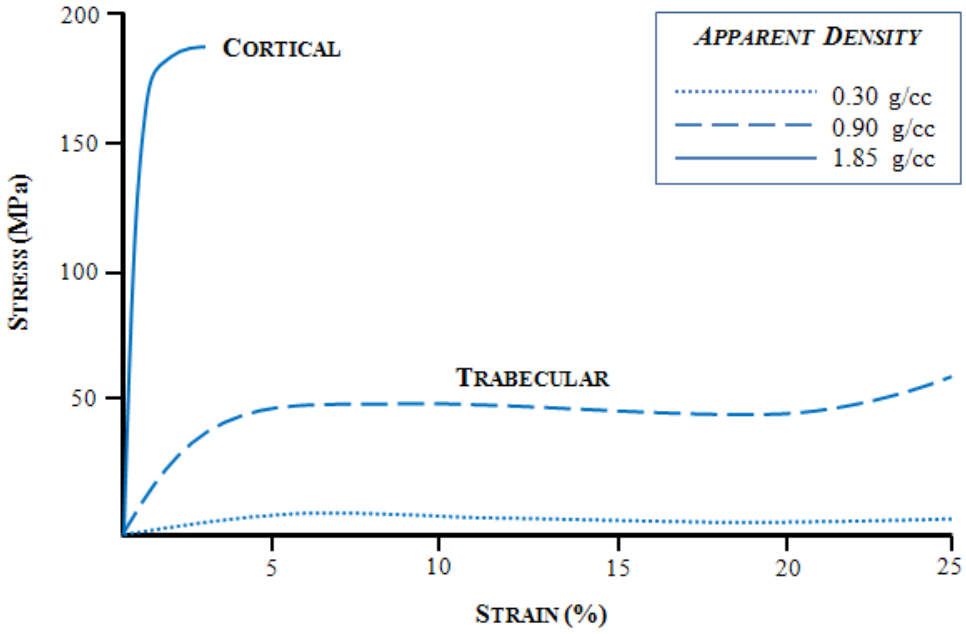


Figure 8. Stress-strain characteristics of macroscopic tissue (adapted from Nordin & Frankel, 2012; Keaveny & Hayes, 1993). Cortical bone is stiffer with a high resistance to stress and low resistance to strain (2% yield). Trabecular bone is porous with a low resistance to stress and high resistance to strain (50% yield).

Stress-strain characteristics differ between macroscopic tissues in response to their underlying microscopic architecture (Main, Lynch & van der Meulen, 2014; Szabo, Zekonyte, Katsamenis, Taylor & Thurner, 2011; Beaupied, Lespessailles & Benhamou, 2007; Wang & Puram, 2004; Yeni & Fyhrie, 2003; Zysset, 2003). Cortical bone is stiffer than trabecular bone, thus can withstand higher stress (~150 MPa) yet lower strain (~2%) prior to failure; whereas the porous nature of trabecular bone provides greater elasticity than cortical bone, thus withstands lower levels of stress (~50 MPa) yet much higher strain (~50%) prior to failure (Nordin & Frankel, 2012; Szabo et al, 2011; Currey, 2003a; Kopperdahl & Keaveny, 1998; Weiner & Wagner, 1998; Keaveny & Hayes, 1993). However, variations in macroscopic composition through-out the skeleton; coupled with

the interaction of different material properties producing different stress-strain characteristics; highlights a complex yet sophisticated relationship between physical load, material deformation and mechanical behaviour (Main, Lynch & van der Meulen, 2014; Seeman 2013; Szabo et al, 2011; Pearson & Leiberman, 2004; Buechner & Lakes, 2003; Hayes & Gerhart, 1995) explored further in Section 2.3.2.

2.3.1.2. Strain Magnitude

Magnitudes of strain received by bone from muscular contraction and gravitational load form the central thesis and most influential feature of bone adaptation (Frost, 2004; Hsieh et al, 2001; Mosley et al, 1997; Turner et al, 1994; Rubin & Lanyon, 1985; Frost, 1983). Conceptually referred to as mechanostat theory (Figure 9); a qualitatively described, dose-response continuum of strain magnitudes can elicit resorptive, regenerative or formative responses in bone (Sugiyama et al, 2012; Robling, Castillo & Turner, 2006; Frost, 2004; Frost, 2003; Cullen, Smith & Akhter, 2001; Turner, 1991). Functionally, the mechanostat serves to modify bone in order to meet mechanical demands; therefore to simply maintain bone mass, a minimum effective strain (MES) is required (Frost, 2004; Frost, 2003; Ehrlich & Lanyon, 2002; Sugiyama, Yamaguchi & Kawai, 2002; Umemura, Baylink, Wergedal, Mohan & Srivastava, 2002). If strain magnitude sits below the MES threshold, mechanical degradation occurs to eliminate unnecessary, excess mass; if strain magnitude exceeds the MES threshold, bone formation occurs to increase bone strength by adding mass and increasing cross-sectional area (Sugiyama et al, 2012; Frost, 2003; Sugiyama, Yamaguchi & Kawai, 2002; Cullen, Smith & Akhter, 2001; Hsieh et al, 2001; Turner & Pavalko, 1998; Turner, 1991; Frost, 1983).

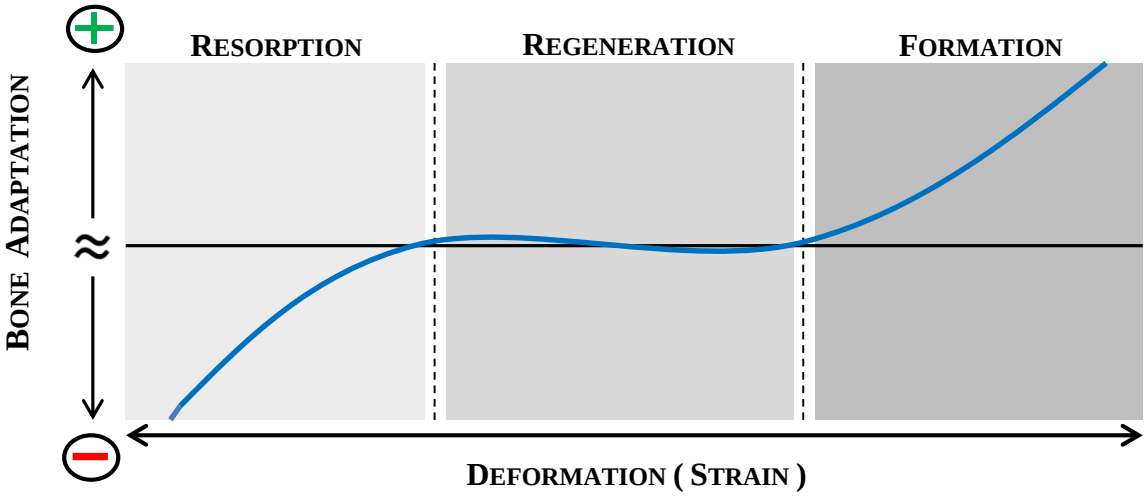


Figure 9. Mechanostat Theory: Resorption represents a region of insufficient strain, where negative adaptation (degradation) occurs; Regeneration represents the minimum strain required to maintain (remodel) bone; Formation represents a region of high strain where positive adaptation (modelling) occurs (adapted from Frost, 2004; Frost 2003; Frost, 1983).

Strain magnitude is not the sole progenitor of, 'nor linearly related to bone adaptation, which highlights an inherent limitation of mechanostat theory in its current form (Wallace et al, 2014; Judex et al, 2003; Ehrlich & Lanyon, 2002; Fritton, McLeod & Rubin, 2000; Turner, Takano & Owan, 1995). Biologically, strain is not sensed and transduced uniformly at the cellular level therefore mechanistically, bone adaptation must respond to various combinations of different strain-related stimuli rather than a specific magnitude of strain itself (Wallace et al, 2014; Sugiyama et al, 2012; Sugiyama, Yamaguchi & Kawai, 2002; Cullen, Smith & Akhter, 2001; Hsieh et al, 2001; Fritton, McLeod & Rubin, 2000). Strain frequency, strain rate and strain distribution are derivatives of strain magnitude, and have therefore been recognised as additional, important determinants of bone adaptation (Judex, Gupta & Rubin, 2009; Robling, Castillo & Turner, 2006; Ehrlich & Lanyon, 2002; Turner, 1998; Gross et al, 1997).

2.3.1.3. Strain Frequency

Strain frequency represents the number of applied cycles-per-second to a given structure (Judex, Gupta & Rubin, 2009; Robling, Castillo & Turner, 2006; Tanaka, Alam & Turner, 2003). The frequency of strain delivered to bone has been established as an influential and programmable determinant of osteogenesis (Judex, Lei, Han & Rubin, 2007; Turner et al, 2005; Warden & Turner, 2004; Rubin et al, 2002; Amidzic et al, 2001; Rubin & McLeod, 1994). Specifically, increases in loading frequency adjust mechanostat thresholds downward; reducing the minimum effective strain required to stimulate osteogenesis, thus enabling strain-related bone formation to occur at lower relative strain magnitudes (Reis et al, 2011; Judex et al, 2003; Cullen, Smith & Akhter, 2001; Hsieh & Turner, 2001). This somewhat inverse relationship between strain frequency and strain magnitude highlights a potential volume-specific adjustable loading mechanism to provide osteogenic stimulus within appropriate, safe and variable strain environments (Robling, Castillo & Turner, 2006; Bacabac et al, 2004; Ehrlich & Lanyon, 2002; Rubin et al, 2002; Tanaka, Alam & Turner, 2003; Hsieh & Turner, 2001).

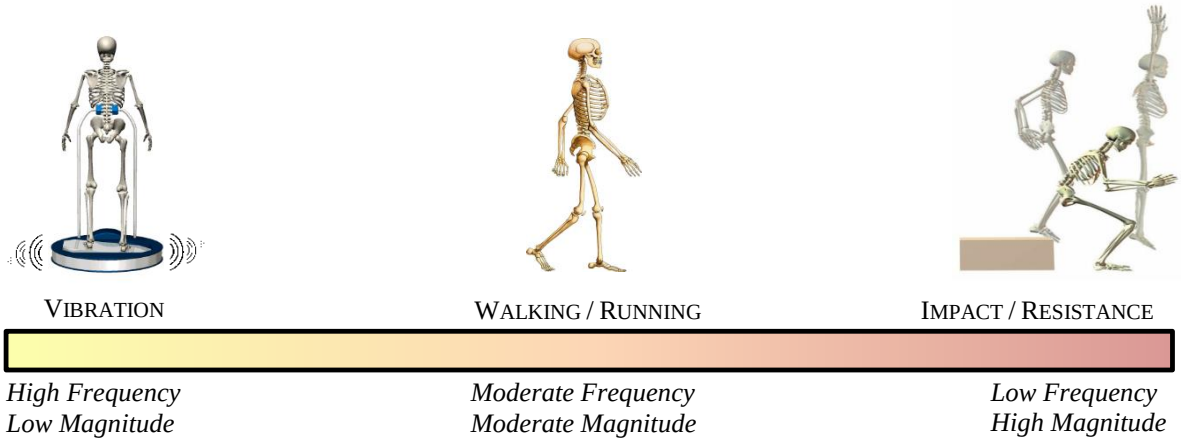


Figure 10. Osteogenic relationship between strain magnitude and strain frequency: Low magnitude, low frequency activities and high magnitude, high frequency activities may lead to maladaptation due to insufficient (resorptive) or excessive (stress reaction) stimuli.

Bone responds in a non-linear fashion to strain frequency, with osteogenic adaptations ceasing to intensify beyond a 10 Hz stimulus cycle due to signal saturation (Reis et al, 2011; Judex, Lei, Han & Rubin, 2007; Warden & Turner, 2004; Hsieh & Turner, 2001). Instead, osteogenic activity interacts with magnitude and frequency loading schemes on a proposed continuum. For example, low magnitude, low frequency strains are likely to result in resorption due to insufficient stimuli; whereas high magnitude, high frequency strains are likely to result in stress reactions or structural failure due to excessive overload. Therefore high-magnitude, low frequency strains (e.g. impact exercise), low magnitude, high frequency strains (e.g. whole-body vibration), or variants of these end-points will optimally yield desirable, formative adaptations (Ozcivici et al, 2010; Bacabac et al, 2004; Ward et al, 2004; Rubin et al, 2002; Tanaka, Alam & Turner, 2003; Judex & Zernicke, 2000).

2.3.1.4. Strain Rate & Distribution

Strain rate and strain distribution represent the temporal and spatial characteristics of strain magnitude respectively (Reis et al, 2011; Judex, Gupta & Rubin, 2009; Turner & Robling, 2005b; Judex et al, 2003; Judex & Zernicke, 2000; Mosley & Lanyon, 1998; Turner, Anne & Pidaparti, 1997). Specifically, strain rate refers to temporal change in strain magnitude within each strain cycle (microstrain per second; με/s), thus measures the rapidity at which alternations in strain application occur (Judex, Gupta & Rubin, 2009; Lamothe, Hamilton & Zernicke, 2005; Turner, Takano & Owan, 1995); whereas strain distribution refers to spatial change in strain magnitude across a given volume of bone (microstrain per linear distance, Δμε/d), quantified circumferentially and longitudinally in each orthogonal axis (Judex, Gupta & Rubin, 2009; Gross et al, 1997; Judex, Gross & Zernicke, 1997). Given the teleological purpose of bone in humans, it seems logical that in order to induce

osteogenic adaptation, strain should be supplied dynamically rather than statically (Turner & Robling, 2005a; Turner & Robling, 2003; Robling, Duijvelaar, Geevers, Ohashi & Turner, 2001; Turner, 1998; Lanyon & Rubin, 1984); therefore variable and volatile strain environments involving these strain parameters should ideologically optimise anabolism in bone (Sugiyama et al, 2012; Judex, Gupta & Rubin, 2009; Robling, Castillo & Turner, 2006; Ehrlich & Lanyon, 2002; Rubin, McLeod & Bain, 1990).

Human and animal models have directly and indirectly established strain rate as a key driver of osteogenesis independent of strain magnitude (Bacabac et al, 2005; Lamothe, Hamilton & Zernicke, 2005; Burr, Robling & Turner, 2002; Judex & Zernicke, 2000; Ferretti, Cointry, Capozza, Capiglioni & Chiappe, 2001; Mosley & Lanyon, 1998; Qin, Rubin & McLeod, 1998; Turner, Takano & Owan, 1995; O'Connor, Lanyon & MacFie, 1982). In particular, adaptive modeling is closely and positively associated with strain rate, such that slowly applied dynamic strains yield minimal adaptations whereas rapidly applied dynamic strains yield significantly intensified adaptations (Turner & Robling, 2003; Burr, Robling & Turner, 2002; Robling et al, 2001; Judex & Zernicke, 2000; Turner, 1998). Similarly, strain location, direction and gradient also contribute to nonlinear outcomes of bone loading paradigms such that irregular and unusual distribution (spatial delivery) of strain is also positively influential to osteogenesis (Reis et al, 2011; Robling, Castillo & Turner, 2006; Gross et al, 1997; Rubin & Lanyon, 1984). Bone cells therefore optimally respond to the net-effect of loading activity that is dominated by high strains (magnitude or frequency) changing at fast rates while presenting in unusual and unbalanced distributions (Russo, 2009; Robling, Castillo & Turner, 2006; Judex et al, 2003; Ehrlich & Lanyon, 2002; Hsieh et al, 2001; Qin, Rubin & McLeod, 1998; Turner, Anne & Pidaparti, 1997; Turner, Owan & Takano, 1995).

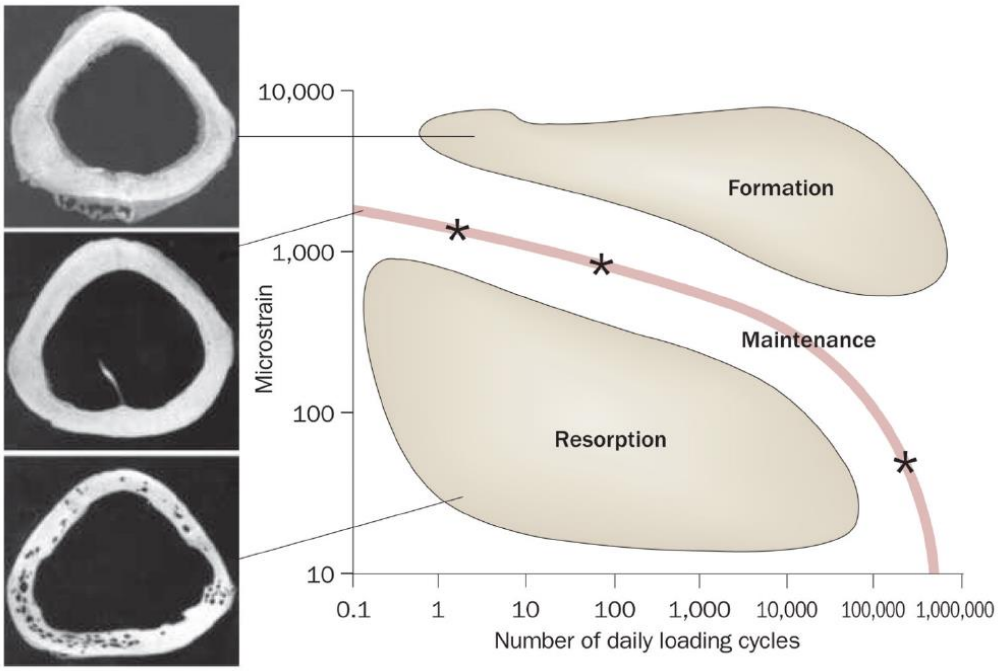


Figure 11. The relationship between daily loading cycles (magnitude, rate and frequency) and subsequent bone adaptation (adapted from Ozcivici et al, 2010). Bone is maintained (red line), formed (superior portion) or resorbed (inferior portion) using a variety of different strain environments.

2.3.1.5. Strain Volume

Strain volume is the durational product of strain magnitude, rate and frequency for a given loading session, often aggregately quantified into a total number of daily loading cycles (Nordin & Frankel, 2012; Ozcivici et al, 2010; Robling, Castillo & Turner, 2006; Qin, Rubin & McLeod, 1998). Specifically, precise amounts of loading cycles at given magnitudes, rates or frequencies generate formative, preservative or resorptive responses in bone dependent upon the strain environment within each session and accumulative strain history within each day (Burr, Robling & Turner, 2002; Ehrlich & Lanyon, 2002; Fritton, McLeod & Turner, 2000). While many combinations of strain magnitude, rate and frequency can interact to provide potent osteogenic stimuli (Figure 11); bone adaptation

does not linearly respond to strain volume (Ozcivici et al, 2010; Robling, Castillo & Turner, 2006; Qin, Rubin & McLeod, 1998). In particular, increases in skeletal loading duration do not elicit proportional changes in bone mass formation; rather, bone responsiveness to mechanical load eventually declines, highlighting an evident suppression of mechanosensitivity (Saxon et al, 2005; Gross et al, 2004; Donahue, Haut, Yellowley, Donahue & Jacobs, 2003; Burr, Robling & Turner, 2002; Robling, Hinant, Burr & Turner, 2002a; Robling, Hinant, Burr & Turner, 2002b; Robling & Turner, 2002; Srinivasan et al, 2002; Robling, Burr & Turner, 2001a; Raab-Cullen, Akhter, Kimmel & Recker, 1994b).

Bone's rapid and acute desensitisation to anabolic stimulus in response to mechanical loading is governed by a law of diminishing returns, such that received load differs from perceived load (Wu et al, 2009; Gross et al 2004; Robling & Turner, 2002; Qin, Rubin & McLeod, 1998). Remarkably small amounts of mechanical stimulation at effective strain thresholds are required to promote osteogenesis prior to a rapid reduction in cellular responsiveness (Robling, Castillo & Turner, 2006; Donahue et al, 2003; Robling et al, 2002a; Umemura, Sogo & Honda, 2002). Specifically, ~95% of mechanosensitivity is dampened after only ~20 to 40 loading cycles at physiologic thresholds (~2000 με in compression), with almost no discernible osteogenic benefit established beyond ~100 loading cycles within equivalent strain environments (Figure 12), at which point strain volume becomes asymptotic (Burr, Robling & Turner, 2002; Umemura, Ishiko, Yamauchi, Kurono & Mashiko, 1997; Rubin & Lanyon, 1984). Indeed, the osteogenic relationship between strain volume and mechanosensitivity is fluid, such that a variety of effective strains along the magnitude-frequency continuum will adjust the number of loading cycles experienced prior to rapid sensory suppression. Nevertheless, the existence of a tangible

saturation point beyond a given cyclical loading threshold has considerable implications for targeted mechanical loading programs (Robling, Castillo & Turner, 2006; Robling et al, 2002b; Umemura et al, 2002; Umemura, Sogo & Honda, 2002; Robling, Burr & Turner, 2001a; Umemura et al, 1997; Umemura et al, 1995).

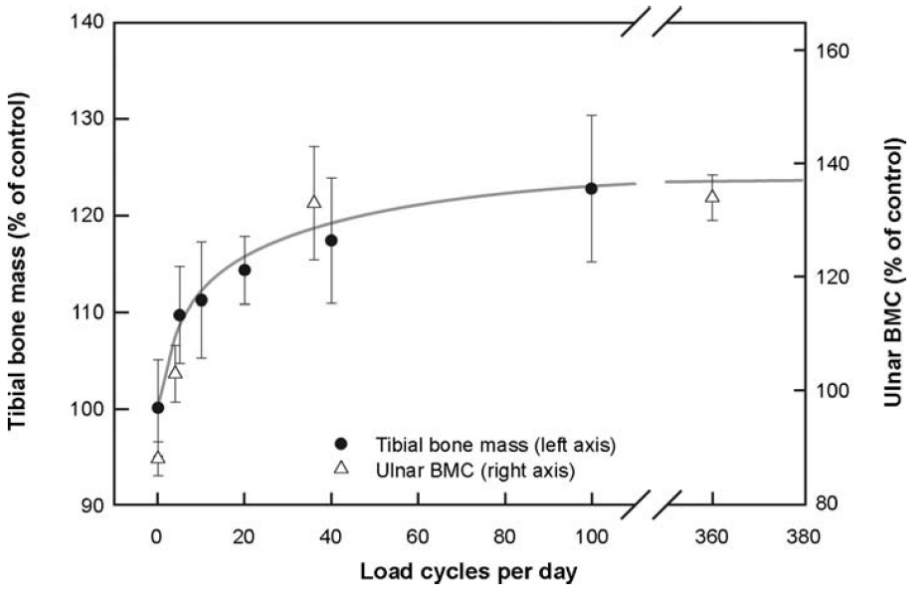


Figure 12. Bone mass of rats (•) and turkeys (∆). Anabolic effect of mechanical loading saturates as the number of loading cycle's increases, with limited benefit above ~40 cycles per day (adapted from Robling, Castillo & Turner, 2006; Burr, Robling & Turner, 2002).

Restoration of mechanosensitivity following previous loading bouts is necessary for bone cells to progressively transduce osteogenic stimuli during successive or future loading bouts (Gross & Srinivasan, 2006; Srinivasan et al, 2003; Robling et al, 2002b; Umemura, Sogo & Honda, 2002; Robling, Burr & Turner, 2000; Raab-Cullen et al, 1994b). In order for resensitisation to occur, the provision of unloaded rest periods is required to afford bone with recovery time; the duration of which is proportionate to the nature of recent loading stimulus incurred (Gross & Srinivasan, 2006; Robling, Castillo & Turner, 2006; Gross et al, 2004; Poliachick, Agans, King, Gross & Srinivasan, 2003). Akin to desensitisation, bone

cell resensitisation presents as a logarithmic function (Figure 13). Specifically, the restoration of mechanosensitivity is also initially rapid, until an inflection point is reached whereby only mild osteogenic improvements occur beyond it (Robling, Burr & Turner, 2001a; Robling, Burr & Turner, 2000). In particular, rest periods spanning ~15 seconds to ~4 hours increase bone formation outcomes by ~65% to 100%; whereas no significant advantage is evident beyond ~8 to 10 hours; and ~98% of mechanosensitivity restored ~24 hours post-loading event (Robling, Castillo & Turner, 2006; Burr, Robling & Turner, 2002; Srinivasan et al, 2002). Rest periods therefore enable an equivalent strain volume to be delivered across several discrete loading blocks; increasing anabolic potency and osteogenic outcomes through targeted mechanical loading schemes (Batra et al, 2005; Gross et al, 2004; Poliachick et al, 2003; Srinivasan et al, 2002; Robling, Burr & Turner, 2000).

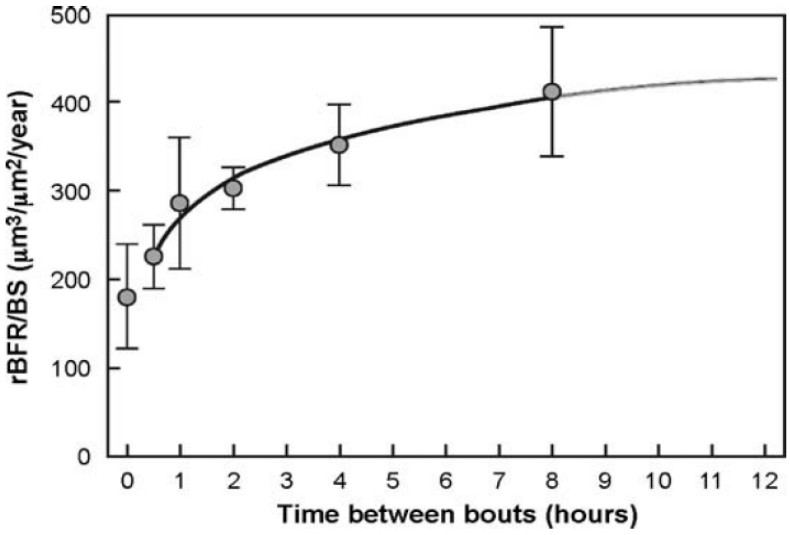


Figure 13. Bone formation (rBFR/BS) of rat tibia after applying loads in 4 bouts of 90-cycles every second day, with various rest provided between bouts; ~4 to 8 hours appears optimal (adapted from Robling, Castillo & Turner, 2006; Robling, Burr & Turner, 2001a).

Cellular accommodation (mechanical acclimatisation) to frequent mechanical loading events creates prolonged cytoskeletal alterations in bone, resulting in longer-term mechanosensitive reductions to familiar strain environments (Wu et al, 2009; Robling, Castillo & Turner, 2006; Saxon et al, 2005; Rubin, Judex & Hadjiargyrou, 2002; Turner, 1999; Turner & Pavalko, 1998; Fyhrie & Schaffler, 1995). Acutely, loading cycles delivered in the first bout of activity provide the greatest opportunity to elicit the largest adaptations within a given session or day, as strain detection and bone adaptation is most responsive at this time (Donahue et al, 2003; Poliachick et al, 2003; Robling et al, 2002a; Robling et al, 2002b; Srinivasan et al, 2002; Umemura, Sogo & Honda, 2002). Chronically, this same principle applies; initial loading blocks within a sequential, long-term loading program also provide the greatest potential for osteogenic adaptation to occur, exemplified when comparing volume-matched regressive and progressive loading schemes (Robling, Castillo & Turner, 2006; Schriefer et al, 2005b; Umemura et al, 2002; Turner & Pavalko, 1998). Akin to acute mechanosensitive suppression; chronic acclimatisation of bone can also be reversed with the provision of unloaded recovery blocks within a broader mechanical loading program (Srinivasan et al, 2007; Saxon et al, 2005; Raab-Cullen et al, 1994b), thus the potency of initial stimulus appears to drive bone adaptation, rather than long-term accumulation of mechanical loads (Srinivasan et al, 2007; Robling, Castillo & Turner, 2006; Saxon et al, 2005; Schriefer et al, 2005b; Turner & Pavalko, 1998). Practitioners must therefore be cognisant of the temporal design and delivery of their prescribed, targeted mechanical loading programs.

2.3.2. Mechanical Behaviour

Bone is structurally complex and hierarchically designed, with diverse arrangements and various layers of biomaterial working co-operatively to meet numerous paradoxical requirements (Fonseca et al, 2014; Hammer, 2014; Brandi, 2009; Clarke, 2008; Seeman & Delmas, 2006; Doblare & Garcia, 2002; Rho, Spearing & Zioupos, 1998). Specifically, the material (mechanical) and structural (geometrical) properties of bone implicitly determines its behaviour under mechanical load, dictating its performance under stress and strain to deliver mechanical rigidity and structural strength to the skeleton (Nordin & Frankel, 2012; Martin & Correa, 2010; Russo, 2009; Bouxsein & Karasik, 2006; Davison et al, 2006; Friedman, 2006; Ammann & Rizzoli, 2003; Weiner & Wagner, 1998). Owing to its anisotropic and viscoelastic design, bones behave and respond uniquely to various loading modalities of differing magnitudes, directions, rates and frequencies (Main et al, 2014; Nordin & Frankel, 2012; Dong & Guo, 2004; Pearson & Leiberman, 2004; Buechner & Lakes, 2003; Zysset, 2003; Garner, Lakes, Lee, Swan & Brand, 2000). While this relationship between mechanical load and mechanical behaviour is multifactorial; bone strength and stiffness are greatest in the direction where loads are most commonly expressed (Cardinale, Newton & Nosaka, 2012; Burr, 2011; Martin & Correa, 2010; Ozcivici et al, 2010; Judex, Gupta & Rubin, 2009; Seeman, 2008a; Frost, 2004; Currey, 2003a; Huiskes, 2000; Wolff, 1892).

2.3.2.1. Loading Types

Bone exhibits distinct mechanical behaviours when loaded across orthogonal axes, as it structurally differs in concentration and arrangement between longitudinal and transverse planes (Cardinale, Newton & Nosaka, 2011; Lynch et al, 2011; Yang, Bruggemann & Rittweger, 2011; Russo, 2009; Leiberman, Polk & Demes, 2004; Pearson & Leiberman,

2004; Doblare & Garcia, 2002; Rho, Kuhn-Spearing & Zioupos, 1998). Consequently, bone strength and stiffness vary across the loading spectrum in an anisotropic and viscoelastic fashion (Table 3), highlighting a context-specific tolerance to mechanical load (Li, Demirci & Silberscmidt, 2013; Beaupied, Lespessailles & Benhamou, 2007; Guedes, Simoes & Morais, 2006; Iyo et al, 2004; Buechner & Lakes, 2003; Doblare & Garcia, 2002; Yamashita, Furman, Rawls, Wang & Agrawal, 2001; Garner et al, 2000; Terrier, Rakotomanana, Ramaniraka & Leyvraz, 1997; Muller & Ruegsegger, 1996; Sasaki & Enyo, 1995; Cowin, Sadegh & Luo, 1992).

Table 3. *Average anisotropic values of ultimate strength (compression, tension, shear), elastic modulus and Poisson's ratio in cortical bone (adapted from Nordin & Frankel, 2012; Reilly & Burnstein, 1975).*

Longitudinal (MPa)	Compression	193
	Tension	133
	Modulus	17,000
	Poisson's Ratio	0.40
Transverse (MPa)	Compression	133
	Tension	51
	Modulus	11,500
	Poisson's Ratio	0.62
Shear (MPa)	Shear	68
	Modulus	3,300

* Trabecular bone: ~50 MPa (compression), ~8 MPa (tension), ~400 MPa (modulus) longitudinally.

Cortical bone is stronger and stiffer in compression than tension; under longitudinal loads than transverse or shear loads; and under higher strain rates than lower strain rates (Li, Demirci & Silberscmidt, 2013; Nordin & Frankel, 2012; Beaupied, Lespessailles & Benhamou, 2007; Shahar et al, 2007; Augat & Schorelemmer, 2006; Bayraktar et al, 2004; Dong & Guo, 2004). By comparison, the mechanical behaviour of trabecular bone is less

predictable and widely volatile, owing to its perforated, variable and less organised lamella arrangement and architectural connectivity (Fonseca et al, 2014; Seeman, 2013; Gong et al, 2010; Beaupied, Lespessailles & Benhamou, 2007; Lai et al, 2005; Zysset, 2003; Jacobs, 2000; Mosekilde, Ebbesen, Tornvig & Thomsen, 2000; Kopperdahl & Keaveny, 1998).

Bone routinely withstands tensile (pulling; positive elongation), compressive (pushing; negative elongation) and shear strains (Lynch et al, 2011; Carter & Beaupre, 2007; Pearson & Lieberman, 2004). Although forces generating strain can act in isolation (uniaxial) or combination (biaxial or triaxial); at any given time bone will still experience all three forms of strain at various locations and magnitudes (Yang, Bruggemann & Rittweger, 2011; Beaupied, Lespessailles & Benhamou, 2007; Lai, Qin, Hung & Chan, 2005; Lai, Qin, Yeung, Lee & Chan, 2005; Milgrom et al, 2000a). The co-existence of linear and angular strains under uniaxial, biaxial and triaxial loading is represented by Poisson's effect; a ratio which describes the susceptibility of bone to deform transversely under given axial loads (Nordin & Frankel, 2012; Shahar et al, 2007; Dong & Guo, 2004). Specifically, bone widens under compression and narrows under tension in accordance with its anisotropic and viscoelastic properties; the sum of which explains the ability and extent of bone to bend and twist under complex or strenuous loads (Cardinale, Newton & Nosaka, 2011; Dong & Guo, 2004; Garner et al, 2000). Bone therefore dynamically responds to forces and moments in various directions (Figure 14), translating compressive, tensile and shear strains into compression, tension, bending, shear and torsional mechanical outputs (Nordin & Frankel, 2012; Lynch et al, 2011; Russo, 2009; Beaupied, Lespessailles & Benhamou, 2007; Shahar et al, 2007; Pearson & Lieberman, 2004).

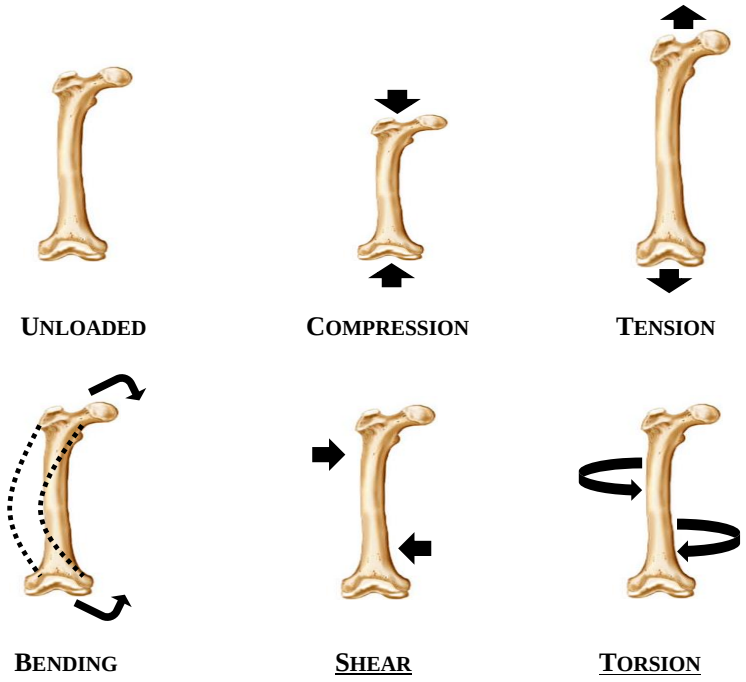


Figure 14. A schematic representation of various loading modes applied to bone in isolation (adapted from Nordin & Frankel, 2012; Pearson & Lieberman, 2004).

2.3.2.2. Material Contribution

Bones are bi-phasic composite materials, with organic and inorganic components (described in section 2.3.1.). The interplay between these materials and their relative composition considerably influences mechanical behaviour and bone strength, independent of geometry, when loaded under static, dynamic or fatiguing conditions (Fonseca et al, 2014; Liu et al, 2010; Bovin et al, 2008; Davison et al, 2006; Peterlik, Roschger, Klaushofer & Fratzl, 2005; Wang & Feng, 2005; Ammann & Rizzoli, 2003; van der Meulen, Jepsen & Mikic, 2001; Rho, Kuhn-Spearing & Zioupos, 1998). Specifically, the degree of mineralisation and porosity (i.e.: apparent density) ultimately determines the quality of bone material, and therefore how it responds to load (Bala, Farlay & Boivin, 2013; Bala, Farlay, Delmas, Meunier & Boivin, 2010; Zebaze et al, 2010; Boivin et al,

2008; Davison et al, 2006; Boskey, 2003b; Currey, 2003b; Su et al, 2003; Rho, Kuhn-Spearing & Zioupos, 1998); influencing its ability to resist deformation (stiffness), absorb stress (elasticity) and absorb energy (toughness) prior to failure (ultimate strength).

Mineralisation refers to the deposition and maturation of mineral content within bone through primary and secondary biomineral phases (Fonseca et al, 2014; Martin & Correa, 2010; Golub, 2009; Friedman, 2006; Ammann & Rizzoli, 2003; Boivin & Meunier, 2002a). Sequentially, newly deposited bone begins to rapidly mineralise within ~5 to 10 days of creation, generating ~60% of its total mineral content during primary mineralisation, prior to gradually advancing toward complete maturation and calcification during secondary mineralisation within ~30 months of initial deposition (Bala, Farlay & Boivin, 2013; Boskey, 2013; Bala et al, 2010; Davison et al, 2006; Boskey, 2003a; Boivin & Meunier, 2002a; Boivin & Meunier, 2002b). This time-course of mineralisation occurs asynchronously and continuously at multiple sites across various regions of bone (Fonseca et al, 2014; Bala, Farlay & Boivin, 2013; Sapir-Koren & Livshits, 2011; Boivin et al, 2008; Davison et al, 2006; Roschger et al, 2003; Boivin & Meunier, 2002a), thus mechanically, the degree to which immature and mature inorganic material (hydroxyapatite crystals) surrounds organic material (type 1 collagen) at any given time will ultimately determine the level of structural flexibility or stiffness conferred to bone, and therefore its mechanical competence (Martin & Correa, 2010; Clarke, 2008; Seeman, 2008a; Allen & Burr, 2007; Friedman, 2006; Wang & Feng, 2005; Follet et al, 2004; Fratzl et al, 2004; Bouxsein, 2003; Currey, 2003a; Currey, 2003b; Boivin & Meunier, 2002b).

Mechanical behaviour is not solely influenced by the degree of bone mineralisation, but also the quality of mineral within the bone matrix (Fonseca et al, 2014; Reis et al, 2011; Liu et al, 2010; Seeman, 2008a; Davison et al, 2006; Peterlik et al, 2005). Indeed, the degree of crystallinity is of behavioural interest as increases in crystal size, number and distribution during secondary mineralisation alter the elastic, plastic and viscoelastic properties of bone in the favour of increased micro-hardness (Bala, Farlay & Boivin, 2013; Boskey, 2013; Golub, 2011; Bala et al, 2010; Farlay et al, 2010; Golub, 2009; Boivin et al, 2008; Yerramshetty & Akkus, 2008; Augat & Schorlemmer, 2006; Davison et al, 2006). If mineralisation and crystallinity are too high, bone may become excessively rigid, stiff and brittle, thus micro-crack initiation, propagation and coalescence may arise at reduced levels of deformation (Bala, Farlay & Boivin, 2013; Boskey, 2013; Burr, 2011; Davison et al, 2006; Boskey, 2003b; Burr, 2003; Currey, 1990). If mineralisation and crystallinity are too low, bone may become fragile and weak; thus a presently undefined, yet evidently optimal ratio of organic-to-inorganic material exists in a U-shaped relationship with bone strength and mechanical competence (Fonseca et al, 2014; Boskey, 2013; Martin & Correa, 2011; Brandi, 2009; Boivin & Meunier, 2003; Boivin & Meunier, 2002a; Boivin & Meunier, 2002b; Weinstein, 2000). This arbitrary conundrum is confounded by the recognition that certain combinations of material properties can improve tolerance to one type of loading, whilst at the same time deleteriously affect another type of loading (Fonseca et al, 2014; Brandi, 2009; Seeman, 2008a; Davison et al, 2006; Peterlik et al, 2005; Su et al, 2003). Fortunately, mineralisation and crystallinity are closely linked, temporally aligned processes; metabolically regulated and mechanically modulated to maintain homeostasis in the absence of pathology or ageing to meet functional requirements (Boskey, 2013; Sapir-Koren & Livshits, 2011; Yerramshetty & Akkus, 2008; Augat & Schorlemmer, 2006).

Porosity represents the prevalence, magnitude and distribution of pores within the bone matrix (Seeman, 2013; Zebaze et al, 2010; Augat & Schorlemmer, 2006; Wang & Ni, 2003; Sikavitsas, Temenoff & Mikos, 2001; Currey, 1988), which characteristically differs between macroscopic tissues. Porosity is a prominent and purposeful architectural feature of trabecular bone (~50 to 90% porous); while minimal in quantity and size within cortical bone (~5 to 10% porous) under normal circumstances (Burr, 2010; Clarke, 2008; Doblare, Garcia & Gomez, 2004; Sikavitsas, Temenoff & Mikos, 2001). The functional merit of porosity in trabecular and cortical bone is provided at the expense of strength, with small increases in porosity equating to disproportionately large decreases in bone mass and density (Fonseca et al, 2014; Seeman, 2013; Davison et al, 2006; Dong & Guo, 2004; Turner, 2002; van der Linden, Homminga, Verhaar & Weinans, 2001; Schaffler & Burr, 1988); the major clinical feature of bone degeneration from ageing, disuse or disease (Giusti & Bianchi, 2015; Lau & Guo, 2011; Zebaze et al, 2010; Dong & Guo, 2004). Trabecular bone is rapidly affected by increased porosity; resulting in progressively thinner, disconnected and separated trabeculae (Fonseca et al, 2014; Fields et al, 2009; Seeman & Delmas, 2006; Siu et al, 2003; Turner, 2002; Laib et al, 2001; Mosekilde et al, 2000); similarly, the weakening of cortical bone is also predominated by increased porosity, resulting in loss of stiffness and reduced load tolerability (Burr, 2010; Seeman et al, 2010; Zebaze et al, 2010; Riggs et al, 2008; Augat & Schorlemmer, 2006; Dong & Guo, 2004; Sevostianov & Kachanov, 2000; McCalden, McGeough, Barker & Court-Brown, 1993; Schaffler & Burr, 1988). Consequently, microarchitectural deterioration of trabecular and cortical bone rapidly compromises mechanical integrity, accounting for ~90% and ~75% of strength loss during ageing respectively (Fonseca et al, 2014; Burr, 2010; Riggs et al, 2008; Seeman & Delmas, 2006; Turner, 2002; Moskilde et al, 2000; McCalden, McGeough &

Court-Brown, 1997; McCalden et al, 1993; Currey, 1988). Bone porosity should therefore be restricted, where possible, to only those cavities required for biological functions such as vascular supply, marrow storage, blood-cell production, biochemical signalling, transduction and remodelling processes (Giusti & Bianchi, 2015; Capozza et al, 2013; Seeman, 2013; Zebaze et al, 2010; Davison et al, 2006; Sevostianov & Kachanov, 2000).

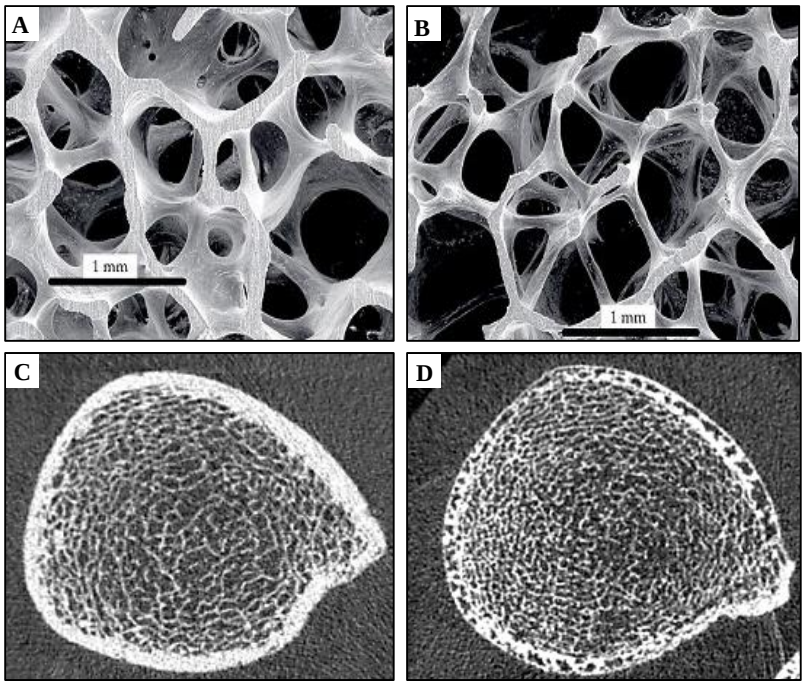


Figure 15. Deterioration of thickness, connectivity and porosity for trabecular (A and B) and cortical (C and D) bone (adapted from Link, 2011; Ritchie, Buehler & Hansma, 2009).

Density is the product of mineralisation and porosity, expressed as mass per unit of volume (Wehrli, Song, Saha & Wright, 2006; Cointry, Capozza, Negri, Roldan & Ferretti, 2004; Rauch & Schoenau, 2001; Rho, Kuhn-Spearing & Zioups, 1998; Seeman, 1998). Specifically, the amount of mineral content per volume of bone (mineralisation), and its ratio of void volume to total volume (porosity) respectively combine to establish apparent bone mineral density (Macdonald, Nishiyama, Kang, Hanley & Boyd, 2011; Jarvinen et al,

2005; Rauch & Schoenau, 2001; Seeman, 1998); the relationship of which exemplifies trabecular and cortical performance under mechanical loads (Fonseca et al, 2014; Main et al, 2014; Macdonald et al, 2011; Brandi, 2009; Petit, Beck & Kontulainen, 2005; Moskilde et al, 2000; Turner et al, 1994). Owing to their architectural and functional differences, components of trabecular and cortical density (surface-to-volume ratios) poorly correlate with each other ($r \approx 0.11$); yet co-operatively influence whole-bone behaviour and strength through separate genetic and environmental mechanisms, the interaction of which remains poorly understood (Fonseca et al, 2014; Paternoster et al, 2013; Kajimura et al, 2011; Paternoster et al, 2010; Jarvinen et al, 2005). Genetically, ~60% of trabecular density and ~40% of cortical density is pre-determined (Paternoster et al, 2013; Havill, Mahaney & Specker, 2007) with unique genomic expressions evident between microarchitectural components; including FMN2/GREM2, RANKL and WNT16 variants effecting trabeculae thickness and number, cortical porosity, and cortical thickness respectively (Paternoster et al, 2013; Estrada et al, 2012; Zheng et al, 2012; Rivadeneira et al, 2009; Richards et al, 2008). Synergistically, this provides scope for environmental mechanisms to separately and aggregately modulate bone density through physical, nutritional and pharmacological mechanisms (discussed in Section 2.4.).

Bone mineral density (BMD) is a frequently used surrogate measure of mechanical competence and bone strength in clinical and experimental contexts, expressed in areal (aBMD) and volumetric (vBMD) terms (Licata, 2009; Wehrli et al, 2006; Jarvinen et al, 2005; Petit, Beck & Kontulainen, 2005; Cointry et al, 2004; Mosekilde et al, 2000). Traditionally, areal BMD (mass per area; g/cm^2) has featured as the central measure of bone quality to establish fracture risk; diagnose osteopenia and osteoporosis; or quantify

interventional efficacy of preventative and remedial programs (Paternoster et al, 2013; Licata, 2009; Rauch & Schonau, 2005; Cummings, Bates & Black 2002; Wilkin, 1999). However, aBMD is limited by its generality; incapable of measuring material volume, composition or structural design; explaining ~50 - 70% of variation in bone strength (Fonseca et al, 2014; Paternoster et al, 2013; Nicks et al, 2012; Toombs, Ducher, Shepherd & Souza, 2012; Clarke, 2008; Havill, Mahaney, Binkley & Specker, 2007; Wehrli et al, 2006; Petit, Beck & Kontulainen, 2005; Rauch & Schonau, 2005; Cointry et al, 2004; Ammann & Rizzoli, 2003). Volumetric BMD (mass per volume; mg/cm^3) has gained ascendency in recent times, owing to its separation of cortical and trabecular compartments; enabling a more refined analysis of tissue composition, adaptation and material contribution to bone strength (Lala et al, 2014; Seeman, 2013; Lala, Cheung, Gordon & Giangregorio, 2012; Sheu et al, 2011; Jarvinen et al, 2005; Petit, Beck & Kontulainen, 2005; Rauch & Schonau, 2005; Rho, Kuhn-Spearing & Zioupos, 1998; Sievanen et al,1998). While this improves upon the limitations of aBMD, all measures of bone mineral density inherently neglect structural properties of bone (architecture, morphology, geometry), which substantially influences mechanical behaviour, and greatly contributes to bone strength and fatigue resistance (Popp et al, 2014; Popp et al, 2012; Martin & Correa, 2010; Seeman, 2008a; Seeman, 2008b; Bouxsein & Karasik, 2006; Friedman, 2006; Boutroy, Bouxsien, Munoz & Delmas, 2005; Rauch & Schonau, 2005). Although bone density provides valuable, modifiable and measureable insights into bone quality; it is only one of several determinants of bone strength (Abel & Macho, 2011; Liu et al, 2010; Brandi, 2009; Engelke et al, 2008; Davison et al, 2006; Jarvinen et al, 2005; Seeman & Delmas, 2006; Cointry et al, 2004; Ammann & Rizzoli, 2003), and should therefore form part of a wider investigative framework which includes structural quantities.

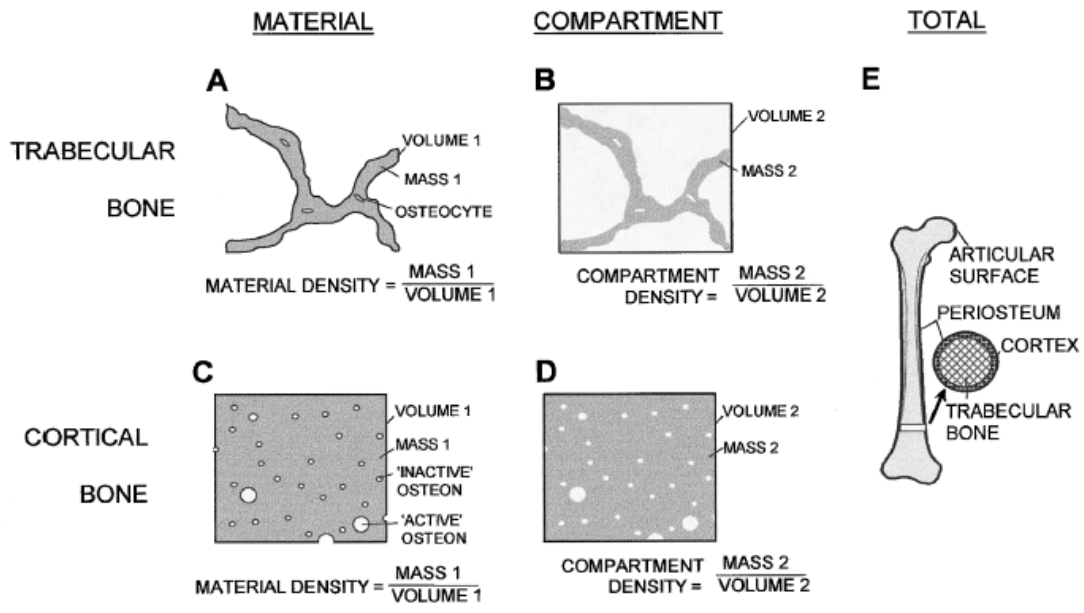


Figure 16. Definitions of mineral density at the material, compartment and whole-bone levels (adapted from Rauch & Schoenau, 2001). Mineralisation and porosity differ between trabecular (A and B) and cortical (C and D) regions. Mass is equal (grey areas); however volume differs (areas encased by black lines).

2.3.2.3. Structural Contribution

Bone has unique geometrical and morphological properties which specifically and functionally adapt to routine mechanical loads in order to enhance bone strength and stiffness in the absence of increased bone mass (Fan et al, 2011; Martin & Correa, 2010; Seeman, 2008a; Daly & Petit, 2007; Bouxsein & Karasik, 2006; Lai, Qin, Hung & Chan, 2005; Pearson & Leiberman, 2004; Frost, 2003). Specifically, bone modifies its structure by adjusting its size (thickness and diameter), shape (contour and dimensions) and architecture (alignment and distribution) to increase cross-sectional area (CSA) and cross-sectional moment of inertia (CSMI) as mechanisms to improve load tolerability and fatigue resistance (Fan et al, 2011; Seeman, 2008a; Seeman, 2008b; Bouxsien & Karasik, 2006; Davison et al, 2006; Lai et al, 2005; Pearson & Leiberman, 2004; Lochmuller, Groll, Kuhn

& Eckstein, 2002; Lochmuller, Lill, Kuhn, Schneider & Eckstein, 2002; Modlesky & Lewis, 2002; Turner, 2002; Davy, 1997). In particular, compressive and tensile strength are proportional to CSA, while bending and torsional strength are exponential to CSMI, such that small amounts of material apposition can significantly improve structural strength (Capozza et al, 2013; Martin & Correa, 2010; Lieberman, Polk & Demes, 2004; Siu, Qin & Leung, 2003; Davy, 1997; McCabe, Zhou, Steele & Marcus, 1991). CSMI is additionally important as it has several bone strength derivatives, including polar moment of inertia (J); section modulus (Z); and bone strength index (BSI).

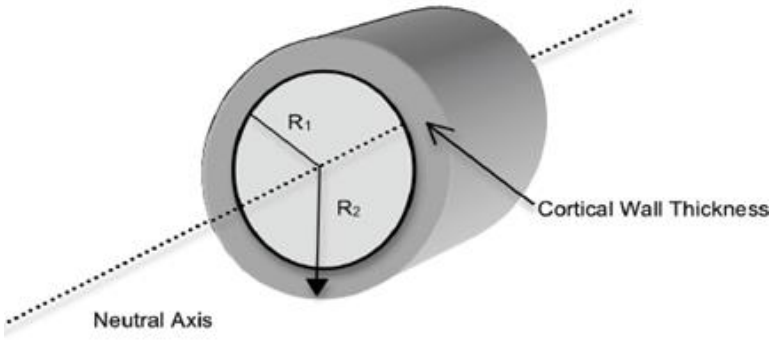
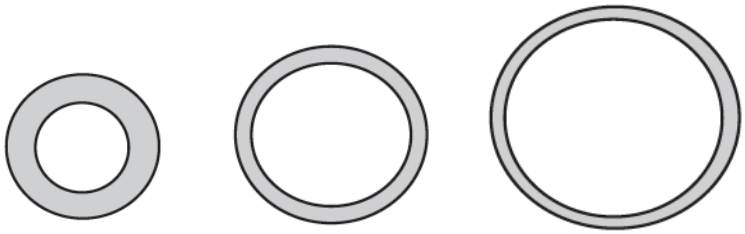


Figure 17. Cross-sectional moment of inertia (CSMI) of a long bone (adapted from Modlesky & Lewis, 2002); where CSMI increases as the cortex widens (R_1 = inner radius; R_2 = outer radius), spreading mass (cortical wall thickness) further from the neutral axis.

Cortex diameter and thickness (i.e. bone size) dramatically influences the mechanical integrity and behaviour of bone when loaded (Fan et al, 2011; Martin & Correa, 2010; Ammann & Rizzoli, 2003; Turner, 2002; Ammann, Rizzoli, Meyer & Bonjour, 1996; Ejersted et al, 1993; Oxlund, Ejersted, Andreassen, Torring & Nilsson, 1993). Specifically, cortex expansion (increased cross-sectional area) advantageously positions material further from the neutral axis of long bones by concomitantly co-ordinating periosteal apposition

with endosteal resorption (Nilsson et al, 2014; Warden et al, 2014; Warden & Roosa, 2014; Capozza et al, 2013; Seeman, 2008a; Modlesky & Lewis, 2002). Mechanically, increases in external and internal diameter of long bone cortices powerfully increases resistance to stress and strain, distributing mechanical forces over a larger area while promoting lightness for efficient movement; accounting for ~55% of bone strength variation (Martin & Correa, 2010; Davison et al, 2006; Ammann & Rizzoli, 2003; Beck et al. 2001; Ammann et al, 1996; Turner & Burr, 1993). In particular, bone strength is proportional to the fourth power of material distance from the neutral axis, such that a doubling in cortex diameter will yield eight-fold increments in mechanical resistance to bending and torsional loads; and modest increments in mechanical resistance to compressive loads; without concomitant changes to mass or density (Capozza et al, 2013; Seeman, 2008b; Davison et al, 2006).



Areal BMD	≈	≈	≈
Compression	≈	↑	↑
Bending	≈	↑↑	↑↑↑

Figure 18. The effect of changes in cortex diameter on bone strength under compression and bending without any change in areal density (adapted from Bouxsein & Karasik, 2006); a limitation of aBMD when assessing the mechanical competence of bone.

Cortex shape and architectural arrangements are also highly adaptive morphological components of bone (Capozza et al, 2013; Abel & Macho, 2011; Fan et al, 2011; Daly & Petit, 2007; Frost, 2004; Yeni et al, 1997; Cheng, Toivanen, Suominen, Toivanen &

Timonen, 1995). Specifically, bone mass asymmetrically and rotationally distributes around the cortex, predominating in areas of high stress, resulting in undulating periosteal and endosteal contours (Nordin & Frankel, 2012; Abel & Macho, 2011; Goldman et al, 2009; Lai et al, 2005; Pearson & Leiberman, 2004; Bass, 2003; Bertram & Biewener, 1988). Indeed, multi-planar bending and torsional forces lead to irregularly distributed increases in diameter and thickness; altering bone size and shape to increase CSA and CSMI; thereby maximising bone strength and stiffness (Capozza et al, 2013; Lieberman, Polk & Demes, 2004; Siu, Qin & Leung, 2003; Modlesky & Lewis, 2002; Davy, 1997). Additionally, cortical and trabecular microarchitecture (collagen fibre organisation) also spatially align in the direction of most commonly expressed stresses to resist customary loads (Fonseca et al, 2014; Seeman 2013; Abel & Macho, 2011; Cardinale, Newton & Nosaka, 2011; Seeman & Delmas, 2006; Frost, 2004). Although these alterations may improve bone strength under common loading scenarios, irregular loading patterns may compromise mechanical competency in the absence of multi-directional, multi-modal and variable stimuli.

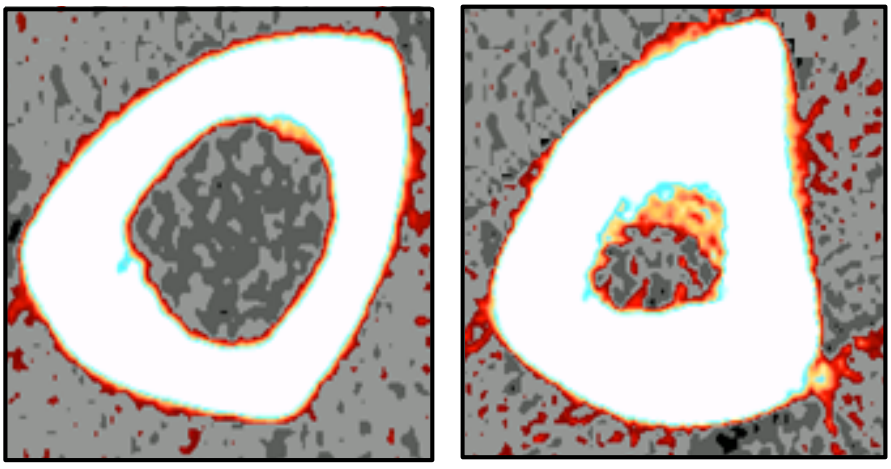


Figure 19. Variations in bone size and shape between age-matched, recreational (left) and elite (right) male athletes illustrating variations in cortical thickness, shape and alignment.

Bone size and shape established during ontogeny determines skeletal robustness or slenderness into adulthood, influencing the format of geometrical co-adaptations to mechanical load during maturation (Capozza et al, 2013; Wallace, Tommasini, Judex, Garland & Demes, 2012; Abel & Macho, 2011; Fan et al, 2011; Goldman et al, 2009; Carter & Beaupre, 2007; Bass, 2003; Bass et al, 2002; Modlesky & Lewis, 2002). Owing to their anthropometric differences (wide versus narrow cortices); material and structural traits of robust and slender bones co-adapt differently to withstand mechanical loads (Jepsen et al, 2013; Tommasini, Nasser, Hu & Jepsen, 2008; Jepsen et al, 2007; Tommasini, Nasser, Schaffler & Jepsen, 2005; Milgrom et al, 1989). Slender bones develop thicker cortices with higher mineral densities than robust bones; conferring additional stiffness at the expense of ductility and toughness in order to compensate for reduced CSA and CSMI dimensions (Wallace et al, 2012; Jepsen et al, 2011; Franklyn, Oakes, Field, Wells & Morgan, 2008; Tommasini et al, 2008; Jepsen et al, 2007; Tommasini et al, 2005; Beck et al, 2000; Beck et al, 1996). Consequently, slender bones exhibit greater susceptibility to damage accumulation (fragility and micro-crack coalescence), whereas robust bones exhibit greater resilience and resistance to fatigue or overload (Jepsen et al, 2013; Franklyn et al, 2008; Tommasini et al, 2005; Warden et al, 2005; Beck et al, 2000; Milgrom et al, 1989). Given the responsiveness of bone mass and radial growth to mechanical loading during ontogeny, it is highly recommended and opportune to maximise robustness within genetic limits where possible (Ireland et al, 2014; Nikander et al, 2010b; Carter & Beaupre, 2007; Janz et al, 2006; Beck & Snow, 2003; MacKelvie, Khan & McKay, 2002; Modlesky & Lewis, 2002). Despite bone strength and stiffness increasing via geometrical means in adulthood; robustness established during ontogeny remains protective through-out life (Nilsson et al, 2014; Warden et al, 2014; Warden & Roosa, 2014; Abel & Macho, 2011).

2.3.2.4. Muscular Contribution

Muscle and bone are inextricably linked by anatomical, mechanical, metabolic and pleiotropic functions (Cianferotti & Brandi, 2014; Ireland, Rittweger & Degens, 2014; Kaji, 2014; Lloyd et al, 2014; DiGirolamo, Kiel & Esser, 2013; Hamrick, 2012; Karasik & Cohen-Zinder, 2012; Hamrick, 2011; Qin, Lam, Ferreri & Rubin, 2010; LeBlanc, Spector, Evans & Sibonga, 2007; Schoenau, 2005). Anatomically, muscle transforms and mobilises skeletal segments into an interlinked system of levers via tendinous junctions (Kaji, 2014; Rabischong, 2014; Marieb & Hoehn, 2013; Karasik & Cohen-Zinder, 2012; Clarke, 2008). Mechanically, muscle exerts contractile forces onto the skeleton in order to effectuate movement, providing bone with its largest voluntary delivery of stimulus; superseding gravitational loads (Ireland, Rittweger & Degens, 2014; Rabischong, 2014; Digirolamo, Kiel & Esser, 2013; Anliker & Toigo, 2012; Schoenau, Neu, Beck, Manz & Rauch, 2002; Rittweger et al, 2000; Schiessl, Frost & Jee, 1998; Schoenau et al, 1996). Metabolically, endocrine-paracrine cross-talk between muscle and bone releases secretory factors capable of modulating each other (muscle to bone; bone to muscle), nearby tissues, and distant organs (Cianferotti & Brandi, 2014; Girgis, Mokbel & DiGirolamo, 2014; Kaji, 2014; DiGirolamo, Kiel & Esser, 2013; Hamrick, 2012; Jahn et al, 2012; Mo, Romero-Suarez, Bonewald, Johnson & Brotto, 2012; Hamrick, 2011; Hadjidakis & Androulakis, 2006; Takeda & Garsenty, 2001). Pleiotropically, muscle and bone share several phenotypic traits, responsive to the same genetic influences and pathways, which if altered, co-operatively contribute to the development of sarcopenia and osteopenia simultaneously, and may explain co-adaptive anabolic and catabolic responses to present or absent mechanical stimulus (Cianferotti & Brandi, 2014; Baud'huin et al, 2012; Karasik & Cohen-Zinder, 2012; Gupta et al, 2011; Karasik & Kiel, 2010; Mikkola et al, 2009).

Adaptation of muscle and bone are interdependent; such that alterations in muscle size, density and strength are temporally linked and positively correlated with alterations in bone size, density and strength (Cianferotti & Brandi, 2014; Ireland, Rittweger & Degens, 2014; Lloyd et al, 2014; Rantalainen, Heinonen, Komi & Linnamo, 2008; Roland, Hanson, Cannon, Stodiec & Ferguson, 2005; Szulc, Beck, Marchand & Delmas, 2005; Rittweger et al, 2000). Specifically, when immobilised; muscle cross-sectional area, volume and strength significantly reduces after ~5 to 7 days; whereas bone thickness, volume and strength significantly reduces after ~14 to 21 days (Lloyd et al, 2014; Wall et al, 2014; Orwoll et al, 2013; Berg, Eiken, Miklavic & Mekjavic, 2007; Carvalho, Louzada & Riso, 2007; LeBlanc et al, 2007; Sibonga et al, 2007; Baecker et al, 2003; Giangregorio & Blimke, 2002). Conversely, when mechanically loaded; muscle cross-sectional area, length and strength significantly increases after ~20 days; whereas bone diameter, thickness and volume significantly increases after ~40 to 80 days (Evans et al, 2012; DeFreitas, Beck, Stock, Dillon & Kasishke, 2011; Seynnes, de Boer & Marici, 2007; Abe et al, 2005; Abe, DeHoyos, Pollock & Garzarella, 2000; Cullen, Smith & Ahkter, 2000). The time-course of adaptation is such that genomic and metabolic alterations occur rapidly and precede morphological adaptations; changes in muscle precede changes in bone (~3:1 to 4:1); and losses of muscle-bone occur more rapidly than accrual (~3:1 to 4:1); thus exercise-induced long-term gains are rapidly reversed and gradually recovered (Lloyd et al, 2014; Nagaraja & Jo, 2014; Armbrecht et al, 2011; Cervinka et al, 2011; Rittweger & Felsenberg, 2009; Baecker et al, 2003; Giangregorio & Blimke, 2002; Goodship et al, 1998).

Muscle is a potent osteogenic stimulant, routinely exerting contractile force onto the skeleton; the frequency, rate, magnitude and distribution of which provides bone with its primary delivery of mechanical load (Avin, Bloomfield, Gross & Warden, 2014; Ireland,

Rittweger & Degens, 2014; Kaji, 2014; Talla, Galea, Lythgo, Angeli & Eser, 2011; El Hage, Courteix, Benhamou, Jacob & Jaffre, 2009; Travison, Araujo, Esche, Beck & McKinlay, 2008; Schiessl, Frost & Jee, 1998; Colletti, Edwards, Gordon, Shary & Bell, 1989). Muscle therefore asserts synergistic dominance over bone, such that bone growth or loss is subservient to muscle hypertrophy or atrophy (Laddu et al, 2014; Lloyd et al, 2014; Qin et al, 2010; Jackowski et al, 2009; LeBlanc et al, 2007; Bitsakos, Kerner, Fisher & Amis, 2005; Ferretti, Cointry, Capozza & Frost, 2003; Burr, 1997). In this regard, muscle and bone are stoichiometric, co-adapting together in response to anabolic or catabolic stimuli; highlighting the importance of muscle size and strength as trainable features to enhance and protect bone size and strength (Avin et al, 2014; Cianferotti & Brandi, 2014; Kaji, 2014; Cardinale, Newton & Nosaka, 2011; Qin et al, 2010; Rantalainen et al, 2008; Khalid, Brannigan & Burke, 2006; Burr, Robling & Turner, 2002). Beyond its osteogenic capabilities, muscle also acts to mechanically alter the distribution of stress applied to bone, utilising short mechanical levers (1:2 to 1:10) to counteract and neutralise tensile forces through partially or wholly equivalent compressive forces as a mechanism to minimise bending moments (Pamukoff & Blackburn, 2015; Avin et al, 2014; Ireland, Rittweger & Degens, 2014; Nordin & Frankel, 2012; Cardinale, Newton & Nosaka, 2011; Martin, Burr & Sharkey, 1998). In particular, volatile forces transmitted through impact loading and agonist muscle contraction create uneven compressive forces onto bone, generating ipsilateral bending moments and contralateral tensile forces; thus antagonist muscle activity serves to actively neutralise tensile forces while evenly distributing compressive forces across the cortex, owing to long-bones superior strength under axial compression (Ireland, Rittweger & Degens, 2014; Milgrom et al, 2007; Pearson & Leiberman, 2004; Duda et al, 1998; Verbitsky, Mizrahi, Voloshin, Treiger & Isakov, 1998; Yoshikawa et al, 1994).

Endocrine-paracrine secretomes hold important implications for muscle-bone biology, providing new opportunities to utilise muscle as a targeted mechanism to cross-regulate and modulate bone. Specifically, molecular cross-talk may independently mediate muscle and bone, separate to mechanical inputs, through secretory factors known as myokines (Kaji, 2014; Hamrick, 2012; Jahn et al, 2012; Lebrasseur, Achenbach, Melton, Amin & Khosla, 2012; Mo et al, 2012; Hamrick, 2011; Hamrick, McNeil & Patterson, 2010; Pedersen, 2009; Walsh, 2009). Myokines (muscle-derived peptides) influence the local activity of neighbouring bone via endocrine-paracrine mechanisms at the muscle-bone interface; an area where muscle fibre inserts directly into the periosteum, thus excluding tendinous and aponeurotic attachments (DiGirolamo, Kiel & Esser, 2013; DiGirolamo, Clemens & Kosteni, 2012; Lebrasseur et al 2012; Hamrick, 2011; Pedersen, 2011). The direct insertion of muscle fibre into bone promotes localised bone formation and reparation activity owing to its collateral delivery of blood and rich supply of secreted trophic factors to the skeleton (Girgis, Mokbel & DiGirolamo, 2014; Hamrick, 2012; Hamrick, McNeil & Patterson, 2010; Walsh, 2009; Vogt et al, 2005; Utvag, Iversen, Grundnes & Reikeras, 2002). In particular, healthy and active muscle tissue positioned alongside and onto the periosteum directly stimulates bone formation without mechanical stimulation; similarly, muscle damage or trauma also delays and impairs bone healing (Liu et al, 2011; Liu, Schindeler & Little, 2010; Harry et al, 2008; Khalid, Brannigan & Burke, 2006; Utvag et al, 2002; Gopal et al, 2000). As a result, the generation, preservation and reparation of bone is interlinked with the health and activity of surrounding muscle, such that cross-regulation has the potential to optimise anabolic and catabolic processes during growth, development, ageing and musculoskeletal rehabilitation (Girgis, Mokbel & DiGirolamo, 2014; DiGirolamo, Kiel & Esser, 2013; Jahn et al, 2012; Lebrasseur et al, 2012; Walsh, 2009).

Table 4. ***Myokines (peptides) secreted by muscle to influence bone, the mechanisms which stimulate release, and the bone metabolism outcomes.***

Myokines	Secretion Stimulants	Bone Metabolism
Growth Factors		
IGF-1	Resistance Exercise	Stimulates Formation
FGF-2	Eccentric Muscle Contraction	Stimulates Formation
GDF-8	Muscle Damage / Atrophy	Supresses Healing / Formation
TGF-β1	Muscle Damage / Atrophy	Supresses Healing / Formation
Matrix Molecules		
SPARC	Resistance Exercise	Promotes Mineralisation
MMP-2	Resistance Exercise	Promotes Healing / Remodelling
BMP-1	Blast trauma to Muscle	Procollagen Cleaving / Bone Formation
Inflammatory Factors		
IL-6	Muscle Contraction	Bone Resorption / Turnover
IL-7	Muscle Contraction	Bone Resorption
IL-15	Resistance Exercise	Increase Bone / Decrease Adiposity

Muscle-derived secretomes influence bone metabolism in a variety of ways, with several growth factors and cytokines importantly linked to bone quality, including interleukin (IL-6, IL-7, IL-15), insulin growth-like factor (IGF-1), fibroblast growth factor (FGF-2), bone morphogenic protein (BMP-1), osteonectin (SPARC), matrix metalloproteinase (MMP-2), transforming growth factor (TGF-β1) and myostatin (GDF-8); exerting anabolic or catabolic effects onto bone in response to physical activity, resistance exercise, muscle damage or trauma (Cianferotti & Brandi, 2014; Kaji, 2014; Baud-huin et al, 2012; Hamrick, 2012; Karasik & Cohen-Zinder, 2012; Hamrick 2011; Pedersen, 2011; Hamrick, McNeil & Patterson, 2010; Karasik & Kiel, 2010; Kitase et al, 2010; Pedersen, 2009).

Conversely, bone-derived secretomes are also capable of influencing muscle metabolism, with recent evidence implicating prostaglandin E2 (PGE2) and undercarboxylated osteocalcin (ucOC) as potential regulators of muscle mass, function and regeneration (Cianferotti & Brandi, 2014; Levinger et al, 2014; Mo et al, 2012; Ducy, 2011). Indeed, endocrine-paracrine cross-talk coupled with mechanical load presents a new and emerging paradigm, whereby muscle and bone closely interact and cross-regulate each other throughout all stages of the lifecycle; highlighting the importance of translational and integrated examinations of muscle and bone biology with growth, development, ageing, exercise and disease (Girgis, Mokbel & DiGirolamo, 2014; DiGirolamo, Clemens & Kosteni, 2012; Hamrick, 2012; Jahn et al, 2012; Walsh, 2009; Wolfe, 2006).

2.3.2.5. Loading Tolerance

Bone mass, material and structure interact with muscle to determine the resultant mechanical behaviour and load tolerability of bone to a given loading environment (Fonseca et al 2014; Ireland, Rittweger & Degens, 2014; Seeman, 2013; Nordin & Frankel, 2012; Burr, 2011; Cardinale, Newton & Nosaka, 2011; Brandi, 2009; Bouxsein & Karasik, 2006; Davison et al, 2006; Friedman, 2006; Ammann & Rizzoli, 2003). Specifically, the interplay between loading magnitude and repetition generates a level of musculoskeletal fatigue and structural vulnerability which, in the absence of suitable rest and recovery, will eventuate in traumatic or overuse injury (Gargac, Turnbull, Roeder & Niebur, 2014; Warden, Davis & Fredericson, 2014; Murgia, 2013; Warden, Burr & Brukner, 2006). The generally inverse relationship between magnitude and repetition describes the causal relationship between mechanical loading and skeletal fatigue on a continuum of high magnitude, low repetition to low magnitude, high repetition loads until structural failure

(Gargac et al, 2014; Nordin & Frankel, 2012; Warden, Burr & Brukner, 2006; Keaveny & Hayes, 1993). To generate and accumulate microdamage, bone must endure strain applications of ~1500 to 10,000 με; the precise magnitude of which is commensurate with resultant microdamage incurred (Warden, Davis & Fredericson, 2014; Nordin & Frankel, 2012; Chen, Beaupre & Carter, 2010; Warden, Burr & Brukner, 2006).

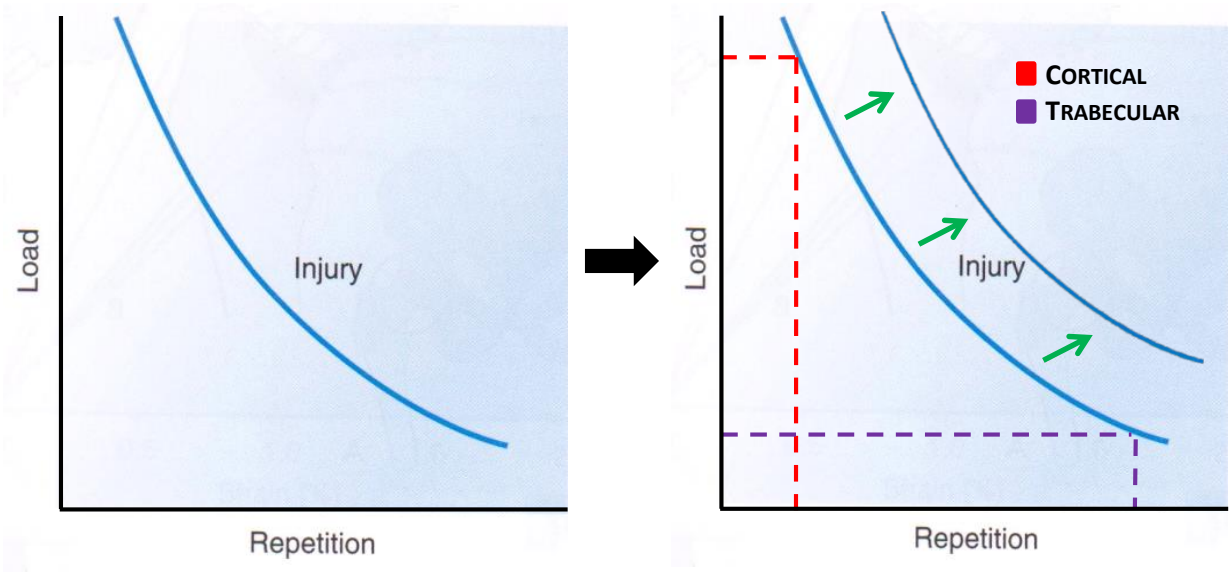


Figure 20. Fatigue curve (adapted from Nordin & Frankel, 2012): The relationship between load, repetition and injury onset (left), with cortical bone and trabecular bone stress-strain properties super-imposed (right). A positive shift in the fatigue-curve demonstrates the benefit of increasing bone strength; a more resilient bone able to handle more stress prior to strain.

Load tolerance and fatigue resistance can be enhanced by increasing bone strength through trainable and modifiable mechanisms (described in section 2.4.); favourably shifting the fatigue curve to the right (Figure 20). Owing to specific material and structural adaptations, stronger and robust bones tolerate higher levels of stress prior to damaging strains, such that equivalent loading environments are less stressful and accumulate less damage than

equally loaded weaker or slender bones, subsequently producing less overall skeletal fatigue (Newshan-West, Lyons & Milburn, 2013; Burr, 2011; Schnakenburg, MacDonald, Ferber, Wiley & Boyd, 2011; Popp et al, 2009; Tommasini et al, 2008; Bouxsein & Karasik, 2006; Tommasini et al, 2005; Franklyn et al, 1998; Beck et al, 1996). Paradoxically, anabolic stimulus required to strengthen bone (long-term) temporarily generates structural vulnerability through acute musculoskeletal fatigue (short-term), implicating muscle fatigue as a covariate to bone fatigue (Figure 21). Specifically, movement quality and efficiency becomes compromised as muscle fatigues (Clansey et al, 2012; Milgrom et al, 2007; Coventry, O'Connor, Hart, Earl & Ebersole, 2006; Mizrahi, Verbitsky, Isakov & Daily, 2000a; Fyhrie et al, 1998; Verbitsky et al 1998; Yoshikawa et al, 1994), resulting in an altered gait; reduced shock absorption; irregular loading; and abnormal stress distribution, such that higher rates and magnitudes of force undesirably transmit direct to the skeleton (Christina, White & Gilchrist, 2001; Mizrahi, Verbitsky, Isakov, 2001; Mizrahi et al, 2000a; Mizrahi, Verbitsky, Isakov, 2000b; Mizrahi, Verbitsky, Isakov, 2000c; Fyhrie et al, 1998; Yoshikawa et al, 1994). In the absence of recovery following strenuous activity, accumulative bone fatigue; microdamage; and eventual bone failure eventuates, highlighting the importance of inserting rest periods within mechanical loading programs designed to promote growth or prevent injury (Corrarino, 2012; McCormick, Nwachukwu & Provencher, 2012; Reshef & Guelich, 2012; Burr, 2011; Harrast & Colonno, 2010; Herman et al, 2010; Taylor, Hazenburg & Lee, 2007; Warden, Burr & Brukner, 2006; Bennell et al, 1999).

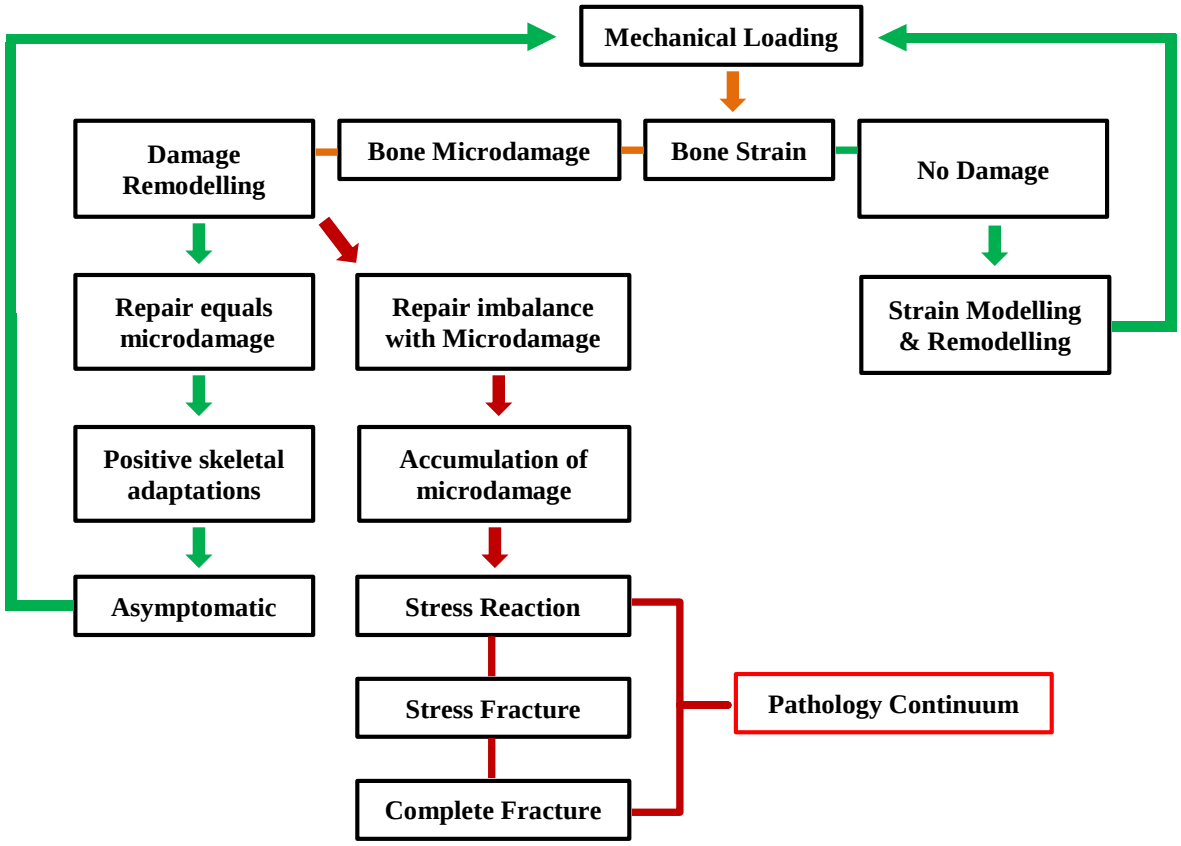


Figure 21. A pathophysiological overview of overuse and fatigue fractures (adapted from Warden, Davis & Fredericson, 2014; Warden, Burr & Brukner, 2006).

2.4. Bone Strength Adaptation

Bone strength explicitly refers to the ability of bone to withstand force prior to catastrophic failure (Fonseca et al, 2014; Davison et al, 2006; Freidman, 2006; Seeman & Delmas, 2006; Pearson & Leiberman, 2004; Ammann & Rizzoli, 2003); and is inextricably linked with fatigue resistance to repetitive loads (Popp et al, 2009; Franklyn et al, 2008; Tommasini et al, 2008; Bouxsein & Karasik, 2006; Tommasini et al, 2005; Warden et al, 2005). Given the complex and multidimensional nature of bone; its strength is ultimately determined by the interaction and adjustment of its material and structural properties (described in Section 2.3.2.) evident at macroscopic, microscopic and nanoscopic levels (Fonseca et al 2014; Seeman, 2013; Brandi, 2009; Seeman, 2008a; Davison et al, 2006;

Friedman, 2006; Rho, Kuhn-Spearing & Zioupos, 1998). The adaptability, modulation and regulation of bone to mechanical and non-mechanical stimuli provides practitioners with the ability to influence bone strength through numerous interdependent mechanisms. Specifically, deterministic and site-specific bone strength adaptations are driven by mechanical loading programs, whereas stochastic non-specific bone strength adaptations are predominantly driven through endocrinological variations, responsive to physical, pharmacological and nutritional interventions (Fonseca et al, 2014; Body, 2011; Sandhu & Hampson, 2011; Martin & Correa, 2010; Nikander et al, 2010b; Karinkanta et al, 2007; Kannus et al, 2005). As all forms of bone adaptation collaboratively determine structural integrity and mechanical competency; it is desirable to optimise and preserve bone strength during growth, development, maturity and advanced age through multi-disciplinary and holistic approaches which importantly address all bone strength determinants.

2.4.1. MEASURING BONE STRENGTH

Bone material, structure and strength must be quantifiable in order to examine, diagnose, monitor and manage skeletal health and bone quality cross-sectionally and longitudinally as a mechanism to establish interventional efficacy of programs designed to enhance or preserve bone strength (Fonseca et al, 2013; Anliker & Toigo, 2012; Seeman & Delmas, 2006; Ashe, Liu-Ambrose, Khan, White & McKay, 2005; Jarvinen et al, 2005). However the accessibility of bone in-vivo remains a constant barrier to scientists. While cadavers are often used to investigate historical events and lasting transactions in bone (Tommasini et al, 2008; Tommasini et al, 2005; Lai, Qin, Yeung, Lee & Chan, 2005; Martin, Severns & Kabo, 2004; Griffin, Gibeling, Martin, Gibson & Stover, 1999; Snyder & Schneider, 1991); understanding the volatile and evolving adaptations of living and responsive hard-tissue

remains elusive (Seeman & Delmas, 2006; Al Nazer, Lanovaz, Kawalilak, Johnston, & Kontulainen, 2012; Lester et al, 2009). Modern-day advancements have attempted to overcome such limitations by developing a multitude of technologies (Figure 22) aimed at non-invasively measuring bone density, structure and strength of various depths, scales and resolutions (Fonseca et al, 2013; Popp et al, 2014; Wehrli, Song, Saha & Wright, 2006; Kang, Paley, Ordidge & Speller, 1999; Ferretti, 1995). Owing to their relative cost, availability and levels of radiation exposure; DXA and pQCT are commonly used bone densitometry devices in clinical and research environments (Sheu et al, 2011; Petit, Beck & Kontulainen, 2005; Cross, Smart & Thomson, 2003; Nijs et al, 1998; Ferretti, 1995; Desforges, Johnston, Slemenda & Melton, 1991); often supported by the collection of biochemical markers through serological and urianalytical samples as surrogate measures of bone metabolism (Banfi, et al, 2011; Rogers et al, 2011; Rantalainen et al, 2009a).

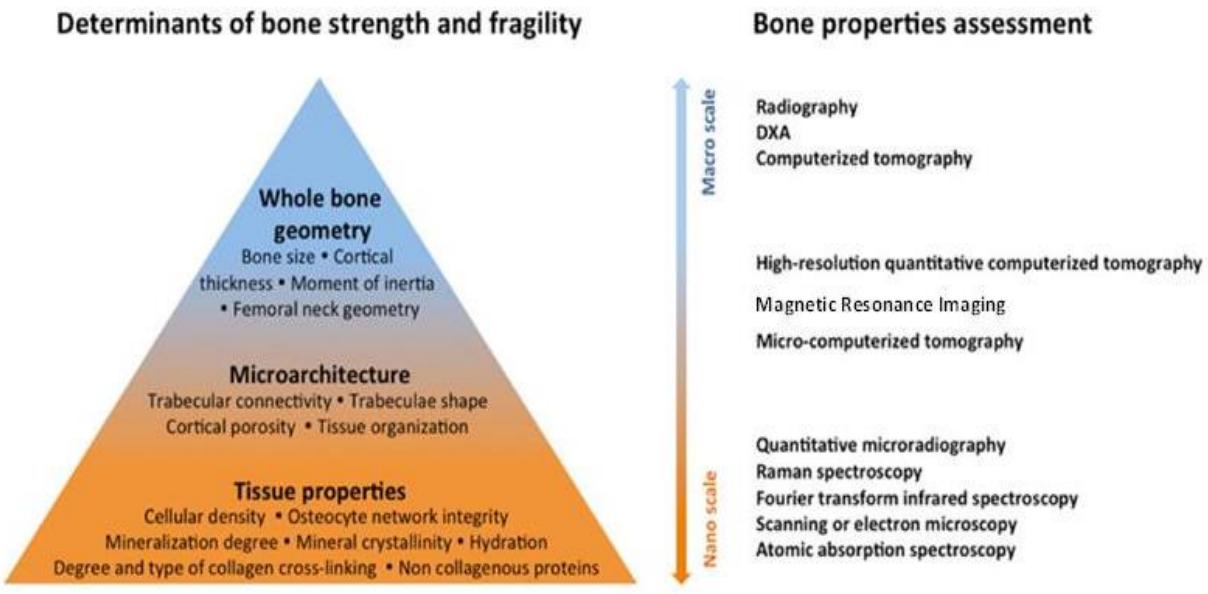


Figure 22. The material and structural determinants of bone strength and fragility [LEFT] with associated technologies required to examine bone properties [RIGHT]; along the macroscopic, microscopic and nanoscopic continuum [top to bottom], (adapted from Fonseca et al, 2014).

2.4.1.1. Dual-energy X-ray Absorptiometry

Dual-energy X-ray Absorptiometry (DXA) is a low-resolution, uniplanar, two-dimensional bone densitometry imaging device (Figure 23) which measures full-body and segmental projections of mass quantities and densities in-vivo using low-level radiation through x-ray technology (Petit, Beck & Kontulainen, 2005; Durkin, Dowling & Andrews, 2002). Specifically, DXA emits two distinct photon energies (140 KeV/70 KeV) via collimated pencil, fan or narrow beams which pass through the individual; the attenuation coefficients and ratios of which differentiate hard tissue from soft tissue, and fat mass from lean mass in an expedient and effective manner (Toombs, Ducher, Shepherd & De Souza, 2011; Durkin, Dowling & Andrews, 2002; Pietrobelli, Wang, Formica & Heymsfield, 1998). Importantly, DXA quantifies areal bone mineral density (aBMD) and its derivatives (bone area and bone mineral content) in order to examine bone quality (Cointry et al, 2004; Licata, 2004; Cummings, Bates & Black, 2002); while also measuring body composition, specifically quantifying soft tissue (fat mass and lean mass) simultaneous with hard tissue (bone mass) in order to concurrently measure materials which co-adapt with each other (Bilsborough et al, 2014b; Rothney et al, 2012; Toombs et al, 2011; Santos et al, 2010). While DXA produces valid and reliable, scan-rescan measures of whole-body bone mass characteristics and body composition components; numerous standardised nutritional, procedural and analytical controls are required to ensure longitudinal integrity of measures when examining interventional efficacy (Bilsborough et al, 2014b; Burkhart, Arthurs & Andrews, 2009; Chen et al, 2007; Stewart & Hannan, 2000; De Lorenzo, Andreoli & Candeloro, 1997; Trevisan et al, 1992).

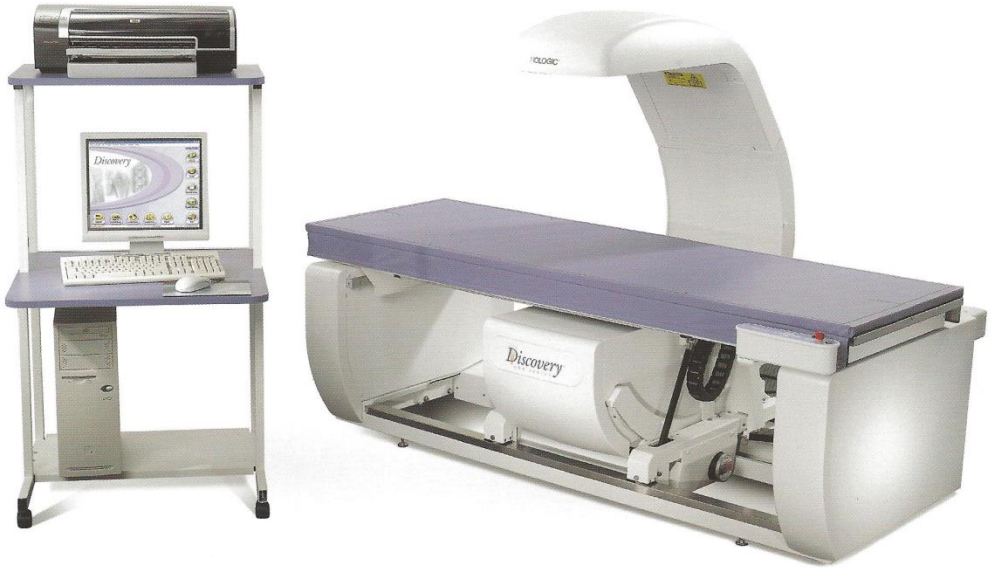


Figure 23. A DXA machine, Hologic QDR-1500 Discovery A model (right); with the operating system and analysis software package (left).

Bone health and skeletal fragility diagnoses of bone disorders are clinically defined by the World Health Organisation (WHO) using DXA-derived aBMD T-scores from population-based reference values, highlighting its established and reputed position as the gold standard in clinical environments (Bianchi et al, 2010; Suman, Subbalakshmi, Pai & Shaila, 2013; Licata, 2004; Gürlek, Bayraktar & Ariyürek, 2000). However, clinical examinations using DXA technology are inherently flawed, as bone material (architecture) and structure (size and shape) cannot be measured (Cointry et al, 2004; Petit, Beck & Kontulainen, 2005; Sievanen et al, 1998). Specifically, DXA's uniplanar, low-resolution images restrict clinicians to descriptions of whole bone mass, which only partially explains bone strength variation (Seeman & Delmas, 2006; Ammann & Rizzoli, 2003; Kroger, Vainio, Nieminen & Kotaniemi, 1995). Inaccurate diagnoses of osteoporosis therefore prevail, with many fragility fractures prevalent in categorically low-to-moderate risk individuals, classified within normal or osteopenic regions (Sheu et al, 2011; Friedman, 2006; Boutroy, Bouxsein, Munoz and Delmas, 2005; Gürlek, Bayraktar & Ariyürek, 2000); further confounded by

regional disparities and T-score variations between measurable sites within a given individual. Indeed, denser bone isn't always stronger, and low density isn't always osteoporotic (Popp et al, 2012; Licata, 2009; Boutroy et al, 2005; Cointry et al, 2004); thus no identifiable total body or site-specific BMD threshold abruptly or disproportionately increases fracture risk; instead, BMD is continuously variable with fracture risk, such that lower BMD equates to higher fracture risk, however does not explicitly predict it (Popp et al, 2012; Sheu et al, 2011; Licita, 2004; Kroger et al, 1995). Therefore, more refined and detailed analyses of bone material and structure are required for more appropriate and predictive diagnoses, potentially deliverable with other technologies (Seeman & Delmas, 2006; Cointry et al, 2003; Cummings, Bates & Black, 2002; Sievanen et al, 1998).

2.4.1.2. peripheral Quantitative Computed Tomography

Quantitative Computed Tomography (QCT, axial; pQCT, peripheral) is a multi-planar, three-dimensional bone densitometry imaging device (Figure 24) which measures the material and structural properties of bone at macroscopic depth; providing clinicians with more accurate descriptions of bone shape, size and quality (Louis et al, 2010; Engelke et al, 2008; Sievanen et al, 1998). Specifically, pQCT transmits targeted collimated beams at selected sites along the length of a given long bone, reconstructing rotational and contiguous two-dimensional samples at each site to deliver a three-dimensional cross-sectional tomographic image of bone, muscle and fat (Jast & Jasiuk, 2013; Willnecker, 2011; Burrows, Cooper, Lu & McKay, 2009). As a result, pQCT devices are able to provide unobstructed circumferential measures of hard- and soft- tissue masses, generating volumetric measures of area, content and density for trabecular bone, cortical bone, marrow, muscle and fat compartments; bone strength indices and fracture loads; periosteal

and endosteal size; cortical thickness; and bone mass (Evans et al, 2012; Willnecker, 2011; Burrows et al, 2009; Kontulainen et al, 2007; Cramer et al, 2007; Genant et al, 1996). Diagnostically, this enables pQCT to address many limitations previously experienced through DXA examinations; providing precise, stable and reliable measures of bone and muscle components (Evans et al, 2012; Louis et al, 2010; Burrows et al, 2009; Cramer et al, 2007; Shields et al, 2006; Cointry, et al, 2004; Sievanen et al, 1998; Nijs et al, 1998).

Figure 24. A pQCT machine with tibial measurement, knee brace and foot holder attachments (right) and the operating system with analysis software package (left).

Bone quality and skeletal fragility examinations using pQCT are superior to those provided by DXA (Sheu et al, 2011; Engelke et al, 2008; Genant et al, 1996). Importantly, applications of mechanical assumptions to quantified material and structural properties across numerous cross-sections allow indices of bone strength to be established, providing better predictive accuracy of fracture risk beyond generic aBMD and vBMD measures (Lala et al, 2014; Lala, Cheung, Gordon & Giangregorio, 2012; Evans et al, 2012; Engelke et al, 2008; Kontulainen et al, 2008; Cointry et al, 2004; Genant et al, 1996). Despite the advantageous diagnostic power afforded to clinicians using pQCT; complexity arises as normative and comparative data for general, specific and special populations scarcely exist

at present, owing to its novel and emerging status as an alternate imaging device in clinical and research environments (Sheu et al, 2011; Rauch & Shonau, 2005; Sievanen et al, 1998). Supplementing DXA measures with pQCT measures may provide a potential short-term solution to combine a detailed insight of bone strength adaptation and fracture risk with clinically relevant reference values. Currently, pQCT is limited to macroscopic depth; however recent technological advancements have led to the creation of micro-scanners (HR-pQCT) with higher resolution images capable of detecting critically important microarchitectural features including trabecular thickness, connectivity and number; cortical porosity; volume fraction; and arterial calcification (Popp et al, 2014; Liu et al, 2010; Lala et al, 2014; Lala et al, 2012). Unfortunately, HR-pQCT is yet to gain ascendency in clinical and research settings due to its infancy in development and high associated cost; however is likely to increase in popularity given the diagnostic importance and catastrophic consequence of microarchitectural deterioration in disease-states and advanced ageing (Brandi, 2009; Liu et al, 2010; Boutroy et al, 2005)

2.4.1.3. Biochemical Markers

Serological and urianalytical provisions of biochemical markers provide clinicians with a useful methodology to examine physiological alterations in bone metabolism; specifically the prevalence of formative and resorptive activity within the skeleton (Srivastava et al, 2005; Singer & Eyre, 2008; Delmas, Eastell, Galnero, Seibel & Stepan, 2000; Miller et al, 1999). Bone mass accrual, maintenance and degradation are explicitly determined by counteracting metabolic processes (formation and resorption) responsive to endogenous (hormones, cytokines, growth factors) and exogenous (mechanical loading) factors (Rogers et al 2011; Clouth & Oremek, 2011; Guadio et al, 2010; Camozzi et al, 2007).

Table 5. ***Available biochemical markers used to examine formative, resorptive and rate of bone metabolism through serological and urianalytical mechanisms.***

Biochemical Marker	Abbreviation	Sample	Bone Metabolism
Bone Alkaline Phosphate	BAP / BALP	Serum	Formation
Osteocalcin	OC / BGP	Serum	Formation
Carboxyterminal, Type I Collagen	PICP	Serum	Formation
Aminoterminal, Type I Collagen	PINP	Serum	Formation
Pyridinoline	PYR	Serum & Urine	Resorption
Deoxypiridoline	DPD / D-PYR	Serum & Urine	Resorption
Carboxyterminal Crosslink, Procollagen I	ITCP	Serum	Resorption
Carboxyterminal Crosslink, Type I Collagen	CTx	Urine	Resorption
Aminoterminal Cross-link, Type I Collagen	NTx	Urine	Resorption
Tartrate-resistant Acid Phosphate	TRAP5	Serum	Resorption
Parathyroid Hormone	PTH	Serum	Turnover Rate

Note: Information adapted from: (Maimoun & Sultan, 2011; Banfi et al, 2010)

Biomarkers become clinically useful to examine bone turnover rates underpinning bone health or skeletal disease; and importantly quantify acute and chronic metabolic alterations to experienced stimulus and targeted interventions (Galliera et al, 2013; Banfi et al, 2010; Lester et al, 2009; Rantalainen et al, 2009a; Singer & Eyre, 2008; Srivastava et al, 2005; Delmas et al, 2000). While biochemical samples are easily collected and analysed; do not involve harmful radiation; and have high sensitivity to change; their diagnostic capabilities in isolation are limited (Banfi et al, 2010; Lester et al, 2009; Allen, 2003; Risteli & Risteli, 1993). In particular, biomarker concentrations and behavioural profiles are highly variable between individuals; and indiscriminately represent global anabolic or catabolic activity of the entire skeleton, such that biomarker analyses cannot provide targeted and localised examinations of formative and resorptive behaviour (Lester et al, 2009; Allen, 2003; Risteli & Risteli, 1993). However, owing to its sensitivity to measure dynamic early onset

alterations; biochemical markers can be complementary to other bone quality and skeletal fragility examinations; performed in conjunction with static morphological measures provided by radiographic and densitometric devices (Rogers et al, 2011; Banfi et al, 2010; Delmas et al, 2000; Seibel & Woitge, 1999; Fujimura et al, 1997).

2.4.2. Effect of Physical Activity

Physical activity confers a plethora of irrefutable benefits to the skeleton (Maurel et al, 2013; Nilsson et al, 2011; Nordstrom, Tervo & Hogstrom, 2011; Schwab & Scalapino, 2011; Pettersson et al, 2010; Guadalupe-Grau, Fuentes, Guerra & Calbet, 2009a; Daly & Petit, 2007; Janz et al, 2006; Warden et al, 2005; Judex & Zernicke, 2000; Pettersson, Nordstrom & Lorentzon, 1999), capitalising on muscular and gravitational loads in combination and isolation to deliver anabolic mechanical stimulus to load-bearing and weight-bearing regions (Maimoun & Sultan, 2011; Rogers et al, 2011; Kemmler & von Stengel, 2011; Ebben, Fauth, Kaufmann & Petushek, 2010; Rantalainen, Linnamo, Komi, Selanne & Heinonen, 2010; Andreoli et al, 2001; Judex & Zernicke, 2000). Although genetics partially determines skeletal growth and development; the final disposition of bone strength and skeletal potential established through-out the lifespan is predominantly governed by mechanical stimuli (Ireland, Rittweger, Schonau, Lamberg-Allardt & Viljakainen, 2014; Boreham & McKay, 2011; Nikander et al, 2010b; Nilsson, Ohlsson, Mellström & Lorentzon, 2009; Janz et al, 2006; Turner & Robling, 2005b; Beck & Snow, 2003; MacKelvie, Khan & McKay, 2002; Modlesky & Lewis, 2002; Haapasalo et al, 2000; Wolff et al, 1999). Specifically, bone accretion and skeletal morphology alterations are responsive to various combinations of strain magnitude, rate, frequency and distribution (described in Section 2.3.1.) driving exercise-orientated research to explore programmable

mechanical paradigms using numerous exercise modalities to optimise bone strength or minimise bone loss. Mechanically driven exercise programs are particularly advantageous; providing long-term and maintainable increases in bone strength with minimal consequence or financial expense in conjunction with other associated physiological and psychological health benefits (Body et al, 2011; Welch, Turner, Devareddy, Arjmandi & Weaver, 2008; Karinkanta et al, 2007; Taylor et al, 2004; Judex & Zernicke, 2000). Conversely, pharmacological interventions are expensive; produce adverse side-effects; require ongoing management; and may be ineffective or harmful to individuals with co-morbidities requiring multiple medications (polypharmacy) resulting in undesirable or contradictory drug-drug interactions (Pountos, Georgouli, Calori & Giannoudis, 2012; Body et al, 2011; Kennel & Drake, 2009; Levy, 2002; Mashiba & Burr, 2001).

Bone primarily adapts to mechanical stresses by changing its size and shape, which are major determinants of fracture and fatigue resistance; developing and restructuring material in regions of high mechanical stress as an efficient means for improving bone strength (Judex & Carlson, 2009; Turner et al, 2009; Warden, Fuchs & Turner, 2004; Judex & Zernicke, 2000). However, dose-response (load-adaptation) mechanical relationships remain poorly defined in humans, with research relying heavily on animal models to isolate variable factors contributing to osteogenic potency under controlled loading conditions. Specifically, animal models provide unique benefits to researchers by enabling direct access to skeletal structures with precise loading histories for use in mechanical tests (Robling, Burr & Turner, 2001b; Aerssens, Boonen, Lowet & Dequeker, 1998; Mosekilde, 1995; Ferretti, 1995). However, animal models cannot replace human models and do not wholly translate to the human condition; instead, they provide novel hypothesis-generating insights to be subsequently tested in humans under relatively comparable situations.

Numerous forms of mechanical tests and physical modalities have been utilised to investigate the effects of mechanical loading to the animal skeleton; including controlled compression and bending tests, electrical stimulation, whole-body vibration, walking, running, jumping and falling activities (Pasqualini et al, 2013; Lambers et al, 2013; Ju et al, 2012; Gonul, Baltaci & Koz, 2011; Swift et al, 2010; Poliachik, Threet, Srinivasan & Gross, 2008; Wallace et al, 2007; Warden et al, 2005; Welch, Weaver & Turner, 2004; Ju, Sone, Fukunga, Lim & Onodera, 2003; Rubin et al, 2002; Kodama et al, 2000; Jamsa, Tuukkanen & Jalovaara, 1998; Barengolts, Curry, Bapna & Kukreja, 1993). Collectively, the general benefits of exercise to bone strength using these methodologies is unequivocal (Ju et al, 2012; Prisby, Lafage-Proust, Malaval, Belli & Vico, 2008; Welch et al, 2008; Warden et al, 2005; Srinivasan et al, 2002; Umemura et al, 2002; Pedersen, Akhter, Cullen, Kimmel & Recker, 1999; Hoshi, Watanabe, Chiba & Inaba, 1998; Umemura et al, 1995; van der Wiel et al, 1995; Wheeler et al, 1995); small materialistic and structural gains exponentially improve bone strength, bending resistance, fracture energy and fatigue resistance (Robling et al, 2006; Warden et al, 2005; Robling et al, 2002; Umemura et al, 2000; Judex & Zernicke, 2000). However, it is of practical importance to understand which loading modalities and methodologies elicit the greatest increments in bone strength in human models; and through which material, structural and muscular mechanisms this occurs (Edwards et al, 2013; James & Carroll, 2010; Guadalupe-Grau et al, 2009a; Judex & Carlson, 2009; Taylor et al, 2004). Specifically, each loading modality exerts osteogenic stimulus through distinct combinations of internal (muscular) and external (gravitational) forces at different magnitudes, rates, frequencies and distributions involving impact and non-impact events (Rogers et al, 2011; Ebben et al, 2010; James & Carroll, 2010; Judex & Carlson, 2009; Robling, 2009); differentially affecting trabecular and cortical bone locally

and regionally across the skeleton. Exercise prescriptions for different populations therefore require appropriate cost-benefit analyses to deliver targeted bone strength adaptations at minimal risk (Body et al, 2011; Guadalupe-Grau et al, 2009a; Karinkanta et al, 2007).

Mechanical loading programs designed for adult populations may not be appropriate for children, adolescents, older adults, elderly or disease-state individuals, whom each present with different stability, mobility or medical contraindications; subsequently classified as special populations which deserve exclusive treatment and investigations respectively. Exercise studies presented in summary tables in subsequent sections are therefore delimited to cross-sectional and longitudinal human models reflecting healthy male and female, adolescent and adult populations, from Tanner Stage II (~12 years) to middle-aged adulthood (~45 years) in order to minimise confounding factors associated with ageing and disease. While adolescent and adult populations have skeletally distinct properties with altered levels of maturity and mechanosensitivity to loading; ~50 to 60% of overall skeletal mass is developed in adolescence (Laudermilk et al, 2012; Hartman et al, 2003; Pitukcheewanont, Safani, Gilsanz & Rubin, 2002; Theintz et al, 1992; Hansen, Overgaard, Riis & Christiansen, 1991; Bonjour et al, 1991), providing a useful model to quantify and exemplify the efficacies of various exercise programs. Additionally, adolescent and adult models are specific and age-appropriate for developmental, sub-elite and elite level athlete populations used in this Thesis.

2.4.2.1. Vibration Exercise

Vibration exercise is a non-impact stimulatory modality which delivers low magnitude, high frequency and variable rates of mechanical strain to the skeleton (Reyes, Hernandez, Holmgren, Sanhueza & Escobar, 2011; Rittweger, 2010; Cardinale & Rittweger, 2006;

Rubin et al, 2002; Rubin, Sommerfeldt, Judex & Qin, 2001). In particular, vibration plates are positioned beneath the individual, at select sites, to produce linear and oscillatory motions at pre-set amplitudes, accelerations and frequencies, which are independently modified to determine signal intensity and osteogenic potency (Gomez-Cabello et al, 2014; Pasqualini et al, 2013; Rittweger, 2010; Cardinale & Wakeling, 2006). While vibration exercise aims to deliver mechanical signals to axial and appendicular regions to increase bone mass; its primary stimulatory effects occur at the point of direct contact, producing a distal-to-proximal delivery of strain which is gradually dampened by biological tissues as it propagates through-out the body (Ligouri, Shoepe & Almsted, 2012; Rittweger, 2010; Cardinale & Wakeling, 2005). Vibration exercise strives to deliver osteogenic benefits in regions proximately located to the vibration plate through two key mechanisms: 1) increasing muscle mass, thereby heightening customary long-term contractile loads; and 2) optimising the strain environment through numerous strain variables, including strain rate, frequency and density, in the absence of high strain magnitude (Miokovic et al, 2014; McKeehen et al, 2013; Pasqualini et al, 2013; Rittweger, 2010; Humphries, Fenning, Dugan, Guinane & MacRae, 2009; Di Loreto et al, 2004; Rubin et al, 2002).

Whole-body vibration has gained ascendency in recent times as a potential therapeutic or adjunctive exercise owing to its low impact and low magnitude stimulatory effects (Miokovic et al, 2014; McKeehen et al, 2013; Gilsanz et al, 2006; Pitukcheewanont & Safani, 2006; Ward et al, 2004; Judex et al, 2003; Torvinen et al, 2003; Srinivasan et al, 2002; Rubin et al, 2001). Specifically, vibration exercise is considered an alternative osteogenic option to promote bone adaptations in higher risk populations who may not be-able to tolerate high-magnitude strains (Miokovic et al, 2014; Lam et al, 2013; Srinivasan et al, 2002; Reyes et al, 2011; Ward et al, 2004; Rubin et al, 2002; Rubin et al, 2001).

Table 6. ***Overview of human model vibration training studies using adolescent and adult males and females.***

Author(s)	Training Protocol	Material Adaptations	Structural Adaptations	Strength Adaptations	Muscular Adaptations
Lam et al. (2013) [Age: ~18 Yrs]	Adult Females (n = 61) Magnitude of 0.3g Frequency of 32-37Hz 20 minutes, 5 days/week 52 weeks (12 months).	Spinal aBMC: +3.5% Femoral aBMC: +2.0% Tibial Tt.vBMD: +2.1% Tibial Tb.vBMD: +1.5% Tibial Ct.vBMD: +1.1%	Tibial Tb.Ar: -0.3% Tibial Ct.Ar: +2.0% Tibial Ct.Th: +1.9%	None Reported.	None Reported.
Ligouri et al. (2012) [Age: ~20 Yrs]	Adult Men (n=6) and Adult Women (n=4) Magnitude not reported. Frequency of 15-26Hz 20-30 minutes, 3 days/week 12 weeks (3 months).	Total aBMD: ±0.0% Spinal aBMD: +1.2%	None Reported.	None Reported.	Total Mass: +0.6%
Humphries et al. (2009) [Age: ~21 Yrs]	Adult Females (n=27) Magnitude not reported Frequency of 50Hz 2-3 minutes, 2 days/week 16 weeks (4 months).	Spinal aBMD: +0.7% Femoral aBMD: +1.6%	None Reported.	None Reported.	None Reported.
Gilsanz et al. (2006) [Age: ~17 Yrs]	Adult Females (n = 48) Magnitude of 0.3g Frequency of 30Hz 2-10 minutes, 7 days/week. 52 weeks (12 months)	Total aBMC: +3.5% Spinal aBMC: +3.9% Spinal Tb.vBMD: +3.8%	Femoral CSA: +2.4% Femoral Ct.Ar: +4.3%	None Reported.	Total Mass: +1.6% Trunk Mass: +2.2%
Torvinen et al. (2003) [Age: ~23 Yrs]	Adult Males (n=21) and Adult Females (n=35) Magnitude of 2 – 8g. Frequency of 25 – 45Hz 4 minutes, 3 – 5 days/week 34 weeks (8 months).	Spinal aBMC: +0.8% Femoral aBMC: +1.1% Calcaneal aBMC: +1.7% Tibial Tb.vBMD: +1.7% Tibial Ct.vBMD: +2.9%	Tibial Ct.Ar: +3.8%	Tibial BSI: +6.1%	Isom.Str: +9.0% Leg Power: +7.2%

Note: **aBMC = areal bone mineral content; aBMD = areal bone mineral density; Tt.vBMD = total volumetric bone mineral density; Tb.vBMD = trabecular volumetric bone mineral content; Ct.vBMD = cortical volumetric bone mineral density; Ma.vBMD = marrow volumetric bone mineral density; Tt.Ar = total area; Tb.Ar = trabecular area; Ct.Ar = cortical area; Ma.Ar = marrow area; CSA = cross-sectional area; Ct.Th = cortical thickness; Circ = circumference; PMI = polar moment of inertia; BSI = bone strength index; total mass = total body lean mass; Isom.Str = isometric strength. All values reported as percent change from baseline.**

Vibration exercise has merit as a potential source of mechanical stimulation, however many limitations exist which substantially diminish its current value as an efficacious loading modality (Verschueren et al, 2011; de Zepetnek, Giangregorio & Craven, 2009; Prisby et al, 2008). In particular, vibration exercise is harmful if directly applied to the head, neck or trunk regions; harmful if excessively applied to any region; may produce physical discomfort to the individual; and has no established standards of use or prescriptive limits for any segment of the human population (Zaki, 2014; Rittweger, 2010; de Zepetnek, Giangregorio & Craven, 2009; Gusi et al, 2006; Cardinale & Rittweger, 2006). Given the expansive range and prescriptive combinations of amplitude, acceleration and frequency signals; and the novelty of vibration as an exercise modality; there is a need to understand the limits of human tolerance and adaptation to vibration exercise prior to pursuing explicit, safe and effective user-delivery recommendations for bone strength adaptation (Rittweger, 2010; de Zepetnek, Giangregorio & Craven, 2009; Prisby et al, 2008; Rubin et al, 2004).

Skeletal adaptations to vibration exercise in adolescent and adult humans are summarised in Table 6, demonstrating positive osteogenic effects for all measured sites in all studies. However, inconsistencies in sample sizes, vibrations delivered, sites measured and variables reported between studies complicate interpretations of efficacy. Specifically, only one study reported bone strength; and only two studies reported material and structural co-adaptations. This is a considerable limitation of the literature, as bone strength and its derivatives are arguably the most valuable measures and primary outcomes of bone adaptation research. Nevertheless, vibration exercise appears to be more effective over longer durations (>8 months); improving tibial strength (~6%) through increased material density (~1 – 3%) and structural cross-sectional area (~2 – 4%); with improvements in muscle mass, strength and power. While these adaptations are positive; the oscillatory

delivery of mechanical stimulus does not functionally optimise bone geometry, owing to the site-specific adaptive properties of the skeleton to mechanical loading (Rubin et al, 2004; Judex et al, 2003; Frost, 2003; Takana, Alam & Turner, 2003; Rubin et al, 2002).

2.4.2.2. Locomotive Exercise

Locomotive exercise is an impact-based, lower-body cyclical activity, producing moderate magnitude, moderate frequency, oddly distributed mechanical strains to the skeleton (Clark, Ryan & Weyand, 2014; Ju, Sone, Ohnaru, Choi & Fukunaga, 2012; Smock et al, 2009; Al Nazer et al, 2008). Specifically, locomotive exercise involves bi-pedal and unilateral bouncing movements consisting of walking, jogging and running; with combined muscular and gravitational loads to deliver highly osteogenic stimuli to the skeleton; subsequently conferring bone mass and bone strength benefits through-out growth, development and adulthood (Roghani et al, 2013; Kohrt, Barry & Schwartz, 2009; Gonul & Koz, 2011; Kiuchi, Arai & Katsuta, 1998; Eliakim, Raisz, Brasel & Cooper, 1997). In particular, owing to the capacity of bone to functionally adapt to routine mechanical loads (Ireland et al, 2014; Karlsson & Rosengren, 2012; Ju et al, 2012; McBride & Silva, 2012; Turner et al, 2009; Frost, 2003); its irregular geometry is predominantly shaped in response to daily locomotive activity and additionally prescribed locomotive exercise, with thicker anterio-posterior cortical walls and stiffer trabeculae to resist frequent anterior bending moments (Lambers et al, 2013; Nikander et al, 2010a; Rantalainen et al, 2010b; Smock et al, 2009). However, these cyclical activities also produce unusual stress patterns which result in odd-impact strains at volatile rates and distributions that may also expose structural weaknesses which can be harmful if running mechanics are jeapordised due to undesirable movement patterns, poor foot-strike strategies, inadequate footwear or heightened neuromuscular fatigue (Breine, Malcolm, Frederick & De Clercq, 2014; Clark, Ryan & Weyand, 2014).

Osteogenic adaptations supplied by prescribed locomotive exercise interventions remain scarcely examined in human models (Table 7). Preliminary evidence using animal models demonstrates generally positive adaptations, with modest improvements in bone mass and strength (Ju et al, 2012; Gonul & Koz, 2011; Ju et al, 2003; Kiuchi, Arai & Katsuta, 1998; van der Wiel et al, 1995; Wheeler et al, 1995; Barengolts et al, 1993). However, locomotive exercise is inherently limited by mechanical saturation, such that longer programs elicit no additional benefits at the expense of increased bone fatigue and microdamage (Clansey, Hanlon, Wallace & Lake, 2012; Scott et al, 2011; Wheeler et al, 1995; van der Wiel et al, 1995); while shorter programs produce lower peak strains and smaller osteogenic adaptations than other exercise modalities of equal duration (Ju et al, 2102; Guadalupe-Grau et al, 2009a; Umemura et al, 1995; Snow-Harter, Bouxsein, Lewis, Carter & Marcus, 1992). Locomotive exercise may also limit the osteogenic influence of muscle, as insufficient overload may restrict muscle hypertrophy (Cianferotti & Brandi, 2014; Smock et al, 2009; Lester et al, 2009); and type II muscle fibres may gradually convert to type I muscle fibres (Wilson et al, 2012; Karp, 2001); concomitantly reducing the magnitude and rate of customary strains supplied to the skeleton via altered contractile properties. While locomotive exercise may appropriately prepare and condition healthy individuals for activities of daily living or demanding athletic pursuits; the inability to wholly control loading parameters using this exercise modality may limit its applicability as a primary option to remediate bone strength in skeletally fragile individuals, or optimally enhance bone strength in the general population (Ju et al, 2012; Smock et al, 2009; Barengolts et al, 1993; Block, Smith, Friedlander & Genant, 1989).

Table 7. ***Overview of human model, locomotive exercise training studies using adolescent and adult males and females.***

Author(s)	Training Protocol	Material Adaptations	Structural Adaptations	Strength Adaptations	Muscular Adaptations
Evans et al. (2012) [Age: ~21 Yrs]	Adult Females (n=14) Steady State + Interval Running Program 30 minutes, 3 days/week 8 weeks (2 months)	Tibial Tb.vBMD: +1.2% Tibial Ct.vBMD: ±0.0%	Tibial Tb.Ar: +0.6% Tibial Ct.Ar: +0.7% Tibial CSA: +1.2% Tibial Ma.Ar: +1.4% Tibial Ps.Circ: ±0.0% Tibial Ec.Circ: ±0.0%	Tibial CSMI.AP: +0.9% Tibial CSMI.ML: +2.0% Tibial PMI: +1.6%	None Reported
Lester et al. (2009) [Age: ~20 Yrs]	Adult Females (n=17) Steady State + Interval Running Program 30-90 minutes, 3 days/week. 8 weeks (2 months).	Total aBMD: +0.7% Leg aBMD: ±0.0% Femoral aBMD: +1.7% Tibial Tt.vBMD: +0.7% Tibial Tb.vBMD: +1.3% Tibial Ct.vBMD: ±0.0%	None Reported	None Reported	Total Mass: +2.2%
Snow-Harter et al (1992) [Age: ~20 Yrs]	Adult Females Aerobic Endurance Training Running Program 30-90 minutes, 3 days/week 34 weeks (8 months)	Spinal aBMD: +1.8% Femoral aBMD: ±0.0%	None Reported	None Reported	Dyn.Leg.Str: +10.0% Dyn.Hip.Str: -13.7%

Note: **aBMD = areal bone mineral density; Tb.vBMD = trabecular volumetric bone mineral content; Ct.vBMD = cortical volumetric bone mineral density; Tb.Ar = trabecular area; Ct.Ar = cortical area; Ma.Ar = marrow area; CSA = cross-sectional area; Ps.Circ = periosteal circumference; Ec.Circ = endocortical circumference; PMI = polar moment of inertia; CSMI = cross-sectional moment of inertia; AP = anterio-posterior; ML = medio-lateral; Total Mass = total-body lean mass; Dyn.Leg.Str = dynamic leg strength; Dyn.Hip.Str = dynamic hip strength; All values reported as percent change from baseline.**

2.4.2.3. Resistance Exercise

Resistance exercise is characterised by low frequency, high magnitude, non-impact activity; using isolated or co-ordinated segments to produce single-joint, multi-joint or full-body movements to displace prescribed external loads, subsequently overcoming additional resistance (Helms, Fitschen, Aragon, Cronin & Schoenfeld, 2014; Ratamess, 2012; Cardinale, Newton & Nosaka, 2011; Nikander et al, 2010b; Ratamess et al, 2009). In particular, lower-body resistance training programs utilise open-kinetic and closed-kinetic chain exercises under isotonic, isometric and isokinetic conditions to overcome maximal or sub-maximal external loads through segmentally co-ordinated muscular contractions at numerous velocities along the force-power spectrum (Helms et al, 2014; Timmons, 2011; Ratamess et al, 2009; Nikols-Richardson, Miller, Wootten, Ramp & Herbert, 2007; Schroeder, Hawkins & Jaque, 2004; Hawkins et al, 1999). As such, resistance exercise is prescriptively advantageous to practitioners, providing precise, programmable, measureable and manageable loading parameters in order to achieve desired adaptive responses under controlled conditions. Specifically, resistance training minimises undesired movement and potentially harmful forces; enabling mechanical load application and resultant force vectors to be targeted toward site-specific regions in order to optimise muscle-bone strength while reducing injury risk (Winters-Stone et al, 2014; Lauersen, Bertelsen & Andersen, 2014; Edwards et al, 2013; Ryan et al, 2004; Heinonen, Sievanen, Kannus, Oja & Vuori, 2002).

Weight-bearing activity is widely recommended as a mechanism to promote bone mass and bone strength (Melo, Tenório, Baratella-Evêncio & Maia, 2012; Schwab & Scalapino, 2011; Nikander et al, 2010b; Turner et al, 2009; Beck & Snow, 2003). While resistance training is non-impact, external loads added to the mass of load-bearing regions (human

body or limb segment) progressively overload the demands of stabilising and mobilising muscle in targeted areas. Osteogenically, this allows high magnitudes of additional mass to be loaded onto the skeleton using pre-planned movements of predictable directions and distributions, while concurrently producing maximal or sub-maximal muscular activations; effectively combining external and internal forces to deliver highly osteogenic mechanical stimuli (Karabulut et al, 2011; Nikander et al, 2010b; Guadalupe-Grau et al, 2009b; James & Carroll, 2006; Suominen, 2006; Frost, 2003; Heinonen et al, 2002; Hakkinen, Sokka, Kotaniemi & Hannonen, 2001; Bemben, Fetters, Bemben, Nabavi & Koh. 2000; Heinonen, Oja, Sievanen, Pasanen & Vuori, 1998; Bennell et al, 1997; Sinaki et al, 1996; Ryan et al, 1994; Menkes et al, 1993; Pruitt, Jackson, Bartels & Lehnhard, 1992; Peterson et al, 1991; Gleeson, Protas, LeBlanc, Schneider & Evans, 1990). Appropriately designed resistance training programs also promote muscle hypertrophy (increased muscle mass), muscular strength and muscular power (Helms et al, 2014; Timmons, 2011; Schoenfeld, 2010; Wernbom, Augustsson & Thomee, 2007; Kraemer & Ratamess, 2004). This is considerably beneficial as muscle strength, density and cross-sectional area closely corresponds with bone strength, density and cross-sectional area, owing to their interdependent relationship (described in section 2.3.2.4). Resistance exercise therefore increases the capacity of muscle to exert higher levels of force at higher rates of development to generate larger mechanical strains with high osteogenic potential (Helms et al, 2014; Lloyd et al, 2014; Judex & Carlson, 2009; Wernbom, Augustsson, Thomee, 2007; James & Carroll, 2006; Suominen, 2006; Ryan et al, 2004; Taylor et al, 2004; Ferretti et al, 2003).

Table 8. ***Overview of human model resistance training studies using adolescent and adult males and females.***

Author(s)	Training Protocol	Material Adaptations	Structural Adaptations	Strength Adaptations	Muscular Adaptations
Lester et al (2009). [Age: ~20 Yrs]	Adult Females (n=17) Free Weights Program 30-90 minutes, 3 days/week. 8 weeks (2 months).	Total aBMD: +0.9% Leg aBMD: ±0.0% Pelvis aBMD: +1.7% Tibial Tt.vBMD: ±0.0% Tibial Tb.vBMD: ±0.0% Tibial Ct.vBMD: ±0.0%	None Reported	None Reported	Total Mass: +2.4%
Nickols-Richardson et al (2007) [Age: ~ 20 Yrs]	Adult Females (n=33) Isokinetic Eccentric Training 40-50 minutes, 3 days/week 20 weeks (5 months)	Total aBMC: +0.6% Total aBMD: +0.2% Femoral aBMC: +1.0% Femoral aBMD: +1.2% Tibial aBMC: +1.0% Tibial aBMD: +0.3%	None Reported	None Reported	Isok.Con.Str: +14.9% Isok.Ecc.Str: +28.9% Total Mass: +1.7% Leg Mass: +2.7%
Nickols-Richardson et al (2007) [Age: ~ 20 Yrs]	Adult Females (n=37) Isokinetic Concentric Training 40-50 minutes, 3 days/week 20 weeks (5 months)	Total aBMC: +0.4% Total aBMD: +0.2% Femoral aBMC: ±0.0% Femoral aBMD: +0.5% Tibial aBMC: +1.3% Tibial aBMD: +0.6%	None Reported	None Reported	Isok.Con.Str: +18.6% Isok.Ecc.Str: +15.6% Total Mass: +1.5% Leg Mass: +2.3%
Ryan et al. (2004) [Age: ~25 Yrs]	Adult Males (n=13) Pneumatic and Free Weights Program 50 minutes, 3 days/week 26 weeks (6 months)	Total aBMD: +0.6% Spinal aBMD: +0.2% Femoral aBMD: +2.4% Ward's aBMD: +3.0%	None Reported	None Reported	Dyn.Con.Ext: +35.0% Dyn.Leg.Str: +25.0% Total Mass: +3.1%
Ryan et al. (2004) [Age: ~26 Yrs]	Adult Females (n=8) Pneumatic and Free Weights Program 50 minutes, 3 days/week 26 weeks (6 months)	Total aBMD: +0.3% Spinal aBMD: +2.7% Femoral aBMD: +1.3% Ward's aBMD: +3.3%	None Reported	None Reported	Dyn.Con.Ext: +29.0% Dyn.Leg.Str: +39.6% Total Mass: +3.7%

Schroeder et al. (2004) [Age: ~24 Yrs]	Adult Females (n = 14) Single-Joint Eccentric Training 3 sets, 6-10 repetitions at 75-125% 40 minutes, 2 days/week 16 weeks (4 months)	Total aBMC: +0.6% Total aBMD: ±0.0% Spinal aBMC: +1.7% Spinal aBMD: ±0.0% Femoral aBMC: +1.6% Femoral aBMD: ±0.0%	None Reported	None Reported	Dyn.Con.Ext: +24.4% Dyn.Con.Flex: +32.2% Total Mass: +2.2%
Hawkins et al. (1999) [Age: ~21 Yrs]	Adult Females (n=12) Isokinetic Eccentric Training 30 minutes, 3 days/week 18 weeks (4 months)	Femoral aBMD: +4.0% Leg aBMD: +0.6%	None Reported	None Reported	Isok.Con.Str: +19.2% Isok.Ecc.Str: +23.8% Thigh Mass: +6.8% Leg Mass: +4.0%
Hawkins et al. (1999) [Age: ~21 Yrs]	Adult Females (n=12) Isokinetic Concentric Training 30 minutes, 3 days/week 18 weeks (4 months)	Femoral aBMD: +1.1% Leg aBMD: ±0.0%	None Reported	None Reported	Isok.Con.Str: +21.3% Isok.Ecc.Str: +19.2% Thigh Mass: +3.5% Leg Mass: +2.3%
Lohman et al. (1995) [Age: ~34 Yrs]	Adult Females (n=22) Free Weights Program 60 minutes, 3 days/week 78 weeks (18 months)	Total aBMD: -1.2% Spinal aBMD: +1.3% Femoral aBMD: +1.5%	None Reported	None Reported	Dyn.Leg.Flex: +57.7% Dyn.Leg.Ext: +99.0% Dyn.Leg.Str: +73.2% Total Mass: +3.1% Leg Mass: +3.2%
Snow-Harter et al (1992) [Age: ~20 Yrs]	Adult Females (n=10) Machines – Isolation Exercises 120 minutes, 3 days/week 36 weeks (8 months)	Spinal aBMD: +0.9% Femoral aBMD: +1.2%	None Reported	None Reported	Dyn.Leg.Str: +53.6% Dyn.Hip.Str: +33.1%
Colletti et al. (1989). [Age: ~25 Yrs]	Adult Males (n=12) Machines and Free Weights Program 60-120 minutes, 3-5 days/week 60-84 months (5-7 years)	Spinal aBMD: +9.6% Femoral aBMD: +13.6%	None Reported	None Reported	None Reported

Note: **aBMC = areal bone mineral content; aBMD = areal bone mineral density; Tt.vBMD = total volumetric bone mineral density; Tb.vBMD = trabecular volumetric bone mineral density; Ct.vBMD = cortical volumetric bone mineral density; total mass = total-body lean mass; leg mass = lower-body lean mass; Isok.Ecc.Str = isokinetic eccentric strength; Isok.Con.Str = isokinetic concentric strength; Dyn.Leg.Flex = dynamic flexion strength; Dyn.Leg.Ext = dynamic extension strength; Dyn.Leg.Str = dynamic leg strength; Dyn.Hip.Str = dynamic hip strength; All values reported as percent change from baseline.**

Examinations involving human models are heterogeneous (Table 8), with different resistance modalities, exercise programs and study designs used to investigate muscle-bone adaptations to resistance exercise. Remarkably, no study reported bone structure or strength adaptations, relying solely on material adaptations to indirectly quantify osteogenesis through changes in aBMD. This is a major limitation as density measures in isolation are inadequate. Specifically, density is a ratio of content per unit of area, therefore concurrent increases in material and structure may be disguised when reporting changes in density despite measureable improvements in bone strength (Bouxsein & Karasik, 2006; Seeman & Delmas, 2006). This could explain the collectively small magnitude of change in aBMD (≤ 1.5%) following resistance training interventions (≤ 18 months) in the literature, as the high magnitudes of change in isokinetic strength (~20%) and dynamic strength (~40%) should be accompanied by evident increments in bone strength. Unfortunately, the absence of bone structure and strength outcomes ultimately misrepresents the osteogenic potential of resistance training. Regardless, resistance exercise appears to deliver positive osteogenic adaptations with large concurrent increases in muscle mass and strength. Specifically, multi-joint, compound, free-weight and closed-kinetic chain exercises appear to produce greater muscle-bone adaptation than single-joint, isolated, isokinetic and open-kinetic chain exercises; owing to the involvement of larger muscle groups, higher magnitudes of external load, higher levels of muscular force, and greater compressive and tensile loads placed upon the skeleton (Helms et al, 2014; Timmons, 2011; Schoenfeld, 2010; Guadalupe-Grau et al, 2009a; Guadalupe-Grau et al, 2009b; Nikols-Richardson et al, 2007; Ryan et al, 2004; Heinonen et al, 2002; Hawkins et al, 1999; Lohman et al, 1994).

2.4.2.4. Impact Exercise

Impact exercise involves low frequency, high magnitude strains produced by high-impact and odd-impact activities, capitalising on the co-contribution of muscular and gravitational loads to deliver high rates of strain with various distributions to weight-bearing regions of the skeleton (Swift et al, 2010; Kohrt, Barry & Schwartz, 2009; Erickson & Vukovich, 2010; Judex & Carlson, 2009; Kato et al, 2006; Johannsen, Binkley, Englert, Neiderauer & Specker, 2003). Specifically, impact exercise addresses several osteogenic sensitivities responsible for maximising bone strength adaptation, using unloaded and loaded plyometric activities, consisting of high accelerating and decelerating movements from habitual and non-habitual directions to sufficiently stimulate the skeleton (Weidauer et al, 2014; James & Carroll, 2010; Welch et al, 2008; Turner & Robling, 2005a; Liu-Ambrose, Khan, Eng, Heinonen & McKay, 2004; Fuchs, Bauer & Snow, 2001; Happasalo et al, 2000; Heinonen et al, 1999; Taaffe, Robinson, Snow & Marcus, 1997). In particular, as bone loss and degradation results from environments of minimal to no gravity (Lloyd et al, 2014; Belavy et al, 2011a; van Oers et al, 2008; Giangregorio & Blimkie, 2002; Vico et al, 2000); it is reasonable to expect that exercises which maximise gravitational loads at high application rates will conversely produce high levels of bone formation, proportionate to the magnitude of impact provided (Umemura et al, 2002; Umemura et al, 2000; Judex & Zernicke, 2000).

Cross-sectional and longitudinal studies using animal models have collectively established impact exercise as an effective and efficient training modality to promote and preserve bone material and strength (Welch et al, 2008; Umemura et al, 2002; Umemura et al, 1997; Umemura et al, 1995). Specifically, impact training produces higher peak strains (~30%) at higher strain rates (~740%), with greater formative adaptations at periosteal (~40%) and

endocortical (~370%) surfaces using considerably fewer loading cycles (~100 cycles) over a markedly smaller duration (~10 minutes) than locomotive exercise modalities (Judex & Zernicke, 2000; Umemura et al, 2000). Given the rapid onset of mechanoreceptor desensitisation in response to sets of mechanical load; impact exercise opportunistically maximises osteogenic stimulation and skeletal adaptation; particularly in site-specific trabecular regions (Ju et al, 2014; Ju et al, 2013; Ju et al, 2008; Kato et al, 2006; Umemura et al, 1997); with considerable formative, preservative and restorative benefits in young, and adult animal models (Honda et al, 2008; Welch et al, 2008; Ju et al, 2008; Umemura et al, 2000). While impact exercise provides prophylactic protections against bone pathology in animals; human studies have been unable to replicate an equivalent magnitude of osteogenic adaptation when using impact loading as a controlled intervention (Table 9).

Athletes participating in high-impact and odd-impact activities demonstrate markedly higher osteogenic outcomes than any of their low-impact or non-impact counterparts (Weidauer et al, 2014; Nilsson, Ohlsson, Mellström & Lorentzon, 2013; Rantalainen et al, 2013; Greene et al, 2012; Weidauer, Eilers, Binkley, Vukovich & Specker, 2012; Quiterio, Carnero, Baptista & Sardinha, 2011; Rantalainen et al, 2011a; Nikander et al, 2010a; Rantalainen et al, 2010a; Rantalainen et al, 2010b); however a comparable adaptive response has yet to be explicitly achieved through targeted impact-centric mechanical programs. Specifically, the loading configuration and structure to best enhance bone strength is largely unknown, owing to the expansive range of loading parameters available, with different impact modalities, intensities, frequencies, durations and rest periods employed by researchers (James & Carroll, 2010; Leppanen Sievanen & Jarvinen, 2008; Wolff, Van Croonenborg, Kemper, Kostense & Twisk, 1999).

Table 9. ***Overview of human model impact training studies using adolescent and adult males and females.***

Author(s)	Training Protocol	Material Adaptations	Structural Adaptations	Strength Adaptations	Muscular Adaptations
Vainionpaa et al. (2005, 2006, 2007, 2009) [Age: ~40 Yrs]	Adult Females (n=60) Stamping, Jumping, Running 60-70 minutes, 3 days/week 52 weeks (12 months)	Total aBMD: ±0.0% Spinal aBMD: +0.1% Femoral aBMD: +1.3% Ward's aBMD: +2.8%	Femoral Ct.Ar: +0.2% Femoral CSA: +0.2% Femoral Ct.Th: ±0.0% Tibial Ct.Ar: ±0.0% Tibial CSA: ±0.0%	Femoral CSMI: ±0.0% Tibial CSMI: +0.4%	None Reported
Kato et al. (2006) [Age: ~20 Yrs]	Adult Females (n=36) Maximal CMJ Efforts 10 jumps/day, 3 days/week 26 weeks (6 months)	Spinal aBMD: +2.4% Femoral aBMD: +2.6% Ward's aBMD: +2.1%	None Reported	None Reported	Leg Power: +8.9%
Bassey et al. (1998) [Age: ~38 Yrs]	Adult Females (n=25) Impact Training 50 jumps, 6 days/week 26 weeks (6 months).	Spinal aBMD: +8.6% Femoral aBMD: +2.1%	None Reported	None Reported	Leg Power: +6.9%
Heinonen et al. (1996) [Age: ~39 Yrs]	Adult Females (n=39) High-impact Exercise 60 minutes, 3 days/week 78 weeks (18 months)	Spinal aBMD: +2.2% Femoral aBMD: +1.8% Tibial aBMD: +2.1% Calcaneal aBMD: +3.7%	None Reported	None Reported	Isom.Str: +5.1% Leg Power: +21.0%
Bassey et al. (1994) [Age: ~32 Yrs]	Adult Females (n=14) High-impact Training 60 minutes, 1 day/week 50 Jumps, 6 days/week 26 weeks (6 months)	Spinal aBMD: +0.5% Femoral aBMD: +3.2%	None Reported	None Reported	Leg Power: 15.8%

Note: **aBMD = areal bone mineral density; Ct.Ar = cortical area; CSA = cross-sectional area; Ct.Th = cortical thickness; CSMI = cross-sectional moment of inertia; Isom.Str = isometric strength. All values reported as percent change from baseline.**

Furthermore, nearly all investigations exclusively reported material adaptations to identify the effect of impact exercise on bone mass, neglecting bone structure and strength; a themed limitation of most exercise intervention studies. This underestimates the effect of exercise on bone strength; insufficiently representing the gamut of adaptations resulting from mechanical loading programs. In particular, adaptations to impact exercise are notably morphometric (Weidauer et al, 2014; Nilsson et al, 2013; Melo et al, 2012; Nikander et al, 2010a; Haapasalo et al, 2000; Wheeler et al, 1995), yet remain largely unquantified in controlled impact environments; nevertheless, higher magnitude increases in material density were evident in all measured regions relative to the other exercise modalities, with concurrent improvements in muscular strength and power.

2.4.2.5. Multi-modal Exercise

Multi-modal exercise integrates numerous modalities within a mechanical loading program to deliver variable osteogenic stimuli of different magnitudes, rates, frequencies, directions and distributions through a combination of mechanisms unique and complimentary to each modality. Specifically, multi-modal exercise combines the muscular benefits of resistance training with the gravitational benefits of impact exercise and locomotive exercise to deliver highly osteogenic outcomes; eliciting high strain magnitudes at high strain rates of high-, odd- and low-impact (Karlsson & Rosengren, 2012; Ebben et al, 2010; Nikander et al, 2010a; Bailey & Brooke-Wavell, 2010; Guadalupe-Grau et al, 2009a; Daly & Petit, 2007; Vainionpaa et al, 2006). As cortical and trabecular bone have different mechanical and behavioural properties (described in Section 2.3.1 and 2.3.2) it seems logical to use multiple loading strategies to target and optimise bone strength in adjacent areas of the

skeleton with different trabecular and cortical compositions. Furthermore, multi-modal exercise concurrently delivers other health benefits, improving balance, mobility, muscular strength, physical function and aerobic fitness (Body et al, 2011; Karinkanta et al., 2007; Beck & Snow, 2003; Karinkanta et al, 2007; Taylor et al, 2004); serving as an attractive interventional model for practitioners to examine and employ.

Mechanical investigations using multiple modes of exercise have typically combined resistance training with impact or locomotive exercise (Table 10). The resultant effects of these mechanical loading programs are encouraging, with larger material and structural adaptations leading to greater increments in bending resistance (~4%) and bone strength (~8%) in ~6 to 9 months. Synergistically, larger muscle adaptations were also evident, with marked improvements in dynamic strength (~70 to 90%), isometric strength (~14 to 20%), isokinetic strength (~18 to 25%), leg power (~7 to 25%) and muscle mass (~4 – 5%). However, unanimous interpretations of multi-modal studies remain limited by variability in duration, design and data reported (Melo et al, 2012; James & Carroll, 2010; Nikander et al, 2010b); centrally focusing on material measures. Nevertheless, multi-modal exercise interventions are notably more effective and efficient than any singular exercise modality when used in isolation.

Table 10. ***Overview of human model mixed-mode training studies using adolescent and adult males and females.***

Author(s)	Training Protocol	Material Adaptations	Structural Adaptations	Strength Adaptations	Muscular Adaptations
Guadalupe-Grau et al. (2009b) [Age: ~24 Yrs]	Adult Males (n=21) Impact and Resistance Training 40 minutes, 3 days/week 9 weeks (2 months).	Spinal aBMC: +2.0% Spinal aBMD: +2.7% Leg aBMC: +0.6% Leg aBMD: ±0.0% Femoral aBMC: ±0.0% Femoral aBMD: -1.8%	None Reported	None Reported	Dyn.Leg.Str: +70.1% Isom.Str: +17.1% Total Mass: +1.6% Leg Mass: +4.5%
Guadalupe-Grau et al. (2009b) [Age: ~23 Yrs]	Adult Females (n=13) Impact and Resistance Training 40 minutes, 3 days/week 9 weeks (2 months).	Spinal aBMC: +1.2% Spinal aBMD: ±0.0% Leg aBMC: +0.5% Leg aBMD: +0.8% Femoral aBMC: +2.0% Femoral aBMD: -1.0%	None Reported	None Reported	Dyn.Leg.Str: +91.5% Isom.Str: +13.8% Total Mass: +1.4% Leg Mass: +5.3%
Ballard et al. (2006) [Age: ~20 Yrs]	Adult Males (n=12) and Adult Females (n=11) Endurance and Resistance Training 45-60 minutes, 5 days/week 26 weeks (6 months).	Total aBMC: +0.5% Tibial Tt.vBMD: +1.2% Tibial Tb.vBMD: +0.4% Tibial Ct.vBMD: +0.5%	Total Tt.Ar: +0.5% Tibial Tt.Ar: -0.6% Tibial Ct.Ar: +0.9% Tibial Ct.Th: +1.5% Tibial Ps.Circ: ±0.0% Tibial Ec.Circ: -1.0%	PMI: +4.3%	None Reported
Winters-Stone et al (2006). [Age: ~40 Yrs]	Adult Females (n=35). Impact and Resistance Training 60 minutes, 3 days/week 52 weeks (12 months).	Total aBMD: +0.8% Spinal aBMD: +1.1% Hip aBMD: +1.5% Femoral aBMD: +1.0%	None Reported	None Reported	Total Mass: +1.9% Leg Mass: +6.2%

Weaver et al. (2001). [Age: ~24 Yrs]	Adult Females (n=37) Impact and Resistance Training 60 minutes, 4 days/week 52 weeks (12 months)	Spinal aBMC: +0.6% Spinal aBMD: +0.4% Femoral aBMD: +0.2%	None Reported	None Reported	Total Mass: +2.7%
Winters et al. (2000). [Age: ~40 Yrs]	Adult Females (n=33) Impact and Resistance Training 60-90 minutes, 3 days/week 52 weeks (12 months)	Total aBMD: +1.0% Spinal aBMD: +1.1% Femoral aBMD: +2.7%	None Reported	None Reported	Isok.Ext.Str: +18.3% Isok.Ab.Str: +27.7% Leg Power: +25.1%
Heinonen et al. (2000) [Age: ~14 Yrs]	Adolescent Females (n=39) Endurance and Impact Training 50 minutes, 2 days/week 39 weeks (9 months)	Spinal aBMC: +5.3% Femoral aBMC: +5.3% Tibial Ct.vBMD: +0.0%	Tibial Ct.Ar: +4.4%	Tibial BSI: +7.5%	Isom.Str: +20.0% Leg Power: +7.0%
Friedlander et al (1995) [Age: ~28 Yrs]	Adult Females (n=32) Endurance, Strength, Impact Training 60 minutes, 3 days/week 104 weeks (24 months)	Spinal aBMD: +1.3% Femoral aBMD: +2.6% Calcaneal aBMD: +5.6%	None Reported	None Reported	Isok.Flex.Str: +25.3% Isok.Ext.Str: +21.1%

Note: **aBMC = areal bone mineral content; aBMD = areal bone mineral density; Tb.vBMD = trabecular volumetric bone mineral content; Ct.vBMD = cortical volumetric bone mineral density; Tt.vBMD = total volumetric bone mineral density; Tt.Ar = total area; Ct.Ar = cortical area; Ct.Th = cortical thickness; CSA = cross-sectional area; Ps.Circ = periosteal circumference; Ec.Circ = endocortical circumference; PMI = polar moment of inertia; CSMI = cross-sectional moment of inertia; BSI = bone strength index; All values reported as percent change from baseline.**

2.4.2.6. Sport Participation

Physical activity in the form of recreational and competitive sporting activities are widely recognised as beneficial to bone mass accretion and bone strength development, owing to the adaptability of bone to increases in habitual mechanical loads (Nikander et al, 2010a; Nilsson et al, 2009; Nevill, Holder & Stewart, 2004; Morris, Naughton, Gibbs, Carlson & Wark, 1997; Heinonen et al, 1995). In particular, sporting activities are highly dynamic and volatile, with non-uniform loading patterns that routinely change in response to external parameters and environmental conditions (Weidauer et al, 2014; Nilsson et al, 2013; Quiterio et al, 2011; Rantalainen et al, 2010b; Zouch et al, 2008; Daly & Petit, 2007). Subsequently, sporting activities share similar osteogenic traits with multi-modal exercise, involving combinations of impact-, resistance- and locomotive-based exercise to deliver high magnitudes and rates of strain with unusual distributions through muscular and gravitational loads under training and competitive contexts (Weidauer et al, 2012; Kohrt, Barry & Schwartz, 2009; Zouch et al, 2008; Nevill, Holder & Stewart, 2004; Haapasalo et al, 2000). However, given the reactive nature of sporting activities, loading parameters are difficult to control; providing a translatory opportunity to transfer bone adaptation principles from prescriptive exercise contexts to habitually unpredictable situations by means of sports participation; whilst conversely providing inherent risks of overload and overuse injury; a cost-benefit consideration for individuals whom may be skeletally fragile.

Regular physical activity through sport delivers sustained and life-long material and structural benefits to the skeleton, independent of bone mass maintenance and recession (Rantalainen et al, 2014; Warden et al, 2014; Warden & Roosa, 2014; Tveit et al., 2012; Rantalainen et al , 2010a; Rantalainen et al 2009b); providing an enjoyable and compliant exercise modality to convey short-term and long-term osteogenic adaptations. However,

mechanical loads expressed through sport are highly dependent upon the nature and style of the chosen competition, specific to their differences in objectives, rules, regulations, field dimensions, participant numbers and tactics used. In order to examine the osteogenic benefits conferred to individuals under various sporting contexts, it is necessary to distinguish between sports with distinct muscular and gravitational loading characteristics. Specifically, sports are qualitatively categorised as high-impact, odd-impact, high-magnitude, low-impact, and non-impact in accordance with activities performed during training and competition (Rantalainen et al, 2011; Nikander et al, 2010a; Rantalainen et al, 2010b; Nikander, Sievanen, Uusi-Rasi, Heinonen & Kannus, 2006; Nikander et al, 2005).

Table 11. ***Classification, definition and sub-category examples of sporting activities involving different muscular and gravitational load profiles***

Sport Classification	Loading Description	Sub-categories or Examples
High-Impact	Events involving maximal vertical jumps, leaps or bounds with corresponding ground impacts.	Volleyball, Gymnastics, High Jump, Triple Jump, Hurdling, Weightlifting
Odd-Impact	Events involving rapid turns, stops, accelerations, decelerations or lateral movement while sprinting or running with corresponding ground impacts	Racquet: (tennis, badminton, squash) Court: (basketball, netball, handball) Field: (hockey, lacrosse, cricket, baseball) Football: (soccer, Australian Football, American Football, Gaelic Football, rugby union, rugby league)
High Magnitude	Events involving maximally applied muscular forces in slow, coordinated movements involving external loads, without any corresponding ground impacts.	Powerlifting and Bodybuilding.
Low-Impact	Events involving ground impacts that occur during longer-lasting running performances at relatively constant speed	Middle-distance: (400m, 800m, 1500m) Endurance: (3000m, marathons, triathlons)
Non-Impact	Events involving applied muscular forces over longer durations without corresponding ground impacts.	Swimming, Cycling

Note: **Sports listed in each sub-category are qualitative additions to those previously defined by Nikander et al (2010a) and Rantalainen et al (2010b). The list is not exhaustive and only indicative.**

Cross-sectional examinations of numerous athletic cohorts demonstrate clear differences in adaptive responses to defined loading classifications (Table 11). Specifically, sports involving impact-based gravitational loading produced markedly greater material, structural and bone strength adaptations at distal and central locations than their non-impact counterparts (Table 12; Figure 25). Furthermore, within impact loading sub-categories; athletes participating in high-impact and odd-impact sports contained the highest tibial bone mineral content (~21 – 39%), cortical area (~20 – 48%), cross-sectional area (~6 - 26%), and polar section modulus (~21 – 39%), subsequently optimising tibial bone strength (~23 - 40%). Interestingly, high-impact sports also delivered large bone strength benefits to the non-weight-bearing fibula (~27%), with all other loading classifications conferring negligible or negative fibular strength adaptations. Lastly, athletes participating in high-impact sports expressed higher levels of muscular strength and power (~35 - 44%) than non-active controls, similar to the effect of high-magnitude sports (~35 – 60%); highlighting the globally superior musculoskeletal benefits of high-impact sports over all other sporting classifications. Despite evident differences in magnitude and composition of adaptation; sports participation is considered to be highly myogenic and osteogenic.

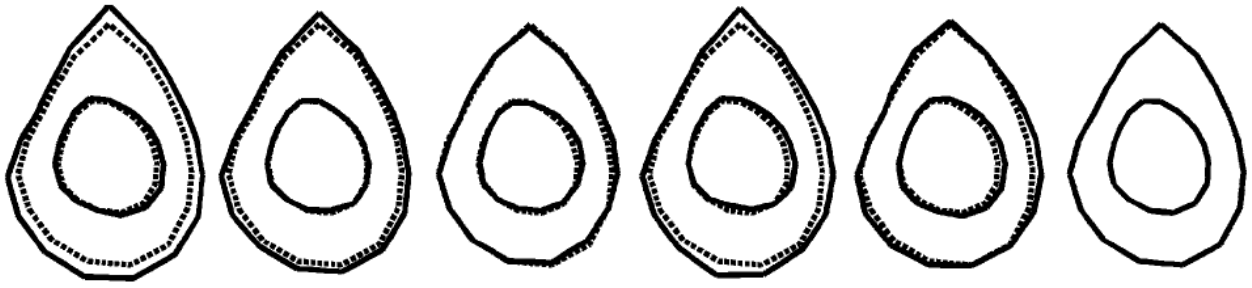


Figure 25. Tibial geometry in athletes (Nikander et al, 2010a) participating in: (A) high-impact, (B) odd-impact, (C) high-magnitude, (D) repetitive low-magnitude, and (E) non-impact sports, with a (F) reference group for comparison (represented by dotted lines from A-E).

Table 12. ***Overview of musculoskeletal adaptations to sports participation stratified by impact-loading characteristics.***

Sport(s)	Category	Material Adaptations	Structural Adaptations	Strength Adaptations	Muscular Adaptations
Volleyball, Hurdling, Triple Jump, High Jump	High-Impact	Distal Tibia vBMC: +31.0% Tibial Shaft vBMC: +38.9%	Distal Tibia CSA: +17.3% Distal Tibia Ct.Ar: +48.5% Distal Tibia PSM: +24.7% Tibial Shaft CSA: +25.9% Tibial Shaft Ct.Ar: +31.8% Tibial Shaft PSM: +38.3%	Tibial SSI: +39.8% Tibial SMA: +9.0% Fibular SSI: +27.0% Fibular SMA: +12.3%	Isom.Str: +35.5% Leg Ab.Power: +44.0% Leg Rel.Power: +34.6%
Soccer, Squash, Tennis, Badminton	Odd-Impact	Distal Tibia vBMC: +20.6% Tibial Shaft vBMC: +27.5%	Distal Tibia CSA: +6.3% Distal Tibia Ct.Ar: +37.4% Distal Tibia PSM: +39.1% Tibial Shaft CSA: +14.5% Tibial Shaft Ct.Ar: +19.6% Tibial Shaft PSM: +20.8%	Tibial SSI: +22.9% Tibial SMA: +3.7% Fibular SSI: +1.6% Fibular SMA: +4.0%	Isom.Str: +27.7% Leg Ab.Power: +19.7% Leg Rel.Power: +15.5%
Powerlifting	High Magnitude	Distal Tibia vBMC: +0.5% Tibial Shaft vBMC: -(22.0)%	Distal Tibia CSA: -(3.1)% Distal Tibia Ct.Ar: +7.6% Distal Tibia PSM: +8.6% Tibial Shaft CSA: +0.5% Tibial Shaft Ct.Ar: +1.4% Tibial Shaft PSM: +1.0%	Tibial SSI: +4.2% Tibial SMA: -(9.8%) Fibular SSI: ±0.0% Fibular SMA: +11.6%	Isom.Str: +60.3% Leg Ab.Power: +40.8% Leg Rel.Power: +34.6%
Endurance Running	Low-Impact	Distal Tibia vBMC: +10.2% Tibial Shaft vBMC: -(7.4)%	Distal Tibia CSA: +6.1% Distal Tibia Ct.Ar: +28.1% Distal Tibia PSM: +12.6% Tibial Shaft CSA: +17.6% Tibial Shaft Ct.Ar: +22.9% Tibial Shaft PSM: +25.3%	Tibial SSI: +29.5% Tibial SMA: +9.4% Fibular SSI: -(5.1)% Fibular SMA: +16.3%	Isom.Str: +20.6% Leg Ab.Power: -(2.3)% Leg Rel.Power: +9.6%
Swimming	Non-Impact	Distal Tibia vBMC: +3.9% Tibial Shaft vBMC: +3.3%	Distal Tibia CSA: +5.9% Distal Tibia Ct.Ar: +1.2% Distal Tibia PSM: +5.1% Tibial Shaft CSA: +6.9% Tibial Shaft Ct.Ar: +5.0% Tibial Shaft PSM: +8.0%	Tibial SSI: +10.2% Tibial SMA: -(5.7)% Fibular SSI: -(2.8)% Fibular SMA: +19.9%	Isom.Str: +15.6% Leg Ab.Power: +18.8% Leg Rel.Power: +13.0%

Note: **vBMC = volumetric bone mineral content; CSA = cross-sectional area; Ct.Ar = cortical area; PSM = polar section modulus; SSI = stress-strain index; SMA = second moment area; Isom.Str = isometric strength; Ab.Power = absolute power; Rel.Power = Relative Power. All values reported as percent difference to non-active controls. Data acquired from Nikander et al. (2010a), Rantalainen et al. (2010b) & Nikander et al. (2006).**

2.4.2.7. Osteogenic Index

Exercise prescriptions use variations of intensity, frequency, duration and recovery to maximise the osteogenic response in bone, capitalising on known relationships between characteristics of loading programs and bone adaptation (Evans et al, 2012; Lester et al, 2009; Santos-Rocha, Oliveira & Veloso, 2006; Erickson & Vukovich, 2010; Robling, Castillo & Turner, 2006; Cullen, Smith & Akhter, 2001). In principle, dynamic activities are more osteogenic than static activities; bone formation is proportional to mechanical intensity (i.e. the interplay between strain magnitude and frequency); and prolonged exercise delivers diminishing returns (Robling, Castillo & Turner, 2006; Santos-Rocha, Oliveira & Veloso, 2006; Turner & Robling, 2003). Using these known relationships, the osteogenic potential of a given activity or exercise could be estimated via the Osteogenic Index; a measure of exercise effectiveness incorporating several known bone biology criteria to reasonably forecast the influence of an exercise protocol on bone mass accretion (Evans et al, 2012; Rantalainen et al, 2010a; Santos-Rocha, Oliveira & Veloso, 2006; Turner & Robling, 2003). Explicitly, the osteogenic index is calculated using the formula: $OI = I * \ln(N + 1)$; where I represents the intensity of exercise and N represents the number of loading cycles performed (Lester et al, 2009; Lau & Pang, 2009; Turner & Robling, 2002). If mechanical loading programs use rest periods between exercise bouts, an additional function is added to the osteogenic index equation recognising mechanical resensitisation; where $-t$ represents the time of rest in hours and r represents a constant of ~6 hours (Erickson & Vukovich, 2010; Turner & Robling, 2003), explicitly written as: $OI = I * \ln(N + 1) * (1 - e^{-t/r})$.

Indirect estimates of exercise effectiveness provide a useful non-invasive platform to quantify osteogenic potential, using external devices (inertial measurement units, accelerometers or force plates) to determine the stimulatory effects of selected exercises (Kelley, Hopkinson, Strike, Luo & Lee, 2014; Tolly, Chumanov & Brooks, 2014; Rantalainen et al, 2011; Lau & Pang, 2009). Specifically, multiples of ground reaction forces are used to provide generalised, non-specific indications of supplied mechanical strain to load-bearing and weight-bearing skeletal regions. While the relative simplicity of measuring and applying the Osteogenic Index to various exercise programs is advantageous; the resultant outcome of mechanical loading programs is different for each bone within the skeleton. Consequently, indirect measures are restricted by an inability to access or isolate skeletal structures; limiting the Osteogenic Index to generalised, global estimations of osteogenic potential (Kelley et al, 2014; Martelli, Kersh, Scache & Pandy, 2014; Al Nazer et al, 2008). Instead, direct measures of mechanical strain could provide a more accurate insight into localised, site-specific and targeted skeletal regions for a given loading sequence (Carriero, Abela, Pitsillides & Shefelbine, 2014; Al Nazer et al, 2012). Specifically, strain gauges applied to individual bones within the skeleton through micro-incision and implantation directly quantify the targeted strain environment for a given exercise at a site-specific location (Al Nazer et al, 2012; Yang, Bruggemann & Ritwegger, 2011; Milgrom et al, 2002; Milgrom et al, 2001). Although invasive and disruptive; precise measures of mechanical strain may further establish explicit dose-response relations between physical load, bone adaptation and injury (Carriero et al, 2014; Martelli et al, 2014; Yang, Bruggemann & Ritwegger, 2011; Al Nazer et al, 2008; Pearce, Richards, Milz, Schneider & Pearce, 2007; Milgrom et al, 2000a; Milgrom et al, 2000b).

2.4.3. EFFECT OF PHARMACOLOGY

Pharmacological strategies to develop and maintain bone strength are commonplace in clinical environments; prophylactically and therapeutically attempting to prevent or manage pathological and degenerative bone conditions such as osteopenia or osteoporosis (Khosla, 2013; Nelson, Wardell & McDonnell, 2013; Han & Wan, 2012; Bukata, 2011; Russell, 2007; Russell, 2006; Bone et al, 2004). Specifically, pharmacological treatment involves the delivery of drug compounds (natural and artificial) into the human body through nasal or oral passageways; subcutaneous, intravenous or intramuscular injections; topical gels or creams; or transdermal patches, attempting to alter the microenvironment of a target area or sub-system in order to exert a desired effect or outcome (Bullock & Manias, 2013; Katzung, Masters & Trevor, 2012; Khosla, Amin & Orwell, 2008). Skeletally, a variety of pharmaceutical products or therapies have been developed to target formative or anti-resorptive mechanisms, including bisphosphonates; denosumab; recombinant estrogen and progesterone (ERT, HRT); selective estrogen receptor modulators (SERMs); recombinant parathyroid hormone (PTH) and calcitonin (Mandema, Zheng, Libanati & Perez Ruixo, 2014; Chiang et al, 2013; Davey & Findlay, 2013; Shiraki, Sugimoto & Nakamura, 2013; Han & Wan, 2012; Nelson, Wardell & McDonnell, 2012; de Villiers & Stevenson, 2012; Blumsohn et al, 2011; Chaiya, Rattanakul, Rattanamongkonkul, Kunpasuruang & Ruktamatakul, 2011; Cremers & Papapoulos, 2011; Jonsson et al, 2011; Rattanakul & Rattanamongkonkul, 2011; Macdonald, Nishiyama, Hanley & Boyd, 2010; Seeman et al, 2010; Kohrt et al, 2010; Bain, Jerome, Shen, Dupin-Roger & Ammann, 2009; Migliaccio, Brama & Spera, 2007; Russell, 2007; Russell, 2006; Bone et al, 2004; Jiang et al, 2003; Paschalis, Boskey, Kassem & Eriksen, 2003; Sato e al, 2002; Roschger et al, 2001; Bonjour, Ammann, Barbier, Caverzasio & Rizzoli, 1995; Ejersted et al, 1993).

Table 13. ***Overview of pharmacological interventions used to treat bone fragility and increase bone strength in humans.***

Treatment	Delivery	Basic Description	Side-Effects
Bisphosphonates: - Alendronate - Ibandronate - Pamidronate - Risedronate - Zoledronic Acid	Oral, SC Injection, IV Injection	Antiresorptive; inhibits osteoclast mediated resorption, supresses remodelling. Selectively binds to hydroxyapatite crystals under active resorption; prevents formation of osteoclasts; promotes osteoclast apoptosis. May also synergistically assist osteoblasts.	Upper Gastrointestinal (nausea, dyspepsia, abdominal pain, and gastritis), Acute Phase Reactions (fever, myalgias, and arthralgias), Musculoskeletal Pain, Transient Hypocalcemia (with secondary hyperparathyroidism), Esophageal Cancer, Ocular Inflammation, Osteonecrosis, Atrial Fibrillation, Sub-trochanteric Femoral Fractures.
ERT and HRT - Estrogen - Progestin - Progesterone	Oral, Topical, Transdermal	Reduces bone turnover and osteoclast activation frequency; second-line therapy due to adverse effects outweighing subtle skeletal benefits.	Breast Discomfort and Swelling; Leg and Foot Swelling; Rapid Weight Gain; Decreased Appetite; Nausea; Vomiting; Fever; Pain; Swelling; Tenderness; Bladder Problems; Abdominal Pain; Yellow Skin or Eyes; Dizziness; Headache
SERMs: - Bazedoxifene - Lasofoxifene - Raloxifene - Tamoxifene	Oral	Non-steroidal compounds, bind to targeted estrogen receptors, may exert agonist and antagonist effects in various tissue. Inhibits bone resorption, minimises bone-turnover. Safer alternative to ERT and HRT.	Abnormal Bleeding; Pain or Pressure in Pelvis; Leg swelling or tenderness; Chest Pain; Shortness of Breath; Weakness; Tingling; Numbness; Sudden Visual Difficulties; Dizziness; Severe Headaches; Fatigue; Night Sweats; Mood Swings; Endometrial Hyperplasia; Fibroids; Polyps.
Denosumab	SC Injection	Monoclonal antibody; blocks binding of RANKL and RANK; Prevents terminal differentiation; Inhibits osteoclast-mediated bone resorption (activation and survival).	Abdominal Pain; Skin Irritation or Blisters; Musculoskeletal Pain; Nausea; Diarrhoea; Headache; Muscular Stiffness, Cramp or Spasms; Numbness; Dizziness; Blurred Vision; Pancreatitis; Mouth or Jaw Pain, Numbness or Swelling.
PTH: - PTH1-34 - PTH1-84 - Teriparatide	SC Injection	Hormonal regulator of calcium; Improves bone mass despite increases in formative and resorptive activity; Develops cortical and trabecular thickness, volume and connectivity.	Muscular Stiffness, Cramps or Spasms; Nausea; Diarrhoea; Indigestion; Fatigue; Weakness; Stomach Pain; Headaches; Dizziness; Loss of Appetite; Pain in Extremities; Back Pain; Metabolic Problems; Constipation.
Calcitonin	SC Injection, Nasal Spray	Hormonal regulator of calcium; amino-acid peptide; released from thyroid; potent inhibitor of bone resorption; assists bone homeostasis.	Muscle Stiffness; Fainting; Nausea; Decreased Appetite; Abdominal Pain; Skin Rash or Itching; Eye Pain; Increased Urination; Foot Swelling; Blurred Vision.

Note: SERMs = selective estrogen receptor modulators; HRT = hormone replacement therapy; ERT = estrogen replacement therapy; SC = subcutaneous; IV = intravenous; Information supplied in this table is not exhaustive; side-effects reported are only indicative of main reported adverse reactions to pharmacological treatment.

Pharmacological treatments for skeletal fragility are increasing in popularity worldwide, owing to their simplicity of administration; relative immediacy of effect; ability to control dose-response; and establishment as an adjunctive or alternative option to exercise or nutrition-based methodologies (Brandi. 2013; Brandi, 2012, Bukata, 2011; Sandhu & Hampson, 2011; Levy, 2002). However, several economical and medical complications arise with drug-based management as pharmaceuticals are expensive to develop, trial, distribute, purchase and consume; require on-going use and supervision to safely maintain therapeutic effects; and only deliver global outcomes in a non-localised, non-specific and stochastic manner. Most catastrophically, all pharmaceuticals have biological consequences with many inherent contraindications, generating dangerous and uncomfortable side-effects which commonly arise during treatment, often requiring secondary management at an additional physiological, psychological and financial cost (Park-Wyllie et al, 2011; Rizzoli et al, 2011a; Rizolli et al, 2011b; Watts & Diab, 2010; Kennel & Drake, 2009). Complexity further arises as drugs also interact with other simultaneously administered medication often prescribed for unrelated conditions (Gosch, Jeske, Kammerlander & Roth, 2012, Kuijpers et al, 2008; Hannan et al, 2004). Specifically, polypharmacy is a negative constraint where drug-drug interactions modify therapeutic potency and impact; contradicting, nullifying or exacerbating their effects; resulting in a blunted, ineffective or toxic response (Gosch et al, 2012; Kuijpers et al, 2008; Hajjar, Cafiero & Hanlon, 2007).

Skeletal adaptations during anti-resorptive and pro-formative treatment primarily restore and maintain bone strength by suppressing osteoclast activity or promoting osteoblast synergy respectively (Perez Ruixo, Zheng & Mandema, 2014; Shiraki, Sugimoto & Nakamura, 2013; Brandi, 2012; Han & Wan, 2012; Cremers & Papapoulos, 2011; Martin

& Correa, 2010; Lindsay et al, 2007; Russell, 2007; Seeman & Delmas, 2006; Bone et al, 2004; Bonjour et al, 1995), increasing bone mineral density through reduced porosity and increased thickness of cortical and trabecular bone (Bukata, 2011; Sandhu & Hampson, 2011; MacDonald et al, 2010; Seeman et al, 2010; Migliaccio et al, 2007; Jiang et al, 2003; Dempster et al, 2001; Ejersted et al, 1993). These adaptations collectively increase bone strength through material contributions at the expense of increased brittleness, subsequently heightening skeletal susceptibility to microdamage during mechanical loading (Chiang et al 2013; Martin & Correa, 2010; Currey, 2005; Roschger et al, 2001). This is problematic for anti-resorptive medications as suppressed remodelling inadvertently blocks microdamage reparation, deleteriously leading to increased microcrack coalescence and reduced mechanical competency (Pountos, Georgouli, Calori & Giannoudis, 2012; Cremers & Papapoulos, 2011; Kohrt et al, 2010; Li, Mashiba & Burr, 2001). As a result, prophylactic use of anti-resorptive agents may be inappropriate; whereas therapeutic use for individuals with high bone turnover rates and low bone density may be optimal (Brandi, 2013; Sandhu & Hampson, 2011; Kennel & Drake, 2009; Migliaccio et al, 2007; Bone et al, 2006; Russell, 2007; Seeman & Delmas, 2006). Conversely, pro-formative agents prophylactically and therapeutically benefit individuals with high or low bone turnover rates of various densities by stimulating bone formation (Han & Wan, 2012; Sandhu & Hampson, 2011; Rosen, 2010; Khosla, Amin & Orwell, 2008; Migliaccio et al, 2007; Seeman & Delmas, 2006; Delmas et al, 2006; Martin, 2004). While broader in application with fewer side-effects; in cases of marked fragility, the smaller remedial effects of pro-formative drugs may not be wholly sufficient (Nelson et al, 2013; Martin & Correa, 2010; Rosen, 2010; Migliacco et al, 2007; Sato et al, 2002), thus informed decisions regarding treatment must consider the underlying cause and skeletal status of the individual.

Anti-resorptive and pro-formative drugs administered in isolation and combination are limited to material and not structural properties through stochastic and not deterministic mechanisms with wide-ranging and deleterious side-effects; subsequently rendering pharmacologically driven adaptations as inferior in magnitude and scale to those established through mechanical loading programs (Body et al, 2011; Kemmler & von Stengel, 2011; Winters-Stone, Schwartz & Nail, 2010; Karinkanta et al, 2007). In particular, complimentary and concurrent exercise and nutrition based interventions provide expansive primary and secondary, direct and indirect health benefits to the musculoskeletal system by explicitly targeting material and structural properties through stochastic and deterministic mechanisms without adverse reactions at markedly reduced costs (Body et al, 2011; Nordstrom et al, 2011; Winters-Stone et al, 2010; Karinkanta et al, 2007). As a result, the modulation and regulation of bone mass and morphology is ideally achieved through non-pharmacologic means, capably delivering skeletal resilience and protective benefits in earlier years, whilst reducing net-resorption and skeletal fragility in later years (Body et al, 2011; Judex, Lei, Han & Rubin, 2007; Kannus et al, 2005; Hannan et al, 2004; Daley, 2002). Although pharmacological treatment is efficacious in cases of advanced ageing, pathological disease, physical injury and periods of immobilisation; non-pharmacological management produces better outcomes at a reduced burden.

2.4.4. Effect of Nutrition

Nutrients supplied by dietary and supplementary sources can substantially promote or impair skeletal growth and development through direct and indirect mechanisms (Rizzoli, Abraham & Brandi, 2014; Price, Langford & Liporace, 2012; Sacco, Horcajada & Offord, 2012; Body et al, 2011; Penteado et al, 2010; Weaver, 2008; Ilich & Kerstetter, 2000).

Directly, nutrients act to promote skeletal integrity and bone strength through material adaptations, with formative and homeostatic adaptations permeating through-out organic and inorganic levels (Horcajada & Offord, 2012; Laudermilk et al, 2012; Sacco et al, 2012; Ahmadieh & Arabi, 2011; Reid, Cornish & Baldock, 2006). In particular, protein compartments reside within the structural components of collagen (organic matrix); and calcium-phosphorous unite to form hydroxyapatite crystals within mineralised bone (inorganic matrix), co-operatively interacting with other nutrients (Table 14) to fortify bone material (Rizzoli et al, 2014; Horcajada & Offord, 2012; Price et al, 2012; Ahmadieh & Arabi, 2011; Bonjour, 2011; Jesudason & Clifton, 2011; Penteado et al, 2010; Weaver, 2008; Palacios, 2006; Bonjour, 2005; Heaney & Weaver, 2005; Devirian & Volpe, 2003; Ilich & Kerstetter, 2000; Holick, 1996). Indirectly, nutrition underpins bone health through the production of growth factors, cytokines and hormones which promote muscle-bone synthesis (Sacco et al, 2012; Jesudason & Clifton, 2011; Holm et al, 2008; Weaver, 2008; Daly & Petit, 2007; Palacios, 2006; Reid et al, 2005); and through the creation of anabolic or catabolic environments by which muscle-bone adaptation or maladaptation occurs (Hattori et al, 2013; Demling, 2009; Tang & Phillips, 2009; Holm et al, 2008; Bonjour, 2005; Heaney & Weaver, 2005; Reid et al, 2005; Schacht, Richy & Reginster, 2005).

Energy availability profoundly impacts bone health, with low levels generating sub-optimal and impaired bodily functions which may compromise muscle-bone anabolism (Loucks, Kiens & Wright, 2011; Loucks, 2007; Nichols, Sanborn & Essery, 2007; Loucks, 2004). Explicitly, energy availability is defined as energy intake, minus energy expenditure during exercise, normalised to fat-free mass (Hattori et al, 2013; Ihle & Loucks, 2004; Loucks, 2004); representing the amount of fuel available for physiological function, including

cellular maintenance, growth, thermogenesis, reproduction, immunity and locomotion (Loucks et al, 2011; Warren & Chua, 2008; Wade & Jones, 2004). Given that energy use is mutually exclusive; when available energy is low (i.e. female triad or male tetrad), limited resources are weighted in a hierarchical fashion towards areas of higher importance, such that sacrificial functions are impaired (Dimitriou et al, 2014; Hattori et al, 2013; Javed, Tebben, Fischer & Lteif, 2013; Laframboise, Borody & Stern, 2013; Swift, Baek, Swift & Bloomfield, 2012; Zach, Machin & Hoch, 2011). Consequently, low energy availability reduces hormonal balance, bone formation and bone mineral density; resulting in decreased bone strength, while compromising skeletal repair and remodelling processes (Hattori et al, 2013; Swift et al, 2012; Sundgot-Borgen & Garthe, 2011).

Nutrient deficiency and toxicity also deleteriously impacts bone health, supressing or inflating biological processes involved in bone metabolism and mineral homeostasis (Laudermilk et al, 2012; Moran et al, 2012b; Ahmadieh & Arabi, 2011; Body et al, 2011; Jesudason & Clifton, 2011; Palacios, 2006; Greer & Krebs, 2005). Consequently, if certain nutrients are chronically reduced or elevated; systemic disturbances can produce altered states of calcium retention and secretion; altered parathyroid hormone activity; reduced insulin growth-like factor production; impaired bone growth and repair; and altered crystallinity; leading to demineralisation, microarchitectural decay and reduced mechanical competency (Viguet-Carrin et al, 2014; Moran et al, 2012b; Greer & Krebs, 2005; Heaney & Weaver, 2005; Shapses et al, 2003). Given the broad range of adversities derived from nutrient deficiency in particular; coupled with the logistical issue of counterbalancing energy intake restrictions with expansive nutrient requirements; supplementation provides an attractive option for practitioners to protect individuals against deficiency driven sub-optimal bone health (Mercer et al, 2012; Price et al, 2012; Loucks et al, 2011; Sandhu &

Hamspon, 2011; Gehrig, Lane & O'Connor, 2008; Holm et al, 2008; Knapen, Schurgers & Vermeer, 2007; Johnston et al, 1992). However, supplementation also carries an inherent risk of toxicity, given its additive effect to nutrients already derived from animal- or plant-based meal sources, and thus should be a secondary option to whole-food sources (Viguet-Carrin et al, 2014; Price et al, 2012; Jesudason & Clifton, 2011; Greer & Krebs, 2005).

Dietary driven adaptations are osteogenically similar in scope to pharmacological treatments, delivering stochastic bone strength adaptations through material gains and mineral maintenance only (Viguet-Carrin et al, 2014; Kukuljan et al, 2011; Sandhu & Hamspon, 2011; Daly & Kukuljan, 2010). Owing to their mechanistic differences, dietary nutrients promote bone growth without the same undesirable side-effects of drugs, establishing nutrition as the preferred strategy to non-mechanically promote bone mass and strength (Body et al, 2011; Daly & Petit, 2007; Knapen et al, 2007). However, nutritional intake provides a supportive rather than dictative role, crucially underpinning the important structural adaptations and deterministic alterations driven by mechanical loading programs during growth, development, maturation and older age (Hattori et al, 2013; Kukuljan et al, 2011; Loucks et al, 2011; Daly & Kukuljan, 2010; Penteado et al, 2010; Daly & Petit, 2007; Palacios, 2006; Lanou, Berkow & Barnard, 2005; Beecher, 1999). As a result, exercise and nutrition jointly form a non-pharmacological, multi-faceted and co-operative strategy that is efficacious, inexpensive, holistic and targeted; with additional and secondary health benefits (Price et al, 2012; Body et al, 2011; Kukuljan et al, 2011; Sandhu & Hampson, 2011; de Kam, Smulders, Weerdesteyn & Smits-Engelsman, 2009; Khosla, Amin & Orwell, 2008; Daly & Petit, 2007; Greer & Krebs, 2005).

Table 14. ***Overview of nutrients influencing Bone health, with benefits, contraindications and toxicity***

Nutrient	Bone Health Mechanisms	Benefits / Contraindications / Toxicity
Protein	Forms part of collagen's structural organic matrix; essential for hormonal and growth factor production which modulate bone synthesis. Positively associated with prevention of fracture	High protein diets may increase calcium secretion however induce net-improvements changes; Low protein diets may decrease calcium absorption thus increase PTH.
Calcium	Main formative mineral of bone; combines with phosphorous to form hydroxyapatite crystals; ~99% stored in skeleton; highly related to peak bone mass, bone strength, and reduced bone loss.	No known skeletal risk with high calcium diets post-maximum retention; However, calcium-deficient diets increase skeletal fragility through demineralisation.
Phosphorous	Essential element involved in bone formation; combines with calcium to mineralise bone (hydroxyapatite crystals); ~85% stored in skeleton.	High phosphorous diets with combined with low calcium levels increases PTH activity. No other marked risks noted.
Magnesium	Influences mineral metabolism through its role in ATP metabolism; a co-factor for ~300 enzymes; decreases crystallinity by reducing crystal size; ~65% stored in skeleton.	Magnesium deficiency results in decreased bone growth, bone strength and bone volume; uncoupling of bone formation and resorption; and altered calcium metabolism.
Flouride	Replaces hydroxyl within mineralised bone (hydroxyapatite crystals); stimulates osteoblast activity, though may also increase brittleness; strong affinity to bone, particularly during growth.	Low flouride levels potentially improve bone density; however, high flouride levels increase crystallinity and brittleness; toxicity may lead to fluorosis.
Zinc	Required for osteoblastic activity, collagen synthesis and phosphatase activity; improves bone synthesis; ~90% located in muscle, bone and skin; important role in connective tissue metabolism.	Low zinc associated with impaired DNA synthesis and protein metabolism; related to osteoporosis, in humans though not yet conclusive. High zinc presents no marked risk to bone health.
Copper	Influences bone formation, mineralisation and connective tissue integrity; essential for cross-linking collagen; increases mechanical strength; influences collagen maturation.	Deficiency of copper is rare, though shown to decrease bone strength; Higher levels reduce bone loss and increase bone density in ageing.

Boron	Aids in forming steroid hormones, thus may be involved in preventing calcium loss and bone demineralisation.	Higher levels of boron reduce excretion of Magnesium and Calcium; increases Calcium absorption; offsets Vitamin D.
Manganese	Required for biosynthesis during bone matrix formation; co-factor of several skeletal enzymes in bone tissue; Influences IGF metabolism.	Deficiency of manganese negatively alters IGF-1 and bone growth. Higher levels associated with increased BMD.
Potassium	Promotes an alkaline environment; reduces reliance on skeletal salts to balance endogenous acid; retention of calcium may also prevent osteoporosis.	Potassium deficient diets may increase calcium secretion and bone fragility. No skeletal adversity with high potassium diet.
Iron	Co-factor in several enzymes involved in collagen matrix synthesis, crosslinking and Vitamin D transformation; affecting calcium absorption.	Iron deficiency negatively impacts bone mass and mechanical strength in animals; yet to be transferred to humans.
Vitamin A	Essential component of remodelling process via retinoic acid receptors found within osteoblasts and osteoclasts; retinol associated with fracture risk; effects are reversible.	High levels of Vitamin A related to lower BMD and fracture risk. Deficiency leads to various bone abnormalities in animals; yet to be translated to humans.
Vitamin B	Vitamin $B_{2,}$ $B_{6,}$ B_{11} and B_{12} known to indirectly influence energy metabolism; modulate effect of Vitamin K; Co-factors in osteoblast-related proteins and homocysteine metabolism; effect on iron metabolism and amino acids.	Adequate levels improve mechanical performance of bone and BMD; however, little evidence available concerning levels of 'B' Vitamins for bone health; goal to avoid deficiency.
Vitamin C	Co-factor in hydroxylation cross-linking collagen fibrils in bone; Stimulates alkaline phosphate activity, potentially osteoblast formation.	Vitamin C intake influences BMD; goal to prevent deficiency. Higher intakes shown to elicit greater BMD outcomes.
Vitamin D	Maintains serum calcium levels; increases calcium absorption efficiency; optimises bone mineral homeostasis.	Low levels of Vitamin D increases risk of fracture (Hypovitaminosis D); High levels decrease bone loss and fracture incidence.
Vitamin K	Co-factor of carboxylation in proteins including osteocalcin, a principal non-collagenous protein of bone.	Deficiency increases immature under-carboxylated osteocalcin, associated with low BMD and high fracture risk.

Note: PTH = parathyroid hormone; ATP = adenosine tri-phosphate; BMD = bone mineral density; IFG = insulin growth-like factor; Information supplied in this table is not exhaustive

2.5. Summary

Bone is a highly adaptive, structurally dynamic and metabolically active biomaterial with many paradoxical and contradictory functional requirements. Specifically, it must be rigid and stiff to withstand force and accommodate load yet be flexible and elastic to deform and absorb energy. It must shorten and widen under compression yet length and narrow under tension, whilst withstanding torsional and sheer forces in isolation and combination. It must also be light yet durable and strong to facilitate locomotion in the absence of catastrophic failure. To simultaneously meet these many requirements, bone has complex and multi-dimensional material and structural arrangements at macroscopic, microscopic and nanoscopic levels which each contribute to the skeleton's mechanical behaviour under load. Importantly, bone is able to model and remodel itself through tightly controlled cellular activity in response to hormonal and mechanical influences; an adaptive mechanism to maintain structural integrity while increasing bone mass and strength through material and structural alterations in order to meet developmental and functional requirements.

Bone material and structure interact with muscle to determine the mechanical behaviour and load tolerability of hard-tissue to a given loading environment. Specifically, muscle protects bone from undesirable bending moments whilst providing the skeleton with a consistently potent osteogenic stimulus in combination with gravitational and impact forces during physical activity and exercise. Indeed, this mechanoreceptive and adaptive feature of bone to routine mechanical stress and strain remains the central focus of intervention for practitioners to heighten musculoskeletal strength and resilience through various exercise modalities. However, the dose-response (load-adaptation) relationship remains poorly

understood in humans, with research relying heavily on animal models to isolate variable osteogenic factors under controlled loading conditions. Collectively, the general benefits of exercise to bone mass and strength is unequivocal, with small material and structural gains expontentially improving ultimate strength, bending resistance, fracture energy and fatigue resistance. Unfortunately, animal models cannot replicate the human condition thus do not wholly translate into meaningful outcomes for humans; instead providing novel hypothesis-generating relationships to be further investigated using human models.

Numerous exercise modalities have been explored in humans, capitalising on variations of strain magnitude, rate, frequency and gradient through vibration, locomotive, resistance, impact and multi-modal exercise interventions to deliver myogenic and osteogenic stimuli to the musculoskeletal system with variable success rates and adaptational outcomes. While each modality is osteogenic in isolation, a multi-modal approach combining resistance training with impact or locomotive exercise appears to be the most effective intervention, providing a broader range of musculoskeletal adaptations, owing to its integration of mechanical stimuli at different mangitudes, rates, frequencies and gradients at any given time; advantageously capitalising on mechanisms complimentary to other modalities in isolation. Unfortunately, human training interventions into bone strength adaptation across modalities are remarkably heterogeneous in design, measurement and scope, heavily relying on material adaptations using areal quantifications as a central focus for training efficacy. This greatly restricts the whole value of results reported and limits the meaningful interpretation of interventional effectiveness; entirely neglecting other important and potent measures including macroscopic tissue, bone structure and geometry, and bone strength

itself as a primary outcome measure. Given that bone material and structure determine bone strength, and interact with muscle to determine mechanical behaviour, it is necessary for all musculoskeletal components to be measured and reported during prescribed mechanical loading programs over longer periods of time and with larger sample sizes to adequately and accurately examine the influence of exercise modalities in isolation or combination.

Strategies to optimise musculoskeletal strength and development through-out the lifespan remain equivocal, owing to the unilateral focus of many research studies through highly controlled investigations. However, bone strength development and preservation must adopt a multidimensional and interdisciplinary approach. Specifically, bone modelling and remodelling processes are regulated by stochastic and deterministic mechanisms which deliver material and structural changes to the skeleton. Nutritional or pharmacological interventions influence stochastic adaptations specific to the quality of bone material, whereas mechanical loading through physical activity and exercise influence deterministic adaptations specific to bone structure and geometry. Indeed, it remains ideal to non-pharmacologically optimise bone strength through material and structural gains by engaging in proper nutritional practices and long-term exercise programs which will deliver quality bone material in a robust geometric arrangement in the absence of undesirable side-effects produced my pharmacological treatments. Importantly, structural adaptations established through mechanical loading programs remain beneficial in older age despite reductions in bone quality, aptly promoting physical activity and exercise as efficacious and preferred activities to pursue from youth into older age to heighten bone strength and mechanical competence.

Sports participation provides an additional, highly compliant, unstructured, dynamic and volatile mechanical environment with habitually non-uniform loading patterns routinely changing in response to external parameters and conditions. Team-based field-sports in particular share similar osteogenic benefits to multimodal exercise, owing to high magnitudes and rates of strain with unusual distribution and various frequencies through muscular, gravitational and impact loads. Although this environment is greatly beneficial to the skeleton, the uncontrollable nature of sport-specific training and competition also provides inherent risks of overload and overuse injury. As a result, practitioners within field-based team-sport environments must carefully monitor training and game-based loads to allow for sufficient recovery. While field-based team-sports are known to provide myogenic and osteogenic stimulus to the musculoskeletal system through training and competition; there are remarkably few studies describing the musculoskeletal characteristics of field-based team-sport athletes of various competitions beyond those provided by limited uniplanar areal measures using DXA; and even fewer studies exploring seasonal musculoskeletal adaptations following annual involvement in training and competition. Consequently, further research is required to characterise muscle and bone morphology in field-based team-sports which simultaneously quantify the material, structural and strength components of the musculoskeletal system and their subsequent adaptations following seasonal participation in high-level sporting environments in order to provide insight into the expected magnitude and type of changes in highly trained athletes. Meaningful bone strength adaptation and musculoskeletal morphology outcomes in healthy athletic populations may provide potential translatory insights to other disease-state or ageing population studies to optimise musculoskeletal robustness and minimise fragility.

CHAPTER THREE - STUDY ONE

NORMATIVE AND COMPARATIVE QUANTIFICATION OF LOWER-BODY MUSCULOSKELETAL CHARACTERISTICS IN ELITE AUSTRALIAN FOOTBALLERS

3.1. Introduction

Skeletal examinations and descriptive profiles of hard-tissue properties in elite Australian Footballers are remarkably scarce (Hart et al, 2013c; Veale, Pearce, Buttifant & Carlson, 2010), exclusively using DXA to provide two-dimensional whole-body and regional examinations of bone area, content and density. While such investigations provide basic insights into bone mass using areal bone mineral content (aBMC) and areal bone mineral density (aBMD) as surrogate measures of bone strength (Fonseca et al, 2014; Sheu et al, 2011; Licata, 2009; Ammann & Rizzoli, 2003; Turner & Robling, 2003), these low-resolution uniplanar images are unable to examine bone structure (shape, size, geometry) or material (macroscopic composition, microscopic architecture); limited solely to frontal plane mass distribution (Popp et al, 2014; Popp et al, 2012; Popp et al, 2009; Bouxsein & Karasik, 2006; Seeman & Delmas, 2006; Rauch & Schonau, 2005; Sievanen et al, 1998). Given the complex array of morphological interactions (structural and material) present within hard-tissue structures; areal measures consequently explain ~50 - 70% of bone strength (Jarvinen et al, 2005; Cointry et al, 2004; Ammann & Rizzoli, 2003), highlighting the need for more comprehensive assessment tools and procedures when quantifying skeletal properties to screen and monitor athlete robustness, training efficacy or injury risk.

Recent technological advancements have led to the development of peripheral Quantitative Computed Tomography (pQCT), a bone densitometry imaging device capable of producing higher resolution and three-dimensional measurements as an alternative to DXA and similar purpose devices (Sheu et al, 2011; Louis et al, 2010; Engelke et al, 2008; Sievanen, 1998). pQCT is particularly advantageous as it allows practitioners to concomitantly measure structural and material properties of bone in order to cross-sectionally estimate bone strength with greater precision (Lala et al, 2014; Lala et al, 2012; Burrows et al, 2009;

Shields et al, 2006; Ashe et al, 2005; Sievanen et al, 1998); and longitudinally monitor morphological adaptations responsible for alterations in bone strength following prescribed interventions or periods of immobilisation (Lam et al, 2013; Evans et al, 2012; Cervinka et al, 2011; Sievanen, 2010; Rittweger et al, 2009; Vainionpaa et al, 2009; Ballard, Specker, Binkley & Vukovich, 2006). Owing to its greater descriptive capabilities and improved measurement outcomes, pQCT has gained ascendency in clinical and research contexts, yet has received minimal attention in sporting contexts. Given this novelty of pQCT in athletic environments, limited normative or descriptive, cross-sectional or longitudinal studies exist (Ireland et al, 2013; Schipilow et al, 2013; Georgeson, Weeks, McLellan & Beck, 2012; Rantalainen et al, 2010b; Wilks et al, 2009; Nikander et al, 2006; Kontulainen, Kontulainen, Sievanen, Kannus, Pasanen & Vuori, 2003; Heinonen et al, 2002), whereby no data is available for Australian Football or equivalent team-based field-sport athletes. This severely complicates screening and monitoring in Australian Football as normative values are critically important and necessary to provide benchmarks and baseline information for comparison (Hart et al, 2013b; Hart et al, 2013c; Veale et al, 2010; Chaouachi et al, 2009; Rauch & Schonau, 2005).

Australian Football is a uniquely fast-paced, dynamic and multidimensional field-based sport, with footballers routinely exposed to unpredictable, volatile and asymmetrical lower-body loading patterns, selectively using a preferred limb for most game-based activities (Coutts et al, 2014; Hart et al, 2014a; Moreira et al, 2014; Pruyn et al, 2012; Ball, 2011; Young & Rath, 2011; Hides et al, 2010; Young et al, 2010; Young & Pryor, 2007; Zakas, 2006; Young et al, 2005). As a result, compressive, torsional, transverse and tensile loads are differentially applied in combination and isolation to hard-tissue structures of each limb within Australian Footballers, exposing the skeleton to stimuli that can lead to positive

bone-specific and site-specific adaptations or subsequent stress reactions and fractures (Rantalainen et al, 2011b; Ekstrand & Torstveit, 2010; Nikander et al, 2010a; Rantalainen et al, 2010b; Kohrt, Barry & Schwartz, 2009; Gabbe et al, 2004; Nevill, Holder & Stewart, 2004). In particular, bone strength adaptations are context specific to loading histories, thus it is logical to expect athletes with higher training ages will illustrate higher bone strength as a result of greater material and structural adaptations than athletes with lower training ages (Kubo et al, 2010; Veale et al, 2010; Hoshikawa et al, 2009; Suominen, 2006; Rhea, Alvar, Burkett & Ball, 2003). Similarly, it is logical to expect a level of lateral dominance and asymmetrical adaptation in elite Australian Footballers on the basis of preferential function (Hart et al, 2014a; Hart et al, 2014b; Hart et al, 2013b; Hides et al, 2010; Gstottner et al, 2009). Repetitious asymmetrical activities have been shown to generate asymmetrical hypertrophic responses in muscle (Hart et al, 2014a; Hart et al, 2013b; Hides et al, 2010; Stewart, Stanton, Wilson & Hides, 2010); however it is not known whether similar long-term adaptations are evident in lower-body hard-tissue structures of Australian Footballers (Ireland et al, 2013; Ireland et al, 2011; McClanahan et al, 2002; Haapasalo et al, 2000).

Bone strength adaptability to mechanical loading provides strength and conditioning practitioners with an important modifiable characteristic to screen, monitor and target with exercise interventions. As bone strength is a measureable and trainable athletic feature, research is required in order to comprehensively characterise lower-body bone strength in Australian Footballers using independent three-dimensional (pQCT) and two-dimensional (DXA) imaging techniques. This will address three key objectives: 1) provide a descriptive set of normative and comparative values for elite Australian Footballers, 2) identify the influence of training exposure (training age) on lower-limb hard-tissue structures, and 3) establish whether developmental laterality exists as a result of sport participation.

3.2. Methods

3.2.1. Subjects

Sixty (n = 60) elite Australian Football players competing in the Australian Football League (AFL) were recruited for participation in this study. Athletes with lower limb injuries or contraindications requiring immobilisation within three months prior to data collection; or with metallic surgical implants located beneath the trunk were excluded from analysis. This rendered five elite players as unsuitable for inclusion, providing a total cohort of fifty-five athletes stratified by their training age at the elite level (in years); less experienced (< 3 years) and more experienced (≥ 3 years) groups (Table 15); owing to heightened injury susceptibility in younger AFL athletes (Fortington et al, 2015). Players wore their club-issued football shorts during the data collection process and were notified of the potential risks involved. Data collection and management procedures conformed to the Code of Ethics (World Medical Association), Declaration of Helsinki, with ethics approval provided by Edith Cowan University's Human Research Ethics Committee.

Table 15. Descriptive characteristics of less experienced (LE, n=27) and more experienced (ME, n=28) elite Australian Footballers.

	LE – (≤ 3 years) [n = 27]	**ME - (> 3 years) [n = 28]**	**Effect (*d*)**	**Significance (*p*)**
Age (yr)	19.1 (± *1.5*)	25.0 (± *3.0*)	2.49 [a]	0.001 [**]
Height (cm)	188.7 (± *6.5*)	189.2 (± *7.8*)	0.07	0.797
Weight (kg)	82.6 (± *7.4*)	88.2 (± *8.3*)	0.71 [b]	0.012 [*]
BMI (kg/m^2)	23.2 (± *1.5*)	24.6 (± *1.2*)	1.03 [b]	0.001 [**]
Bone Mass (%)	4.0 (± *0.3*)	4.2 (± *0.3*)	0.67 [b]	0.013 [*]
Lean Mass (%)	85.4 (± *1.4*)	85.9 (± *1.8*)	0.31 [c]	0.316
Fat Mass (%)	10.6 (± *1.5*)	9.9 (± *1.8*)	0.42 [c]	0.166
Tibial Length (mm)	435.6 (± *24.8*)	435.0 (± *31.7*)	0.02	0.947

Note: Values reported as Mean (± SD); BMI = body mass index; Bone Mass = whole-body bone mineral content; Effect = effect size; ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect (d ≥ 1.2); b = moderate effect (d ≥ 0.6); c = small effect (d ≥ 0.2).

3.2.2. Experimental Design

This acute, cross-sectional study commenced with anthropometric measures including height (cm), weight (kg) and tibial length (mm), followed by a series of whole-body composition and lower-body bone densitometry scans performed at the commencement of preseason training. Specifically, whole-body and segmental appendicular mass (lean, fat, bone and total) was examined using DXA; while lower-body bone material, structure and strength was assessed for both limbs using pQCT.

3.2.3. Anthropometry

Stature was recorded to the nearest 0.1 cm using a wall-mounted stadiometer (Model 222, Seca, Hamburg, DE), with body mass recorded to the nearest 0.1 kg using an electronic weighing scale (AE Adams CPW Plus-200, Adam Equipment Inc., CT, USA). Tibial length of the kicking leg was assessed using a retractable measuring tape (Model 4414, Tech-Med Services, NY, USA), from the tibial plateau at the knee joint (proximal end), to the medial malleolus of the Tibia (distal end), and was recorded to the nearest 0.1 cm. Stature and tibial length measures were performed three times for each participant, with the average of each variable retained for analysis. All measures were reliably performed by the same accredited exercise scientist ($CV \leq 0.23\%$; $ICC \geq 0.996$).

3.2.4. Scan Procedures

3.2.4.1. DXA

Whole-body scans were performed using DXA (QDR-1500, Hologic Discovery A, Waltham, MA). Subjects assumed a stationary, supine position on the scan bed with both arms pronated by their side. To ensure consistent and reproducible subject positioning, the same DXA operator manually assisted all subjects to straighten their head, torso and pelvis;

internally rotate and fixate their legs and feet at 45°; and position their arms next to the body within the scanning zone (Figure 26). Subjects were not permitted to perform exercise within ~24 hours of their assigned scan, with pre-scan nutrition and hydration managed by an accredited sports dietician. This has produced a scan/re-scan coefficient of variation below 1% in our laboratory (Hart et al, 2014a; Hart et al, 2013b; Pfeiffer et al, 2010).

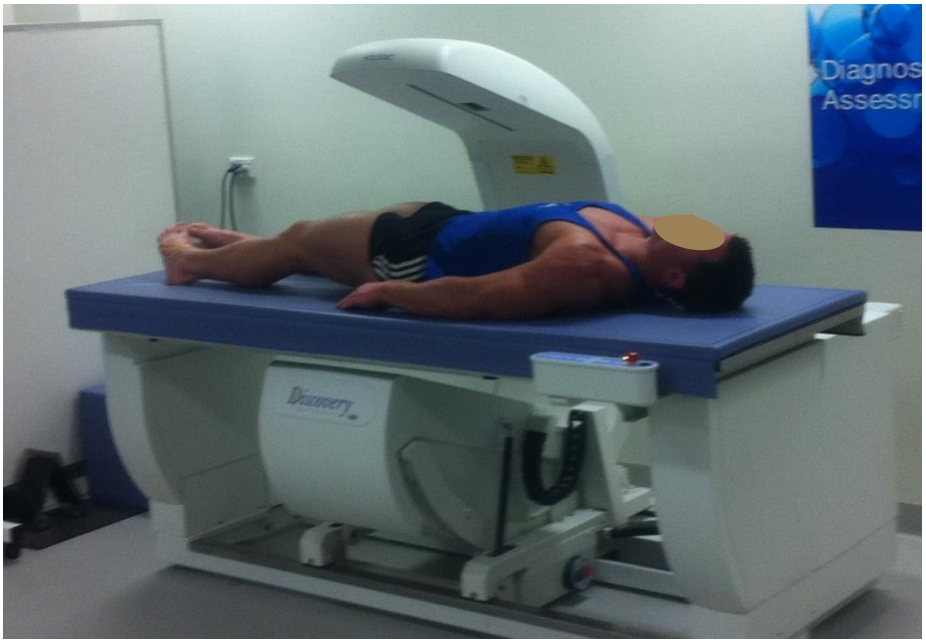


Figure 26. A whole-body DXA scan with the subject positioned supine, arms pronated by their side, with both legs internally rotated and fixated together.

Using the in-built scan analysis software (Version 12.4; QDR for Windows, Hologic, Waltham, MA), full-body images were defined in accordance with Hologic's whole body model (Hart et al, 2014a; Hologic, 2004). Two sub-regions were also created using the sub-region analysis tool in order to quantify the shank segments for each limb (Hart et al, 2014a), from the tibiofemoral joint (knee axis) through to the talocrural joint (ankle axis). All hard-tissue and soft-tissue variables for the whole-body segment and shank segments were retained for analysis. Specifically, bone area, bone mineral content (aBMC), bone mineral density (aBMD), fat mass, lean mass and total mass.

3.2.4.2. pQCT

Tibial scans were performed on each limb using pQCT (XCT-3000, Stratec Medizintechnik Pforzheim, Germany), set at a slice thickness of 2.4 mm, tube voltage of 46kV and operated at 0.3 mA (Willnecker, 2011). Subjects were required to sit on a height-adjustable chair with their lower limb fully extended through the acrylic cylinder and central gantry of the pQCT, and fixated to the foot-hold attachment (Figure 27). Four pQCT scan slices were then measured at 4%, 14%, 38% and 66% of tibial length (distal-to-proximal) quantified in section 3.2.3. Prior to scan commencement, the central gantry was positioned at the base of the medial malleolus to acquire a 30mm image identifying the talocrural joint; used as the internal reference point for scan progression (Figure 27). This has previously produced a scan re-scan CVRMS below 1.6% for bone structural variables (Rantalainen et al, 2010a; Rantalainen et al, 2008). Analysis thresholds were set at 181 mg/ccm for trabecular bone (4%); 280 mg/ccm for cortical bone (14%, 38%, 66%); and 41 mg/ccm for muscle (66%).

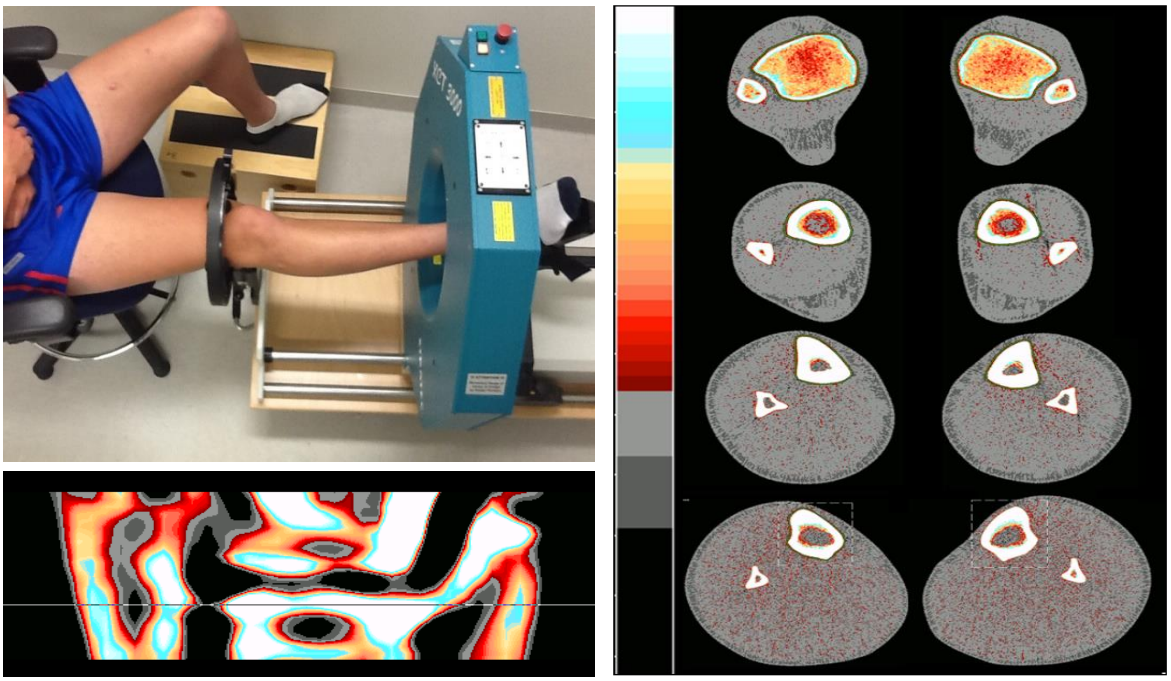


Figure 27. A tibial scan of the right lower limb using pQCT (top), with the talocrural joint identified (bottom), producing cross-sectional tibial slices at 4%, 14%, 38% and 66% of tibial length (right).

Variables across all tibial slices were retained for analysis. Trabecular density (Tb.vBMD) and trabecular area (Tb.Ar) were obtained from the 4% slice; cortical density (Ct.vBMD), cortical area (Ct.Ar), cortical thickness (Ct.Th), periosteal area (Ps.Ar) and endocortical area (Ec.Ar) were averaged across the 14% and 38% tibial slices; marrow density (Ma.vBMD), marrow area (Ma.Ar), muscle density (Mu.Den) and muscle area (Mu.Ar) were obtained from the 66% slice; and total density (Tt.vBMD), total area (Tt.Ar) and tibial mass were averaged across the 4%, 14% and 38% tibial slices. Stress-strain index (SSIPOL) and fracture loads (FL.Ab) in the sagittal and frontal planes were averaged to represent whole bone strength for each limb. Relative fracture load (FL.Rel) was subsequently determined by dividing the absolute fracture load (N) by the body mass of the athlete (N). The resultant fracture load (FL.Ratio) was established by dividing the sagittal plane fracture load by frontal plane fracture load, thus a value above one (> 1.0) reflects greater strength in the sagittal plane and a value below one (< 1.0) reflects greater strength in the frontal plane.

3.2.5. Symmetry Index

The symmetry index (SI) was determined for tibial mass, total density (Tt.vBMD), total area (Tt.Ar) and stress-strain index (SSIPOL) using a previously established calculation (Hart et al, 2014a; Gouwanda and Senanayake, 2011; Sadeghi et al., 2000):

$$SI = \frac{\text{Support Leg} - \text{Kicking Leg}}{0.5 \times (\text{Support Leg} + \text{Kicking Leg})} \times 100$$

These skeletal variables were chosen to represent a primary material, structural and strength measure. A negative score represents lateral dominance towards the kicking leg, while a positive score represents lateral dominance towards the support leg.

3.2.6. Statistical Analysis

Independent t-tests were conducted to determine whether significant differences were evident between groups for: 1) subject characteristics 2) muscle-bone characteristics of the kicking limb; 3) muscle-bone characteristics of the support limb; and 4) symmetry index. Independent t-tests were also conducted to determine whether significant differences were evident between the kicking and support limbs with-in each group for all muscle-bone characteristics. Post-hoc adjustment for multiple comparisons was performed using Holm-Bonferonni Sequential Corrections. Effect sizes were also calculated (Cohen, 1988) to determine the magnitude of difference between variables in accordance with Hopkins (2002): $d \geq 0.2$ is small; $d \geq 0.6$ is moderate; $d \geq 1.2$ is large. Statistical computations were performed using a statistical program (SPSS, Version 17.0; Chicago, IL).

3.3. Results

Descriptive characteristics of less experienced and more experienced elite Australian Footballers are provided in Table 15. More experienced players were significantly heavier ($p = 0.012$) than less experienced players, displaying a moderate effect ($d = 0.71$), despite no evident difference in height or tibial length. When expressed relative to weight, only bone mass was significantly higher in the more experienced group ($p = 0.013$) with a moderate effect ($d = 0.67$). Soft-tissue masses (lean and fat) only provided small effects ($d = 0.31$ to 0.42) with no significance difference between groups.

3.3.1. Training Age

Muscle-bone characteristics of the lower-body for less experienced and more experienced elite Australian Footballers are provided in Tables 16, 17 and 18. More experienced players exhitbited significantly higher material properties, with greater tibial mass ($p < 0.001$),

trabecular vBMD ($p \leq 0.009$), cortical vBMD ($p \leq 0.001$) and total vBMD ($p \leq 0.001$) with moderate to large effects ($d = 0.79 – 1.22$). More experienced players also had higher structural properties than their less experienced counterparts, with significantly greater cortical area and cortical thickness ($p \leq 0.003$) of moderate effect ($d = 0.92 – 1.07$); higher trabecular, total and periosteal areas of small effect ($d = 0.21 – 0.40$) and lower endocortical area of small effect ($d = 0.22 – 0.26$). The combination of higher periosteal area and lower endocortical area in more experienced players explains their greater cortical thickness values. The only material and structural component with no significant difference or notable effect with training age were marrow vBMD and marrow area.

Material and structural properties subsequently delivered significantly higher bone strength in more experienced players, with greater stress-strain indices ($p \leq 0.007$) and absolute fracture loads ($p \leq 0.018$) producing small to moderate effects ($d = 0.57 – 0.75$) across both limbs. Relative fracture load exhibited a small positive effect between training ages in the support leg only ($d = 0.23$). Furthermore, DXA-derived areal measures of bone mineral content (aBMC) and bone mineral density (aBMD) of the shank segments were also significantly higher in more experienced players ($p \leq 0.004$) with moderate to large effects ($d = 1.00 – 1.20$), while whole bone area (BA) exhibited a small positive effect ($d = 0.53$). Soft-tissue measures were favourable toward more experienced players, with significantly higher muscle area ($p \leq 0.009$) and significantly lower fat area ($p \leq 0.028$) in more experienced players with moderate effect ($d = 0.69 – 0.99$). This was similarly evident when evident for lean mass ($p = 0.028$) and fat mass ($d = 0.31$ to 0.68) of the shank segments using DXA. Muscle density was lower in more experienced players but with only a small magnitude of effect ($d = 0.41 – 0.45$).

3.3.2. Limb Function

Muscle-bone comparisons between kicking and support limbs within each training age category are also provided in Tables 16, 17 and 18. Differences were observed between limbs for one material (cortical vBMD), two structural (cortical area, periosteal area), and two strength variables (stress-strain index, FL Ratio) in less experienced players of small effect (d = 0.20 – 0.25); whereas two material (tibial mass, cortical vBMD), five structural (trabecular area, cortical area, total area, periosteal area, cortical thickness) and three strength variables (stress-strain index, absolute fracture load, FL Ratio) were notably different in more experienced players of small effect (d = 0.20 – 0.44). In all cases, the support leg exhibited favourable material, structural and strength values over the kicking leg for less experienced and more experienced players alike; a general trend evident in all Australian Footballers. Soft-tissue differences were also evident between limbs, with lower muscle density in the support limb for less experienced and more experienced players (d = 0.23 – 0.24), and lower fat area in the support leg of more experienced players only (d = 0.20). Interestingly, no clear differences were detected using areal, DXA-derived measures of hard tissue or soft-tissue between limbs for either group of footballers, highlighting the inadequacy of DXA to appropriately quantify morphological musculoskeletal adaptations.

Skeletal asymmetry between kicking and support limbs was notably higher in more experienced players, as conveyed in Figure 28. Tibial mass, total vBMD, total area and stress-strain index were chosen as representative variables of material (mass and density), structure (cross-sectional area) and strength (bending resistance) to avoid repetitious reporting of similarly behaved variables. Significantly higher asymmetries were evident in tibial mass and total area ($p \leq 0.047$; d = 0.51 – 0.53), with a small effect also evident in stress-strain indices (d = 0.42). The only variable with no clear difference in asymmetry

between limbs, or magnitude of asymmetry between training ages was total vBMD. Specifically, these variables exhibited higher asymmetries as a result of greater material, structure and strength values in the support leg relative to the kicking leg of a higher magnitude in more experienced players compared to less experienced players. Indeed, the trend of favourable adaptation to the support leg relative to the kicking leg within each group is further evident as training age increases.

3.4. Discussion

Lower-body skeletal examinations of Australian Footballers are scarce (Hart et al, 2013c; Veale et al, 2010). Consequently, this study sought to provide normative and comparative musculoskeletal data of the kicking and support limbs for less experienced and more experienced elite Australian Footballers using independent three-dimensional (pQCT) and two-dimensional (DXA) imaging techniques. In particular, as bone is highly adaptive and responsive to mechanical loading, normative values were stratified by training age and limb function in order to account for the influence of training exposure and asymmetrical loading on bone strength and its derivatives. Accordingly, this study was able to describe the characteristically different musculoskeletal profiles of more experienced and less experienced players, such that higher training ages exhibited greater relative whole-body skeletal mass proportional to body mass and greater lower-body bone strength commensurate with greater exposure to mechanical loading over longer periods of time. Similarly, this study was able to successfully demonstrate the existence of unique and distinct morphological adaptations prevalent between the kicking and support limbs of Australian Footballers in response to repetitious asymmetrical loading patterns experienced as a consequence of their functional differences within the context of Australian Football.

Table 16. **Normative pQCT derived skeletal values for LE (n=27) and ME (n=28), elite Australian Footballers.**

	Less Experienced – (≤ 3 years)			More Experienced - (> 3 years)			Effect: (LE ↔ ME)	
	Kicking Leg	Support Leg	Effect	Kicking Leg	Support Leg	Effect	Kicking	Support
MATERIAL PROPERTIES								
Tibial Mass (g/cm)	4.51 (± *0.3*)	4.57 (± *0.4*)	0.17	4.94 (± *0.4*)	5.06 (± *0.4*)	0.30 [c]	1.22 [**/a]	1.22 [**/a]
Tb.vBMD (mg/cm^3)	279.4 (± *28.4*)	277.2 (± *25.9*)	0.08	303.9 (± *33.5*)	303.0 (± *33.4*)	0.03	0.79 [**/b]	0.86 [**/b]
Ct.vBMD (mg/cm^3)	1102.7 (± *12.2*)	1099.9 (± *14.8*)	0.21 [c]	1127.2 (± *14.9*)	1122.9 (± *14.5*)	0.30 [c]	1.80 [**/a]	1.57 [**/a]
Ma.vBMD (mg/cm^3)	21.0 (± *7.2*)	21.3 (± *8.7*)	0.04	22.2 (± *6.4*)	22.0 (± *6.1*)	0.03	0.18	0.09
Tt.vBMD (mg/cm^3)	608.7 (± *35.2*)	607.0 (± *28.7*)	0.05	646.7 (± *45.4*)	645.7 (± *43.1*)	0.02	0.94 [**/b]	1.06 [**/b]
STRUCTURAL PROPERTIES								
Tb.Ar (mm^2)	635.0 (± *70.7*)	638.9 (± *67.2*)	0.06	650.1 (± *72.8*)	665.5 (± *81.2*)	0.20 [c]	0.21 [c]	0.36 [c]
Ct.Ar (mm^2)	324.3 (± *25.3*)	331.6 (± *35.7*)	0.24 [c]	351.4 (± *29.6*)	361.9 (± *30.2*)	0.35 [c]	0.98 [**/b]	0.92 [**/b]
Ma.Ar (mm^2)	231.0 (± *66.1*)	235.2 (± *67.9*)	0.06	229.1 (± *89.7*)	230.2 (± *77.1*)	0.01	0.02	0.06
Tt.Ar (mm^2)	860.4 (± *78.6*)	870.5 (± *79.4*)	0.12	883.5 (± *91.5*)	906.8 (± *99.1*)	0.25 [c]	0.27 [c]	0.40 [c]
Ps.Ar (mm)	85.6 (± *3.5*)	86.5 (± *3.7*)	0.25 [c]	86.9 (± *4.6*)	88.2 (± *4.8*)	0.28 [c]	0.31 [c]	0.40 [c]
Ec.Ar (mm)	55.7 (± *4.2*)	56.2 (± *4.0*)	0.12	54.4 (± *5.7*)	55.1 (± *5.8*)	0.12	0.26 [c]	0.22 [c]
Ct.Th (mm)	4.77 (± *0.4*)	4.83 (± *0.4*)	0.15	5.17 (± *0.4*)	5.26 (± *0.4*)	0.23 [c]	1.00 [**/b]	1.07 [**/b]
STRENGTH PROPERTIES								
SSI (mm^3)	2458.8 (± *256.6*)	2564.6 (± *340.3*)	0.35 [c]	2673.0 (± *353.8*)	2836.3 (± *384.7*)	0.44 [c]	0.69 [**/b]	0.75 [**/b]
FL.Ab (N)	5691.7 (± *689.8*)	5773.0 (± *818.9*)	0.11	6156.6 (± *929.2*)	6284.4 (± *890.0*)	0.14	0.57 [*/c]	0.60 [**/b]
FL.Rel (N/kg)	7.00 (± *0.5*)	7.10 (± *0.7*)	0.16	7.10 (± *0.7*)	7.26 (± *0.7*)	0.23 [c]	0.16	0.23 [c]
FL Ratio (X/Y)	1.18 (± *0.1*)	1.20 (± *0.1*)	0.20 [c]	1.16 (± *0.1*)	1.18 (± *0.1*)	0.20 [c]	0.20 [c]	0.20 [c]

Note: Values reported as Mean (± SD); Tb = trabecular; Ct = cortical; Ma = marrow; Tt = total; Ps = periosteal; Ec = endocortical; vBMD = volumetric bone mineral density; Ar = area; Th = thickness; SSI = stress-strain index; FL = fracture load; Ab = absolute; Rel = relative; X = medio-lateral, Y = anterio-posterior; effect = effect size;
***** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).***

Table 17. **Normative pQCT derived soft-tissue values for LE (n=27) and ME (n=28) elite Australian Footballers.**

	Less Experienced – (≤ 3 years)			More Experienced – (> 3 years)			Effect: (LE ↔ ME)	
	Kicking Leg	**Support Leg**	**Effect**	**Kicking Leg**	**Support Leg**	**Effect**	**Kicking**	**Support**
Mu.Ar (mm^2)	8498.7 (± *1059.6*)	8400.9 (± *1108.9*)	0.09	9457.8 (± *1177.1*)	9487.2 (± *1094.5*)	0.03	0.86 **/b	0.99 **/b
Mu.Den (mg/cm^3)	78.7 (± *1.2*)	78.4 (± *1.4*)	0.23 c	78.1 (± *1.7*)	77.7 (± *1.7*)	0.24 c	0.41 c	0.45 c
Fat.Ar (mm^2)	1377.7 (± *425.0*)	1319.2 (± *419.4*)	0.14	1095.5 (± *387.4*)	1012.9 (± *456.0*)	0.20 c	0.69 */b	0.70 */b

Note: Values reported as Mean (± SD); Mu = muscle; Ar = area; Den = density; ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 18. **Normative DXA derived shank values for LE (n=27) and ME (n=28) elite Australian Footballers.**

	Less Experienced – (≤ 3 years)			More Experienced – (> 3 years)			Effect: (ME ↔ LE)	
	Kicking Leg	**Support Leg**	**Effect**	**Kicking Leg**	**Support Leg**	**Effect**	**Kicking**	**Support**
BA (cm)	204.9 (± *19.5*)	205.8 (± *18.0*)	0.05	216.8 (± *25.2*)	217.6 (± *26.0*)	0.03	0.53 c	0.53 c
aBMC (g)	270.5 (± *28.6*)	270.7 (± *29.7*)	0.01	308.9 (± *44.5*)	311.7 (± *44.5*)	0.06	1.03 **/b	1.08 **/b
aBMD (g/cm^2)	1.32 (± *0.1*)	1.31 (± *0.1*)	0.10	1.42 (± *0.1*)	1.43 (± 0.1)	0.10	1.00 **/b	1.20 **/a
Lean Mass (g)	3043.5 (± *308.5*)	3056.1 (± *321.9*)	0.04	3294.8 (± *421.6*)	3300.3 (± *396.0*)	0.01	0.68 */b	0.68 */b
Fat Mass (g)	422.0 (± *144.3*)	409.9 (± *152.1*)	0.08	376.9 (± *99.3*)	367.9 (± *114.2*)	0.08	0.36 c	0.31 c

Note: Values reported in absolute values as Mean (± SD); BA = bone area; aBMC = areal bone mineral content; aBMD = areal bone mineral density, ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

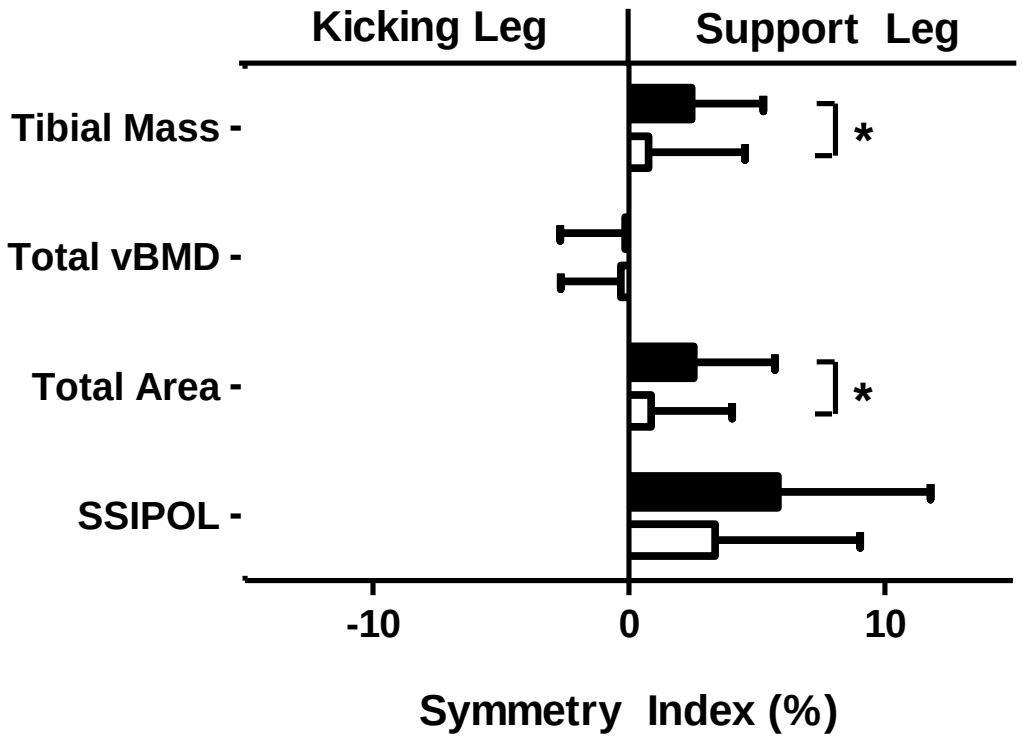


Figure 28. Symmetry index of more experienced (black bars) and less experienced (white bars) elite Australian Footballers for material, structural and strength measures between the kicking and support limbs. Asterix (*) represents statistical significance ($p \leq 0.05$).

3.4.1. Training Age

Professional athletes engage in full-time training and competitive workloads at the elite level; striving to maximise physical capacity, heighten performance and minimise injury in pursuit of success (Colby, Dawson, Heasman, Rogalski & Gabbett, 2014; Coutts et al, 2014; Moreira et al, 2014; Gastin, Fahrner, Meyer, Robinson, & Cook, 2013; Rogalski et al, 2013). Practitioners subsequently prescribe training programs using various exercise modalities to explicitly increase musculoskeletal resilience; driven to optimise muscle size, strength, power and endurance concomitantly with bone size, strength and fatigue resistance (Lauersen, Bertelsen & Andersen, 2014; Ratamess, 2012; Cardinale, Newton & Nosaka, 2011; Rhea et al, 2003; Abe et al, 2000; Milgrom et al, 2000b). Accordingly,

Australian Football athletes engage in structured combinations of locomotive exercise (walking, running, changing direction); resistance exercise (weight training); and impact exercise (jumping, kicking, tackling) each week in controlled training environments in order to better withstand the volatile and unpredictable competitive demands of the sport. These annual programs capitalise on the variety of benefits afforded to the musculoskeletal system by multi-modal exercise (Section 2.4.2.5) in addition to the plethora of benefits conveyed through sports participation (Section 2.4.2.6); extrapolated over concurrent annual cycles through-out a footballers career to develop a robust and resilient athlete.

Dose-response, load-adaptation relationships between external stimuli and biomaterial properties implies that Australian Footballers with greater acute and chronic exposure to training and competitive loading regimens should have proportionally higher magnitudes and broader ranges of favourable musculoskeletal adaptations than those with lower exposure (Chahal, Lee & Luo, 2014; Fortington et al, 2015; Moreira et al, 2014; Weatherholt, Fuchs & Warden, 2013; Skerry, 2006; Cussler et al, 2003; Rhea et al, 2003; Smith & Gilligan, 1996). Predictably, the relationship between training age and muscle-bone morphology was positive toward more experienced players in this study. Specifically, more experienced players exhibited higher periosteal area and lower endocortical area owing to greater periosteal apposition and lower endocortical resorption overtime; a stimulatory characteristic of deterministic modeling and re-modelling processes through mechanical loading (Fonseca et al, 2014; Nilsson et al, 2014; Capozza et al, 2013; Herman et al, 2010; Clarke, 2008; Seeman 2008a; Seeman, 2008b; Bouxsein & Karasik, 2006; Friedman 2006; Skerry, 2006; Szulc et al, 2006; Warden et al, 2005). Subsequently, these larger external diameters and smaller marrow cavities provide more experienced players

with higher tibial mass, greater cortical thickness, higher cross-sectional area and higher material density; ultimately delivering higher bone strength than less experienced players. Similarly, muscle cross-sectional area and lean mass volume were also significantly higher in more experienced players; an important protective co-adaptation to assist managing load dispersion through the skeleton while neutralising repetitious bending moments in the lower limbs during sports participation (Pamukoff & Blackburn, 2015; Ireland, Rittweger & Degens, 2014; Seeman, 2008b; Milgrom et al, 2007; Bouxsein & Karasik, 2006; Davison et al, 2006; Friedman 2006; Pearson & Leiberman, 2004; Yoshikawa et al, 1994).

3.4.2. Limb Function

Australian Football is characterised as an odd-impact sport (Section 2.4.2.6); involving rapid turns, stops, jumps, tackles, accelerations, decelerations and lateral movements while sprinting, running, or kicking; simultaneously requiring footballers to constantly react to situational events within the field of play (Kempton et al, 2015; Coutts et al, 2014; Hart et al, 2014b; Moreira et al, 2014; Ball, 2013; Rogalski et al, 2013). Consequently, footballers develop and selectively use preferred limbs for most game-based activities, such as kicking, changing direction and jumping (Hart et al, 2014a; Hart et al, 2014b; Hart et al, 2013b; Ball, 2013; Ball, 2011; Young & Rath, 2011). Most prevalent is the kicking skill which requires players to adopt uni-pedal postures in order to powerfully strike the ball with the kicking limb while forcefully planting the support limb to provide stability, balance and support (Hart et al, 2014a; Ball, 2013; Paillard et al., 2006). While it is advantageous to be equally proficient across both limbs; time, space, and accuracy constraints place pressure on players to use their most dominant movement patterns in order to produce desirable outcomes. Accordingly, asymmetrical loading patterns are commonplace in Australian

Football; transmitting differential strain magnitudes, rates and distributions of varying frequencies to each limb independently. Specifically, the support limb experiences combinations of high-grade gravitational, impact and muscular forces simultaneously (Ball, 2013; Orloff et al, 2008), whereas the kicking limb experiences high-grade muscular forces when swinging the limb, and low-grade impact forces when striking the ball (Hart et al, 2014a; Hart et al, 2013b; Ball, 2011; Young & Rath, 2011).

Morphological adaptations respond differently to varying combinations of muscular, impact and gravitational forces (Weidauer et al, 2014; Maimoun & Sultan, 2011; Rogers et al, 2011; Ebben et al, 2010; Nikander et al, 2010b; Kohrt, Barry, & Schwartz, 2009; Judex & Zernicke, 2000). Consequently, the dampened osteogenic stimulus afforded to the kicking limb from low-grade impacts and absent gravitational loads during the kicking skill will likely develop asymmetrical osteogenic adaptations in favour of the support limb when extrapolated overtime. Rather expectantly, in this study, morphological asymmetries were observable between limbs for less experienced and more experienced players, with the support limb exhibiting greater bone strength (stress-strain index, absolute and relative fracture loads) and higher bone mass relative to the kicking limb. Specifically, the increased strength of the support limb is symptomatic of its structural superiority; developing thicker cortices with wider cross-sectional areas than the kicking limb. The support limb did exhibit lower density values, however this was not detrimental or unsurprising, as equivalent materials dispersed over larger areas will be considered less dense despite delivering aggregate strength benefits, as was the case in the support limb for this cohort. This also highlights an evident limitation of using bone mineral density as a surrogate measure in isolation (Fonseca et al, 2014; Nicks et al, 2012; Bouxsein & Karasik,

2006; Davison et al, 2006; Seeman & Delmas, 2006; Petit, Beck & Kontulainen, 2005; Ammann & Rizzoli, 2003; Sievanen et al, 1998). Indeed, cross-sectional area was the primary morphological adaptation afforded to the support limb; a potent adaptation which improves load tolerance proportional to the fourth power of material distance from its neutral axis, such that a two-fold increment in cross-sectional area would yield an eight-fold increment in bone strength, notwithstanding other changes in mass or density parameters (Capozza et al, 2013; Seeman, 2008a; Seeman, 2008b; Davison et al, 2006; Warden et al, 2005).

Loading exposure over longer periods was shown to differentiate less experienced and more experienced players of differing training ages. Interestingly, this same relationship was evident between kicking and support limbs within players; whilst also magnified by training age. That is, more experienced players produced larger morphological asymmetries than less experienced players, with higher magnitude benefits afforded to the support limb. This interlimb difference in adaptation provides a useful loading model, as it uses individual athletes as their own internal control to establish which loading profiles promote particular morphological, musculoskeletal changes overtime. In this regard, repetitious high-impact gravitational loading evidently favours cross-sectional area as a morphological adaptation to potently enhance skeletal robustness, bone strength and fatigue resistance (Weidauer et al, 2014; James & Carroll, 2010; Nikander et al, 2010a; Rantalainen et al, 2010b; Welch et al, 2008; Warden et al, 2005; Umemura et al, 2002; Judex & Zernicke, 2000); with bone density exhibiting no discernible additional benefit between limbs irrespective of training age effects (Figure 28). This presents strength and conditioning professionals with an opportunity to target the kicking leg with high-impact, gravitational

loading in controlled settings to promote skeletal development and physical resilience bilaterally. Importantly, areal measures supplied by DXA were unable to identify any notable asymmetry between limbs within each group despite clear material, structural and strength differences identified by pQCT. This was expected, given that DXA is uni-planar; measures only frontal plane mass distribution; and is unable to measure bone structure which was the primary asymmetrical adaptation of note.

Musculoskeletal differences evident between training ages in this study are confounded by biological age (Section 3.4.1), with morphological variations partially influenced by differences in skeletal maturity. Regardless of this, mechanical loading programs confer additional bone material, structural and strength benefits to the skeleton beyond those evident during ageing and maturation, thus the findings of this study must be considered in context. To consolidate this relationship between training exposure and musculoskeletal development examined in the current study, differential adaptations evident between limbs were examined using a within-subject design to compare the kicking and support limbs between training ages (Section 3.4.2). This internal comparison supported the influence of context-specific loading exposure, highlighting the developmental effect of asymmetrical loads unique to Australian Football, with larger differences in musculoskeletal adaptations evident in athletes of higher training age. Further strengths of this study also include the large sample size and use of elite level athletes often scarce in research contexts; the novel application of pQCT to elite Australian Football athletes; and the unique comparison of lower-body musculoskeletal adaptations between limbs based on differential function.

3.5. Summary

Normative and comparative musculoskeletal data of the lower-body was developed for less experienced and more experienced elite Australian Footballers using DXA and pQCT imaging techniques. Dose-response, load-adaptation relationships between levels of training exposure (less experienced vs. more experienced) and asymmetrical loading exposure (kicking limb vs. support limb) were evident, with distinct morphological adaptations noted. Specifically, greater training exposure leads to greater material, structural and strength adaptations commensurate with controlled multi-modal exercise interventions and participation in high-impact, odd-impact sporting competitions over time. Similarly, longer-term exposure to asymmetrical loading between limbs developed different morphological features for the kicking limb relative to the support limb; emphasising the potent benefit of cross-sectional area as a key attribute to deliver greater bone strength in response to routine, high-impact gravitational loads within the support limb. Indeed, to increase musculoskeletal resilience in both limbs, practitioners should focus on training modalities which increase muscle and bone cross-sectional area; a potent contributor to biomaterial strength. It is also strongly recommended to measure and monitor structural and material properties in combination using pQCT in order to appropriately examine various musculoskeletal factors that contribute to load tolerance in sport.

CHAPTER FOUR – STUDY TWO

INJURED AND NON-INJURED COMPARISONS OF LOWER-BODY MUSCULOSKELETAL CHARACTERISTICS IN ELITE AUSTRALIAN FOOTBALLERS

4.1. Introduction

Skeletal injuries in Australian Football have continued to rise over the past decade (Orchard, Seward & Orchard, 2013; Orchard et al, 2012; Orchard & Seward, 2003). Despite this concerning incremental trend, injury prevention and rehabilitation research in Australian Football has exclusively directed attention towards soft tissue injuries, consequently neglecting hard-tissue pathology (Duhig, 2014; Hickey et al, 2014; Freckleton, Cook & Pizzari, 2014; Opar et al, 2014a; Opar et al, 2014b; Opar et al, 2014c; Serpell et al, 2014; Verrall, Estermann & Hewett, 2014; Pizzari, Taylor & Coburn, 2013; Orchard et al, 2012; Schache et al, 2011; Taylor et al, 2011; Warren et al, 2010; Watsford et al, 2010; Cochrane et al, 2007; Hrysomallis, McLaughlin & Goodman, 2007; Hoskins & Pollard, 2005; Verrall, Slavotinek & Barnes, 2005; Gabbe, Bennell & Finch, 2006a; Gabbe et al, 2006b; Orchard, Farhart & Leopold, 2004; Cameron, Adams & Maher, 2003; Orchard, 2002; Orchard, 2001; Orchard, Seward & McGivern, 2001; Verrall et al, 2001; Orchard et al, 1999; Bennell et al, 1998). Accordingly, subtle reductions in the incidence, recurrence and prevalence of soft-tissue injuries have occurred simultaneously with increments in traumatic and overuse hard-tissue injuries (Orchard, Seward & Orchard, 2013; Orchard, Seward & Orchard, 2012). Given that lower-body skeletal injuries currently generate an approximate competition-wide expense of ~$1.5 million in lost player wages each year (calculation detailed in Chapter 1); this paucity of research is surprising and justifies the need for further scientific investigation. In particular, the ability to comprehensively examine lower-body skeletal properties provides practitioners with an opportunity to characterise, screen and monitor Australian Football players for injury risk; and measure the efficacy of prophylactic or remedial strength and conditioning programs aimed at minimising skeletal injury in conjunction with other load management practices.

Traumatic (acute onset, impact-based) and overuse (gradual onset, stress-based) skeletal injuries result from sudden high-grade or cyclical low-grade forces respectively (Shindle et al, 2012; Ekstrand, Hagglund & Walden, 2011; Smoljanovic et al, 2009). While traumatic injuries can never truly be eliminated; overuse injuries are considered to be highly preventable given their aetiological response to prescribed mechanical load and recovery which underpin injury onset (Lauersen, Bertelsen & Andersen, 2014; Corrarino, 2012; McCormick, Nwachukwu & Provencher, 2012; Shindle et al, 2012; Harrast & Colonno, 2010; Rauh, Macera, Trone, Shaffer & Brodine, 2006; Warden, Burr & Brukner, 2006; Jones et al, 2002; Milgrom et al, 2000b; Bennell et al, 1999). Specifically, unaccustomed (excessive or unusual) skeletal loading generates and propagates tissue damage in the form microcracks; whereby the absence of sufficient recovery leads to an accumulation and coalescence of microcracks into macrocracks or complete fractures (Beck et al, 2015; Lester et al, 2009; Taylor, Hazenburg & Lee, 2007; Davison et al, 2006; Noble, 2003; Hsieh & Silva, 2002; Noble et al, 1997; Burr et al, 1989). Accordingly, stress reactions, fractures and related syndromes eventuate through prolonged hard-tissue degradation in response to chronic disturbances between bone resorption and formation such that a net-resorptive environment is created; an accumulative consequence of reparation to eliminate microdamage (Warden, Davis & Fredericson, 2014; Moran et al, 2012a; Burr, 2011; Herman et al, 2010; Warden, Burr & Brukner, 2006). Given that bone reparation requires damaged tissue to be removed and then replaced at multiple locations simultaneously; the progressive weakening of bone through excessive remodelling has significant microstructural consequences, compromising structural integrity and mechanical competency (Fonseca et al, 2014; Clansey et al, 2012; Burr, 2011; Taylor, Hazenburg & Lee, 2007; Friedman, 2006; Schell et al, 2006; Seeman & Delmas, 2006; Burr et al, 1997).

Overuse skeletal injuries are multifactorial with isolated, interactive and interdependent risk factors; however, the intrinsic musculoskeletal properties of an athlete will ultimately determine their extrinsic ability to tolerate mechanical load (Beck, Rudolph, Matheson, Bergman & Norling, 2015; Leppänen, Aaltonen, Parkkari, Heinonen & Kujala, 2014; Lauersen, Bertelsen & Andersen, 2014; Corrarino, 2012; Rauh et al, 2006; Jones et al, 2002; Milgrom et al, 2000b; Bennell et al, 1998). Accordingly, skeletal fragility is directly related to injury risk (Lauersen, Bertelsen & Andersen, 2014; Popp et al, 2009; Franklyn et al, 2008; Tommasini et al, 2008; Tommasini et al, 2005; Burr et al, 1997); proportionately heightening athlete susceptibility to traumatic and overuse skeletal injuries through a reduced capacity to manage applied forces (Newsham-West, Lyons & Milburn, 2013; Wallace et al, 2012; Burr, 2011; Jepsen et al, 2011; Schnakenburg et al, 2011; Jepsen et al, 2007; Ammann & Rizzoli, 2003; Beck et al, 2001). Consequently, athletes with low bone mass, muscle mass and slender structural proportions will acquire and accumulate greater amounts of microdamage and musculoskeletal fatigue in response to loading than athletes with high bone mass, muscle mass and robust structural proportions (Warden, Davis & Fredericson, 2014; Jepsen et al, 2013; Tommasini et al, 2008; Tommasini et al, 2005; Warden et al, 2005; Beck et al, 2000). Given the individuality of training history and morphological development between players of any sport; and the subsequent exclusivity of muscle-bone characteristics established through-out growth and maturation; complexity arises as no single athlete will exhibit the same capacity to tolerate mechanical loads within a given team. It is therefore pertinent that practitioners quantify muscle and bone morphology of all players within a team or sport during routine physical screening procedures in order to identify and stratify skeletal risk; and accordingly, to individualise and modify load management programs.

Bone strength is also a highly trainable musculoskeletal characteristic; modified through targeted mechanical loading programs aimed at developing and optimising material and structural skeletal components (Ireland, Rittweger & Degens, 2014; Warden et al, 2014; Robling, 2012; Sugiyama et al, 2012; Bergmann et al, 2011; Martin & Correa, 2010; Judex, Gupta & Rubin, 2009; Kohrt, Barry & Schwartz, 2009; Turner, 2007; Robling, Castillo & Turner, 2006; Suominen, 2006; Warden et al, 2005; Ammann & Rizzoli, 2003). Specifically, morphological adaptations which lead to increments in bone strength demonstrably reduce skeletal fatigue and damage susceptibility to customary loads while concomitantly increasing resistance to undesirable bending moments (Fonseca et al, 2014; Seeman, 2008a; Bouxsein & Karasik, 2006; Davison et al, 2006; Tommasini et al, 2008; Warden et al, 2005; Pearson & Leiberman, 2004) such that players with comparatively low bone mass and slender structural proportions may benefit from prophylactic bone strengthening programs as a mechanism to enhance skeletal robustness and load tolerance. However, research is required to identify which morphological characteristics inherently predispose some Australian Footballers to overuse skeletal injuries in comparison to those who are skeletally resilient; and therefore which physical components should be targeted and monitored through prophylactic and remedial training programs to reduce injury incidence, severity or recurrence within this population. This study serves to comprehensively examine the lower-body musculoskeletal properties of elite Australian Footballers using independent three-dimensional (pQCT) and two-dimensional (DXA) imaging techniques. This serves to: 1) provide a set of normative and comparative values for injured and non-injured Australian Footballers, and 2) identify whether observed differences between injured and non-injured players were further evident between injured and non-injured limbs within the injured cohort.

4.2. Methods

4.2.1. Subjects

Sixty (n = 60) elite Australian Football players were recruited from the Australian Football League (AFL) competition for participation in this study. Athletes with lower limb injuries or contraindications requiring immobilisation within 3 months prior to data collection; or with metallic surgical implants located beneath the trunk were excluded from analysis. This rendered five players as unsuitable for inclusion, providing a total cohort of fifty-five athletes stratified by stress fracture injury incidence during the prior AFL season (injured versus non-injured). Players wore their club-issued football shorts during the data collection process and were notified of the potential risks involved. Data collection and management procedures conformed to the Code of Ethics (World Medical Association), Declaration of Helsinki, with ethics approval provided by Edith Cowan University's Human Research Ethics Committee.

Table 19. Descriptive characteristics of injured (n=13) and non-injured (n=42) elite Australian Footballers.

	Injured [n = 13]	**Non-Injured [n = 42]**	**Effect (*d*)**	**Significance (*p*)**
Age (yr)	20.2 (± *2.1*)	22.6 (± *3.9*)	0.77 [b]	0.059
Height (cm)	185.5 (± *8.6*)	189.4 (± *6.5*)	0.51 [c]	0.109
Weight (kg)	80.9 (± *4.6*)	86.4 (± *8.5*)	0.80 [b]	0.045 [*]
BMI (kg/m^2)	23.6 (± *1.6*)	24.0 (± *1.5*)	0.26 [c]	0.354
Bone Mass (%)	4.0 (± *0.3*)	4.1 (± *0.3*)	0.33 [c]	0.175
Lean Mass (%)	84.7 (± *1.5*)	85.7 (± *1.6*)	0.64 [b]	0.124
Fat Mass (%)	11.3 (± *1.4*)	10.2 (± *1.7*)	0.71 [b]	0.144
Tibial Length (mm)	422.7 (± *38.3*)	437.8 (± *24.9*)	0.47 [c]	0.111

Note: Values reported as Mean (± SD); BMI = body mass index; Bone Mass = whole-body bone mineral content; Effect = effect size; ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect (d ≥ 1.2); b = moderate effect (d ≥ 0.6); c = small effect (d ≥ 0.2).

4.2.2. Experimental Design

This acute, cross-sectional study commenced with anthropometric measures including height (cm), weight (kg), and tibial length (mm), followed by a series of whole-body composition and lower-body bone densitometry scans conducted at the commencement of preseason training. Specifically, whole-body and segmental appendicular mass (lean, fat, bone and total) was examined using Dual-energy X-ray Absorptiometry (DXA); while lower-body bone material, structure and strength measures were assessed using peripheral Quantitative Computed Tomography (pQCT). All anthropometry measurements, bone densitometry operations and analyses, and symmetry index calculations were performed in accordance with descriptions and illustrations provided in prior sections 3.2.3 (Anthropometry), 3.2.4 (Scan Procedures) and 3.2.5 (Symmetry Index).

4.2.3. Injury Analysis

All injuries were recorded if the identified concern or medical condition caused the player to miss a training session or competitive match. In this study, only stress-related bone injuries identified during the previous AFL season were considered for retrospective analysis. Injuries were determined through detailed physical assessment and medical examination provided by physiotherapists and medical doctors of the football club respectively. Players who presented with stress-related tibial bone injuries during the previous season were used to establish an injured group (n = 13) to compare with those who were, in skeletal terms, the non-injured group (n = 42). The injured limb of players who sustained stress-related bone injures was also recorded for comparison against their non-injured limb. All stress fractures were acquired ~6 to 12 months prior to data collection thus players were fully rehabilitated and prophylactically re-strengthened.

4.2.5. Statistical Analysis

Independent t-tests were conducted to determine whether significant differences were evident between groups for: 1) subject characteristics 2) muscle-bone characteristics of the kicking limb; 3) muscle-bone characteristics of the support limb; and 4) symmetry index. Independent t-tests were also conducted to determine whether significant differences were evident between injured and non-injured limbs of the injured players for all muscle-bone characteristics. Post-hoc adjustment for multiple comparisons was performed using Holm-Bonferonni Sequential Corrections. Effect sizes were also used for all comparisons (Cohen, 1988) to determine the magnitude of difference between variables in accordance with Hopkins (2002): $d \geq 0.2$ is small; $d \geq 0.6$ is moderate; $d \geq 1.2$ is large. Statistical computations were performed using SPSS (Version 17.0; Chicago, IL).

4.3. Results

Descriptive characteristics of injured and non-injured elite Australian Footballers recruited to this study are provided in Table 19. Non-injured players were significantly heavier of a moderate effect than injured players ($p = 0.045$, $d = 0.80$). Furthermore, non-injured players were also older, with greater relative lean mass and lower relative fat mass than injured players of a moderate effect ($d = 0.64 – 0.77$) despite not reaching significance ($p = 0.590 – 0.144$). Non-injured players were slightly taller with longer tibias and greater relative bone mass of small effect than injured players ($d = 0.26 – 0.51$) whilst also not reaching statistical significance ($p = 0.109 – 0.354$).

4.3.1. Player Comparison

Muscle-bone characteristics of the kicking and support limbs for injured and non-injured elite Australian Footballers are provided in Tables 20, 21 and 22. Non-injured players

exhibited significantly higher tibial mass (p = 0.019), with a moderate effect evident across both limbs (d = 0.68 – 1.04). Further, non-injured players also exhibited higher cortical density (d = 0.38 – 0.46) and higher marrow density of a small effect (d = 0.21). While non-injured players displayed higher values for three material variables; they were markedly higher across all seven structural and all four strength variables, illustrating the greater contribution of structural properties to bone strength in this cohort. Specifically, non-injured players exhibited significantly higher cortical area and periosteal area (p = 0.034 – 0.039) of moderate effect (d = 0.63 – 0.86) than injured players; with markedly higher trabecular area, marrow area, total area and endocortical area of small effects (d = 0.22 – 0.59). Cortical thickness was only higher in the support leg for non-injured players of a small effect (d = 0.43); potentially indicative of greater susceptibility within the support limb of the injured group.

Material and structural properties combined to deliver higher bone strength across both limbs of non-injured players, with an emphasis toward the support leg. In particular, non-injured players had significantly higher stress-strain indices, absolute fracture loads and relative fracture loads than injured athletes in the support leg (p = 0.007 – 0.043) of a moderate effect (d = 0.70 – 1.04). Similarly, non-injured players also exhibited higher stress-strain indices, absolute fracture loads and relative fracture loads in the kicking leg of moderate effect (d = 0.48 – 0.87) reaching statistical significance only for absolute fracture load (p = 0.024). Further, DXA-derived areal bone mineral content (aBMC) was significantly higher in non-injured players (p = 0.017 – 0.020) with moderate effects evident across bone mineral content and bone area (d = 0.64 – 0.91). Areal density (aBMD) displayed small magnitude positive effects in non-injured players (d = 0.50). Soft-tissue

measures were also favourable for non-injured players, with significantly higher muscle area and higher muscle mass (p = 0.009 – 0.034) of moderate effect (d = 0.79 – 0.96) than their injured counterparts. Conversely, injured players contained slightly higher muscle density at the expense of muscle area (d = 0.28 – 0.32), with higher fat mass of small magnitude comparative to non-injured players (d = 0.30 – 0.31).

4.3.2. Limb Comparison

Muscle-bone characteristics of the injured and non-injured limbs within injured elite Australian Footballers are provided in Tables 23. Differences were observed between limbs of injured players for two material (tibial mass, total vBMD), two structural (cortical area and thickness), and two strength variables (stress-strain index, relative fracture load), with lower values reported for the injured limb comparative to the non-injured limb of a small magnitude (d = 0.20 – 0.55) except for cortical area which displayed a moderate effect (d = 0.70). Interestingly, muscle area was not clearly different between limbs; with muscle density and fat mass reportedly lower in the injured limb of a small magnitude (d = 0.29 – 0.54). While DXA-derived areal measures were similar to pQCT-derived volumetric measures with moderate magnitude effects (d = 0.34 – 0.47) for bone area and bone mineral content, it was not possible to establish a clear difference in bone mineral density (aBMD). DXA was also unable to detect any notable disparity between hard-tissue and soft-tissue measures between injured and non-injured players when stratified by limb function (kicking and support), despite small magnitude effects evident in several material, structural and strength components. This supports the notion that DXA is unable to detect subtle morphological, musculoskeletal adaptations also expressed earlier in Chapter 3.

Table 20. **Comparative pQCT derived skeletal values for injured (n=13) and non-injured (n=42) elite Australian Footballers.**

	Injured			Non-Injured			Effect: (I ↔ NI)	
	Kicking Leg	**Support Leg**	**Effect**	**Kicking Leg**	**Support Leg**	**Effect**	**Kicking**	**Support**
MATERIAL PROPERTIES								
Tibial Mass (g/cm)	4.51 (± *0.3*)	4.51 (± *0.2*)	0.00	4.75 (± *0.4*)	4.84 (± *0.4*)	0.23 [c]	0.68 [b]	1.04 [*/b]
Tb.vBMD (mg/cm^3)	290.8 (± *46.4*)	288.0 (± *46.1*)	0.06	292.8 (± *30.2*)	290.7 (± *29.1*)	0.07	0.05	0.07
Ct.vBMD (mg/cm^3)	1108.7 (± *19.3*)	1105.9 (± *17.0*)	0.15	1116.2 (± *12.2*)	1112.7 (± *18.6*)	0.22 [c]	0.46 [c]	0.38 [c]
Ma.vBMD (mg/cm^3)	21.0 (± *6.0*)	20.7 (± *5.2*)	0.05	21.7 (± *6.9*)	22.1 (± *7.8*)	0.05	0.11	0.21 [c]
Tt.vBMD (mg/cm^3)	631.7 (± *64.5*)	622.2 (± *58.7*)	0.15	627.3 (± *38.7*)	626.3 (± *36.5*)	0.03	0.08	0.08
STRUCTURAL PROPERTIES								
Tb.Ar (mm^2)	627.8 (± *72.8*)	634.3 (± *63.2*)	0.10	643.8 (± *70.3*)	652.5 (± *74.8*)	0.12	0.22 [c]	0.26 [c]
Ct.Ar (mm^2)	325.1 (± *16.2*)	326.0 (± *13.8*)	0.06	338.9 (± *25.3*)	348.3 (± *33.8*)	0.31 [c]	0.65 [b]	0.86 [*/b]
Ma.Ar (mm^2)	190.0 (± *66.7*)	206.1 (± *74.9*)	0.23 [c]	236.7 (± *78.7*)	237.0 (± *70.5*)	0.00	0.59 [c]	0.43 [c]
Tt.Ar (mm^2)	840.5 (± *79.3*)	851.0 (± *72.6*)	0.14	875.2 (± *83.5*)	891.9 (± *88.5*)	0.20 [c]	0.43 [c]	0.51 [c]
Ps.Ar (mm)	84.0 (± *3.9*)	84.6 (± *3.8*)	0.16	86.5 (± *4.0*)	87.6 (± *4.1*)	0.27 [c]	0.63 [b]	0.76 [*/b]
Ec.Ar (mm)	53.0 (± *6.3*)	54.0 (± *5.9*)	0.16	55.3 (± *4.6*)	55.9 (± *4.6*)	0.13	0.42 [c]	0.36 [c]
Ct.Th (mm)	4.93 (± *0.5*)	4.88 (± *0.4*)	0.11	4.97 (± *0.4*)	5.05 (± *0.4*)	0.20 [c]	0.09	0.43 [c]
STRENGTH PROPERTIES								
SSI (mm^3)	2402.0 (± *226.1*)	2423.8 (± *233.4*)	0.09	2584.3 (± *322.4*)	2729.5 (± *363.5*)	0.42 [*/c]	0.65 [b]	1.00 [**/b]
FL.Ab (N)	5387.7 (± *564.6*)	5386.5 (± *565.4*)	0.00	5990.7 (± *803.6*)	6102.4 (± *790.0*)	0.14	0.87 [*/b]	1.04 [**/b]
FL.Rel (N/kg)	6.78 (± *0.6*)	6.78 (± *0.6*)	0.00	7.07 (± *0.6*)	7.20 (± *0.6*)	0.22 [c]	0.48 [c]	0.70 [*/b]
FL Ratio (X/Y)	1.14 (± *0.1*)	1.13 (± *0.1*)	0.10	1.18 (± *0.1*)	1.20 (± *0.1*)	0.20 [c]	0.40 [c]	0.70 [b]

Note: Values reported as Mean (± SD); Tb = trabecular; Ct = cortical; Ma = marrow; Tt = total; Ps = periosteal; Ec = endocortical; vBMD = volumetric bone mineral density; Ar = area; Th = thickness; SSI = stress-strain index; FL = fracture load; Ab = absolute; Rel = relative; X = medio-lateral, Y = anterio-posterior; effect = effect size; ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 21. **Comparative pQCT derived soft-tissue values between injured (n=13) and non-injured (n=42) elite Australian Footballers.**

	Injured			Non-Injured			Effect: (I ↔ NI)	
	Kicking Leg	**Support Leg**	**Effect**	**Kicking Leg**	**Support Leg**	**Effect**	**Kicking**	**Support**
Mu.Ar (mm^2)	8166.6 (± *883.1*)	8242.7 (± *971.6*)	0.08	9145.5 (± *1192.3*)	9102.6 (± *1200.8*)	0.04	0.93 **/b	0.79 */b
Mu.Den (mg/cm^3)	78.7 (± *0.7*)	78.4 (± *1.2*)	0.31 c	78.3 (± *1.6*)	78.0 (± *1.6*)	0.20 c	0.32 c	0.28 c
Fat.Ar (mm^2)	1216.3 (± *225.1*)	1158.2 (± *204.2*)	0.13	1245.1 (± *455.2*)	1173.5 (± *495.8*)	0.15	0.08	0.04

Note: Values reported as Mean (± SD); Mu = muscle; Ar = area; Den = density; ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 22. **Comparative DXA derived shank segment values for injured (n=13) and non-injured (n=42) elite Australian Footballers.**

	Injured			Non-Injured			Effect: (I ↔ NI)	
	Kicking Leg	**Support Leg**	**Effect**	**Kicking Leg**	**Support Leg**	**Effect**	**Kicking**	**Support**
BA (cm)	199.0 (± *21.2*)	198.1 (± *17.2*)	0.05	213.3 (± *23.3*)	214.8 (± *23.1*)	0.06	0.64 b	0.82 b
aBMC (g)	264.0 (± *28.1*)	264.4 (± *30.9*)	0.01	295.8 (± *43.2*)	298.9 (± *43.5*)	0.07	0.87 */b	0.91 */b
aBMD (g/cm^2)	1.33 (± *0.1*)	1.34 (± 0.1)	0.10	1.38 (± *0.1*)	1.39 (± *0.1*)	0.10	0.50 c	0.50 c
Lean Mass (g)	2913.9 (± *298.3*)	2935.9 (± *271.8*)	0.01	3236.6 (± *372.5*)	3246.5 (± *366.0*)	0.03	0.96 **/b	0.96 **/b
Fat Mass (g)	371.7 (± *60.9*)	363.1 (± *46.9*)	0.16	402.7 (± *131.2*)	395.0 (± *141.9*)	0.06	0.31 c	0.30 c

Note: Values reported in absolute values as Mean (± SD); BA = bone area; aBMC = areal bone mineral content; aBMD = areal bone mineral density. ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 23. **Comparison of musculoskeletal characteristics of injured and non-injured limbs for injured (n = 13) elite Australian Footballers.**

	Injured Limb	Non-Injured Limb	Effect
MATERIAL PROPERTIES			
Tibial Mass (g/cm)	4.44 (± *0.3*)	4.58 (± *0.2*)	0.55 [c]
Tb.vBMD (mg/cm^3)	286.7 (± *47.4*)	292.0 (± *44.9*)	0.11
Ct.vBMD (mg/cm^3)	1106.1 (± *17.8*)	1108.5 (± *18.6*)	0.13
Ma.vBMD (mg/cm^3)	20.9 (± *5.0*)	20.7 (± *6.2*)	0.04
Tt.vBMD (mg/cm^3)	619.3 (± *60.6*)	634.7 (± *62.0*)	0.25 [c]
STRUCTURAL PROPERTIES			
Tb.Ar (mm^2)	629.3 (± *69.5*)	632.9 (± *67.0*)	0.05
Ct.Ar (mm^2)	320.6 (± *15.5*)	330.5 (± *12.8*)	0.70 [b]
Ma.Ar (mm^2)	198.1 (± *69.7*)	198.0 (± *73.0*)	0.00
Tt.Ar (mm^2)	843.3 (± *77.2*)	848.1 (± *75.2*)	0.06
Ps.Ar (mm)	84.2 (± *3.7*)	84.4 (± *4.0*)	0.05
Ec.Ar (mm)	53.9 (± *5.7*)	53.1 (± *6.5*)	0.13
Ct.Th (mm)	4.82 (± *0.4*)	4.99 (± *0.5*)	0.38 [c]
STRENGTH PROPERTIES			
SSI (mm^3)	2382.7 (± *243.3*)	2443.1 (± *211.8*)	0.26 [c]
FL.Ab (N)	5345.8 (± *552.2*)	5428.4 (± *574.4*)	0.15
FL.Rel (N/kg)	6.73 (± *0.5*)	6.84 (± *0.6*)	0.20 [c]
FL Ratio (X/Y)	1.15 (± *0.1*)	1.12 (± *0.1*)	0.30 [c]
SOFT-TISSUE PROPERTIES			
Mu.Ar (mm^2)	8217.5 (± *869.7*)	8191.8 (± *985.0*)	0.03
Mu.Den (mg/cm^3)	78.3 (± *1.1*)	78.8 (± *0.7*)	0.54 [c]
Fat.Ar (mm^2)	1183.0 (± *191.1*)	1191.5 (± *239.8*)	0.04
AREAL MEASURES			
BA (cm)	194.1 (± *17.5*)	203.0 (± *20.0*)	0.47 [c]
aBMC (g)	259.3 (± *33.5*)	269.1 (± *23.9*)	0.34 [c]
aBMD (g/cm^2)	1.33 (± *0.1*)	1.33 (± 0.1)	0.00
Lean Mass (g)	2918.8 (± *284.2*)	2931.0 (± *286.8*)	0.04
Fat Mass (g)	358.7 (± *43.4*)	373.7 (± *58.9*)	0.29 [c]

Note: Values reported as Mean (± SD); Tb = trabecular; Ct = cortical; Ma = marrow; Tt = total; Ps = periosteal; Ec = endocortical; vBMD = volumetric bone mineral density; Ar = area; Th = thickness; SSI = stress-strain index; FL = fracture load; Ab = absolute; Rel = relative; X = medio-lateral, Y = anterio-posterior; Mu = muscle; Ar = area; Den = density; BA = bone area; aBMC = areal bone mineral content; aBMD = areal bone mineral density; effect = effect size; ** = statistical significance (p ≤ 0.01); * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

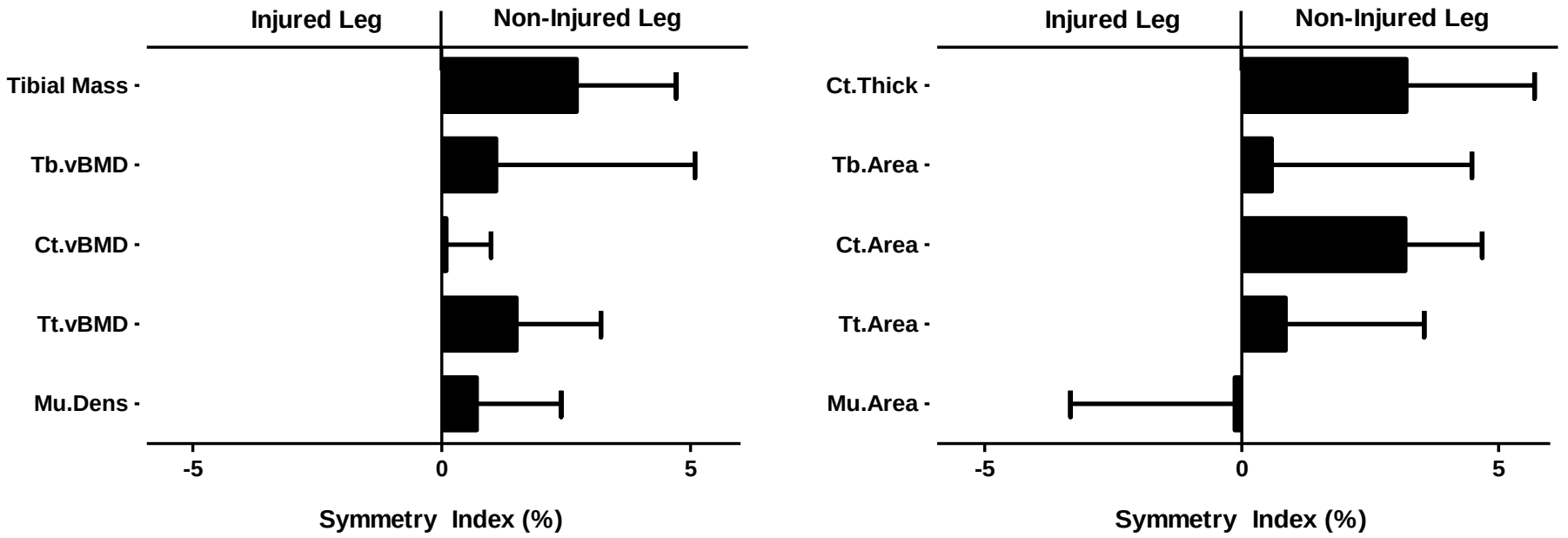


Figure 29. **Symmetry index of material (left) and structural (right) measures between injured and non-injured limbs of injured elite Australian Footballers.**

Musculoskeletal asymmetry between injured and non-injured limbs of injured players illustrated demonstrably favourable properties toward the non-injured limb, with material and structural properties displayed in Figure 29. Similar to comparisons drawn between players; the non-injured limb contained greater tibial mass (~2.7%) and greater volumetric density (~0.2 – 1.5%) for all materials (trabecular, cortical and total) with the exception of marrow which was higher in the injured limb (~3.2%). Similarly the non-injured limb contained a thicker cortex (~3.2%), owing to wider periosteal (~0.6%) and smaller endocortical areas (~1.1%). Furthermore, the non-injured limb contained greater cross-sectional area (~0.6 – 3.0%) for all materials (trabecular, cortical, total and marrow). Indeed, the concomitant superiority of material density and structural cross-sectional area in the non-injured limb perhaps exposes the inherent weaknesses of the injured limb; a slender bone with greater susceptibility to microdamage generation and accumulation overtime. As such, the non-injured limb had greater resistance to bending moments and greater ultimate strength, owing to higher stress-strain indices (~3.0%) and fracture loads (~2.2%).

4.4. Discussion

Skeletal injuries continue to rise in Australian Football (Orchard, Seward & Orchard, 2013; Orchard et al, 2012; Orchard & Seward, 2003) in the absence of context specific hard-tissue injury prevention, minimisation or rehabilitation research. While traumatic injuries are difficult to wholly prevent, overuse skeletal injuries are aetiologically considered to be highly preventable given the causative premise of excessive mechanical load and inadequate recovery (Beck et al, 2015; Fortington et al, 2015; Corrarino, 2012; McCormick, Nwachukwu & Provencher, 2012; Shindle et al, 2012; Harrast & Colonno, 2010; Rauh et al, 2006; Warden, Burr & Brukner, 2006; Jones et al, 2002; Milgrom et al,

2000b; Bennell et al, 1999). Despite an expansive array of reported risk factors; intrinsic musculoskeletal properties are potentially the most influential, owing to their dominant role in mechanical behaviour, microdamage accumulation and load tolerability (Beck et al, 2015; Leppänen et al, 2014; Lauersen, Bertelsen & Andersen, 2014; Corrarino, 2012; Rauh et al, 2006; Jones et al, 2002; Milgrom et al, 2000b; Bennell et al, 1998). Presently, no scientific data exists to describe the lower-body musculoskeletal morphology of elite Australian Football athletes when stratified by injury incidence. Accordingly, this study has provided a comprehensive musculoskeletal examination of the lower-body morphology of elite Australian Football athletes with and without stress fractures using DXA and pQCT imaging devices to explicitly identify which morphological traits are associated with overuse skeletal injuries between players; and between the injured and non-injured limbs of injured players.

4.4.1. Player Comparison

Repetitious and cyclical low-grade forces prevalent in land-based locomotive activities deliver sub-threshold mechanical loads to lower-body skeletal structures that inevitably generate and propagate hard-tissue microdamage beyond its intrinsic reparation capabilities in the absence of appropriate nutrition and recovery. However, the ability to extrinsically strengthen bone through training interventions attractively reduces sub-threshold stresses, producing lower relative microdamage and higher relative resistance to fatigue at equivalent loading volumes (Fonseca et al, 2014; Ireland, Rittweger & Degens, 2014; Burr, 2011; Nikander et al, 2010a; Seeman, 2008a; Warden et al, 2005; Burr, 2003; Milgrom et al, 2000b). In the absence of longitudinal training and injury data, the relationship between bone strength and its derivatives to injury incidence can be investigated using cross-

sectional comparisons of individual players exposed to similar loading conditions within their sporting environment. As Australian Football is a unique, volatile, odd-impact sport delivering compressive, torsional, transverse and tensile loads in isolation and combination; Australian Footballers will have distinct lower-body musculoskeletal characteristics, inevitably creating different maximal and submaximal load tolerance thresholds prior to injury onset which may predispose some players to greater risk of injury than others. Expectantly, this study was able to demonstrate this general relationship, with different lower-body morphological profiles between injured and non-injured players.

Australian Footballers who acquired stress fractures were lower across nearly all musculoskeletal measures in this study, demonstrating a general inferiority and global physical weakness in comparison to their non-injured counterparts. Skeletally, non-injured players were ~10 to 12% stronger than injured players in response to greater cross-sectional area and robust structural properties across all macroscopic tissues, despite only modest differences in material density. This is particularly noteworthy as structural adaptations are potent contributors to bone strength, whereby ~2-fold increases in cross-sectional area and bone geometry can yield an ~8-fold and ~100-fold increase in bone strength and fatigue resistance respectively without any concomitant change in mass or density (Seeman, 2008a; Seeman, 2008b; Bouxsein & Karasik, 2006; Davison et al, 2006; Warden et al, 2005). Indeed, skeletal slenderness, owing to smaller cross-sectional areas and thinner cortices, is directly linked to skeletal fragility and microdamage accumulation (Wallace et al, 2012; Burr, 2011; Tommasini et al, 2008; Ruffing et al, 2006; Ural & Vashishth, 2006; Tommasini et al, 2005; Beck et al, 2000); an observed structural deficiency within injured Australian Footballers in this study. Specifically, slender bones produce higher material

densities to accommodate for lower cross-sectional areas; a mechanism used to confer strength to the skeleton through structural rigidity at the unfortunate expense of ductility (Jepsen et al, 2013; Wallace et al, 2012; Jepsen, 2011; Jepsen et al, 2011; Jepsen et al, 2007; Tommasini et al, 2008; Peterlik et al, 2005; Tommasini et al, 2005). Accordingly, players with slender bones accumulate more damage and require longer recovery periods at equivalent mechanical loads than their resilient counterparts; a consequence of increased mineralisation and heightened brittleness subsequently altering mechanical behaviour and increasing overuse injury risk through reduced mechanical competency (Herman et al, 2010; Ritchie, Buehler & Hansma, 2009; Tommasini et al, 2008; Tommasini, Nasser & Jepsen, 2007; Peterlik et al, 2005; Turner, 2002; Currey, 1984). This, in part, explains why injured players with lower tibial masses, narrower cortices and smaller geometrical properties possessed similar material densities than non-injured players.

Despite global differences in skeletal properties between injured and non-injured Australian Footballers; there are specific morphological characteristics worthy of attention. Non-injured players in this study contained favourable geometric properties specific to cross-sectional area in trabecular and cortical regions; with greater periosteal, endocortical and marrow areas illustrating wider external and internal cortex diameters. Specifically, radial expansion of bone favourably positions mineral material further away from its neutral axis to confer greater strength (Capozza et al, 2013; Fan et al, 2011; Bouxsein & Karasik, 2006; Davison et al, 2006; Pearson & Leiberman, 2004); evidenced by higher stress-strain indices (resistance to bending) and fracture loads (resistance to fatigue and impact) in non-injured Australian Footballers. This is a potent structural adaptation, markedly increasing resilience to potentially dangerous bending and torsional moments; the highest and most damaging

stresses imposed onto the appendicular skeleton (Martin & Correa, 2010; Doube, Wiktorowicz-Conroy, Christiansen, Hutchinson & Shefelbine, 2009; Bouxsein & Karasik, 2006; Davison et al, 2006; Pearson & Leiberman, 2004). Previous stress fracture research using military recruits, distance runners and triathletes align with our findings, showing evident dispositions between geometrical properties and stress fracture histories specific to narrower cortices; thinner anterio-posterior or medio-lateral walls; and smaller cortical areas (Newsham-West, Lyons & Milburn, 2013; Moran et al, 2012a; Schnakenburg et al, 2011; Popp et al, 2009; Franklyn et al, 2008; Cowan et al, 1996). Importantly, these morphological skeletal components are measureable and modifiable through targeted mechanical loading programs; highlighting the need for improved screening methodologies and prophylactic training protocols to promptly identify players at risk of injury, remediate physical weaknesses and modify loading schemes accordingly.

Muscle is tightly linked to bone (Cianferotti & Brandi, 2014; Kaji, 2014; Lloyd et al, 2014; Mikkola et al, 2009), functionally attenuating mechanical load to prevent undesirable bending moments, whilst also exerting osteogenic forces onto the skeleton to produce movement (Pamukoff & Blackburn, 2015; Avin et al, 2014; Ireland, Rittweger & Degens, 2014; Milgrom et al, 2007; Martin, Burr & Sharkey, 1998; Yoshikawa et al, 1994). Specifically, alterations in muscle size, density and strength are sequentially linked to alterations in bone size, density and strength (Cianferotti & Brandi, 2014; Ireland, Rittweger & Degens, 2014; Lloyd et al, 2014; Mikkola et al, 2009; Szulc et al, 2006; Crepaldi & Maggi, 2004; Rittweger et al, 2000). Interestingly, this relationship is also evident in the current study, as the production of higher bone density to accommodate for lower bone area in slender players was extrapolated to muscle; with injured players

producing higher muscle density to counteract lower muscle area than non-injured players. Indeed, this may implicate muscle density as a less desirable trait than muscle area, highlighting the greater value of muscle cross-sectional area to subsequent bone adaptation and mechanical behaviour. This seems logical given the strong link between muscular cross-sectional area and subsequent muscular strength (Edwards et al, 2013; Hoshikawa et al, 2013; Jones, Bishop, Woods & Green, 2008; Suominen, 2006) demonstrating the value of muscle size and strength as targetable and trainable features to enhance and protect bone size and strength. While previous stress fracture investigations have not reported muscle density values, their findings corroborate those of the current study with injured cohorts containing substantially less muscle in mass and area measures than their non-injured colleagues (Clarke, Tobias, Murray & Boreham, 2011; Schnackenburg et al, 2011; Popp et al, 2009; Cesari et al, 2006; Szulc et al, 2006; Beck et al, 2000). Areal measures supplied by DXA were generally able to differentiate between injured and non-injured players with lower bone area, bone mass and lean mass evident in injured players. However, areal measures were unable to identify any notable differences between limbs when stratified by function despite clear material, structural and strength differences identified by pQCT.

4.4.2. Limb Comparison

Injury prevention and rehabilitation research routinely compares measureable biomechanical and physiological characteristics between injured and non-injured populations in an effort to identify common factors which contribute to resilience or susceptibility; establishing normative data for benchmarking and comparative interpretation. While these investigations are necessary and provide unique insights into potentially modifiable deficiencies within athletes susceptible to injury; they are also

limited by confounding extraneous factors such as variations in genetic phenotypes, age, gender, ethnicity, nutritional history, training history, and other environmental developments established between players over time. Subsequently, it becomes difficult to isolate which developmental musculoskeletal factors directly and potently contribute to injury incidence between players of varying backgrounds. To address this limitation, prior studies have compared biomechanical and physiological characteristics between injured and non-injured limbs of injured athletes (Ardern, Taylor, Feller & Webster, 2014; Opar et al, 2014; Lee, Reid, Elliot & Lloyd, 2009; Sugiura, Saito, Sakuraba, Sakuma & Suzuki, 2008; Paterno, Ford, Myer, Heyl & Hewett, 2007; Nash, Mickan, Del Mar & Glasziou, 2004; Holder-Powell & Rutherford, 2000; Holder-Powell & Rutherford, 1999). This serves as a useful investigative model, enabling players to act as their own internal control in an attempt to identify specific, common and isolated musculoskeletal factors that contribute to heightened fragility in particular populations. Importantly, information provided by these internal comparisons enable practitioners to preferentially select characteristics during medical screening protocols in order to identify which limb is most at risk within descriptively fragile athletes. Accordingly, prophylactic training programs can be targeted towards localised remediation of an individual limb within the broader strength and conditioning program, in addition to globalised strengthening of the skeleton as a whole.

Injured limbs were morphologically different to non-injured limbs within injured elite Australian Footballers, containing musculoskeletal characteristics that may predispose the injured limb to higher rates of skeletal microdamage and potential injury than the contralateral, non-injured limb. Specifically, injured limbs contained narrower and thinner cortices, lower mineral density and lower bone mass than non-injured limbs within

skeletally fragile players. Although these material and structural relationships were similarly observed between injured and non-injured players more globally (Section 4.4.1); this internal comparison illustrates the preferential and specific importance of cortical area and thickness as structural and geometrical contributors to bone strength in presently fragile players. Indeed, the narrow and slender cortices of injured limbs highlight a greater weakness within skeletally vulnerable individuals, further highlighting a common theme whereby structural adaptations offer the greatest trainable and protective benefit to prevent skeletal injury in elite Australian Footballers through improvements to mechanical behaviour and competency under volatile physical loads. Accordingly, the greater slenderness of the injured limb in fragile players offers a measurable and modifiable skeletal property for practitioners to identify and target using detailed screening procedures and controlled loading sequences within prophylactic and remedial training programs.

Bone strength and mechanical behaviour are ultimately determined by the co-contribution of material and structural properties (Fonseca et al, 2014; Nordin & Frankel, 2012; Davison et al, 2006; Friedman, 2006; Seeman & Delmas, 2006; Jarvinen et al, 2005; Ammann & Rizzoli, 2003). Specifically, for a given magnitude of mechanical load, bone structure will determine the relative magnitude of stress experienced, whereas bone material will determine the ability of bone to resist stress under strain (Ireland, Rittweger & Degens, 2014; Bouxsein & Karasik, 2006; Warden et al, 2005; Pearson & Leiberman, 2004; Beck et al, 1996); highlighting the value of both skeletal properties toward mechanical competency under load. Using symmetry analysis (Figure 29), the heightened fragility of the injured limb is evident as the non-injured limb was superior across all structural measures and nearly all material measures. Indeed, the non-injured limb generally contained greater

volumes and densities of bone material which were structurally distributed over wider areas. The only exception was marrow density which was higher in the injured limb as a consequence of reduced marrow area in the injured limb owing to its narrow and slender cortex. As a result, the non-injured limb experiences lower relative stresses for a given mechanical load, and lower relative microdamage for a given mechanical stress. While muscle area was nearly symmetrical between limbs, the non-injured limb contained higher muscle density; a potential protective mechanism to neutralise unexpected stress distributions. Interestingly, areal measures supplied by DXA did not detect any difference in bone density or muscle mass despite evident differences in volumetric measures supplied by pQCT, specifically for total bone mineral density and muscle density. This further highlights the morphological limitations of DXA, reducing its diagnostic power during screening procedures when aiming to detect subtle or meaningful differences between limbs within athletes.

Musculoskeletal differences observed between injured and non-injured players as well as injured and non-injured limbs could be a consequence of recent injury history generating a level of muscle and bone resorption and atrophy. However, all retrospective stress fracture injuries used in this study were acquired 6 – 12 months prior; therefore at the time of measurement, all players were fully rehabilitated and provided with further prophylactic intervention. While some residual degradation following injury may still exist, it is believed that the effect of this was minimal between injured and non-injured players given the magnitude of observed difference (Section 4.4.1). To consolidate the relationship between injured and non-injured players, a within-subject design to compare injured and non-injured limbs of injured players (Section 4.4.2). Further strengths of this study also include the

modest sample size of injured players; the use of elite level athletes often scarce in research contexts; the novel application of pQCT to examine lower-body musculoskeletal injuries in Australian Football athletes; and the unique comparison of lower-body musculoskeletal characteristics between limbs based on injury history.

4.4. Summary

Australian Footballers contain different lower-body musculoskeletal characteristics and therefore different load tolerance thresholds prior to injury onset. Accordingly, the ability of practitioners to promptly, comprehensively and accurately examine the lower-body musculoskeletal properties of elite Australian Footballers is notably advantageous; providing useful screening and monitoring information as a mechanism to enhance injury risk stratification, modify load management practices, and optimise prophylactic or remedial training programs. Specifically, practitioners should focus on measuring a combination of material and structural musculoskeletal variables when interpreting skeletal robustness or fragility, focusing on bone area, bone mineral content and lean mass when using DXA; or tibial mass, total density, cortical area, cortical thickness, stress-strain index, fracture load and muscle area when using pQCT. Given the markedly high contribution, potency and direct importance of bone cross-sectional area and geometry to bone strength and skeletal fatigue resistance in Australian Footballers, it is strongly recommended that practitioners use pQCT to investigate musculoskeletal resilience; particularly as DXA cannot measure bone structure or estimate skeletal slenderness, limited solely to frontal plane mass distribution as a surrogate reflection of bone area or mineral content. To prevent injury incidence or minimise injury severity, it is recommended that practitioners focus on training modalities which enhance muscle-bone cross-sectional area and muscle-bone mass.

CHAPTER FIVE – STUDY THREE

IN-SEASON AND OFF-SEASON LOWER-BODY MUSCULOSKELETAL ADAPTATIONS IN ELITE AUSTRALIAN FOOTBALLERS

5.1. Introduction

Australian Football is a fast-paced and multi-dimensional field based sport which places high physical demands on athletes in order to produce a successful outcome (Kempton et al, 2015; Johnston et al, 2012; Pruyn et al, 2012; Ball, 2011; Young et al, 2010; Young et al, 2005). Given the substantive investment of finances, time and resources devoted to developing individual athletes; the importance of effective training practices to enhance performance, reduce injuries, and optimise musculoskeletal robustness are clearly evident (Fortington et al, 2015; Hickey et al, 2014; Moriera et al, 2014; Lauersen, Bertelsen & Andersen, 2014; Gastin et al, 2013; Orchard, Seward & Orchard, 2012). Indeed, elite professional Australian Footballers engage in annual, full-time training and competitive schedules involving high intensity and high volume training loads necessary for elite athletes to elicit desired physiological adaptations (Buchheit, Morgan, Wallace, Bode & Poulos, 2015; Bilsborough et al, 2014a; Colby et al, 2014; Coutts et al, 2014; Moriera et al, 2014; Buchheit et al, 2013; Rogalski et al, 2013). However, this training-performance, dose-response relationship is complex, requiring careful manipulations of training volume and intensity with short-term unloading periods as a mechanism to maintain the precarious position between under- and over-training. Owing to the sustained evolution of Australian Football; physiological demands are highly variable, complicating physical development and injury reduction endeavors within the confines of scarce time and resource availability (Kempton et al, 2015; Rogalski et al, 2013; Orchard, Seward & Orchard, 2012; Norton, Craig & Olds, 1999). Accordingly, practitioners must establish tightly controlled and individualised load monitoring and management practices which deliver appropriate mechanical dosages to each athlete within their own physical capacities and musculoskeletal tolerance levels that promote positive adaptation in the absence of injury.

Muscle and bone are highly adaptive, structurally dynamic and metabolically active biomaterials, inextricably linked by anatomical, mechanical, metabolic and pleiotropic functions (Cianferotti & Brandi, 2014; Ireland, Rittweger & Degens, 2014; Kaji, 2014; Lloyd et al, 2014; Hamrick, 2012; Karasik & Cohen-Zinder, 2012; LeBlanc et al 2007; Schoenau, 2005). Specifically, the structure, size and strength of musculoskeletal tissues are reliant upon, and responsive to the physiological and mechanical demands placed upon them; thus the prevalence or absence of mechanical stimuli can deliver hypertrophic or atrophic signals to muscle and bone respectively, creating anabolic or catabolic adaptational microenvironments (Girgis, Mokbel & DiGirolamo, 2014; Ireland, Rittweger & Degens, 2014; Ju et al, 2014; Wall et al, 2014; Gomez-Cabello et al, 2012; Klein-Nulend, Bacabac & Bakker, 2012; Belavy, Armbrecht, Richardson, Felsenberg & Hides, 2011b; Chen et al, 2010; Skerry, 2006; Warner, Shea, Miller & Shaw 2006; Frost, 2004; Giangregorio & Blimkie, 2002). Indeed, sports participation itself is considered to be highly beneficial to muscle-bone development, owing to the adaptability and responsiveness of these biomaterials to increases in habitual mechanical loads (Warden & Roosa, 2014; Greene et al, 2012; Tveit et al, 2012; Weidauer et al, 2012; Quiterio et al, 2011; Rantalainen et al, 2011a; Janz et al 2006; Ducher et al, 2005; Janz et al, 2004; Nevill, Holder & Stewart, 2004; Kontulainen et al, 2003; Modlesky & Lewis, 2002; Petit et al, 2002). Specifically, sporting activities share similar myogenic and osteogenic traits with prescribed multi-modal exercise (Section 2.4.2.5), involving combinations of impact-, resistance- and locomotive-based exercise to deliver high magnitudes and rates of strain with unusual distributions through impact, muscular and gravitational loads under training and competitive contexts (Weidauer et al, 2014; Nilsson et al, 2013; Schipilow et al, 2013; Weidauer et al, 2012; Nikander et al, 2010a; Nikander et al, 2010b; Rantalainen et al, 2011b; Rantalainen et al,

2010a; Rantalainen et al, 2010b; Nikander et al, 2006; Bass et al, 2002; Nara-Ashizawa et al, 2002). Subsequently, the plastic properties of muscle and bone to regular mechanical stimuli provides practitioners with a modifiable characteristic to screen, monitor and target with exercise interventions as an adjunctive modality alongside sports participation to optimise the physical resilience of athletes, or minimise tissue disruption following injury.

Sport participation delivers mechanical loads that are highly dependent upon the nature and style of the chosen competition; specific to the unique objectives, rules, regulations, field dimensions, participant numbers and tactics used within it. Indeed, hypertrophic benefits conferred to the musculoskeletal system under various contexts are a result of the distinct impact, muscular and gravitational loading profiles of the sport itself (Rantalainen et al, 2011a; Rantalainen et al, 2010a; Nikander et al, 2006). Categorically, Australian Football is considered an odd-impact sport with athletes routinely exposed to various, unpredictable and volatile lower-body loading patterns spanning from cyclical low-grade forces when walking or running, to sudden high-grade forces when jumping, landing, kicking or changing direction. Consequently, Australian Footballers experience compressive, torsional, transverse and tensile loads in combination and in isolation, exposing the skeleton to stimuli that can lead to positive bone-specific and site-specific adaptations; or in the absence of suitable conditioning, recovery and nutrition, an increased likelihood of lower limb injury (Hughes et al, 2014; Schipilow et al, 2013; Clansey et al, 2012; Moran et al, 2012a; Moran et al, 2012b; Rantalainen et al, 2011b; Ekstrand & Torstveit, 2010; Nikander et al, 2010a; Milgrom et al, 2002). Unfortunately, longitudinal investigations into muscle-bone adaptations in field-based team-sports through-out annual programs remain scarce (Georgeson et al, 2012; Beck & Doecke, 2005), rendering the association between sports participation and musculoskeletal adaptation or maladaptation unclear.

Australian Football provides players with prolonged exposure to myogenic and osteogenic mechanical environments similar to other field-based team-sports (Baker, 2013; Hart et al, 2014a; Hart, Dobbin, Weber, Nimphius & Newton, 2013a; Hart et al, 2013b; McMaster, Gill, Cronin & McGuigan, 2013; Nilsson et al 2013; Appleby, Newton & Cormie, 2012; Georgeson et al, 2012; Nimphius, Hart & Newton, 2012; Quiterio et al, 2011; Baker & Newton, 2008; Baker & Newton, 2006; Daly & Bass, 2006; Suominen, 2006; Vicente-Rodríguez, 2006; Beck & Doecke, 2005; Nevill, Holder & Stewart, 2004; Godfrey, Madgwick & Whyte, 2003). While numerous cross-sectional and context-specific Australian Football studies demonstrate favourable musculoskeletal properties comparative to other populations with others demonstrating larger conferred benefits to Australian Footballers of higher training age than lower training age (evident in Chapter 3; Bilsborough et al, 2014a; Gastin, et al 2013; Hart et al, 2013c; Veale et al, 2010; Young et al, 2005); there is a distinct absence of longitudinal or seasonal investigations. Consequently, it is not yet known whether annual participation at the elite level of Australian Football confers aggregate seasonal improvements, maintenance or decrements in lower-body musculoskeletal characteristics to players; thus the relationship between seasonal muscle-bone adaptations to seasonal game-based and training-based loading schemes require scientific investigation. Specifically, this study serves to quantify the lower-body musculoskeletal characteristics of elite Australian Footballers following a full in-season and off-season annual program in order to examine: 1) whether Australian Footballers positively or negatively adapt to seasonal loading demands; 2) whether differential adaptations between limbs exist across each season; and 3) whether a detraining effect results following a self-guided and unmonitored off-season training program.

5.2. Methods

5.2.1. Subjects

Forty (n = 40) elite Australian Football players were recruited from the Australian Football League (AFL) for participation in this study to quantify in-season adaptations (Table 24), with only twenty-two (n = 22) players retained to quantify off-season adaptations due to club-imposed restrictions (Table 25). Athletes with lower limb injuries or contraindications requiring immobilisation within 3 months prior to data collection; or with metallic surgical implants located beneath the trunk were excluded from analysis. Players wore their club-issued football shorts during the data collection process and were notified of the potential risks involved. Data collection and management procedures conformed to the Code of Ethics (World Medical Association), Declaration of Helsinki, with ethics approval provided by Edith Cowan University's Human Research Ethics Committee.

Table 24. **Descriptive characteristics of forty (n = 40) elite Australian Footballers at the beginning and end of an AFL in-season phase (~26 weeks).**

	Baseline	Change	SWC	Effect
Age (yr)	23.0 (± *3.6*)	+ 0.44 **	± 0.10	0.14
Height (cm)	187.7 (± *6.7*)	± 0.00	± 0.00	0.00
Weight (kg)	84.0 (± *6.6*)	+ 2.06 **	± 0.49	0.32 c
BMI (kg/m^2)	23.9 (± *1.5*)	+ 0.57 **	± 0.13	0.42 c
Bone Mass (%)	4.2 (± *0.3*)	+ 0.02 **	± 0.02	0.07
Lean Mass (%)	85.8 (± *1.4*)	– 0.64 **	± 0.19	0.53 c
Fat Mass (%)	10.0 (± *1.4*)	+ 0.62 **	± 0.20	0.46 c
Tibial Length (mm)	430.2 (± *26.3*)	± 0.00	± 0.00	0.00

Note: Values reported as Mean (± SD); BMI = body mass index; Bone Mass = whole-body bone mineral content; SWC = smallest worthwhile change; Effect = effect size; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 25. **Descriptive characteristics of twenty-two (n = 22) elite Australian Footballers at the beginning and end of an AFL off-season phase (~10 weeks).**

	Baseline	Change	SWC	Effect
Age (yr)	22.3 (± *3.3*)	+ 0.22 **	± 0.08	0.09
Height (cm)	188.2 (± *6.4*)	± 0.00	± 0.00	0.00
Weight (kg)	84.7 (± *6.9*)	+ 0.25	± 0.30	0.04
BMI (kg/m^2)	23.9 (± *0.9*)	+ 0.08	± 0.09	0.12
Bone Mass (%)	4.2 (± *0.3*)	– 0.04 **	± 0.02	0.15
Lean Mass (%)	84.9 (± *1.5*)	– 0.72 **	± 0.25	0.56 c
Fat Mass (%)	10.9 (± *1.6*)	+ 0.77 **	± 0.25	0.51 c
Tibial Length (mm)	432.8 (± *6.7*)	± 0.00	± 0.00	0.00

Note: Values reported as Mean (± SD); BMI = body mass index; Bone Mass = whole-body bone mineral content; SWC = smallest worthwhile change; Effect = effect size; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

5.2.2. Experimental Design

This longitudinal study spanned over complete in-season (~26 week) and off-season (~10 week) programs within the elite AFL competition. This required three collection periods: 1) start of competitive season; 2) end of competitive session, start of off-season; and 3) end of off-season. Collection phases commenced with anthropometric measures including height, weight and tibial length, followed by a series of whole-body composition and lower-body bone densitometry scans. Specifically, whole-body and segmental appendicular mass (lean, fat, bone and total) was examined using Dual-energy X-ray Absorptiometry (DXA); while lower-body bone material, structure and strength measures were assessed using peripheral Quantitative Computed Tomography (pQCT). All anthropometry measurements, bone densitometry operations and analyses, and percent change calculations were performed in accordance with descriptions and illustrations provided in prior sections 3.2.3 (Anthropometry), 3.2.4 (Scan Procedures) and 3.2.5 (Symmetry Index) respectively.

5.2.3. Statistical Analysis

Dependent (paired) t-tests were conducted to determine whether significant differences were evident following one in-season and off-season phase for: 1) subject characteristics 2) muscle-bone characteristics of the kicking limb; 3) muscle-bone characteristics of the support limb; and 4) symmetry index. Independent t-tests were also conducted to determine whether significant differences were evident between the kicking and support limbs with-in each group for all muscle-bone characteristics for each season. Post-hoc adjustment for multiple comparisons was performed using Holm-Bonferonni Sequential Corrections. Effect sizes were calculated for all comparisons (Cohen, 1988) to determine the magnitude of difference between variables in accordance with Hopkins (2002): $d \geq 0.2$ is small; $d \geq 0.6$ is moderate; $d \geq 1.2$ is large; $d \geq 2.0$ is very large. Smallest worthwhile changes (SWC) for each seasonal phase and all variables were calculated in accordance with Hopkins (2004) as 20% of the between-subject standard deviation of seasonal adaptations (0.2 x SD). Statistical computations were performed using SPSS (Version 17.0; Chicago, IL).

5.3. Results

Baseline and post-season descriptive characteristics of elite Australian Footballers following an in-season and off-season competitive phase are provided in Table 1 and Table 2 respectively. Players were ~2 kg heavier following the in-season, with body mass remaining relatively stable during the off-season. While absolute mass increased, relative expressions of composite tissues changed both positively and negatively throughout. Specifically, soft-tissues uniformly changed across both periods with relative increases in fat mass and relative decreases in lean mass of small effect ($d = 0.32 – 0.56$). In contrast, while there was a relative increase in bone mass during the in-season phase; this was counterbalanced by a relative decline in bone mass during the off-season phase.

5.3.1. In-season Adaptations

Muscle-bone characteristics and adaptations following the in-season are provided in Tables 26, 27 and 28; with asymmetrical material and structural adaptations illustrated between the kicking and support limbs in Figure 30. Favourable osteogenic adaptations were apparent across both limbs despite notably different morphological changes between limbs. Indeed, the support limb exhibited a broader range of material and structural adaptations at higher magnitudes beyond the smallest worthwhile change than the kicking limb, with a greater emphasis on structural gains; a potent contributor to bone strength. Specifically, total density increased in both limbs as a result of trabecular changes in the kicking limb, and cortical changes in the support limb with small effect (d = 0.22). Marrow density decreased in the kicking limb at a small magnitude (d = 0.26). Structurally, only cortical thickness improved in the kicking leg; whereas trabecular area, total area, periosteal area, endocortical area and cortical thickness all favourably adapted in the support leg. Despite small absolute magnitudes of change, the percent change of skeletal adaptations were significantly different between limbs for trabecular density (p = 0.047; d = 0.47), cortical density (p = 0.023; d = 0.59), total density (p = 0.037; d = 0.51) and trabecular area (p = 0.049; d = 0.46); demonstrating markedly different skeletal responses to in-season participation between limbs.

Bone strength increments of ~44 N and ~50 N were evident for the kicking and support limbs respectively, with small decrements in relative fracture load (d = 0.22 – 0.23), owing to larger concurrent changes in total body mass. While DXA-derived areal measures of bone area and bone mineral content (aBMC) illustrated small magnitude increases (d = 0.25 – 0.47) following the in-season period; no identifiable changes in areal bone mineral

density were apparent despite volumetric evidence supplied by pQCT, highlighting the limitation of aBMD as a surrogate measure of bone strength. Similarly, soft-tissue adaptations were evident in the support leg only, with favourable increases in muscle area and decreases in fat area respectively. No identifiable change in areal measures of lower-body lean or fat mass quantities was evident. Despite small absolute changes in soft-tissue within each limb, the percent change of muscle area between limbs was moderately significant (p = 0.046; d = 0.81), demonstrating asymmetrical adaptations between limbs in response to differential in-season loading patterns.

5.3.2. Off-season Adaptations

Muscle-bone characteristics and seasonal adaptations following the off-season are provided in Tables 29, 30 and 31; with asymmetrical material and structural adaptations illustrated between the kicking and support limbs in Figure 31. A general detraining effect was evident with a notable loss of bone material, reduced muscle mass and geometric re-arrangement of bone structure across both limbs. In particular, material adaptations considerably regressed while structural adaptations were partially preserved or improved over the ~10 week off-season. Specifically, tibial mass, trabecular density, cortical density and total density all decreased beyond the smallest worthwhile change in both limbs; with marrow density increasing in the kicking leg yet decreasing in the support leg. Interestingly, a favourable increase in trabecular area with a reduction in cortical area for the kicking leg were observed; whereas for the support leg, a favourable increase in cortical area with a reduction in trabecular area was observed; possibly a functional adaptation in response to limb recruitment post-season. Although small magnitudes of change were evident, moderate differential adaptations were significant between limbs for percent change in marrow density (p = 0.035; d = 0.68) and trabecular area (p = 0.043; d = 0.67).

Table 26. **Seasonal pQCT derived skeletal adaptations over a ~26 week in-season phase for forty (n=40) elite Australian Footballers.**

	Kicking Leg				Support Leg			
	Baseline	**Change**	**SWC**	**Effect**	**Baseline**	**Change**	**SWC**	**Effect**
MATERIAL PROPERTIES								
Tibial Mass (g/cm)	4.75 (± *0.4*)	+ 0.01 **	± 0.01	0.03	4.78 (± *0.4*)	+ 0.03 **	± 0.01	0.08
Tb.vBMD (mg/cm^3)	301.2 (± *33.8*)	+ 2.25 **	± 0.85	0.07	297.6 (± *33.1*)	+ 0.96	± 1.12	0.03
Ct.vBMD (mg/cm^3)	1121.4 (± *16.6*)	+ 0.18	± 0.98	0.01	1118.4 (± *16.7*)	+ 3.54 **	± 1.41	0.22 c
Ma.vBMD (mg/cm^3)	22.9 (± *7.5*)	– 1.87 **	± 1.29	0.26 c	23.3 (± *8.0*)	+ 0.07	± 0.65	0.01
Tt.vBMD (mg/cm^3)	638.9 (± *45.8*)	+ 1.12 **	± 0.89	0.03	632.8 (± *43.9*)	+ 3.59 **	± 1.24	0.08
STRUCTURAL PROPERTIES								
Tb.Ar (mm^2)	639.8 (± *64.9*)	+ 0.37	± 3.18	0.01	646.9 (± *65.4*)	+ 6.25 **	± 1.82	0.11
Ct.Ar (mm^2)	335.7 (± *28.6*)	+ 0.47	± 0.77	0.02	339.7 (± *30.0*)	+ 0.73	± 1.19	0.06
Ma.Ar (mm^2)	217.7 (± *59.0*)	+ 2.44	± 5.05	0.04	218.5 (± *57.8*)	– 1.06	’± 1.64	0.02
Tt.Ar (mm^2)	862.2 (± *76.9*)	+ 0.36	± 2.34	0.01	875.0 (± *77.7*)	+ 3.18 **	± 1.44	0.04
Ps.Ar (mm)	85.4 (± *4.0*)	+ 0.01	± 0.08	0.03	86.2 (± *4.0*)	+ 0.16 **	± 0.07	0.05
Ec.Ar (mm)	54.0 (± *5.3*)	– 0.04	± 0.12	0.08	54.8 (± *5.2*)	– 0.35 **	± 0.16	0.08
Ct.Th (mm)	5.00 (± *0.5*)	+ 0.01 **	± 0.01	0.02	5.01 (± *0.5*)	+ 0.03 **	± 0.02	0.07
STRENGTH PROPERTIES								
SSI (mm^3)	2535.3 (± *303.1*)	– 7.30	± 9.88	0.03	2630.6 (± *350.9*)	– 7.72	± 9.66	0.02
FL.Ab (N)	5748.4 (± *732.2*)	+ 43.81 **	± 31.65	0.07	5798.6 (± *726.9*)	+ 49.47 **	± 37.85	0.07
FL.Rel (N/kg)	6.97 (± *0.6*)	– 0.12 **	± 0.05	0.22 c	7.04 (± *0.6*)	– 0.13 **	± 0.07	0.23 c
FL Ratio (X/Y)	1.14 (± *0.1*)	+ 0.01 **	± 0.01	0.10	1.16 (± *0.1*)	– 0.01 **	± 0.01	0.10

Note: Values reported as Mean (± SD); Tb = trabecular; Ct = cortical; Ma = marrow; Tt = total; Ps = periosteal; Ec = endocortical; vBMD = volumetric bone mineral density; Ar = area; Th = thickness; SSI = stress-strain index; FL = fracture load; Ab = absolute; Rel = relative; X = medio-lateral, Y = anterio-posterior; effect = effect size; SWC = smallest worthwhile change; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 27. **Seasonal pQCT derived soft-tissue values over a ~26 week in-season phase for forty (n=40) elite Australian Footballers.**

	Kicking Leg				Support Leg			
	Baseline	**Change**	**SWC**	**Effect**	**Baseline**	**Change**	**SWC**	**Effect**
Mu.Ar (mm^2)	8985.6 (± *1327.2*)	+ 27.99	± 79.83	0.02	8913.2 (± *1249.2*)	+ 80.81 **	± 68.09	0.07
Mu.Den (mg/cm^3)	78.2 (± *1.5*)	– 0.16	± 0.47	0.14	78.0 (± *1.7*)	+ 0.16	± 0.43	0.12
Fat.Ar (mm^2)	1175.3 (± *382.6*)	– 37.65	± 67.44	0.11	1131.3 (± *424.7*)	– 76.34 **	± 67.59	0.18

Note: Values reported as Mean (± SD); Mu = muscle; Ar = area; Den = density; effect = effect size; SWC = smallest worthwhile change; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 28. **Seasonal DXA derived values over a ~26 week in-season phase for forty (n=40) elite Australian Footballers.**

	Kicking Leg				Support Leg			
	Baseline	**Change**	**SWC**	**Effect**	**Baseline**	**Change**	**SWC**	**Effect**
BA (cm)	208.4 (± *20.6*)	+ 8.05 **	± 2.44	0.47 c	208.7 (± *19.2*)	+ 3.81 **	± 2.16	0.26 c
aBMC (g)	287.2 (± *38.7*)	+ 11.05 **	± 3.17	0.31 c	286.1 (± *35.6*)	+ 7.39 **	± 3.46	0.25 c
aBMD (g/cm^2)	1.38 (± *0.1*)	± 0.00	± 0.01	0.00	1.37 (± *0.1*)	± 0.00	± 0.01	0.00
Lean Mass (g)	3113.0 (± *328.9*)	+ 11.85	± 21.25	0.04	3136.6 (± *329.2*)	+ 12.66	± 20.17	0.04
Fat Mass (g)	387.1 (± *95.9*)	+ 2.83	± 13.18	0.04	370.8 (± *98.3*)	+ 8.97	± 12.08	0.09

Note: Values reported in absolute values as Mean (± SD); BA = bone area; aBMC = areal bone mineral content; aBMD = areal bone mineral density; effect = effect size; SWC = smallest worthwhile change; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 29. **Seasonal pQCT derived skeletal adaptations over ~10 week off-season phase for twenty-two (n=22) elite Australian Footballers.**

	Kicking Leg				Support Leg			
	Baseline	**Change**	**SWC**	**Effect**	**Baseline**	**Change**	**SWC**	**Effect**
MATERIAL PROPERTIES								
Tibial Mass (g/cm)	4.71 (± *0.3*)	– 0.01 **	± 0.01	0.03	4.75 (± *0.3*)	– 0.01 **	± 0.01	0.03
Tb.vBMD (mg/cm³)	301.8 (± *34.0*)	– 1.21 **	± 0.56	0.04	296.2 (± *35.4*)	– 1.22 **	± 0.49	0.04
Ct.vBMD (mg/cm³)	1121.1 (± *16.4*)	– 1.56 **	± 1.05	0.10	1123.9 (± *13.3*)	– 3.94 **	± 1.35	0.31 c
Ma.vBMD (mg/cm³)	21.0 (± *7.7*)	+ 1.67 **	± 0.60	0.09	22.4 (± *7.6*)	– 1.48 **	± 0.93	0.21 c
Tt.vBMD (mg/cm³)	640.1 (± *44.9*)	– 1.21 **	± 0.56	0.03	636.9 (± *40.2*)	– 1.30 **	± 0.85	0.04
STRUCTURAL PROPERTIES								
Tb.Ar (mm²)	629.9 (± *60.9*)	+ 4.17 **	± 3.14	0.07	645.6 (± *61.2*)	– 6.07 **	± 2.90	0.10
Ct.Ar (mm²)	332.1 (± *29.5*)	– 0.36	± 0.87	0.01	335.2 (± *27.4*)	+ 1.44 **	± 0.79	0.06
Ma.Ar (mm²)	219.2 (± *60.3*)	– 1.18	± 2.31	0.02	218.6 (± *64.7*)	+ 4.81 **	± 3.53	0.07
Tt.Ar (mm²)	851.5 (± *76.6*)	+ 2.94 **	± 2.34	0.04	868.2 (± *77.4*)	– 2.92 **	± 2.33	0.04
Ps.Ar (mm)	85.0 (± *3.9*)	– 0.02	± 0.07	0.00	85.6 (± *3.9*)	+ 0.18 **	± 0.06	0.05
Ec.Ar (mm)	53.7 (± *5.0*)	+ 0.04	± 0.12	0.00	54.2 (± *4.9*)	+ 0.10	± 0.12	0.02
Ct.Th (mm)	4.99 (± *0.4*)	– 0.01	± 0.02	0.03	5.01 (± *0.4*)	+ 0.01	± 0.02	0.02
STRENGTH PROPERTIES								
SSI (mm³)	2484.4 (± *306.6*)	– 7.48	± 9.08	0.03	2577.5 (± *333.1*)	+ 3.14	± 9.91	0.01
FL.Ab (N)	5622.7 (± *727.9*)	– 42.46 **	± 36.09	0.06	5699.7 (± *630.8*)	– 3.10	± 24.75	0.00
FL.Rel (N/kg)	6.75 (± *0.4*)	– 0.08 **	± 0.05	0.22 c	6.85 (± *0.4*)	± 0.00	± 0.04	0.00
FL Ratio (X/Y)	1.16 (± *0.1*)	+ 0.01 **	± 0.01	0.10	1.16 (± *0.1*)	+ 0.02 **	± 0.01	0.20 c

Note: Values reported as Mean (± SD); Tb = trabecular; Ct = cortical; Ma = marrow; Tt = total; Ps = periosteal; Ec = endocortical; vBMD = volumetric bone mineral density; Ar = area; Th = thickness; SSI = stress-strain index; FL = fracture load; Ab = absolute; Rel = relative; X = medio-lateral, Y = anterio-posterior; effect = effect size; SWC = smallest worthwhile change; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 30. **Seasonal pQCT derived soft-tissue values over ~10 week off-season phase for twenty-two (n=22) elite Australian Footballers.**

	Kicking Leg				Support Leg			
	Baseline	**Difference**	**SWC**	**Effect**	**Baseline**	**Difference**	**SWC**	**Effect**
Mu.Ar (mm^2)	8746.3 (± *1230.9*)	– 110.08 **	± 70.61	0.09	8753.6 (± *1211.1*)	– 121.00 **	± 58.73	0.10
Mu.Den (mg/cm^3)	78.6 (± *1.1*)	– 0.32 **	± 0.22	0.34 c	78.6 (± *1.3*)	– 0.90 **	± 0.43	0.67 c
Fat.Ar (mm^2)	1236.8 (± *372.2*)	+ 125.00 **	± 47.81	0.34 c	1184.5 (± *457.9*)	+ 145.57 **	± 65.08	0.33 c

Note: Values reported as Mean (± SD); Mu = muscle; Ar = area; Den = density; a = statistical significance (p ≤ 0.01); SWC = smallest worthwhile change; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

Table 31. **Seasonal DXA derived shank values over a ~10 week off-season phase for twenty-two (n=22) elite Australian Footballers.**

	Kicking Leg				Support Leg			
	Baseline	**Difference**	**SWC**	**Effect**	**Baseline**	**Difference**	**SWC**	**Effect**
BA (cm)	203.7 (± *33.5*)	+ 2.03 **	± 1.64	0.06	204.2 (± *29.2*)	+ 3.21 **	± 1.65	0.12
aBMC (g)	277.9 (± *43.0*)	+ 1.53	± 2.22	0.04	279.4 (± *42.6*)	+ 1.81	± 2.34	0.04
aBMD (g/cm^2)	1.31 (± *0.2*)	– 0.01 **	± 0.01	0.06	1.32 (± *0.2*)	– 0.01 **	± 0.01	0.06
Lean Mass (g)	2937.5 (± *451.0*)	– 31.10 **	± 17.54	0.07	2938.8 (± *435.7*)	– 13.21 **	± 12.44	0.03
Fat Mass (g)	384.1 (± *114.1*)	+ 52.61 **	± 10.23	0.48 c	382.7 (± *123.3*)	+ 16.48 **	± 6.90	0.15

Note: Values reported in absolute values as Mean (± SD); BA = bone area; aBMC = areal bone mineral content; aBMD = areal bone mineral density. SWC = smallest worthwhile change; ** = actual change ≥ SWC; * = statistical significance (p ≤ 0.05); a = large effect size (d ≥ 1.2); b =moderate effect size (d ≥ 0.6); c = small effect size (d ≥ 0.2).

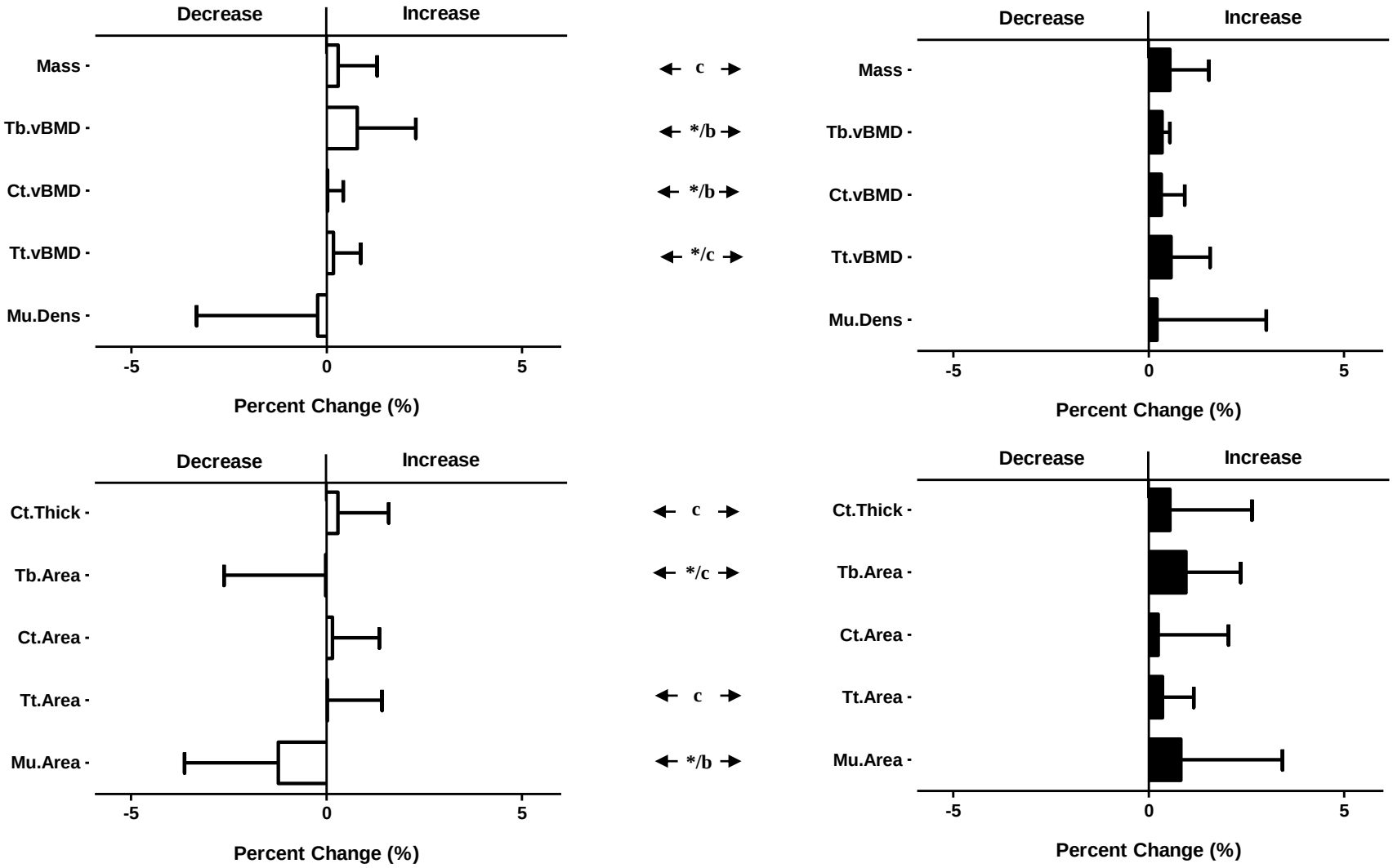


Figure 30. **Material (top) and structural (bottom) adaptations of the kicking (white) and support (black) limbs over a ~26 week in-season, expressed as percent change: * = statistical significance ($p \leq 0.05$), a = large effect ($d \geq 1.2$), b = moderate effect ($d \geq 0.6$), c = small effect ($d \geq 0.2$).**

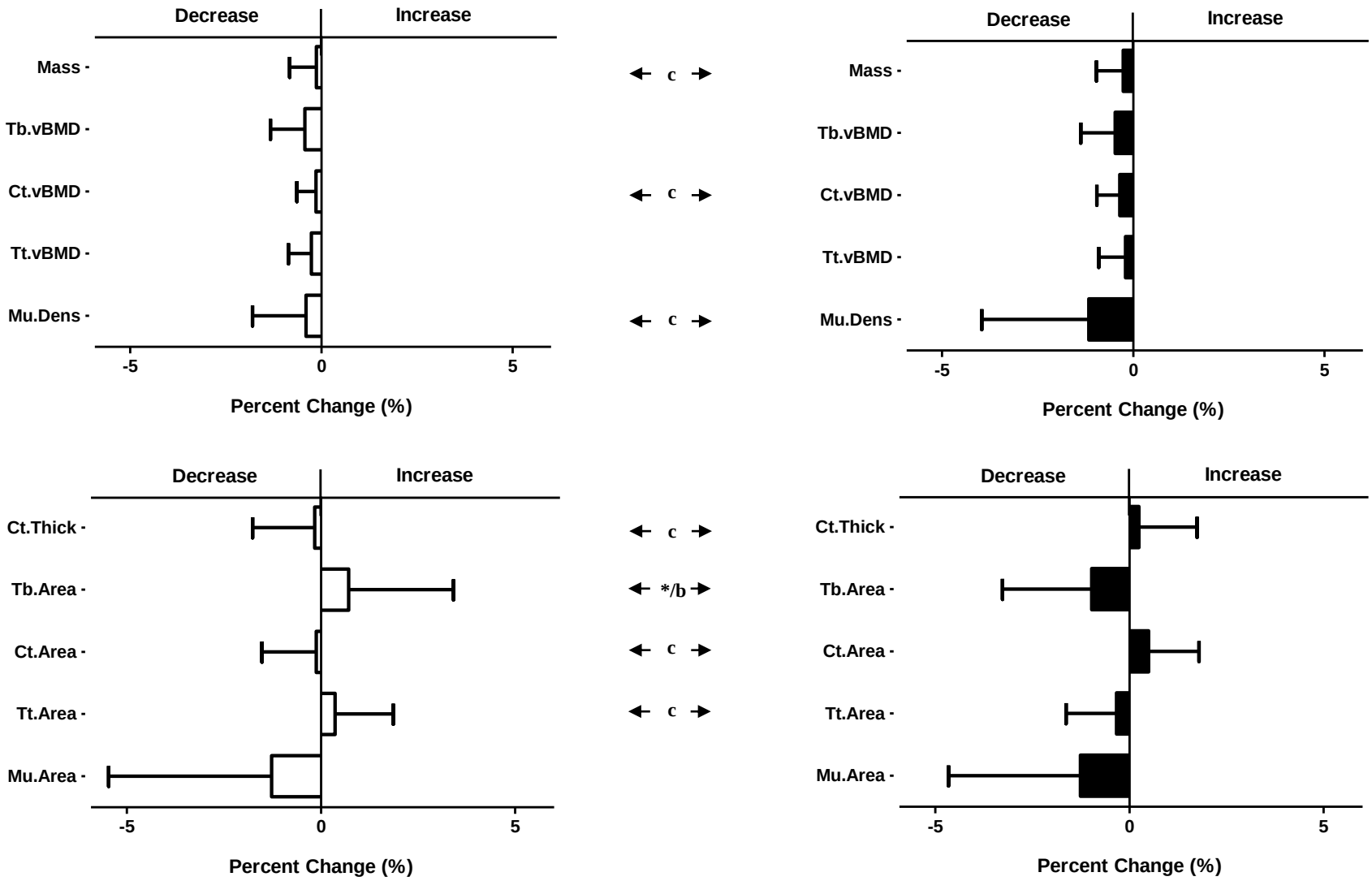


Figure 31. **Material (top) and structural (bottom) adaptations of the kicking (white) and support (black) limbs over a ~10 week off-season, expressed as percent change: * = statistical significance ($p \leq 0.05$), a = large effect ($d \geq 1.2$), b = moderate effect ($d \geq 0.6$), c = small effect ($d \geq 0.2$).**

Asymmetrical material and structural changes produced different bone strength adaptations between limbs. Specifically, the kicking limb weakened in absolute and relative terms, reversing the osteogenic response provided during the in-season phase; whereas the support limb preserved and maintained its strength, potentially due to an increase in periosteal area despite concurrent endocortical resorption; an indication of new bone formation to widen the cortex. Furthermore, DXA measures generally agreed with pQCT, demonstrating a subtle increase in bone area and decrease in bone density, commensurate with the smallest worthwhile change; with a slightly larger change in bone area noted for the support limb. Soft-tissue adaptations were similar between limbs, with a notable loss of muscle area, muscle density and muscle mass; in addition to a notable gain of fat area and fat mass; evidently undesirable adaptations indicating a detraining effect on soft-tissue as well. Despite small absolute changes in soft-tissue within each limb tracking negatively together, the differences in percent change of muscle density between limbs was still of a small magnitude (d = 0.34).

5.4. Discussion

Musculoskeletal robustness and physical resilience are the developmental cornerstones of injury prevention and performance enhancement strategies in elite Australian Football. Unfortunately, the unique seasonal configuration of the elite competition severely complicates interventional and managerial endeavours for strength and conditioning practitioners striving to develop and improve often disparate physical requirements and athletic components of players (Kempton et al, 2015; Bilsborough et al 2014a; Gastin et al, 2014; Hart et al, 2014a; Hart et al, 2014b; Gastin et al, 2013; Wong, Chaouachi, Chamari, Dellal & Wisloff, 2010; Pyne et al, 2008; Young & Pryor, 2007; Gamble, 2006; Pyne et al, 2006; Pyne et al, 2005; Young et al, 2005; Gamble, 2004; Baker, 2001). Accordingly,

strength and conditioning practitioners must manipulate their training programs differently through-out the preseason, in-season and off-season periods to account for numerous time, travel and resource restrictions. Subsequently, different seasonal adaptations will arise to deliver progressive, neutral and regressive musculoskeletal adaptations across the preseason, in-season and off-season respectively; producing a training, maintenance or detraining effect (Buchheit et al, 2015; Koundourakis et al, 2014; Moreira et al, 2014; Buchheit et al, 2013; Georgeson et al, 2012; Weiler, Keen & Wolman, 2012; Rønnestad, Nymark & Raastad, 2011; Hansen, Cronin, Pickering & Newton, 2011; Chad, 2010; Wong et al, 2010; Hoffman et al, 2009; Kelly & Coutts, 2007; Gamble, 2006; Gabbett, 2005; Moore, Hickey & Reiser, 2005; Gabbett, 2004; Baker, 2001; Baker, 1998). Indeed, the explicit aim of strength and conditioning practitioners in this environment is to optimise and maintain physical development during the preseason and in-season respectively, whilst minimising physical deterioration during the off-season. Unfortunately, limited investigations exist which canvas seasonal musculoskeletal adaptations in field-based team-sports (Appleby, Newton & Cormie, 2012; Georgeson et al, 2012; Beck & Doecke, 2005; Bolonchuk, Lukaski & Siders, 1991), with an evident absence in Australian Football. As a result, this study quantified the lower-body musculoskeletal changes of elite Australian Footballers during the course of an in-season and off-season phase, demonstrating unique and specific material and structural adaptations to each limb and each phase within an annual plan respectively.

5.4.1. In-season Adaptations

Australian Football traditionally includes an in-season spanning ~23 to 26 weeks of competitive matches; the length of which is reliant upon qualification into, and progression through the finals campaign. Subsequently, training sessions reduce from ~3 – 4 sessions

per week during the preseason to ~1 – 2 sessions per week with competitive matches during the in-season. As a result, training structure and composition shifts emphasis from developing physical capacity and musculoskeletal resilience during the preseason, to preparing for competition and promoting recovery between matches during the in-season (Georgeson et al, 2012; Kelly & Coutts, 2007; Gamble, 2006). Accordingly, previous levels of musculoskeletal mass, size and strength established during the preseason could become compromised owing to a reduction in training volume and intensity, or could continue to experience myogenic and osteogenic adaptations in response to benefits afforded by multi-modal exercise (Section 2.4.2.5) and sports participation (Section 2.4.2.6) abundantly prevalent in an Australian Football in-season. Indeed, muscle and bone adapt at different rates (Lloyd et al, 2014; Wall et al, 2014; Evans et al, 2012; DeFreitas et al, 2011; Berg et al, 2007; Seynnes, de Boer & Narici, 2007; Abe et al, 2000; Cullen, Smith & Ahkter, 2000); whereby the length of an Australian Football in-season may prove insufficient in time to see considerable changes in skeletal properties using DXA or pQCT despite potentially marked changes in soft-tissue properties. Instead, subtle skeletal changes may indicate trending data which if extrapolated over time, could lead to marked adaptational differences between limbs; general osteogenic benefits to the skeleton; and could indicate the prevalence of early, significant and important microscopic changes not detectable by these two technologies (Popp et al, 2014; Liu et al, 2010; Lala et al, 2014; Lala et al, 2012; Boutroy et al, 2005).

Lower-body morphological adaptations were evident for the in-season phase in the current study, with asymmetrical responses apparent between kicking and support limbs. Expectantly, the magnitude of adaptation was trivial to small across both limbs but with

many material, structural and strength characteristics exceeding the smallest worthwhile change; indicating a preliminary maintenance or favourable osteogenic effect in response to participation in elite training and competition practices. Despite general improvements for both limbs; in accordance with our earlier study (Section 3.4.2.), the support limb exhibited higher magnitude changes than the kicking limb for bone mass, density and cross-sectional area; promoting the osteogenic potency of regular high impact, gravitational and muscular forces on the skeleton. Specifically, the support limb developed notably higher tibial mass, trabecular area and cortical density than the kicking limb; all preferential adaptations resulting from larger volumes of axial compression and bending moments commensurate with gravitational, impact loading (Nilsson et al, 2014; Warden et al, 2014; Weidauer et al, 2014; Schipilow et al, 2013; Weatherhold, Fuchs & Warden, 2013; Lynch et al, 2011; Judex & Carlson, 2009; Ural & Vashishth, 2006; Pearson & Leiberman, 2004; Petit et al, 2002; Haapasalo et al, 2000). Similarly, the support limb displayed larger increases in periosteal area and larger decreases in endocortical area; indicating new bone formation at periosteal and endosteal regions to concomitantly thicken and widen the cortex; improving structural resistance to stress (Fonseca et al, 2014; Ireland, Rittweger & Demens 2014; Ireland et al, 2013; Kato, Niwa, Yamashita, Matumoto & Umemura, 2014; Melo et al, 2012; Fan et al, 2011; Ireland et al, 2011; Martin & Correa, 2010; Seeman, 2008b; Bouxsein & Karasik, 2006; Davison et al, 2006; Friedman, 2006; Warden et al, 2005; Ammann & Rizzoli, 2003; Bass, 2003).

Bone strength increased across both limbs at a similar magnitude despite different morphological adaptations, achieving higher absolute fracture loads. This is intriguing given the support limb contained greater material and structural improvements; however also unsurprising, as each limb was differentially loaded and so will uniquely adapt to

increase skeletal strength. Further, bones tend to adapt differently along the slenderness-robustness continuum (Jepsen et al, 2013; Wallace et al, 2012; Jepsen et al, 2011; Tommasini et al, 2008; Jepsen et al, 2007; Tommasini et al, 2007; Tommasini et al, 2005); as the support limb is more robust than the kicking limb, this may also explain the different adaptational strategies of each limb to confer strength to the skeleton. Despite the trivial to small absolute adaptations within each limb; their unique morphological profiles were further evident when comparing percent changes (Figure 1); with small and moderately significant adaptational differences in nearly all material and structural variables between limbs. Over time, these trends would continue to extrapolate to greater significance, as evidenced in Chapter 3. Surprisingly, despite an approximate ~2 kilogram increase in total body mass; only the support limb showed slightly greater muscle area and lower fat area beyond the smallest worthwhile change, with no change in the kicking limb. This could be undesirable as rapid increments in mass above the shank segments may generate higher repetitive stresses during low-grade cyclical activities known to predispose athletes to overuse skeletal injury, evidenced by the reductions in relative fracture load.

5.4.2. Off-season Adaptations

Collective bargaining agreements (CBA) established between the players association (AFLPA) and the Australian Football League (AFL) defines the explicit nature of interaction allowable between players and football clubs during the off-season period (AFL-AFLPA, 2011). Specifically, players cannot be monitored, investigated or contacted by any member of the football club regarding their training behaviour, requiring football clubs to trust players to attentively and conscientiously self-manage their own motivation and compliance levels, as well as correctly self-guide their exercise progressions inherent within their training programs. Indeed, failure to adhere to training programs during the

offseason has potentially deleterious musculoskeletal consequences for players, likely resulting in a detraining effect with the potential to completely reverse positive adaptations experienced during the in-season; the explicit preventative goal of strength and conditioning practitioners (Buchheit et al, 2015; Koundourakis et al, 2014; Smart & Gill, 2013; Weiler, Keen & Wolman, 2012; Caldwell & Peters, 2009; Hoffman et al, 2009). This is particularly important in team-based field-sports as musculoskeletal deterioration will heighten injury risk during the subsequent preseason, which may predispose footballers to higher rates and severities of acute or traumatic injuries; a consequence of weakening biomaterial in combination with the reintroduction of excessively volatile or incremental loads (Buhcheit et al, 2015; Lauersen, Bertelsen & Andersen, 2014; Weiler, Keen & Wolman, 2012).

Muscle-bone loss occurs more rapidly than accrual at an approximate rate of 3:1, with measurable and significant losses of muscle and bone evident within 5 to 14 days of disuse respectively (Lloyd, et al, 2014; Wall et al, 2013; Seynnes, de Boer & Narici, 2007; Abe et al, 2000; Cullen, Smith & Akhter, 2000), highlighting the enormous challenge for strength and conditioning practitioners to prevent deterioration over a seventy day (~10 week) off-season. Expectantly, despite the provision of self-guided training programs, elite Australian Footballers in this study experienced notable detraining in muscle and bone across material and structural parameters for both limbs. While the breadth and depth of skeletal deterioration differed between material and structural properties; morphological detraining between kicking and support limbs was also intriguingly different. Specifically, nearly all material components (mass and density) decreased by a similar yet opposite magnitude to the benefits conferred during the in-season; a concerning and counterproductive regression. Conversely, most structural components (area and thickness) were maintained or increased,

with the exception of trabecular area in the support leg. Indeed, the preservation of structural properties despite concurrent material loss is fortunate given that cross-sectional area is a potent contributor to bone strength (Fonseca et al, 2014; Bouxsein & Karasik, 2006; Davison et al, 2006; Friedman, 2006; Weidauer et al, 2012; Warden et al, 2005; Ammann & Rizzoli, 2003; Danova et al, 2003; Orwoll, 2003); while somewhat expected, given that material is a more volatile and transient component of skeletal morphology in contrast to structural configurations during detraining, disuse or ageing (Nilsson et al, 2014; Warden et al, 2014; Warden & Roosa, 2014; Bloomfield, 2010; Honda, Sogo, Nagasawa, Kato & Umemura, 2008; Umemura , Nagasawa, Sogo & Honda, 2008; Nordstrom, Olsson & Nordstrom, 2005; Fujie et al, 2004).

Bone strength alterations varied between the kicking and support limbs, primarily in response to differences in structural preservation and adaptation. Specifically, the kicking limb only increased trabecular area; whereas the support limb increased cortical area and periosteal area with new bone formation increasing cortical thickness. As a result, the kicking limb weakened over the offseason while the support limb maintained its strength. Despite the trivial to small absolute changes of each limb; their distinct morphological profiles were further evident when comparing percent changes (Figure 2); with small and moderately significant differences in several material and most structural variables between limbs. Interestingly, trabecular and cortical adaptations were specific to each limb during the in-season and off-season which may be a consequence of function. Indeed, the kicking limb is routinely loaded at the highly trabecular ankle-foot complex when striking a ball; whereas the support limb is commonly loaded in axial compression during unilateral planting and jumping activities with bending moments promoting cortical expansion. Intriguingly, independent increases in trabecular and cortical density during the in-season

converted into limb-specific increases in trabecular and cortical area following the off-season; a possible sequential morphological change where material gains precede structural gains in a macroscopic and site-specific manner. Expectantly, undesirable changes in soft-tissue composition were evident over the offseason with decreases in muscle area, density and mass commensurate with increases in fat area and mass; indicative of deconditioning.

Musculoskeletal adaptations evident during in-season and off-season phases occur with the caveat that two different cohorts were used. Although forty athletes were used to describe in-season adaptations, only twenty-two athletes were permitted to attend an additional collection session to describe off-season adaptations due to club restrictions. Regardless, the general relationship and morphological changes between the in-season and off-season provide a unique insight into training and de-training effects evident during these seasonal periods. It is a strength of the current study to have a large cohort (n = 40) of elite athletes monitored over ~26 weeks, and a moderate cohort (n = 22) further monitored over an additional ~10 weeks to deliver a robust and comprehensive description of muscle and bone adaptation during these phases. Further strengths of this study include the novel application of pQCT to elite Australian Football athletes at multiple stages of their annual program; as well as the between-limb comparison of morphological lower-body adaptations based on differential loading patterns through-out an in-season and off-season period.

5.4. Summary

Training structure and composition differ across the preseason, in-season and off-season periods in Australian Football, complicating efforts to aggregately develop and improve musculoskeletal robustness overtime. While the preseason forms the primary developmental phase to optimise physical resilience and conditioning; adaptations may be

compromised or maintained during the in-season and off-season owing to reduced training loads, evidenced by Australian Footballers in this study. In particular, players produced contrasting adaptations between the in-season and off-season, whilst producing asymmetrical changes in muscle-bone morphology between kicking and support limbs. Specifically, participation in an elite Australian Football in-season produced favourable yet subtle skeletal increases in lower-body material and structural properties for each limb; with larger magnitudes and broader ranges of morphological adaptations evident in the support limb, particularly specific to cross-sectional area in only ~26 weeks. Unfortunately, an elite Australian Football off-season was partially regressive, producing a detraining effect by reversing most material adaptations established during the in-season while also reducing muscle area and mass at the expense of increased fat area and mass in only ~10 weeks. Fortunately, there was a preservation of structural properties in the kicking leg and a sustained increase in structural properties in the support leg. Indeed, during the off-season, bone strength developed in the in-season was completely reversed for the kicking leg yet was wholly maintained by the support leg. Accordingly, the favourable osteogenic adaptations of the support limb during the in-season coupled with its preservation of strength during the off-season promotes the osteogenic potency of regular impact-based gravitational loading experienced by the support limb. Furthermore, these differential adaptations illustrate disparities between kicking and support limb which might explain developmental asymmetries when extrapolated overtime in accordance with training age and training exposure. If available, future studies could utilise HR-pQCT technology to identify early microarchitectural adaptations prevalent in this population over similar time periods.

6.0 – CHAPTER SIX – SUMMARY / CONCLUSIONS

The purpose of this thesis was to examine the association between lower-body bone strength and lower-body loading patterns with injury risk and seasonal adaptations in field-based team-sports. In particular, the series of studies in this thesis comprehensively examined lower-body musculoskeletal properties of Australian Football athletes using sophisticated imaging techniques to provide two-dimensional and three-dimensional representations of muscle and bone morphology. These detailed lower-body examinations provided unique insights into modifiable and trainable musculoskeletal components, identifying common factors that may predispose Australian Footballers to heightened injury risk or alternatively promote athlete resilience and physical robustness. Accordingly, this thesis provides information designed to guide prophylactic and remedial programs devised by strength and conditioning practitioners through the provision of measureable and targetable musculoskeletal parameters discoverable during routine screening procedures. Three expansive studies were designed to quantify muscle-bone morphology in order to examine the: 1) influence of training age and limb function on musculoskeletal development; 2) morphological parameters predisposing Australian Footballers to overuse skeletal injury; and 3) influence of seasonal adaptations on lower-body morphology through-out an in-season and off-season period in elite Australian Football.

The first study sought to provide normative and comparative data of lower-body musculoskeletal properties for the kicking and support limbs of elite Australian Footballers using pQCT and DXA. Specifically, this study quantified the effect of training exposure and limb function on lower-body muscle-bone morphology in elite Australian Footballers.

Greater training exposure led to greater material, structural and strength adaptations commensurate with controlled multi-modal exercise and uncontrolled participation in high-impact, odd-impact sports; whereas longer-term exposure to asymmetrical loads developed disparate morphological features between the kicking and support limbs, providing a unique model to examine differential adaptations to various loading profiles. Specifically, cross-sectional area was the key attribute which delivered greater bone strength and skeletal robustness between limbs, owing to routine gravitational and impact loads evident in the support leg. This study: 1) promotes the ability to increase musculoskeletal resilience and mechanical load tolerance through training modalities which increase muscle-bone cross-sectional area as potent contributors to biomaterial strength; 2) highlights the necessity to measure and monitor structural and material properties in combination to appropriately examine various musculoskeletal factors that contribute to physical capacity and load tolerance; and 3) provides normative values for benchmarking and comparison during screening procedures as a tool to stratify potential injury risk; and guide prophylactic or remedial training programs.

The second study sought to provide a comprehensive musculoskeletal examination of lower-body morphology between non-injured and previously injured elite Australian Football athletes using pQCT and DXA. Specifically, this study quantified the differences between injured and non-injured players in addition to injured and non-injured limbs to establish commonalities and disparities between skeletally fragile or robust Australian Footballers; and skeletally fragile or robust limbs. Players who acquired stress fractures were lower across nearly all musculoskeletal measures, demonstrating a general inferiority and global weakness in comparison to non-injured players. Injured players contained lower

tibial mass, narrower cortices and smaller geometrical properties despite containing similar material densities than non-injured players. Interestingly, injured limbs also contained lower tibial mass, narrower cortices and smaller geometrical properties than the non-injured limb within already fragile individuals; highlighting the importance of cortical area and thickness as contributors to strength as a key difference between injured and non-injured limbs. This study: 1) highlights structural adaptations as the greatest trainable and protective benefit to prevent skeletal injury or develop physical robustness in elite Australian Footballers; 2) offers measurable and modifiable skeletal properties for practitioners to identify and target using detailed screening procedures and controlled loading sequences within prophylactic and remedial training programs; and 3) provides normative values and benchmarks during screening procedures to identify players at risk of overuse skeletal injury, enhancing load management and injury reduction strategies.

The third and final study sought to quantify lower-body musculoskeletal adaptations of the kicking and supports limbs in elite Australian Footballers following an in-season and off-season phase using pQCT and DXA. Given that training structure and emphasis differs across the preseason, in-season and off-season in Australian Football; the ability to aggregately develop and improve musculoskeletal robustness overtime is complicated. While the preseason is the primary phase to optimise physical development; earned adaptations may be subsequently compromised during the in-season and off-season as a result of reduced training loads. Expectantly, favourable yet subtle skeletal increases in lower-body material and structural properties were evident following the in-season with larger magnitudes and broader ranges of morphological adaptations evident in the support limb; emphasising cross-sectional area. Unfortunately, the off-season was partially

regressive, with a detraining effect reversing most material adaptations. Fortunately, structural properties were preserved in the kicking limb and increased in the support limb, thus bone strength was completely reversed for the kicking leg yet wholly maintained by the support leg. Accordingly, favourable osteogenic adaptations of the support limb during the in-season coupled preservation of strength during the off-season promotes the osteogenic potency of regular impact-based gravitational loading. Further, differential adaptations illustrate disparities between kicking and support limb which might explain developmental asymmetries when extrapolated overtime in accordance with training age and training exposure outlined in the first study. This study: 1) illustrates expected myogenic and osteogenic adaptations of the lower-body through-out the in-season; 2) demonstrates a level of reversibility and regression experienced by players during the off-season; and 3) describes the asymmetrical morphological adaptation and maladaptation of the kicking and support limbs during the in-season and off-season phases.

In summary, the overriding conclusion drawn from the collection of experimental studies presented in this thesis promotes the importance of bone structure and bone geometry as potent contributors to skeletal robustness, microdamage resistance and bone strength development. In particular, elite Australian Footballers with higher levels of training exposure (training age) and physical resilience (non-injured) exhibited greater tibial mass, higher cortical density and thicker cortical walls radially expanded over wider transverse areas; distributing densely packed bone further from its neutral longitudinal axis to considerably reduce received mechanical strain for a given mechanical stress. By extension, similar internal parameters differentiated non-injured and injured limbs of individual players, with particular emphasis on cross-sectional area and cortical thickness as primary

structural and geometrical properties delivering heightened protection to the non-injured limb against skeletal fatigability.

Collectively, these experimental studies also provided novel insight into the individuality of musculoskeletal adaptation between limbs within Australian Football players, illustrating the effect of differential loading patterns expressed by limbs based on their routine functional engagement. Specifically, kicking and support limbs experience asymmetrical morphological adaptation and maladaptation through in-season and off-season phases, which if extrapolated annually, generates incremental disparities between limbs as training exposure (age) increases. Indeed, the interlimb functional loading model highlights the value of axial compression under combined gravitational, impact loads to develop favourable material and structural adaptations; specifically with regard to radial expansion of the cortex through incremental periosteal and endosteal activity in response to bending moments known promote new bone formation at targeted, site-specific regions.

Together, these findings ultimately endorse the need to concurrently quantify and report material, structural and strength variables when examining musculoskeletal properties and morphological change. Given that material or structural components can independently only explain ~50% of bone strength variance, neither property should be used as a surrogate measure in isolation, particularly as bone strength is a quantifiable primary measure examinable through advanced technologies such as pQCT. More specifically, the mechanical behaviour of bone under load is considerably influenced by both material and structural adaptations which often occur sequentially. Accordingly, the measurement and dissemination of material, structural and strength variables importantly enhances

practitioner insight into the true efficacy of training interventions to optimise bone strength and mechanical competency; specific to the magnitude, breadth and characteristics of morphological change. By extension, this limits the practicality of DXA in this regard; restricted by areal measures of frontal mass distribution which cannot provide suitably detailed analyses into skeletal robustness or bone strength. Indeed, denser bone isn't always stronger, whereby DXA cannot provide insight into structural variables necessary to produce thorough and detailed examinations of muscle-bone quality.

The precise nature of these cross-sectional outcomes provides a foundation for future longitudinal studies to establish training interventions using human models which may strive to heighten musculoskeletal resilience through numerous controlled exercise modalities in addition to sports participation using higher-resolution, three-dimensional bone densitometers to appropriate measure and monitor morphological change over time.

7.0 – CHAPTER SEVEN – FUTURE RESEARCH

The series of three studies provided in this thesis resulted in several interesting findings, however, the review of the literature and presented experimental outcomes have revealed a number of potential areas for future research opportunities:

1) Bone structure and geometry are known factors involved in the development of stress fractures and skeletal fragility more broadly. Given the unique movement demands and loading patterns required by players in Australian Football, in addition to the site-specific adaptability of bone, it is of interest to establish whether Australian Football players who acquire tibial stress fractures or stress-related syndromes have sector-specific material or structural weaknesses which could be identifiable during skeletal screening procedures and remedied through intervention. To address this, future research may pursue a comprehensive sectoral analysis at multiple tibial sites between injured and non-injured players, as well as injured and non-injured limbs within injured players.

2) Differential loading patterns experienced by the kicking and support limbs of Australian Footballers generate functional yet asymmetrical musculoskeletal adaptations. Given the importance of structure and geometry to skeletal robustness and physical resilience; the differences in bone strength between kicking and support limbs; and the site-specific adaptability of bone to mechanical load, it is of interest to identify the material, structural and geometrical distribution of site-specific adaptations along the Tibia in response to participation in Australian

Football. Specifically, future research may explore a comprehensive sectoral analysis at multiple tibial sites between the kicking and support limbs of Australian Footballers; stratifying players by training age and biological age to understand the general effect of loading exposure while investigating potential seasonal adaptations or changes in sectoral configuration overtime.

3) Normative and comparative lower-body musculoskeletal data using pQCT is scarce in sporting populations, particularly in field-based team-sports. The availability of such data is incredibly important for both athletes and practitioners alike, providing benchmark and baseline information as a basis of comparison, interpretation and stratification internally within a sport, or externally between different sports; heightening the meaning and value of such musculoskeletal investigations for use during medical screening and monitoring protocols. Accordingly, future research is required to establish normative lower-body and upper-body musculoskeletal parameters using pQCT on an expansive range of different individual- and team-sports with different loading characteristics in male and female athletes and squads across the junior to senior, amateur to elite developmental spectrum.

4) Human training interventions driving bone strength adaptations across various modalities (vibration, locomotive, resistance, impact, multi-modal) are remarkably heterogeneous in design, measurement and scope. Indeed, the majority of existing studies (reviewed in Section 2.4.2.) have measured and reported material adaptations in bone using areal quantifications only, subsequently neglecting macroscopic tissue, bone structure, bone geometry and bone strength. Further, small sample sizes and short-term interventions have often been used, limiting the known

efficacy of such exercise modalities. In order to fully understand the time-course of osteogenic adaptation and morphological change in hard-tissue in response to various exercise modalities, there is a need for greater homogeneity in study design and program delivery in order to isolate genuine adaptations resulting from explicit mechanical loading structures. Accordingly, future studies using human models should: 1) recruit larger sample sizes, 2) employ longer interventions, 3) measure and report bone material, structural and strength variables simultaneously, 4) report muscle and bone data together, 5) enhance mechanical loading program design, 6) measure and report relevant load-specific data (e.g. the magnitude and rate of ground reaction forces if investigating impact loading); 7) measure multiple time-periods to improve temporal and sequential morphological changes; and 8) measure multiple sites of long bones, and multiple bones of the axial and appendicular skeleton where possible.

5) Examinations of bone quality and interventional efficacy primarily use DXA or pQCT, relying on areal and volumetric measures as surrogate markers of bone strength, limited to macro-architectural depth (ie: cortical and trabecular). However, micro-architectural features of cortical bone (porosity and mineralisation) and trabecular bone (connectivity and thickness) are critically important to hard-tissue quality, structural integrity and the mechanical competency of tissues under load. Indeed, recent technological advancements have led to the development of high-resolution pQCT devices (HR-pQCT) capable of measuring micro-architectural features of macroscopic tissue; subsequently affording practitioners with the capacity to detect important morphological changes and osteogenic adaptations

earlier. Accordingly, future research may wish to examine musculoskeletal and morphological changes using human models with various exercise modalities, sports participation and controlled training interventions.

6) Numerous exercise modalities are commonly used by strength and conditioning practitioners in sporting environments to produce myogenic and osteogenic adaptations for prophylactic, remedial or rehabilitative purposes. Given the high reliance and importance of load management in field-based team-sports; it is of interest to examine which modality yields the greatest muscle and bone adaptations, specific to material and structural gains, in the safest manner. In particular, athletes at risk of stress fracture, or athletes with recent stress fracture history may benefit from a greater emphasis toward resistance exercise and impact exercise (i.e. weight training, plyometrics and weightlifting) to provide a potent osteogenic stimulus using muscle, gravitational and impact forces in controlled loading environments rather than locomotive exercise (walking, jogging or running) during aerobic conditioning activities which may instead heighten skeletal fatigue and injury susceptibility due to microdamage accumulation and muscular fatigue during less controllable and highly cyclical field-based activities. Future research could attempt to examine these training modalities in the context of elite, field-based team sport environments. Furthermore, future studies may provide rehabilitation case-studies following stress-related syndromes to address which modalities produce optimal morphological adaptations during musculoskeletal restoration after immobilisation.

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APPENDIX A: Conference Poster – (ASCA - 2012) – Gold Coast, AUS

LOWER-BODY BONE MASS CHARACTERISTICS OF ELITE, SUB-ELITE AND AMATEUR AUSTRALIAN FOOTBALLERS

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INTRODUCTION

Skeletal fragility is directly related to injury risk in football sports. Athletes with lower bone mass and slender bones are more vulnerable to impact fracture (trauma) and stress fracture (overuse) than athletes with greater bone mass and more robust bones [1].

Mechanical loading provided by weight-bearing exercise and resistance training programs produce direct osteogenic effects which subsequently lead to advantageous bone mass and bone strength adaptations. Specifically, dynamic and explosive multi-planar activities involving impact loads are considered to be highly osteogenic due to a coupling of large muscle contraction forces and large ground reaction forces [2], often seen in football sports.

In Australian Football, athletes are routinely exposed to a variety of lower body loading patterns under training and competitive contexts, exposing footballers to stimuli that can lead to either positive bone adaptations, or in the absence of suitable strength and conditioning programs, an increased incidence of lower limb injuries. This paper seeks to assess lower-body bone mass characteristics of elite, sub-elite and amateur Australian Footballers in order to examine the influence of various training and game-based loading schemes on lower body fragility or robustness across the different levels of competition.

PARTICIPANTS

45 elite, sub-elite and amateur Australian Footballers were evenly recruited from the AFL, WAFL and WAAFL competitions respectively (Table 1). Any athletes with lower limb injuries or contraindications requiring immobilisation within 3 months prior to data collection; or any athletes with metallic surgical implants located beneath the trunk were excluded from the study

Table 1. Subject characteristics of elite, sub-elite and amateur athletes.

	AFL (n = 15)	WAFL (n = 15)	WAAFL (n = 15)
Age (yr) [A]	25.4 (± 3.5)	21.1 (± 3.3)	23.1 (± 1.9)
Height (cm) [A,B]	188.5 (± 3.6)	181.5 (± 7.1)	180.3 (± 6.9)
Weight (kg) [A]	89.5 (± 4.7)	80.5 (± 8.3)	88.5 (± 15.3)
Body Fat (%) [B,C]	9.1 (± 1.0)	10.7 (± 1.6)	18.1 (± 4.9)

[A] Significant difference between AFL and WAFL (P ≤ 0.05)
[B] Significant difference between AFL and WAAFL (P ≤ 0.05)
[C] Significant difference between WAFL and WAAFL (P ≤ 0.05)

METHODS

Experimental Approach:
Testing sessions commenced with anthropometric measures (height and weight), followed by an assessment of whole-body composition and lower body bone mass characteristics (bone area [BA], bone mineral content [BMC], bone mineral density [BMD]) of the kicking and support limbs using Dual-energy X-ray Absorptiometry (DXA).

Scan Protocol:
Whole-body scans were performed using DXA (QDR-1500; Hologic Discovery A, Waltham, WA) to assess lower body bone mass characteristics and full-body composition using previously established, standardised and reliable body positioning procedures [3].

Scan Analysis:
Scans were analysed using the inbuilt analysis software (Version 12.4; QDR for Windows, Hologic, Waltham, WA). To determine body composition, a standardised whole-body model was applied to the scan image, separating the body into axial and appendicular sections [3]. To determine lower body bone mass, two sub-regions were drawn to capture both limbs from the pelvis to the distal phalanges (Figure 1) using previously described anatomical boundaries [4].

Statistical Analysis
One-way between-group ANOVA's were performed for all subject and bone mass characteristics. Bonferonni's post-hoc sequential corrections were applied to establish the level of significance ($\alpha < 0.05$) between each group.

Figure 1. Lower body boundaries used to define the kicking and support limbs during scan analysis.

RESULTS

Table 2. Bone mass characteristics of the lower limbs within elite (AFL), sub-elite (WAFL) and amateur (WAAFL) athletes.

	AFL	WAFL	WAAFL
Kicking Leg:			
Bone Area (cm^2)	530.1 (± 27.2) [A,B]	477.4 (± 39.4)	470.7 (± 38.0)
BMC (g)	819.8 (± 77.8) [A,B]	669.3 (± 91.2)	648.2 (± 93.2)
BMD (g/cm^2)	1.545 (± 0.09) [A,B]	1.398 (± 0.09)	1.372 (± 0.11)
Support Leg:			
Bone Area (cm^2)	536.8 (± 29.7) [A,B]	483.1 (± 39.6)	478.6 (± 39.0)
BMC (g)	838.4 (± 74.0) [A,B]	679.2 (± 88.2)	656.7 (± 83.8)
BMD (g/cm^2)	1.561 (± 0.08) [A,B]	1.402 (± 0.9)	1.369 (± 0.9)

[A] Significant difference between AFL and WAFL (P ≤ 0.05)
[B] Significant difference between AFL and WAAFL (P ≤ 0.05)
[C] Significant difference between WAFL and WAAFL (P ≤ 0.05)

CONCLUSION

The examination of bone mass in athletes provides strength and conditioning practitioners with an insight into bone health and hard-tissue injury risk stratification. BMD in particular, is a commonly used surrogate measure for bone strength [5]. In the current study, elite Australian Footballers contained significantly stronger and more robust bones when compared to sub-elite and amateur populations, demonstrating greater BA, BMC and BMD in both kicking and support limbs.

Despite an evident trend between all competition levels, there were no significant differences observed between sub-elite and amateur ranks. This may be due to an evident disparity between full-time structured conditioning programs provided to elite athletes and part-time semi-structured conditioning programs provided to sub-elite athletes. Recruitment of full-time strength and conditioning professionals at state level football clubs might expedite the physical preparation of sub-elite athletes for elite level lower body loading demands.

PRACTICAL APPLICATION

Athletic progression from sub-elite and amateur competitions toward the elite level may require Australian Footballers to engage in training activities which generate lower body bone mass characteristics similar to those expressed by elite Australian Footballers. To generate optimal bone strength improvements, programs focusing on exercises which use large muscular forces, large ground reaction forces, and include impact loading are recommended. Consideration must also be given to nutrition; specifically Calcium and Vitamin D intake levels.

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Comparison of support and kicking leg tibial bone strength strain indices in professional football players

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Introduction

In sport, the assessment of physical characteristics allows coaches and strength and conditioning professionals to determine both athlete potential and readiness to play. The assessment of muscular imbalance has been previously identified in athletes that must repeatedly perform single leg or single arm actions[1]. Although such an imbalance is often thought of as a negative characteristic, these specific adaptations are often due to years of sport specific stress that cause differential adaptation to the limbs due to different loads being chronically placed on the system. In Australian Rules Football (ARF), as for other kicking sports such as Soccer and Rugby, players will have a preferred kicking leg and support leg that will be exposed to different types of repetitive loads. Understanding if the skeletal system also preferentially adapts could be of use when monitoring and determining volume loads for specific activities and training. While dual energy xray absorptiometry has traditionally been used to assess bone and body composition in athletes, peripheral quantitative computed tomography (pQCT) provides much higher resolution imaging of the extremities and can be used to estimate actual fracture strength. Further, it is suggested that the use of pQCT may be a better predictor of bone fracture risk[2] and that specific measures of the bone morphology instead of BMD or BMC may be better determinants of bone strength[3,4]. A very novel aspect of this study is the application of this technique in athlete research. Therefore, it was the purpose of this study to examine if there are significant differences present in bone strength of the support limb versus the kicking limb in elite ARF players.

Methods

Subjects
Forty-six (age: 22.9 ± 3.8 years; height: 188.3 ± 6.6 cm; body mass: 85.5 ± 8.3 kg) professional ARF players participated in this study. Thirty of these players (Group A) were listed in the main squad and 16 (Group B) were categorized as less experienced with shorter training history and striving to be elevated to the main squad. Data was collected as part of the athlete's employment as a professional and all procedures and data management conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Testing
pQCT (XCT3000, Stratec, Germany) was used to scan the tibia of both the support and kicking limb at distances of 14% and 38% from the distal end. Structural strength of the bone was then determined using the Strength Strain Index (SSI) which is a density weighted bone section modulus. A composite SSI measure was determined as the average of the two sites.

Statistical Analysis
Statistical difference between groups for kicking leg, support leg and difference between legs was evaluated using one-way ANOVA with alpha set at 0.017 after Bonferroni adjustment for multiple variable comparisons. Differences between kicking and support limbs within each group were evaluated using paired t-tests with alpha similarly adjusted. Further, the relationship between the SSI of the kicking and support leg was assessed using Pearson product moment correlation coefficient.

Results

Bone measures are provided in Table 1. SSI of both the kicking and support legs was significantly higher ($p < 0.001$) for Group A compared to Group B. SSI of the support leg was significantly greater than the kicking leg for Group A ($p<0.001$) but not Group B ($p=0.256$). The percentage difference between the two legs was 3.6 times greater for Group A than Group B but this was not statistically significant ($p=0.074$). For Group A there was a significant correlation ($r=0.898$, $p<0.001$) between SSI of support and kicking legs as well as the relationship of support leg SSI and percentage difference between the two legs ($r=0.573$, $p=0.001$). The same pattern was apparent for Group B between legs ($r=0.820$, $p<0.001$) and support leg SSI and difference between legs ($r=0.608$, $p=0.13$). To show the relationship between increasing magnitude of support leg SSI and increasing percentage difference between kicking and support limb see Figure 1. Due to the bimodal distribution of Group A versus Group B SSI indices, the relationships were assessed within group as previously presented to prevent false inflation of the relationship. There was no relationship between kicking leg SSI and difference between legs for either group.

Table 1. Strength Strain Index (mean ± sd) of kicking and support leg tibias of football players

	Kicking	Support	% Difference
Group A (n=30) (elite)	2683 ± 316	2831 ± 404	4.74 ± 6.15[a]
Group B (n=16) (sub-elite)	2295 ± 183	2333 ± 225	1.31 ± 5.84
% Difference	14.5[b]	17.6[b]	3.43[c]

[a] indicates significant difference between kicking and support leg
[b] indicates significant difference between elite and sub-elite
[c] indicates non-significant ($p=0.074$) difference between elite and sub-elite

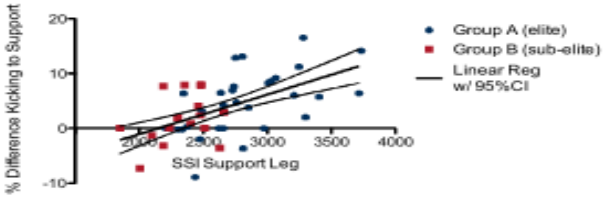

Figure 1
Comparison of percentage difference between kicking and support limb to the SSI of the support leg for both Group A and Group B. In this figure, it can be noted the "clustering" of lower level support leg SSI indices in Group B (extended squad) professional football players. However, there was a similar magnitude relationship between percentage difference in kicking and support SSI and SSI support leg magnitude in both Group A ($r=0.573$, $p=0.001$) and Group B ($r=0.608$, $p=0.13$).

Discussion

There appears to be a long-term adaptation of the bone strength of both the support and kicking limbs as a result of repeated kicking during football training and competition as indicated by significantly higher SSI for the more experienced athletes with longer training and playing history. Further, the more experienced players exhibited a significant difference in SSI between the two legs which is most likely due to the support limb being exposed to large and repetitive eccentric loads during the plant phase of the kick. Interestingly the less experienced players had not yet developed such asymmetry. Bone strength of kicking and support limbs is strongly correlated suggesting genetic factors in combination with career training loads result in increased SSI of both limbs. However, the difference between limbs is only correlated with support leg SSI suggesting it is the volume of kicking and other unilateral activities preferentially loading the support leg that induces the asymmetry.
Similar to other research associated with sidedness and bone adaption in athletes[4], the current research demonstrates that beneficial adaptations can occur not only to the muscle[1] but also to the bone, potentially to assist with load absorption. Of interest in these findings, is the potential to enhance bone strength of any limb by repeated eccentric load exposure such as those incurred by the support limb during kicking. This has implications for strength and conditioning practice as some athletes may exhibit low bone strength and thus higher fracture risk. Activities such as kicking and exercises that place similar eccentric loads on the supporting limb may be of benefit though longitudinal rather than cross sectional research is required to confirm this. This study suggests that bone morphology should be assessed in these professional athletes as it could have implications for bone injury risk and training program design[3].

Conclusion

Experience, training and competition history contribute to significantly higher bone strength of the lower limbs of football players. The tendency for these athletes to kick more frequently with a given leg results in markedly higher bone strength in the support leg which we hypothesize is due to the high eccentric loads occurring during foot plant. A high number of the better athletes exhibit greater asymmetry in bone strength most likely a result of longer history of kicking in training and competition. pQCT analysis should be considered for professional football players and appropriate strength and conditioning interventions should be implemented if markedly low SSI are determined as this may place the athlete at greater risk of fracture.

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APPENDIX C: Conference – (ASCA - 2013) – Melbourne, AUS

PHYSICAL LOAD TOLERANCE DIFFERS BETWEEN KICKING AND SUPPORT LIMBS IN AUSTRALIAN FOOTBALLERS

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INTRODUCTION

Repetitious asymmetrical activities have been shown to generate asymmetrical hypertrophic responses in muscle (1-4). It is not yet known whether similar long-term adaptations are evident in hard-tissue structures. While it is logical to expect a level of lateral dominance in the lower limbs of elite Australian Footballers on the back of preferential function during sport participation (4-6), this has yet to be quantified. It is therefore not yet known whether developmental laterality exists; or whether load tolerance capability (fracture load) differs between hard-tissue structures of the lower limbs. The purpose of this study is to quantify tibial fracture load and stress-strain indices of an elite Australian Football cohort.

METHODS

PARTICIPANTS:

Fifty-one elite Australian Footballers were recruited from the Australian Football League (AFL). Athletes with lower limb injuries or contraindications requiring immobilisation within 3 months prior to data collection; or with metallic surgical implants located beneath the knee compartment were excluded from analysis. This rendered four players as unsuitable for inclusion, providing a total cohort of forty-seven footballers (age: 22.4 ± 3.8 yrs; mass: 84.2 ± 8.0 kg; height: 188.2 ± 7.0 cm; tibial length: 432.1 ± 28.2 mm).

Figure 1. Subject positioning for pQCT scan, with the talocrural joint identified at high-resolution (left); The drop punt kick, used to demonstrate differential loading imposed upon each limb (right).

EXPERIMENTAL DESIGN:

Anthropometric measures including height, weight and tibial length were recorded. To examine lower-body bone strength, a volumetric tibial bone scan was performed on each leg using peripheral Quantitative Computed Tomography (pQCT; XCT3000, Stratec, Germany). Four sites were examined at 4%, 14%, 38% and 66% from the distal end of the Tibia. Data was collected as part of the athlete's employment as a footballer. All procedures and data management conformed to the Code of Ethics of the World Medical Association.

STATISTICAL ANALYSIS:

Paired t-tests ($p \leq 0.05$) were used to determine significant differences of bone strength between kicking and support limbs within subjects. Independent t-tests ($p \leq 0.05$) and effect sizes (ES) were calculated to provide a measure of magnitude and significance of difference between groups.

RESULTS

Table 1. Bone strength profile, comparing the kicking and support limbs.

	Kicking Leg	Support Leg	Diff (%)	ES (d)
Tibial Mass (g/cm)	4.75 (± 0.4)	4.83 (± 0.4)	1.7%	0.20 *
Stress-Strain Index (mm^3)	2529.8 (± 303)	2634.2 (± 389)	4.1%	0.31 *
Absolute Fracture Load (N)	5766.4 (± 734)	5865.7 (± 846)	1.7%	0.13
Relative Fracture Load (N/N)	7.03 (± 0.6)	7.13 (± 0.7)	1.5%	0.15

Note: Values expressed as mean ± SD; Diff(%) represents percent difference between limbs.
* Small effect size (≥ 0.2)

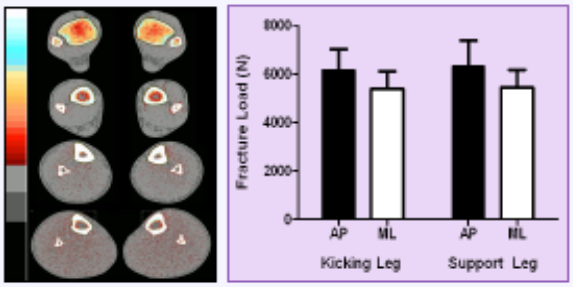

Figure 2. Cross-sectional, density-weighted images of each limb at 4%, 14%, 38% and 66% length (left); with a comparison of load tolerance from anterior-posterior (AP) and medio-lateral (ML) force application between limbs (Right).

KEY INFORMATION

- The support leg was higher in all measures of bone strength.
- Previous bone adaptation research (8,9) has shown that very small structural changes produce very large improvements in fatigue resistance. (≤ 2-fold change can elicit a ≥ 100-fold benefit).
- Australian Footballers can withstand 15% more force (impact) in the sagittal plane relative to the frontal plane.

CONCLUSION

Physical loads generated by weight-bearing exercise and resistance training programs produce advantageous bone mass and bone strength adaptations at site-specific load-bearing regions (8,9). As footballers preferentially use a specific limb for kicking, and a specific limb for unilateral support, each leg is exposed to different types and magnitudes of repetitive stress (beyond cyclical running tasks).

This could, in part, explain the slightly higher bone mass and strength measures evident in the support leg of an elite Australian Football cohort (1.6 – 4.1%). Despite not reaching statistical significance, the small effect evident in mass and stress-strain index has practical significance as small improvements in bone geometry can elicit large protective benefits (≤ 2-fold change, ≥ 100-fold benefit, (8)).

PRACTICAL APPLICATION

Skeletal fragility is directly related to hard-tissue injury risk. While it is not yet known which loading parameters best provide osteogenic benefits to bone; the greater adaptations seen in the support leg may implicate activities requiring rapid, dynamic, high load, high impact exercise, utilising high muscular forces and high variants in gravitational loading (3,9). In athletes with characteristically low bone mass; the kicking limb may be at most risk of fracture. In the absence of regular bilateral kicking; other conditioning interventions could be appropriate.

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APPENDIX D: Conference – (SPRINZ - 2014) – Auckland, NZ

APPENDIX E: Conference – (ASCA - 2014) – Melbourne, AUS.

MUSCLE-BONE DIFFERENCES BETWEEN ELITE AUSTRALIAN FOOTBALL AND RUGBY UNION PLAYERS

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[3] David G. Joyce, [3] Charlie Higgins, [1] G. Gregory Haff, [1] Robert U. Newton

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INTRODUCTION

Muscle and bone are inextricably linked, with alterations in muscle size, density and strength temporally linked and positively correlated to alterations in bone size, density and strength [1-3]. Specifically, changes in muscle precede changes in bone; and losses of muscle and bone occur faster than accrual; thus exercise-induced gains are rapidly reversed yet gradually recovered [4-6]. Indeed, muscle asserts synergistic dominance over bone, such that bone growth or loss is subservient to muscle hypertrophy or atrophy [1-6]. In this regard, the importance of muscle size and strength as trainable features to enhance and protect bone size and strength is evident. Given the markedly higher prevalence and severity of bone injury (traumatic and stress fracture) in Australian Football (AFL) over Rugby Union (SuperRugby); it is of interest to compare muscle-bone profiles of these two distinct sporting codes, owing to the greater emphasis of gym-based, strength and power training prevalent in Rugby Union relative to Australian Football.

METHODS

PARTICIPANTS:

60 elite Australian Football and 37 elite Rugby Union players were recruited from the AFL and Super Rugby competitions respectively. Athletes with lower limb injuries or contraindications requiring immobilisation within three months prior to data collection; or with metallic surgical implants beneath the knee compartment were excluded from analysis. This rendered four AFL players and one Super Rugby player as unsuitable for inclusion. Descriptive data is provided in Table 1.

Table 1. Subject characteristics of elite AFL and Rugby Union players

	AFL [n=56]	Rugby [n=36]
Age (yrs) *	22.0 (± 3.8)	24.2 (± 2.5)
Height (cm)	188.8 (± 7.1)	186.8 (± 6.3)
Weight (kg) *	85.2 (± 8.3)	105.1 (± 10.7)
Body Mass Index (BMI) *	23.9 (± 1.5)	30.1 (± 3.1)
Whole Body Fat (%) *	10.3 (± 1.6)	14.8 (± 3.0)
Leg Length (mm)	435.9 (± 27.9)	430.9 (± 18.8)

Note: Values are expressed as mean ± SD.
* Statistical significance ($p \leq 0.01$) between groups.

EXPERIMENTAL DESIGN:

Height, weight and leg length were measured by an accredited exercise scientist with whole-body composition quantified using Dual-energy X-ray Absorptiometry (DXA). Tibial bone strength (fracture load and stress-strain index), tibial volumetric density, tibial cross-sectional area, muscle density and muscle cross-sectional area were quantified using peripheral Quantitative Computed Tomography (pQCT; XCT3000, Stratec, Germany). All procedures and data management conformed to the Code of Ethics of the World Medical Association. Data was collected as part of the athlete's employment with their respective sporting organisation.

STATISTICAL ANALYSIS:

Independent t-tests were used to determine significant differences between Australian Football and Rugby Union players for all subject, muscle and bone characteristics. Statistical significance was set at $p \leq 0.01$.

RESULTS

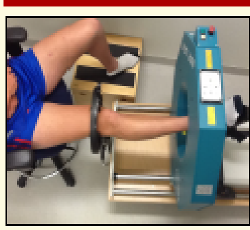


Figure 1. Tibial scan positioning for pQCT.

- Bone strength was significantly greater in Rugby Union players ($p \leq 0.001$).
- Muscle and bone morphology co-adapted with both tissues exhibiting similar traits:-
  - Density was not statistically different for muscle or bone between groups ($p \geq 0.891$).
  - Cross-sectional area was significantly higher for muscle and bone ($p \leq 0.001$) in Rugby Union players.

RESULTS

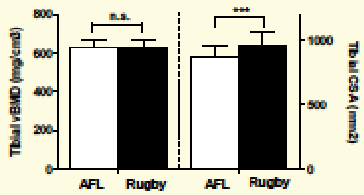
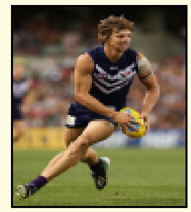
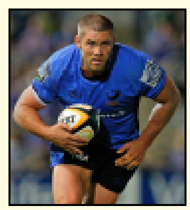


Figure 2. Tibial density (left) and cross-sectional area (right).





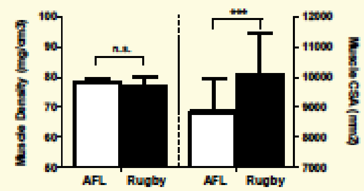


Figure 3. Muscle density (left) and cross-sectional area (right).

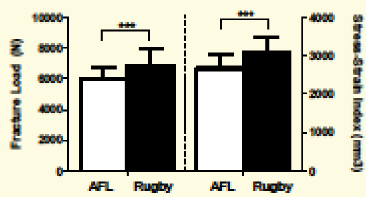
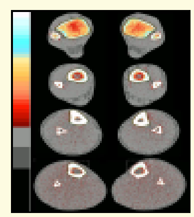


Figure 4. Tibial bone strength, fracture load (left), SSI (right).



CONCLUSION

Bone strength was significantly greater in Rugby Union players compared to Australian Football players. Although this was somewhat expected, the difference in bone strength was attributable to variations in cross-sectional area only, and not density for muscle and bone. This is an important adaptation as increases in cross-sectional area improves load tolerance proportional to the fourth power of material distance from the neutral axis, such that a ~2-fold increment in cross-sectional area yields an ~8-fold increment in bone strength without any concomitant change in bone mass or density (7,8). This also highlights the glaring inadequacy of using density measures in isolation. Cross-sectional area may be a potent morphological adaptation to enhance musculoskeletal robustness in field-based team-sports.

PRACTICAL APPLICATION

To increase musculoskeletal resilience, practitioners should focus on training modalities which increase muscle and bone cross-sectional area; a potent contributor to biomaterial strength. It is strongly recommended to measure and monitor structural and material properties in combination in order to appropriately examine various musculoskeletal factors that contribute to load tolerance in sport.

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Eligible for the Student Poster Award

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APPENDIX F: Human Ethics Approval

Research Ethics Details
9384 HART Ethics approval
23 April 2013 8:59 AM

Dear Nicolas

Project Number: 9384 HART
Project Name: Bone strength, load tolerance and injury risk in Australian Football
Student Number: 10022791

The ECU Human Research Ethics Committee (HREC) has reviewed your application and has granted ethics approval for your research project. In granting approval, the HREC has determined that the research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

The approval period is from 23 April 2013 to 30 June 2015.

The Research Assessments Team has been informed and they will issue formal notification of approval. Please note that the submission and approval of your research proposal is a separate process to obtaining ethics approval and that no recruitment of participants and/or data collection can commence until formal notification of both ethics approval and approval of your research proposal has been received.

All research projects are approved subject to general conditions of approval. Please see the attached document for details of these conditions, which include monitoring requirements, changes to the project and extension of ethics approval.

Please feel free to contact me if you require any further information.

Regards
Sue

Sue McDonald, Research Ethics Support Officer, Office of Research & Innovation,
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