

9-1-2020

Biological basis of bone strength: Anatomy, physiology and measurement

Nicolas H. Hart
Edith Cowan University

Robert U. Newton
Edith Cowan University

Jocelyn Tan

Timo Rantalainen
Edith Cowan University

Paola Chivers
Edith Cowan University

See next page for additional authors

Follow this and additional works at: <https://ro.ecu.edu.au/ecuworkspost2013>



Part of the [Medicine and Health Sciences Commons](#)

Hart, N. H., Newton, R. U., Tan, J., Rantalainen, T., Chivers, P., Siafarikas, A., & Nimphius, S. (2020). Biological basis of bone strength: anatomy, physiology and measurement. *Journal of Musculoskeletal and Neuronal Interactions*, 20(3). <http://www.ismni.org/jmni/index.php>

This Journal Article is posted at Research Online.

<https://ro.ecu.edu.au/ecuworkspost2013/8650>

Authors

Nicolas H. Hart, Robert U. Newton, Jocelyn Tan, Timo Rantalainen, Paola Chivers, Aris Siafarikas, and Sophia Nimphius

Review Article

Biological basis of bone strength: anatomy, physiology and measurement

Nicolas H. Hart^{1,2,3,4}, Robert U. Newton^{1,4}, Jocelyn Tan^{2,3,5}, Timo Rantalainen^{1,2,3,4,6}, Paola Chivers^{1,2,3,4}, Aris Siafarikas^{1,2,3,7,8}, Sophia Nimphius^{3,4}

¹Exercise Medicine Research Institute, Edith Cowan University, Perth, W.A., Australia; ²Institute of Health Research, The University of Notre Dame Australia, Fremantle, W.A., Australia; ³Western Australian Bone Research Collaboration, Perth, W.A., Australia; ⁴School of Medical and Health Sciences, Edith Cowan University, Perth, W.A., Australia; ⁵School of Health Sciences, The University of Notre Dame Australia, Perth, W.A., Australia; ⁶Gerontology Research Center, University of Jyväskylä, Jyväskylä, Finland; ⁷Department of Endocrinology and Diabetes, Perth Children's Hospital, Perth, W.A., Australia; ⁸School of Paediatrics and Child Health, University of Western Australia, Perth, W.A., Australia

Abstract

Understanding how bones are innately designed, robustly developed and delicately maintained through intricate anatomical features and physiological processes across the lifespan is vital to inform our assessment of normal bone health, and essential to aid our interpretation of adverse clinical outcomes affecting bone through primary or secondary causes. Accordingly this review serves to introduce new researchers and clinicians engaging with bone and mineral metabolism, and provide a contemporary update for established researchers or clinicians. Specifically, we describe the mechanical and non-mechanical functions of the skeleton; its multidimensional and hierarchical anatomy (macroscopic, microscopic, organic, inorganic, woven and lamellar features); its cellular and hormonal physiology (deterministic and homeostatic processes that govern and regulate bone); and processes of mechanotransduction, modelling, remodelling and degradation that underpin bone adaptation or maladaptation. In addition, we also explore commonly used methods for measuring bone metabolic activity or material features (imaging or biochemical markers) together with their limitations.

Keywords: Cortical, Imaging, Modelling, Remodelling, Trabecular

Introduction

Bone is a remarkable and exquisite biomaterial. It is highly adaptive, structurally dynamic and metabolically active, and is superior to all other biomaterials in terms of strength and toughness¹⁻⁴. In particular, bone structure, size and strength are reliant upon and responsive to the routine physiological and mechanical demands placed upon it⁵⁻¹². Mechanical stimuli thus initiate or inhibit bone modelling and remodelling processes in response to

variations in internal or external forces or as a consequence of immobilisation¹³⁻¹⁷. 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 mass¹⁸⁻²⁴. This is achieved through a sophisticated process involving the careful cellular regulation and coordination of osteoblasts (bone matrix deposit) and osteoclasts (bone matrix resorption) in order to remove damaged or extraneous bone material and subsequently replace it with new robust material^{19-21,25-30}. As bone remodelling is a continuous 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 load tolerance capabilities²⁹⁻³⁵. In particular, the mechanical integrity and performance of bone under various loading conditions is directly affected by its mechanical properties and geometric characteristics^{1,7,12,13,18,36} which are both

The authors have no conflict of interest.

Corresponding author: Dr. Nicolas H. Hart – PhD, AES, CSCS, ESSAM, Senior Research Fellow, Edith Cowan University, 270 Joondalup Drive, JOONDALUP, Perth, WA, Australia, 6027

Edited by: G. Lyritis

Accepted 24 April 2020



indicators of bone health and underpin bone strength.

The ability of bone to withstand forces and moments (mechanical loads) differs substantially across the loading spectrum under various loading conditions, specific to the mode, magnitude, direction, rate and frequency of load applied^{3,12,16,17,37-39}. As bone is anisotropic in nature, it has different thresholds of load tolerability across different planes of action^{2,18,40,41}. Indeed, habitual human behaviours routinely expose bones to various, often unpredictable loading patterns spanning from cyclical low-grade forces when walking or running, to sudden high-grade forces when jumping, landing or changing direction. As a result, compressive, torsional, transverse and tensile loads in combination and isolation are routinely applied to bone, exposing the skeleton to stimuli that can lead to positive bone-specific and site-specific adaptations^{16,42-49}, or in the absence of suitable conditioning, recovery and nutrition, an increased likelihood of injury⁵⁰⁻⁵⁷.

Despite the complex and multidimensional relationship between various loading schemes and bone mechanical properties (beyond the scope of this review, and published earlier¹²), bone strength and stiffness are greatest in the direction by which loads are most commonly expressed^{13,44,49,58}. The prevailing bone structure reflects an appropriate adaptation to mechanical loading highlighting a specificity of adaptation (site-specific) as force transmission regulates osteogenic (anabolic) bone formation outcomes concomitantly with other stochastic (spatially non-specific) adaptations^{2,16,20,21,59}. 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 mechanotransduction⁵⁹⁻⁶². Proportionate to mechanical stimulation, osteocytes biochemically promote osteogenesis by coordinating osteoblast and osteoclast activity so that overall bone morphology and bone shape positively adapts in favour of greater bone strength⁶³⁻⁶⁵. Within this process, 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^{7,19-21,66,67}.

As reviewed below, bone loss and bone accrual are not necessarily co-located and occur in a targeted or site-specific manner around bone circumference and along its length, additional to observable coadaptive bone morphological traits. A thorough understanding of these cellular and physiologic processes and their contribution to determining and maintaining bone strength will facilitate clinical diagnostics, designing appropriate interventions, and evaluating clinical musculoskeletal outcomes of pharmacological and non-pharmacological interventions⁶⁸. Accordingly, this review aims to provide a comprehensive update of current scientific literature and our understanding of these processes for clinicians and researchers, in companionship with the mechanical basis of bone strength¹² published earlier.

Bone strength

Bone strength explicitly refers to the ability of bone to withstand force prior to catastrophic failure^{1,24,69-72}, and is inextricably linked with fatigue resistance to repetitive loads⁷³⁻⁷⁸. Given the complex and multidimensional nature of bone, its strength is ultimately determined by the interaction and adjustment of its material and structural properties evident at macroscopic, microscopic and nanoscopic levels^{1,70,72,79-82}. At the material level, the collagenous extracellular matrix of bone provides resistance to tension, whereas the mineral inorganic phase of bone provides resistance to compression. Indeed, variations in collagen (such as osteogenesis imperfecta) or mineralisation (such as anti-resorptive drugs) can weaken or strengthen bone. Microscopically, the trabeculae in trabecular meshwork have implications on bone structural strength, and macroscopically, varying the shape of the bone will increase or decrease the amount of bending and torsion a bone can withstand given a particular amount of total mineral mass.

The adaptability, modulation and regulation of bone to mechanical and non-mechanical stimuli provides practitioners with the ability to directly influence and target bone strength through numerous interdependent mechanisms. Specifically, deterministic site-specific bone strength adaptations are driven by habitual mechanical loading, whereas general and non-specific bone strength adaptations are predominantly driven through endocrinological variations, responsive to physical, pharmacological and nutritional interventions^{1,32,33,83-86}. 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. The biological basis of bone strength is determined by its structure and function through its anatomy and physiology.

Bone anatomy

Skeletal function

Our skeletons are responsible for several important mechanical and non-mechanical functions^{22,36,87}. Mechanically, they provide a structural framework and stable foundation for human movement and locomotion to occur, generating mechanical rigidity and kinematic connectivity within the body^{22,36,88-90}. 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, and serves to protect the brain, spinal cord and internal organs^{2,18,26,36,91,92}. Non-mechanically, bone 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^{22,26,36,91,93}. In order to fulfil these many functions

simultaneously, bone has unique structural, morphological and mechanical properties that are highly dynamic, metabolically active and physiologically adaptive to the environment in which they're exposed^{21,23,88,94}. Bone is also highly vascular, facilitating the perfusion of oxygenated blood to enable the removal of metabolites and provision of nutrient availability required by bone 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 strength in order to meet its functional requirements^{18,19,24,79,89}.

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^{22,95}. Long bones, however, are the most commonly loaded structures and therefore strongest load-bearing bones in the body, predominantly in the appendicular skeleton. They comprise of a hollow cylindrical shaft known as the diaphysis, a cone-shaped proximal and distal metaphysis, and rounded proximal and distal epiphysis^{22,96-98}, each portion has different architectural features which are organised and configured to withstand and manage different physical loads during regular activities of daily living^{79,80,88,99}.

Macroscopic architecture

Bone is a structurally complex and sophisticated biomaterial^{1,2,4,33}. It must be rigid and stiff to withstand forces and accommodate loading, yet be flexible and elastic to deform and absorb energy^{24,80,100,101}. It must shorten and widen under compression, yet lengthen and narrow under tension, whilst also withstanding torsional and shear forces in isolation and in combination without experiencing catastrophic failure^{24,79}. In order to manage these contradictory and paradoxical requirements, the skeleton contains two macroscopic osseous tissues (trabecular and cortical bone) which are architecturally and functionally different^{33,81,102-105}. In its entirety, skeletal mass consists of approximately 20% trabecular tissue and 80% cortical tissue, which co-exists at various proportions in all bones through-out the body in accordance with the functional and regional demands of each individual bone^{18,22,79,80,105,106}. The structural intricacies and interactions between these two osseous tissues, enable long bones to be remarkably light yet durable and strong in order to facilitate locomotion^{24,79,82,107,108}.

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^{22,79,81,109,110}. Texturally, trabecular tissue presents as a meshwork of bone (trabeculae) with many interconnecting spaces through-out which contain

red bone marrow^{88,102,111-114}. 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 design best suited for the mechanical loading of bone^{7,89,101,109,114-116}. The spongy and porous architecture of trabecular bone enables it to store large amounts of energy prior to yielding^{18,23,105,117,118}, thus allowing it to routinely tolerate cyclical low-grade forces.

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^{2,22,95,119}. Cortical bone encapsulates trabecular bone, however the relative co-existence and composition of each tissue varies between bones through-out the skeleton^{1,18,99,102}. 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^{79,95,97,111,119-122}. Both surfaces contain important cells (osteoclasts, osteoblasts and osteocytes) responsible for modelling and remodelling processes essential to bone adaptation and osteogenesis^{17,24,25,97,123}. The endosteum additionally lines the central cavity with yellow marrow^{88,95,111,112,122}. Structurally, cortical bone is highly organised, densely packed, rigid, and texturally smooth^{18,23,111,120}, with mineralized lamellar bone and collagen fibre matrix most prominently arranged in the direction of routine mechanical stress^{69,101,119,120,124,125}. This provides cortical bone with an increased capability to tolerate sudden, high impact forces i.e. a sample of cortical bone is ~25% stronger than a sample of trabecular bone^{1,18,23,119,126}.

Microscopic architecture

Bone also has microscopic and sub-microscopic levels which, together with the macroscopic level, form a multidimensional architectural biomaterial with a deliberate mass (size, geometry and density) aimed at achieving optimal structural strength^{1,33,70,73,80}. Microscopically, bone presents in the form of woven and lamellar bone at the tissue level^{81,98,127-129}, and consists of organic and inorganic components at the material level^{26,33,59,130-132}.

Tissue level

Bone presents in the form of immature (woven) and mature (lamellar) tissue at different stages of the modelling and remodelling processes at the microscopic level^{22,100,127,129,133-135}. 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^{100,104}. It is formed rapidly, producing a highly unorganised and porous structure^{22,127,128}. Woven bone features primarily through-out development, exclusively forming the entire skeleton at

birth prior to a gradual transformation into mature lamellar bone during growth and physical maturation^{22,98,100,136}. 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^{2,127,137-139}. 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. Lamellar tissue is characterised by a precise and deliberate parallel and concentric arrangement of lamellae sheets produced slowly due to a low turnover rate^{2,81,98,134}. 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^{1,81,95,128,134}. Lamellar bone is therefore denser and stronger than woven bone^{22,100,101,140}.

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^{1,18,33,124,130,141}. 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^{59,70,132}. The extracellular organic component is mostly collagenous, conferring flexibility and resilience to bone by solidifying in tension as a protection against stretching, twisting and torsion¹⁴²⁻¹⁴⁶. Conversely, the mineralised inorganic component is primarily calcium and phosphate in the form of an insoluble salt known as hydroxyapatite^{130,147-152}, giving bone its hardness and rigidity, particularly in compression¹⁵³⁻¹⁵⁵. As a result, the overall structural strength of bone relies upon the joint contribution and inter-play of these organic and inorganic material properties^{1,2,24,148,153}, such that variations of inorganic mineral density will potentially adjust stiffness and flexibility arrangements in bone^{24,130,156}, the optimal balance of which remains largely unknown. That is, highly mineralised bone can become brittle (e.g. atypical femoral fractures), whereas less mineralised bone will be tougher yet less stiff (e.g. greenstick fracture). 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.

Bone physiology

Historically, bone has been regarded as the domain of anatomical study. However mechanically receptive, biologically adaptive and metabolically active features of bone have since solidified it as a biomaterial well-suited for physiological and biomechanical investigation^{2,12,69,89,157}. 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^{20,21,24,25,91,93,158}.

Cellular mechanisms

Bone is generated, regulated and maintained by an interaction of four key cells: osteoblasts, osteoclasts, osteocytes and extra-cellular lining cells^{13,19,26-28,159}. Osteoblasts are anabolic in nature, producing new bone material by synthesizing and calcifying newly generated collagen^{2,21,23,141}. 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^{25,160-162}. Conversely, osteoclasts are a catabolic cell which degrades, dissolves and resorbs bone material, often as a response to material damage or disuse^{21,29,123,163}. Osteoclasts have a limited lifespan, undergoing apoptosis (programmed cell death) within 2 to 4 weeks of osteoclastogenesis^{25,123,164}. 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).

Osteocytes are central to bone development and renewal as the most abundant residential cell in bone, accounting for approximately 90% to 95% of all bone cells^{66,141,162,165,166}. Specifically, osteocytes are descendants of osteoblasts produced during osteogenesis, which subsequently become entombed within the mineralised collagen matrix^{25,27,66,109,162}. 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^{13,136,165,167,168}. This network is explicitly formed by dendritic connections (~60 to 80 per osteocyte) which proliferate through canalculated passages to provide a functional and mechanosensitive platform integral to the detection of mechanical load and associated microdamage^{13,66,158,165,167}. This mechanically sensitive function, known as mechanotransduction, enables bone to physiologically detect and convert mechanical energy into proportionate biochemical signals in order to promote growth and repair processes^{59,60,65,158,168}. The process of mechanotransduction, including how bones sense mechanical changes, are described further under the Bone Adaptation section of this review.

Hormonal mechanisms

Bone growth, development and preservation is largely reliant upon hormonal regulation, globally controlling skeletal homeostasis somewhat independently of mechanical loads through-out the lifespan in order to facilitate non-mechanical functions of bone^{33,169-173}. Specifically, the endocrine system serves to maintain bone mineral deposition and homeostatic cellular balance through continual, non-mechanically induced generation and regeneration of bone during biological growth and maturation^{24,174-177}. While the endocrine system does

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, suppresses 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

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^{172,173,178-183}. Endocrine activity therefore forms a central component of a complex biological system that mediates calcium-phosphate balance, energy metabolism and bone mineralisation in response to dynamic and volatile physiological requirements^{179,184-190}. In this regard, endocrine function majorly influences bone health and metabolism, ascending into domination through adulthood and advanced ageing^{169,175,178,182,183,191,192}.

Endocrinological regulation of bone metabolism is highly influenced and tightly controlled by sub-categories of growth, gonadal and calcitropic hormones (Table 1), with varying levels of contribution and relative dominance through-out life^{170,174,175,178,187-206}. 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^{171,178,179,183-186,189,192,207-213}. 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^{24,34,71,173,214}. 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^{21,23,123,191,215}. As a result, hormonal imbalances and environmental irregularities underpinning deficient endocrine function form the nutritional and pharmacological basis of bone preservation strategies^{34,214,216-218}, utilising natural and artificial suppression and stimulation of bone

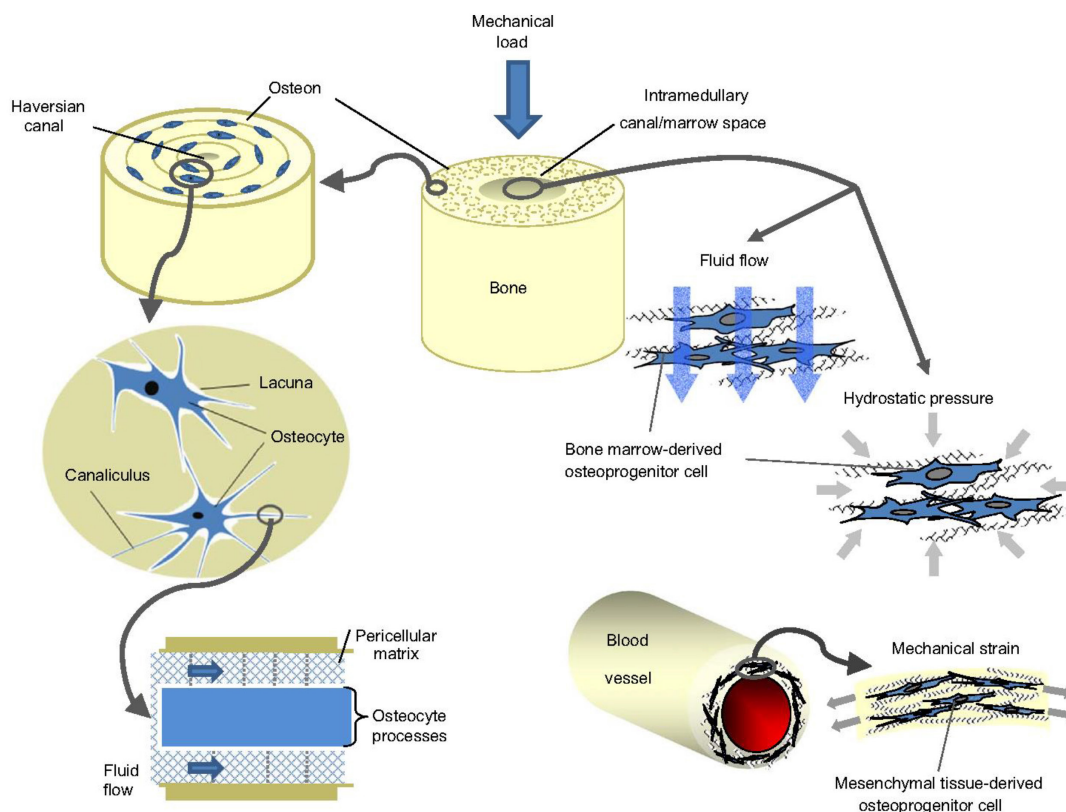


Figure 1. Mechanotransduction (adapted from ^{14,15}): illustrating the hierarchical structure of bone and the organizational structure of osteocytes within (left); and the mechanically induced fluid flow from hydrostatic pressure and osteoprogenitors through which biochemical signals proliferate (right).

resorption and formation to prevent and manage pathogenic conditions through-out the life-span.

Bone adaptation

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 and contemporary research^{11,89,219-233}. Their meritorious work collectively describes the ability of bone to alter its mass and structure in response to routine mechanical loads^{15,69,92,106,234-238}. However, scientific understanding of this mechanobiological relationship remains elusive and poorly understood. The conceptual basis of mechanical events stimulating and mediating bone formation, adaptation, maintenance and repair is widely accepted^{2,15,61,141,239}. 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^{15,59,62,67,240,241}.

In principle, mechanotransduction (Figure 1) 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^{13,63-65,158,242,243}. This biologic 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^{60,63,98,133,244}. Specifically, forces which lead to bone deformation create interstitial fluid movement within canaliculi, stimulating biochemical activity via mechanosensory cells^{64,245-251}. Piezoelectric signals are then transmitted through comprehensive lacuno-canalicular networks of osteocytes, lining cells and osteoblasts to determine the format and magnitude of cellular response relative to the perceived dose of mechanical load^{59,65,98,113,141,252-255}. This fundamental dose-response relationship between mechanical load and structural bone adaptation provides the foundation of bone modelling and re-modelling theory^{63-65,158,240,243,256}.

Modelling

Modelling is a dynamic and constructive process which adjusts the size, shape and strength of bone in order to

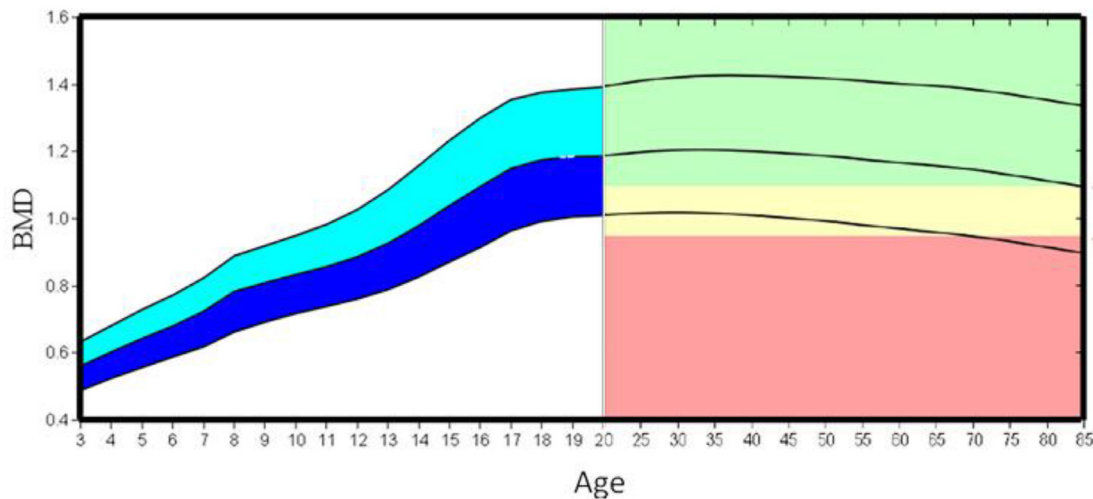


Figure 2. Bone mineral density accrual, maintenance and loss through-out the life-span as indication of bone mass alterations; with approximately 50–60% of total adult bone mass gained during adolescent years preceding peak bone mass and skeletal maturity at ~30 years of age. Bone mass deteriorates gradually following peak bone mass into older age to within normal (green), osteopaenic (yellow) or osteoporotic (red) bone density ranges.

achieve its structural potential during ontogeny, specifically in response to physiological and mechanical influences through-out physical maturation^{22,79,111,122,257-259}. It comprises of a complex and multifarious array of cellular and material activity which interact to position and configure cells and matrices during growth and development^{7,69,239}. At the cellular level, osteoblasts work independently from osteoclasts to create an environment where matrix deposition exceeds matrix resorption^{11,15,22,111,260,261}. At the tissue level, this is expressed through periosteal apposition and simultaneous yet slower endocortical resorption^{22,73,82,97,107,111,122,261,262}, leading to the formation of new bone material and partial preservation of old bone material to deliver a net increase in bone mass^{15,24,79,243,263,264}.

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^{22,69,79,82,97,107,122,265}. These morphological alterations structurally enhance bone strength through two key mechanisms: 1) increasing the bony (i.e. excluding any cavities) cross-sectional area, and 2) by placing the material farther from the centre of the bone, which increases the polar moment of inertia^{1,22,69,73,82,258}. Increasing the amount of bone material in a given cross-section improves bone strength in compression and tension, whereas distributing bone material farther from the centre of the bone improves strength in bending and torsion. For further details on bone mechanics, refer to our companion review¹². Ultimately, these morphological alterations keep

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^{69,72,73,107,266-268}.

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 mass²⁶⁹⁻²⁷¹. 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 development^{73,82,97,257,262,267,272-277}. 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^{216,278-282}. 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^{83,267,283-290}. Despite this apparent ceiling of bone mass augmentation (Figure 2), bone strength is able to increase through other spatially relevant mechanisms in maturity using a regulatory process known as re-modelling^{33,73,79,91,269,291,292}.

Remodelling

Remodelling is an on-going, homeostatic and restorative process which replaces old and damaged bone with new and healthy material (Figure 3) to maintain and improve structural integrity and mechanical competency^{19-21,23,26,29,82,107,159,293}. The regulatory nature of

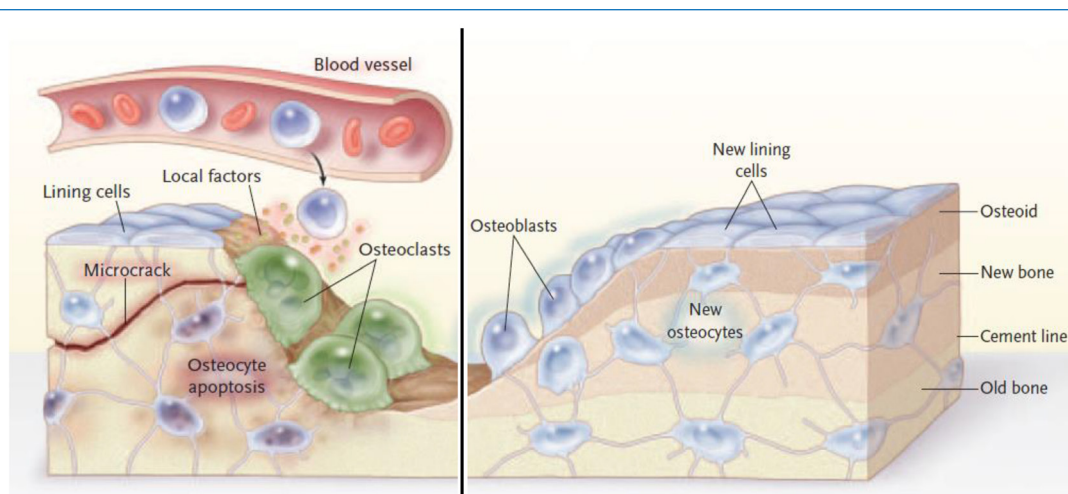


Figure 3. A graphical representation of the remodelling cycle (adapted from ²⁴). Bone resorption (left) is stimulated by a micro-crack which severs canaliculi channels between osteocytes leading to osteocytic apoptosis. Lining cells and osteocytes release signals attracting cells from blood and marrow 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).

Table 2. Adult bone remodelling (adapted from ^{96,109,110,123}).

• Lifespan of BMU: ~6-9 months
• Duration of remodelling: ~4-6 months
• Speed of remodelling: ~25 $\mu\text{m}/\text{day}$
• 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 $[0.75 \times 4] + [0.25 \times 28] = 10\%$; BMU = basic multicellular unit.

re-modelling relies upon integrated sensory signals in order to provide a feedback-controlled modulation of skeletal structure; a mechanism designed to sustain current and future functional requirements^{20-24,79,80,91,111}. This complex and multidimensional process is essential to ensure bone structure remains 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^{17,25,29,82,107,123}.

Remodelling occurs through stochastic and deterministic mechanisms^{19,20,59,80,91,294}. Stochastic remodelling describes randomly delivered and spatially non-specific forms of regeneration via the endocrine system, whereas deterministic remodelling forms the morphological and

mechanosensitive basis of bone strength adaptation through-out the lifespan^{15,17,123,293,295}. Specifically, deterministic remodelling represents a precisely assigned, targeted and site-specific form of remediation to repair damaged bone or initiated as a consequence of mechanical behaviour^{2,19,237,292,293,296,297}. 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^{21,59,79,80,297}. As a result, bone is resorbed in regionally and temporally distinct locations, detected and driven at the cellular level by osteocytes through mechanotransduction in order to target, repair and replace damaged material at the tissue-level^{19,20,24,29,79,293,296}.

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^{19,29,33,111,159,242}. 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^{11,21,26,82,110,219,298,299}. Biologically, these multicellular units are similar between cortical and trabecular bone, following a standard activation-resorption-formation sequence via osteocyte-osteoclast-osteoblast integration^{23,25,123,242,294,299,300}. 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^{7,17,20,23,242}. 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^{23,27,110,123}.

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^{17,296,301-304}. This occurs through non-mechanical and mechanical mechanisms in isolation and combination. Non-mechanical degradation represents bone loss during advanced biological ageing and associated pathological conditions such as osteopenia, osteoporosis and other disease-states^{26,33,34,79,84,305-308}; whereas mechanical degradation refers to environments of disuse (immobilisation and microgravity) or overuse (repetitive loading) which are preventable and reversible^{17,309-315}. As the cellular governance of bone generation, regeneration and repair is mainly responsive to mechanical load^{11,17,24,157,277,296,304,306,316}, the absence or overload stimulus can lead to net-resorptive activity and subsequent bone degradation^{26,303,307,312,317-319}.

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^{303,309,312,315,320-332}. 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 musculoskeletal injury^{17,26,303,319,321,322,333-338}. 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^{1,36,70,73,80,103,316,339}. 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^{17,26,103,115,307,308}. In reversible situations, the time-course and magnitude of recovery is markedly slower and more gradual than loss^{17,309,315,319,326,327,340,341}.

Bone loss is also uniquely layer specific within the skeleton, eloquently demonstrated in ageing and spinal cord injury cohorts^{303,342}. Specifically, through aging or following spinal cord injury, bone cross-sectional area observably loses material from the endosteal border and intra-cortically, with no clear evidence at the periosteal level^{102,343,344}. For example, individuals with traumatic paralysis prior to growth cessation develop smaller periosteal circumferences relative to non-paralysed referents, however individuals paralysed after growth cessation have similar periosteal circumferences to non-paralysed referents^{303,342,345-347}. Conversely, bone accretion can occur at the endosteal and periosteal surfaces³⁴⁸⁻³⁵⁰, however whether or not age-related endosteal and intracortical bone resorption can be reduced or prevented with skeletal loading is currently unclear^{351,352}. In contrast to deterministic mechanical loading effects, antiresorptive and proformative drugs exert their effects systemically (stochastically) through-out bone material³⁵³⁻³⁵⁵. Taken together, while cellular processes are tightly coupled, whole organ bone resorption and accretion may be situated at different locations within and along the bone, and that particular surfaces may be preferentially affected. This complex inter-play of bone loss and bone accretion across bone cross-sectional areas and along bone lengths requires dutiful consideration when designing and evaluating mechanical, dietary or pharmacological interventions.

Excessive mechanical loads supplied through repetitive and cyclical activity may also yield net-resorptive and degradative effects on bone^{38,52,74,75,356}. 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^{51,75,296,357-359}. 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^{38,51,52,74,91,356,358}. 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^{57,76,157,301,304,317,358-360}. 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^{1,17,70,157,306,361}.

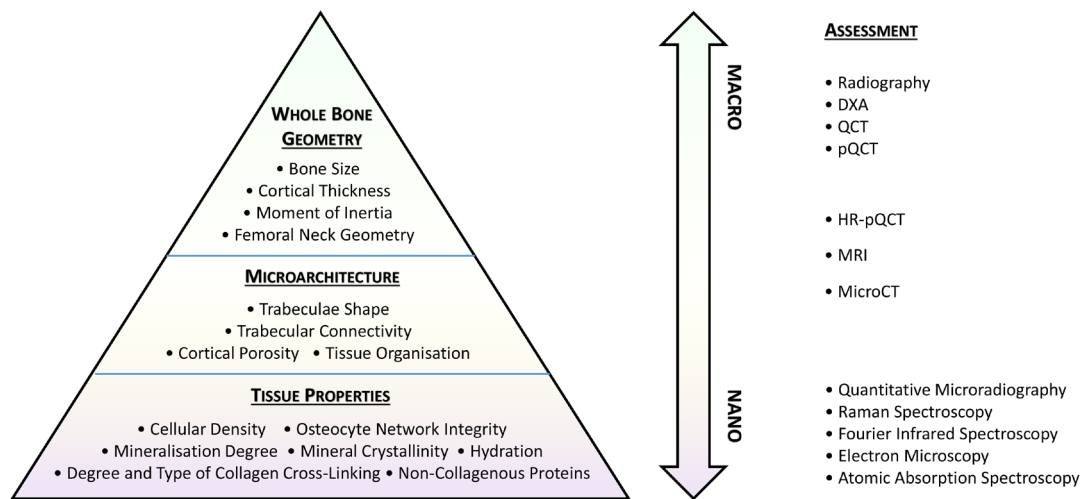


Figure 4. Material and structural determinants of bone strength or fragility (left) with associated technologies required to examine bone properties (right); along the macroscopic, microscopic and nanoscopic continuum [top to bottom], (adapted from ¹).

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^{1,24,36,362,363}. 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^{76,78,364-366}, understanding the volatile and evolving adaptations of living and responsive hard-tissue remains elusive^{24,367,368}. Modern-day advancements have attempted to overcome such limitations by developing a multitude of technologies (Figure 4) aimed at non-invasively measuring bone density, structure and strength of various depths, scales and resolutions^{1,369-372}. Owing to their relative cost, availability and levels of radiation exposure, DXA and pQCT are commonly used bone densitometry devices in clinical and research environments³⁷²⁻³⁷⁷, often supported by the collection of biochemical markers through serological and urinalytical samples as surrogate measures of bone metabolism^{87,378,379}.

Dual-energy X-ray absorptiometry

Dual-energy X-ray Absorptiometry (DXA) is a low-resolution, uniplanar, two-dimensional bone densitometry imaging device which measures full-body and segmental projections of mass quantities and densities in-vivo using low-level radiation through x-ray technology^{374,380}. 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 manner³⁸⁰⁻³⁸². Importantly, DXA quantifies areal bone mineral density (aBMD) and its derivatives (bone area and bone mineral content) in order to examine bone quality³⁸³⁻³⁸⁵, 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^{381,386-388}. 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^{386,389-394}.

Bone health and skeletal fragility diagnoses of bone disorders are clinically defined by the World Health Organisation using DXA-derived aBMD T-scores from population-based reference values, highlighting its established and reputed position as the gold standard in clinical environments^{384,395-397}. However, clinical examinations using DXA technology are inherently flawed, as bone material (architecture) and structure (size and shape) cannot be measured^{374,383,398,399}. Specifically, DXA's uniplanar, low-resolution images restrict clinicians to descriptions of whole bone mass, which only partially explains bone strength variation^{24,398,400-402}. Inaccurate diagnoses of osteoporosis therefore prevail, with many fragility fractures prevalent in categorically low-to-moderate risk individuals, classified within normal or osteopenic regions^{72,275,373,397,403}, 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

Table 3. Available biochemical markers used to examine formative, resorptive and rate of bone metabolism through serological and urinal analytical mechanisms^{87,431}.

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
Deoxypyridoline	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 ^{69,431}.

always osteoporotic^{383,384,403,404}, 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^{373,384,401,404}. Therefore, more refined and detailed analyses of bone material and structure are required for more appropriate and predictive diagnoses, potentially deliverable with other technologies^{24,383,385,399,405,406}.

peripheral Quantitative Computed Tomography

Quantitative Computed Tomography (QCT, axial; pQCT, peripheral) is a multi-planar, three-dimensional bone densitometry imaging device which measures the material and structural properties of bone at macroscopic depth, providing clinicians with more accurate descriptions of bone shape, size and quality^{399,407,408}. 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 fat⁴⁰⁹⁻⁴¹¹. 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 mass⁴¹⁰⁻⁴¹⁴. Diagnostically, this enables pQCT to address many limitations previously experienced through DXA examinations which provide precise, stable and reliable measures of bone and muscle components^{333,376,383,399,407,411,412,415}.

Bone quality and skeletal fragility examinations using pQCT are superior to those provided by DXA^{373,408,414,416}. 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^{383,408,412-415,417,418}. 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 emerging status as an alternate imaging device in clinical and research environments^{373,399,419-422}. Supplementing DXA measures with pQCT measures has been suggested as a potential solution for a detailed insight of bone strength adaptation and fracture risk with clinically relevant reference values⁴²³. Some forms of pQCT are limited to macroscopic depth, however the emerging use of micro-scanners (HR-pQCT) provides higher resolution images that are capable of detecting critically important microarchitectural features including trabecular thickness, connectivity and number; cortical porosity; volume fraction; and arterial calcification^{127,369,417,418}. HR-pQCT is still gaining ascendancy in clinical and research settings due to its relative infancy in development, high associated cost, and limited ability to access an array of peripheral skeletal sites. HR-pQCT is likely to increase in popularity given the diagnostic importance and catastrophic consequence of microarchitectural deterioration in disease-states and advanced ageing, particularly as its technology and capabilities evolve^{80,127,275,403,424}.

Biochemical markers

Serological and urinal analytical 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 skeleton⁴²⁵⁻⁴²⁸. 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^{318,378,429,430}.

Biomarkers become clinically useful to examine bone turnover rates underpinning bone health or skeletal disease (Table 3) and importantly quantify acute and chronic metabolic alterations to experienced stimulus and targeted interventions^{87,368,379,425-427,432}. 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^{87,368,433,434}. 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^{368,433,434}. 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^{87,378,427,435,436}.

Conclusion and future research

Bone is impressive in its design, architecture and maintenance as a living biomaterial with distinct porosities (trabecular and cortical), tissues (woven and lamellar) and materials (organic and inorganic) that, together, form a robust multidimensional structure (macroscopic to nanoscopic) with a deliberate mass (size, geometry and density) aimed at achieving optimal mechanical strength to support locomotion and activities of daily living. Growth, development and homeostasis is eloquently achieved through tightly coupled cellular processes (osteoblasts, osteoclasts, osteocytes and bone lining cells) which underpin bone quality and the continual generation and regeneration of bone in response to mechanical loading and damage acquisition through mechanotransduction.

Although, broadly speaking, bone resorption and formation are tightly coupled, the balance between these two processes can tilt to favour one or the other resulting in net gain or net loss. Key reasons for shifts in otherwise homeostatic balance can be due to the presence or absence of mechanical loading, metabolism (for example, withdrawal of female reproductive hormones through menopause), or pathology. Moreover during growth and development, formation and resorption are not necessarily co-localised in bone (for example, transformative morphological narrowing of long bone metaphyses to become diaphyseal). In addition to understanding the net effect, it is important to realise that the timing and duration of bone resorption and formation do not necessarily happen concurrently. Rather, bone resorption takes less time than formation and typically precedes formation. Additionally, bone formation occurs across essentially two phases: 1) laying down the collagen

meshwork, and 2) subsequent mineralisation (explained further in our companion review paper¹²). In terms of the gross bone morphology, it bears repeating that responses to mechanical loads are site-specific. That is, it is entirely possible to have strong lower limb skeletal structures yet weak upper limb skeletal structures as is the case in endurance runners for example. Moreover, even within a long bone, at a particular site-specific location along the length of the bone, it is possible to lay new bone material in particular directions, while the direction at a right angle remains unmodified by loads, and similarly, the diaphysis may adapt while no changes are observed in the epiphysis.

This review highlights the complexity of evolving bone morphology, specific to bone anatomy and physiology, underpinning the biological basis of bone strength, and the many cooperative or competing processes required to delicately maintain bone health. Taking the above together, we assert the need for clinicians and researchers to understand and thus consider the underlying physiology and technical limitations of assessing bone as paramount in devising appropriate clinical measurement and active monitoring strategies to allow timely yet accurate assessments which capture the properties of interest. For example, attempting to capture bone formation with x-ray-based, bone densitometric methods will fail unless sufficient time for mineralisation is allowed as only the mineral incorporated into the bone contributes meaningfully to absorbing the radiation used to assess the bone. To this end, for clinical or research interventions aiming to evaluate observed x-ray based, densitometric changes in such properties, a minimum of 6 to 12 months would be our recommendation. Similarly, in-vivo and non-invasive methodologies to assess the quality and properties of type 1 collagen at given bone sites or skeletal regions is a potentially necessary yet presently absent assessment, relying solely on systemic biomarkers (from serum or urine) or bone biopsy, thus limiting the accessibility and our understanding of the organic matrix of bone. Owing to the dynamic nature of bone biology, and its complex and routine interaction and communication between bone cells and other bodily organs, a deeper recognition and understanding of the governance and subservience of various processes and organs within the human body, such as muscle-bone interactions (described in our companion review¹²), will continue to produce new knowledge and assist clinicians and researchers in the development new therapeutic approaches to bone diseases, and management of bone health across the lifespan.

References

1. Fonseca H, Moreira-Gonçalves D, Coriolano H-JA, Duarte JA. Bone quality: The determinants of bone strength and fragility. *Sports Med* 2014;44(1):37-53.
2. Cardinale M, Newton R, Nosaka K. Strength and conditioning: Biological principles and practical applications. Portland, OR: John Wiley & Sons; 2011.

3. Manske SL, Lorincz CR, Zernicke RF. Bone health: Part 2, physical activity. *Sports Health* 2009;1(4):341-6.
4. Ritchie RO, Buehler MJ, Hansma P. Plasticity and toughness in bone. *Phys Today* 2009;62(6):41-7.
5. Korhonen MT, Heinonen A, Siekkinen J, Isolehto J, Alén M, Kiviranta I, et al. Bone density, structure and strength, and their determinants in aging sprint athletes. *Med Sci Sports Exerc* 2012;44(12):2340-9.
6. Greene DA, Naughton GA, Bradshaw E, Moresi M, Ducher G. Mechanical loading with or without weight-bearing activity: influence on bone strength index in elite female adolescent athletes engaged in water polo, gymnastics, and track-and-field. *J Bone Miner Metab* 2012;30(5):580-7.
7. Gong H, Zhu D, Gao J, Lv L, Zhang X. An adaptation model for trabecular bone at different mechanical levels. *Biomed Eng Online* 2010;9:32-49.
8. Turner CH. Skeletal adaptation to mechanical loading. *Clin Rev Bone Miner Metab* 2007;5(4):181-94.
9. Greene D, Naughton G, Briody J, Kemp A, Woodhead H. Assessment of bone strength at differentially-loaded skeletal regions in adolescent middle-distance runners. *J Sci Med Sport* 2006;9(3):221-30.
10. Lorentzon M, Mellström D, Ohlsson C. Association of amount of physical activity with cortical bone size and trabecular volumetric BMD in young adult men: the GOOD study. *J Bone Miner Res* 2005;20(11):1936-43.
11. Frost HM. A 2003 update of bone physiology and Wolff's Law for clinicians. *Angle Orthod* 2004;74(1):3-15.
12. Hart NH, Nimphius S, Rantalainen T, Ireland A, Siafarikas A, Newton RU. Mechanical basis of bone strength: influence of bone material, bone structure and muscle action. *J Musculoskelet Neuronal Interact* 2017;17(3):114-39.
13. Nguyen J, Tang SY, Nguyen D, Alliston T. Load regulates bone formation and Sclerostin expression through a TGF β -dependent mechanism. *PLoS One* 2013;8(1):e53813.
14. Belavý DL, Beller G, Armbrrecht G, Perschel FH, Fitzner R, Bock O, et al. Evidence for an additional effect of whole-body vibration above resistive exercise alone in preventing bone loss during prolonged bed rest. *Osteoporos Int* 2011;22(1581-1591).
15. Chen J-H, Liu C, You L, Simmons CA. Boning up on Wolff's Law: mechanical regulation of the cells that make and maintain bone. *J Biomech* 2010;43(1):108-18.
16. Kohrt WM, Barry DW, Schwartz RS. Muscle forces or gravity: What predominates mechanical loading on bone? *Med Sci Sports Exerc* 2009;41(11):2050-5.
17. Robling AG, Castillo AB, Turner CH. Biomechanical and molecular regulation of bone remodeling. *Annu Rev Biomed Eng.* 8. Palo Alto: Annual Reviews; 2006. p. 455-98.
18. Nordin M, Frankel VH. Basic biomechanics of the musculoskeletal system. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2012.
19. Crockett JC, Rogers MJ, Coxon FP, Hocking LJ, Helfrich MH. Bone remodelling at a glance. *J Cell Sci* 2011;124:991-8.
20. Eriksen EF. Cellular mechanisms of bone remodeling. *Rev Endocr Metab Disord* 2010;11(4):219-27.
21. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. *J Biol Chem* 2010;285(33):25103-8.
22. Clarke B. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol* 2008;3(Supplement 3):S131-9.
23. Hadjidakis DJ, Androulakis II. Bone remodeling. *Ann N Y Acad Sci* 2006;1092(1):385-96.
24. Seeman E, Delmas PD. Bone quality: The material and structural basis of bone strength and fragility. *N Engl J Med* 2006;354(21):2250-61.
25. Singh A, Mehdi AA, Srivastava RN, Verma NS. Immunoregulation of bone remodelling. *Int J Crit Illn Inj Sci* 2012;2(2):75-81.
26. Feng X, McDonald JM. Disorders of bone remodeling. *Annu Rev Pathol-Mech* 2011;6:121-45.
27. Hill PA, Tumber A. Ceramide-induced cell death/survival in murine osteoblasts. *J Endocrinol* 2010;206:225-33.
28. Seeman E. Bone modeling and remodeling. *Crit Rev Eukaryot Gene Expr* 2009;19(3):219.
29. Filvaroff E, Derynck R. Bone remodelling: a signalling system for osteoclast regulation. *Curr Biol* 1998; 8(19):R679-R82.
30. Erlebacher A, Filvaroff EH, Gitelman SE, Derynck R. Toward a molecular understanding of skeletal development. *Cell* 1995;80(3):371-8.
31. Giusti A, Bianchi G. Treatment of primary osteoporosis in men. *Clin Interv Aging* 2015;10:105-15.
32. Body JJ, Bergmann P, Boonen S, Boutsen Y, Bruyere O, Devogelaer JP, et al. Non-pharmacological management of osteoporosis: A consensus of the Belgian Bone Club. *Osteoporos Int* 2011;22(11):2769-88.
33. Martin RM, Correa PHS. Bone quality and osteoporosis therapy. *Rev Assoc Med Bras.* 2010;54(2):186-99.
34. Khosla S, Amin S, Orwoll E. Osteoporosis in men. *Endocr Rev* 2008;29(4):441-64.
35. Orwoll ES, Klein RF. Osteoporosis in men. *Endocr Rev* 1995;16(1):87-116.
36. Järvinen TLN, Sievänen H, Jokihaara J, Einhorn TA. Revival of bone strength: The bottom line. *J Bone Miner Res* 2005;20(5):717-20.
37. Kemmler W, von Stengel S. Exercise and osteoporosis-related fractures: Perspectives and recommendations of the sports and exercise scientist. *Phys Sportsmed* 2011;39(1):142-57.
38. Edwards WB, Taylor D, Rudolphi TJ, Gillette JC, Derrick TR. Effects of stride length and running mileage on a probabilistic stress fracture model. *Med Sci Sports Exerc* 2009;41(12):2177-84.
39. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. American College of Sports Medicine position stand: Physical activity and bone health (Special Communications). *Med Sci Sports Exerc* 2004;36(11):1985-96.

40. Iyo T, Maki Y, Sasaki N, Nakata M. Anisotropic viscoelastic properties of cortical bone. *J Biomech* 2004;37(9):1433-7.
41. Doblaré M, Garcia JM. Anisotropic bone remodelling model based on a continuum damage-repair theory. *J Biomech* 2002;35(1):1-17.
42. Rantalainen T, Nikander R, Daly RM, Heinonen A, Sievänen H. Exercise loading and cortical bone distribution at the tibial shaft. *Bone* 2011;48(4):786-91.
43. Nikander R, Kannus P, Rantalainen T, Uusi-Rasi K, Heinonen A, Sievänen H. Cross-sectional geometry of weight-bearing tibia in female athletes subjected to different exercise loadings. *Osteoporos Int* 2010a;21(10):1687-94.
44. Rantalainen T, Nikander R, Heinonen A, Suominen H, Sievänen H. Direction-specific diaphyseal geometry and mineral mass distribution of tibia and fibula: A pQCT study of female athletes representing different exercise loading types. *Calcif Tissue Int* 2010;86(6):447-54.
45. Ducher G, Hill B, Angeli T, Bass SL, Eser P. Comparison of pQCT parameters between ulna and radius in retired elite gymnasts: the skeletal benefits associated with long-term gymnastics are bone- and site-specific. *J Musculoskelet Neuronal Interact* 2009;9(4):247-55.
46. Hart NH, Nimphius S, Weber J, Spiteri T, Rantalainen T, Dobbin M, et al. Musculoskeletal asymmetry in football athletes: A product of limb function over time. *Med Sci Sports Exerc* 2016;48(7):1379-87.
47. Hart NH, Dobbin M, Weber J, Nimphius S, Newton RU. Physical load tolerance differs between kicking and support limbs in Australian footballers. *J Aust Strength Cond* 2013a;21(S2):102-4.
48. Hart NH, Nimphius S, Weber J, Dobbin M, Newton RU. Lower body bone mass characteristics of elite, sub-elite and amateur Australian footballers. *J Aust Strength Cond* 2013b;21(1):50-3.
49. Lambert C, Beck BR, Harding AT, Watson SL, Weeks BK. Regional changes in indices of bone strength of upper and lower limbs in response to high-intensity impact loading or high-intensity resistance training. *Bone* 2019.
50. Corrarino JE. Stress fractures in runners. *Nurse Pract* 2012;37(6):18-28.
51. Moran DS, Finestone AS, Arbel Y, Shabshin N, Laor A. A simplified model to predict stress fracture in young elite combat recruits. *J Strength Cond Res* 2012;26(9):2585-92.
52. Harrast MA, Colonna D. Stress fractures in runners. *Clin Sports Med* 2010;29(3):399.
53. Twomey D, Finch C, Roediger E, Lloyd DG. Preventing lower limb injuries: Is the latest evidence being translated into the football field? *J Sci Med Sport* 2009;12(4):452-6.
54. Gabbe B, Bennell KL, Finch CF, Wajswelner H, Orchard JW. Predictors of hamstring injury at the elite level of Australian Football. *Scand J Med Sci Sports* 2006b;16:7-13.
55. Murphy D, Connolly D, Beynon B. Risk factors for lower extremity injury: a review of the literature. *Br J Sports Med* 2003;37(1):13-29.
56. Taylor D, Lee TC. Microdamage and mechanical behaviour: predicting failure and remodelling in compact bone. *J Anat* 2003;203(2):203-11.
57. Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. *J Bone Miner Res* 1997;12(1):6-15.
58. Vainionpää A, Korpelainen R, Väänänen HK, Haapalahti J, Jämsä T, Leppäluoto J. Effect of impact exercise on bone metabolism. *Osteoporos Int* 2009;20(10):1725-33.
59. Reis J, Capela e Silva F, Queiroga M, Lucena S, Potes J. Bone mechanotransduction: A review. *J Biomed Bioeng* 2011;2.
60. Bonewald LF. Mechanosensation and transduction in osteocytes. *Bonekey Osteovision* 2006;3:7-15.
61. Klein-Nulend J, Bacabac R, Mullender M. Mechanobiology of bone tissue. *Pathol Biol (Paris)* 2005;53(10):576-80.
62. Robling AG, Turner CH. Mechanotransduction in bone: genetic effects on mechanosensitivity in mice. *Bone* 2002;31(5):562-9.
63. Humphrey JD, Dufresne ER, Schwartz MA. Mechanotransduction and extracellular matrix homeostasis. *Nat Rev Mol Cell Biol* 2014.
64. Thompsona WR, Rubinb CT, Rubina J. Mechanical regulation of signaling pathways in bone. *Gene* 2012;503(2):179-93.
65. Ozcivici E, Luu YK, Adler B, Qin Y-X, Rubin J, Judex S, et al. Mechanical signals as anabolic agents in bone. *Nat Rev Rheumatol* 2010;6(1):50-9.
66. Bonewald LF. The amazing osteocyte. *J Bone Miner Res* 2011;26(2):229-38.
67. Bonewald LF. Osteocytes as dynamic multifunctional cells. *Ann N Y Acad Sci* 2007;1116:281-90.
68. Jenkins M, Hart NH, Nimphius S, Chivers P, Rantalainen T, Rothacker KM, et al. Characterisation of peripheral bone mineral density in youth at risk of secondary osteoporosis - a preliminary insight. *J Musculoskelet Neuronal Interact* 2020;20(1).
69. Pearson OM, Lieberman DE. The aging of Wolff's "law": Ontogeny and responses to mechanical loading in cortical bone. *Am J Phys Anthropol* 2004;125(S39):63-99.
70. Davison KS, Siminoski K, Adachi J, Hanley DA, Goltzman D, Hodsman AB, et al. Bone strength: The whole is greater than the sum of its parts. *Semin Arthritis Rheum* 2006;36(1):22-31.
71. Seeman E. Pathogenesis of bone fragility in women and men. *Lancet* 2002;359(9320):1841-50.
72. Friedman AW. Important determinants of bone strength: Beyond bone mineral density. *J Clin Rheumatol* 2006;12(2):70-7.
73. Bouxsein ML, Karasik D. Bone geometry and skeletal fragility. *Curr Osteoporos Rep* 2006;4(2):49-56.

74. Popp KL, Hughes JM, Smock AJ, Novotny SA, Stovitz SD, Koehler SM, et al. Bone geometry, strength, and muscle size in runners with a history of stress fracture. *Med Sci Sports Exerc* 2009;41(12):2145-50.
75. Warden SJ, Hurst JA, Sanders MS, Turner CH, Bur DB, Li J. Bone adaptation to a mechanical loading program significantly increases skeletal fatigue resistance. *J Bone Miner Res* 2005;20(5).
76. Tommasini SM, Nasser P, Hu B, Jepsen KJ. Biological co-adaptation of morphological and composition traits contributes to mechanical functionality and skeletal fragility. *J Bone Miner Res* 2008;23(2).
77. Franklyn M, Oakes B, Field B, Wells P, Morgan D. Section modulus is the optimum geometric predictor for stress fractures and medial tibial stress syndrome in both male and female athletes. *Am J Sports Med* 2008;36(6):1179-89.
78. Tommasini SM, Nasser P, Schaffler MB, Jepsen KJ. Relationship between bone morphology and bone quality in male tibias: Implications for stress fracture risk. *J Bone Miner Res* 2005;20(8):1372-80.
79. Seeman E. Age- and menopause-related bone loss compromise cortical and trabecular microstructure. *J Gerontol A Biol Sci Med Sci* 2013;68(10):1218-25.
80. Brandi ML. Microarchitecture, the key to bone quality. *Rheumatology* 2009;48:8.
81. Rho J-Y, Kuhn-Spearing L, Zioupos P. Mechanical properties and the hierarchical structure of bone. *Med Eng Phys* 1998;20(2):92-102.
82. Seeman E. Bone quality: The material and structural basis of bone strength. *J Bone Miner Metab* 2008; 26(1):1-8.
83. Nikander R, Sievänen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. *BMC Med* 2010;8(1):47.
84. Sandhu SK, Hampson G. The pathogenesis, diagnosis, investigation and management of osteoporosis. *J Clin Pathol* 2011;64:1042-50.
85. Karinkanta S, Heinonen A, Sievänen H, Uusi-Rasi K, Pasanen M, Ojala K, et al. A multi-component exercise regimen to prevent functional decline and bone fragility in home-dwelling elderly women: randomized, controlled trial. *Osteoporos Int* 2007;18(4):453-62.
86. Kannus P, Uusi-Rasi K, Palvanen M, Parkkari J. Non-pharmacological means to prevent fractures among older adults. *Ann Med* 2005;37(4):303-10.
87. Banfi G, Lombardi G, Colombini A, Lippi G. Bone metabolism markers in sports medicine. *Sports Med* 2010;40(8):697-714.
88. Taichman RS. Blood and bone: two tissues whose fates are intertwined to create the hematopoietic stem-cell niche. *Blood* 2005;105(7):2631-9.
89. Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec* 2003;275(2):1081-101.
90. Burr DB. Muscle strength, bone mass, and age-related bone loss. *J Bone Miner Res*. 1997;12(10):1547-51.
91. Harada S-I, Rodan GA. Control of osteoblast function and regulation of bone mass. *Nature* 2003; 423(6937):349-55.
92. Turner CH, Pavalko FM. Mechanotransduction and functional response of the skeleton to physical stress: The mechanisms and mechanics of bone adaptation. *J Orthop Sci* 1998;3(6):346-55.
93. Schwab P, Scalapino K. Exercise for bone health: Rationale and prescription. *Curr Opin Rheumatol* 2011;23(2):137-41.
94. Karlsson MK, Rosengren BE. Physical activity as a strategy to reduce the risk of osteoporosis and fragility fractures. *Int J Clin Endocrinol Metab* 2012;10(3):527-36.
95. Marieb E, Hoehn K. *Human Anatomy & Physiology*. 9th ed: Pearson Education; 2013.
96. White TD, Black MT, Folken PA. *Human osteology*. 3rd ed. San Francisco: Elsevier; 2012.
97. Orwoll ES. Toward an expanded understanding of the role of the periosteum in skeletal health. *J Bone Miner Res* 2003;18(6):949-54.
98. Sikavitsas VI, Temenoff JS, Mikos AG. Biomaterials and bone mechanotransduction. *Biomaterials* 2001;22(19):2581-93.
99. Beaupied H, Lespessailles E, Benhamou C-L. Evaluation of macrostructural bone biomechanics. *Joint Bone Spine* 2007;74(3):233-9.
100. Currey JD. How well are bones designed to resist fracture? *J Bone Miner Res* 2003;18(4):591-8.
101. Currey JD. The many adaptations of bone. *J Biomech* 2003;36(10):1487-95.
102. Zebaze RMDD, Ghasem-Zadeh A, Bohte AP, Iuliano-Burns SP, Mirams MP, Price RIP, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. *Lancet* 2010;375(9727):1729-36.
103. Mosekilde L, Ebbesen E, Tornvig L, Thomsen J. Trabecular bone structure and strength-remodelling and repair. *J Musculoskelet Neuronal Interact* 2000;1(1):25-30.
104. Weiner S, Wagner HD. The material bone: Structure-mechanical function relations. *Annu Rev Mater Sci* 1998;28(1):271-98.
105. Keaveny TM, Hayes WC. A 20-year perspective on the mechanical properties of trabecular bone. *J Biomech Eng* 1993;115(4B):534-42.
106. Huiskes R. If bone is the answer, then what is the question? *J Anat* 2000;197(02):145-56.
107. Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. *Rheumatology* 2008;47(4):iv2-iv8.
108. Yeni YN, Brown CU, Wang Z, Norman TL. The influence of bone morphology on fracture toughness of the human femur and tibia. *Bone* 1997;21(5):453-9.
109. Huiskes R, Ruimerman R, Van Lenthe GH, Janssen JD. Effects of mechanical forces on maintenance and adaptation of form in trabecular bone. *Nature* 2000;405(6787):704-6.

110. Parfitt AM. Osteonal and hemi-osteonal remodeling: The spatial and temporal framework for signal traffic in adult human bone. *J Cell Biochem* 1994a;55(3):273-86.
111. Szulc P, Seeman E, Duboeuf F, Sornay-Rendu E, Delmas PD. Bone fragility: Failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. *J Bone Miner Res* 2006;21(12).
112. Travlos GS. Normal structure, function and histology of bone marrow. *Toxicol Pathol* 2006;34(5):548-65.
113. Ruimerman R, Hilbers P, Rietbergen Bv, Huiskes R. A theoretical framework for strain-related trabecular bone maintenance and adaptation. *J Biomech* 2005;38:931-41.
114. Jacobs CR. The mechanobiology of cancellous bone structural adaptation. *J Rehabil Res Dev* 2000;37(2):209-16.
115. Ruimerman R, Rietbergen BV, P.Hilbers, Huiskes R. The effects of trabecular-bone loading variables on the surface signaling potential for bone remodeling and adaptation. *Ann Biomed Eng* 2005;33(1):71-8.
116. Ruimerman R, Huiskes R, Van Lenthe G, Janssen J. A computer-simulation model relating bone-cell metabolism to mechanical adaptation of trabecular architecture. *Comput Methods Biomech Biomed Engin* 2001;4(5):433-48.
117. Kopperdahl DL, Keaveny TM. Yield strain behavior of trabecular bone. *J Biomech* 1998;31(7):601-8.
118. Ding M, Dalstra M, Danielsen CC, Kabel J, Hvid I, Linde F. Age variations in the properties of human tibial trabecular bone. *J Bone Joint Surg Br* 1997;79(6):995-1002.
119. Augat P, Schorlemmer S. The role of cortical bone and its microstructure in bone strength. *Age Ageing* 2006;35(S2):ii27-ii31.
120. Carnelli D, Vena P, Dao M, Ortiz C, Contro R. Orientation and size-dependent mechanical modulation within individual secondary osteons in cortical bone tissue. *J R Soc Interface* 2013;10(81).
121. Techawinboonwong A, Song HK, Leonard MB, Wehrli FW. Cortical bone water: *In vivo* quantification with ultrashort echo-time MR Imaging 1. *Radiology* 2008;248(3):824-33.
122. Seeman E. The periosteum - A surface for all seasons. *Osteoporos Int* 2007;18(2):123-8.
123. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis 1. *Endocr Rev* 2000;21(2):115-37.
124. Burr D. The contribution of the organic matrix to bone's material properties. *Bone* 2002;31(1):8-11.
125. Sevostianov I, Kachanov M. Impact of the porous microstructure on the overall elastic properties of the osteonal cortical bone. *J Biomech* 2000;33:881-8.
126. Bayraktar HH, Morgan EF, Niebur GL, Morris GE, Wong EK, Keaveny TM. Comparison of the elastic and yield properties of human femoral trabecular and cortical bone tissue. *J Biomech* 2004;37(1):27-35.
127. Liu XS, Zhang XH, Sekhon KK, Adams MF, McMahon DJ, Bilezikian JP, et al. High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. *J Bone Miner Res* 2010;25(4):746-56.
128. Su X, Sun K, Cui FZ, Landis WJ. Organization of apatite crystals in human woven bone. *Bone* 2003;32(2):150-62.
129. Turner CH, Forwood M, Rho JY, Yoshikawa T. Mechanical loading thresholds for lamellar and woven bone formation. *J Bone Miner Res* 1994;9(1):87-97.
130. Bala Y, Farlay D, Boivin G. Bone mineralization: from tissue to crystal in normal and pathological contexts. *Osteoporos Int* 2013;24(8):2153-66.
131. Yeni Y, Brown C, Norman T. Influence of bone composition and apparent density on fracture toughness of the human femur and tibia. *Bone* 1998;22(1):79-84.
132. Hangartner TN, Gilsanz V. Evaluation of cortical bone by computed tomography. *J Bone Miner Res* 1996;11(10):1518-25.
133. Shapiro F. Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. *Eur Cell Mater* 2008;15:53-76.
134. Weiner S, Traub W, Wagner HD. Lamellar bone: Structure-function relations. *J Struct Biol* 1999;126(3):241-55.
135. Forwood M, Turner C. Skeletal adaptations to mechanical usage: results from tibial loading studies in rats. *Bone* 1995;17(4):S197-S205.
136. Kusuzaki K, Kageyama N, Shinjo H, Takeshita H, Murata H, Hashiguchi S, et al. Development of bone canaliculi during bone repair. *Bone* 2000;27(5):655-9.
137. McBride SH, Silva MJ. Adaptive and injury response of bone to mechanical loading. *BoneKey Rep* 2012;1:192.
138. Marsell R, Einhorn TA. The biology of fracture healing. *Injury* 2011;42:551-5.
139. Fazzalari NL. Bone fracture and bone fracture repair. *Osteoporos Int* 2011;22(6):2003-6.
140. Zioupos P, Currey JD. The extent of microcracking and the morphology of microcracks in damaged bone. *J Mater Sci* 1994;29(4):978-86.
141. Burger EH, Klein Nulend J. Mechanotransduction in bone—role of the lacuno-canalicular network. *FASEB J* 1999;13(9001):S101-S12.
142. Martin E, Shapiro JR. Osteogenesis Imperfecta: Epidemiology and pathophysiology. *Curr Osteoporos Rep* 2007;5(3):91-7.
143. Viguet-Carrin S, Garnero P, Delmas P. The role of collagen in bone strength. *Osteoporos Int* 2006;17(3):319-36.
144. Fratzl P, Gupta HS, Paschalis EP, Roschger P. Structure and mechanical quality of the collagen-mineral, nano-composite in bone. *J Mater Chem* 2004;14(14):2115-23.
145. Wang X, Puram S. The toughness of cortical bone and its relationship with age. *Ann Biomed Eng* 2004;32(1):123-35.
146. Yamashita J, Li X, Furman BR, Rawls HR, Wang X,

- Agrawal CM. Collagen and bone viscoelasticity: A dynamic mechanical analysis. *J Biomed Mater Res* 2002;63(1).
147. Golub EE. Biomineralization and matrix vesicles in biology and pathology. *Semin Immunopathol* 2011;33(5):409-17.
 148. Farlay D, Panczer G, Rey C, Delmas PD, Boivin G. Mineral maturity and crystallinity index are distinct characteristics of bone mineral. *J Bone Miner Metab* 2010;28(4):433-45.
 149. Golub EE. Role of matrix vesicles in biomineralization. *Biochimica et Biophysica Acta (BBA)-General Subjects* 2009;1790(12):1592-8.
 150. Bouxsein ML. Bone quality: Where do we go from here? *Osteoporos Int* 2003;14(S5):118-27.
 151. Boivin G, Meunier PJ. Changes in bone remodeling rate influence the degree of mineralization of bone. *Connect Tissue Res* 2002;43(2-3):535-7.
 152. Boivin G, Meunier PJ. The degree of mineralization of bone tissue measured by computerized quantitative contact microradiography. *Calcif Tissue Int* 2002;70(6):503-11.
 153. Boivin G, Bala Y, Doublier A, Farlay D, Ste-Marie L, Meunier P, et al. The role of mineralization and organic matrix in the microhardness of bone tissue from controls and osteoporotic patients. *Bone* 2008;43(3):532-8.
 154. Allen MR, Burr DB. Three years of alendronate treatment results in similar levels of vertebral microdamage as after one year of treatment. *J Bone Miner Res* 2007;22(11):1759-65.
 155. Follet H, Boivin G, Rumelhart C, Meunier PJ. The degree of mineralization is a determinant of bone strength: a study on human calcanei. *Bone* 2004;34(5):783-9.
 156. Bala Y, Farlay D, Delmas PD, Meunier PJ, Boivin G. Time sequence of secondary mineralization and microhardness in cortical and cancellous bone from ewes. *Bone* 2010;46(4):1204-12.
 157. Taylor D, Hazenberg JG, Lee TC. Living with cracks: Damage and repair in human bone. *Nat Mater* 2007;6(4):263-8.
 158. Stern AR, Nicoletta DP. Measurement and estimation of osteocyte mechanical strain. *Bone* 2013;54(2):191-5.
 159. Parfitt AM. The two faces of growth: Benefits and risks to bone integrity. *Osteoporos Int* 1994b;4(6):382-98.
 160. Karsenty G, Kronenburg HM, Settembre C. Genetic control of bone formation. *Annu Rev Cell Dev Biol* 2009;25:629-48.
 161. Karsenty G. Transcriptional control of skeletogenesis. *Annu Rev Genom Hum* 2008;9:183-96.
 162. Franz-Odenaal TA, Hall BK, Witten PE. Buried alive: How osteoblasts become osteocytes. *Dev Dyn* 2006;235(1):176-90.
 163. Mizoguchi T, Muto A, Udagawa N, Arai A, Yamashita T, Hosoya A, et al. Identification of cell cycle-arrested quiescent osteoclast precursors *in vivo*. *J Cell Biol* 2009;184(4):541-54.
 164. Yavropoulou MP, Yovos JG. Osteoclastogenesis - Current knowledge and future perspectives. *J Musculoskelet Neuronal Interact* 2008;8(3):204-16.
 165. Lu XL, Huo B, Chiang V, Guo XE. Osteocytic network is more responsive in calcium signaling than osteoblastic network under fluid flow. *J Bone Miner Res* 2012;27(3):563-74.
 166. Marotti G. The structure of bone tissues and the cellular control of their deposition. *Ital J Anat Embryol* 1996;101(4):25.
 167. Bonewald LF. Generation and function of osteocyte dendritic processes. *J Musculoskelet Neuronal Interact* 2005;5(4):321-4.
 168. Aarden EM, Burger EH, Nijweide PJ. Function of osteocytes in bone. *J Cell Biochem* 1994;55(3):287.
 169. Sapir-Koren R, Livshits G. Bone mineralization and regulation of phosphate homeostasis. *IBMS BoneKey* 2011;8(6):286-300.
 170. Leppanen M, Aaltonen S, Parkkari J, Heinonen A, Kujala UM. Interventions to prevent sports related injuries: A systematic review and meta-analysis of randomised controlled trials. *Sports Med* 2014;44(4):473-86.
 171. Venken K, Callewaert F, Boonen S, Vanderschueren D. Sex hormones, their receptors and bone health. *Osteoporos Int* 2008;19(11):1517-25.
 172. Lindsay R. Hormones and bone health in postmenopausal women. *Endocrine* 2004;24(3):223-30.
 173. Rizzoli R, Bonjour J, Ferrari S. Osteoporosis, genetics and hormones. *J Mol Endocrinol* 2001;26(2):79-94.
 174. Imai Y, Youn M-Y, Inoue K, Takada I, Kouzmenko A, Kato S. Nuclear receptors in bone physiology and diseases. *Physiol Rev* 2013;93(2):481-523.
 175. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol* 2013;9(12):699-712.
 176. Karsenty G, Yadav V. Regulation of bone mass by serotonin: Molecular biology and therapeutic implications. *Annu Rev Med* 2011;62:323-31.
 177. Fukumoto S, Martin TJ. Bone as an endocrine organ. *Trends Endocrinol Metab* 2009;20(5):230-6.
 178. Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. *Trends Endocrinol Metab* 2012;23(11):576-81.
 179. Ducy P. The role of osteocalcin in the endocrine cross-talk between bone remodelling and energy metabolism. *Diabetologia* 2011;54(6):1291-7.
 180. Hamilton EJ, Ghasem-Zadeh A, Gianatti E, Lim-Joon D, Bolton D, Zebaze R, et al. Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. *J Clin Endocrinol Metab* 2010;95(12):E456-E63.
 181. Ribot CA, Trémollières FA. Effect of estrogens on bone and other systems and hormonal substitute treatment. *Curr Opin Orthop* 1997;8(5):45-52.
 182. Lanyon L. Using functional loading to influence bone mass and architecture: objectives, mechanisms, and relationship with estrogen of the mechanically adaptive process in bone. *Bone* 1996;18(1):S37-S43.
 183. Britto JM, Fenton AJ, Holloway WR, Nicholson GC.

- Osteoblasts mediate thyroid hormone stimulation of osteoclastic bone resorption. *Endocrinology* 1994;134(1):169-76.
184. Fuqua JS, Rogol AD. Neuroendocrine alterations in the exercising human: Implications for energy homeostasis. *Metabolism* 2013;62(7):911-21.
 185. Sinnesael M, Claessens F, Boonen S, Vanderschueren D. Novel insights in the regulation and mechanism of androgen action on bone. *Curr Opin Endocrinol Diabetes Obes* 2013;20(3):240-4.
 186. Colaianne G, Sun L, Di Benedetto A, Tamma R, Zhu L-L, Cao J, et al. Bone marrow oxytocin mediates the anabolic action of estrogen on the skeleton. *J Biol Chem* 2012;287(34):29159-67.
 187. Karsenty G. Bone endocrine regulation of energy metabolism and male reproduction. *CR biologies* 2011;334(10):720-4.
 188. Karsenty G. Convergence between bone and energy homeostases: Leptin regulation of bone mass. *Cell Metab* 2006;4(5):341-8.
 189. Godfrey RJ, Madgwick Z, Whyte GP. The exercise-induced growth hormone response in athletes. *Sports Med* 2003;33(8):599-613.
 190. Ohlsson C, Bengtsson B-Ak, Isaksson OG, Andreassen TT, Sootweg MC. Growth hormone and bone 1. *Endocr Rev* 1998;19(1):55-79.
 191. Agas D, Sabbieti MG, Marchetti L. Endocrine disruptors and bone metabolism. *Arch Toxicol* 2013;87(4):735-51.
 192. Esbrit P, Alcaraz MJ. Current perspectives on parathyroid hormone (PTH) and PTH-related protein (PTHrP) as bone anabolic therapies. *Biochem Pharmacol* 2013;85(10):1417-23.
 193. Colaianne G, Tamma R, Di Benedetto A, Yuen T, Sun L, Zaidi M, et al. The oxytocin-bone axis. *J Neuroendocrinol* 2014;26(2):53-7.
 194. Csakvary V, Puskas T, Oroszlan G, Lakatos P, Kalman B, Kovacs GL, et al. Hormonal and biochemical parameters correlated with bone densitometric markers in prepubertal Hungarian children. *Bone* 2013;54(1):106-12.
 195. Dhanwal DK. Thyroid disorders and bone mineral metabolism. *Indian J Endocrinol Metab* 2011;15:S107.
 196. Isaacs CM, Zaidi M, Blair HC. ACTH is a novel regulator of bone mass. *Ann N Y Acad Sci* 2010;1192(1):110-6.
 197. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. *J Clin Invest* 2008;118:3820-8.
 198. Fukushima N, Hanada R, Teranishi H, Fukue Y, Tachibana T, Ishikawa H, et al. Ghrelin directly regulates bone formation. *J Bone Miner Res* 2005;20(5):790-8.
 199. Elmquist JK, Stewler GJ. Physiology: Do neural signals remodel bone? *Nature* 2005;434(7032):447-8.
 200. Misra M, Miller KK, Bjornson J, Hackman A, Aggarwal A, Chung J, et al. Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. *J Clin Endocrinol Metab* 2003;88(12):5615-23.
 201. Olney RC. Regulation of bone mass by growth hormone. *Med Pediatr Oncol* 2003;41(3):228-34.
 202. Pfeifer M, Begerow B, Minne H. Vitamin D and muscle function. *Osteoporos Int* 2002;13(3):187-94.
 203. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster J-Y, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344(19):1434-41.
 204. Langdahl BL, Eriksen EF. The influence of thyroid hormones on bone turnover in health and osteopetrosis. *Eur J Endocrinol* 1998;139(1):10-1.
 205. Gallagher JC, Kinyamu HK, Fowler SE, Dawson-Hughes B, Dalsky GP, Sherman SS. Calcitropic hormones and bone markers in the elderly. *J Bone Miner Res* 1998;13(3):475-82.
 206. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: A meta-analysis. *J Clin Endocrinol Metab* 1996;81(12):4278-89.
 207. Delhanty PJ, Eerden BC, Leeuwen JP. Ghrelin and bone. *Biofactors* 2014;40(1):41-8.
 208. Legiran S, Brandi ML. Bone mass regulation of leptin and postmenopausal osteoporosis with obesity. *Clin Cases Miner Bone Metab* 2012;9(3):145.
 209. Williams GR. Actions of thyroid hormones in bone. *Endokrynol Pol* 2009;60(5):380-8.
 210. Grote FK, Van Suijlekom-Smit LW, Mul D, Hop WC, Ten Cate R, Oostdijk W, et al. Growth hormone treatment in children with rheumatic disease, corticosteroid induced growth retardation, and osteopenia. *Arch Dis Child* 2006;91(1):56-60.
 211. Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu J-L, et al. Circulating levels of IGF-1 directly regulate bone growth and density. *J Clin Invest* 2002;110(6):771-81.
 212. Kroll MH. Parathyroid hormone temporal effects on bone formation and resorption. *Bull Math Biol* 2000;62(1):163-88.
 213. MacDonald B, Gallagher J, Russell R. Parathyroid hormone stimulates the proliferation of cells derived from human bone. *Endocrinology* 1986;118(6):2445-9.
 214. Bone HG, Hosking D, Devogelaer J-P, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004;350(12):1189-99.
 215. Takeda S, Karsenty G. Central control of bone formation. *J Bone Miner Metab* 2001;19:195-8.
 216. Weaver CM. The role of nutrition on optimizing peak bone mass. *Asia Pac J Clin Nutr* 2008;17(S1):135-7.
 217. Palacios C. The role of nutrients in bone health, from A to Z. *Crit Rev Food Sci Nutr* 2006;46:621-8.
 218. Levy R. Costs and benefits of pharmaceuticals: The value equation for older Americans. *Care Manage J* 2002;3(3):135-43.
 219. Frost HM. From Wolff's law to the Utah paradigm: insights about bone physiology and its clinical applications. *Anat Rec* 2001;262(4):398-419.

220. Frost HM. Why do bone strength and "mass" in aging adults become unresponsive to vigorous exercise? Insights of the Utah paradigm. *J Bone Miner Metab* 1999;17(2):90-7.
221. Frost HM. From Wolff's law to the mechanostat: a new "face" of physiology. *J Orthop Sci* 1998;3(5):282-6.
222. Frost HM. Perspectives: A proposed general model of the "mechanostat"(suggestions from a new skeletal-biologic paradigm). *Anat Rec* 1996;244(2):139-47.
223. Frost HM. Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians. *Angle Orthod* 1994;64(3):175-88.
224. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's law: the bone modeling problem. *Anat Rec* 1990;226(4):403-13.
225. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 2. Redefining Wolff's law: the remodeling problem. *Anat Rec*. 1990;226(4):414-22.
226. Wolff J, Maquet P, Furlong R. The law of bone remodeling. Berlin: Springer-Verlag; 1986.
227. Frost HM. A determinant of bone architecture: the minimum effective strain. *Clin Orthop Relat Res* 1983;175:286-92.
228. Frost HM. Tetracycline-based histological analysis of bone remodeling. *Calcif Tissue Res* 1969;3(1):211-37.
229. Roux W. Beitrage zur morphologie der funktionellen anpassung. *Arch Anat Physiol Anat Abt* 1885;9:120-58.
230. Wolff J. Das gesetz der transformation der knochen. Berlin: A. Hirschwild; 1892.
231. Roux W. Der kampf der teile im organismus. Leipzig: Engelmann; 1881.
232. Wolff J. Uber die bedeutung der architektur der spongiosen Substanz. *Zentralblatt fur die medizinische Wissenschaft* 1869;6:223-34.
233. Wolff J. Uber die innere architektur der knochen und ihre bedeutung fur die frage vom knochenwachstum. *Archi fur pathologische Anatomie und Physiologie und Kinische Medizin* 1870;50:389-453.
234. Hammer A. The paradox of Wolff's theories. *Ir J Med Sci* 2014;1-10.
235. Stoltz JF. Response of cells and tissues to mechanical stimulation. *Series Biomech* 2012;27(1-2):17-32.
236. Ruff C, Holt B, Trinkaus E. Who's afraid of the big bad Wolff?: "Wolff's law" and bone functional adaptation. *Am J Phys Anthropol* 2006;129(4):484-98.
237. Skerry TM. One mechanostat or many? Modifications of the site-specific response of bone to mechanical loading by nature and nurture. *J Musculoskelet Neuronal Interact* 2006;6(2):122-7.
238. Lee T, Taylor D. Bone remodelling: Should we cry wolff? *Ir J Med Sci*. 1999;168(2):102-5.
239. Turner CH. Three rules for bone adaptation to mechanical stimuli. *Bone* 1998;23(5):399-407.
240. Wu Q, Sample SJ, Baker TA, Thomas CF, Behan M, Muir P. Mechanical loading of a long bone induces plasticity in sensory input to the central nervous system. *Neurosci Lett* 2009;463(3):254-7.
241. Turner CH. Toward a mathematical description of bone biology: The principle of cellular accommodation. *Calcif Tissue Int* 1999;65:466-71.
242. van Oers RF, Ruimerman R, Tanck E, Hilbers PA, Huiskes R. A unified theory for osteonal and hemi-osteonal remodeling. *Bone* 2008;42(2):250-9.
243. Järvinen T, Kannus P, Pajamäki I, Vuohelainen T, Tuukkanen J, Järvinen M, et al. Estrogen deposits extra mineral into bones of female rats in puberty, but simultaneously seems to suppress the responsiveness of female skeleton to mechanical loading. *Bone* 2003;32(6):642-51.
244. Duncan RL, Turner CH. Mechanotransduction and the functional response of bone to mechanical strain. *Calcif Tissue Int* 1995;57(5):344-58.
245. Bacabac RG, Smit TH, Mullender MG, van Loon JJWA, Klein Nulend J. Initial stress-kick is required for fluid shear stress-induced rate dependent activation of bone cells. *Ann Biomed Eng* 2005;33(1):104-10.
246. Ciani C, Doty SB, Fritton SP. Mapping bone interstitial fluid movement: Displacement of ferritin tracer during histological processing. *Bone* 2005;37(3):379-87.
247. Bacabac RG, Smit TH, Mullender MG, Dijcks SJ, Van Loon JJ, Klein-Nulend J, editors. Fluid shear stress-induced activation of bone cells is rate dependent and requires an initial stress kick. 50th Annual Meeting of the Orthopaedic Research Society; 2004; Anaheim, CA.
248. Han Y, Cowin SC, Schaffler MB, Weinbaum S. Mechanotransduction and strain amplification in osteocyte cell processes. *Proceedings of the National Academy of Sciences* 2004;101(47):16689-94.
249. Knoth Tate ML, Adamson JR, Tami AE, Bauer TW. The osteocyte. *Int J Biochem Cell Biol* 2004;36(1):1-8.
250. Bacabac RG, Dijcks SJ, Mullender MG, Smit TH, Van Loon JJ, Klein-Nulend J, editors. Rapid nitric oxide production by fluid flow treated bone cells is fluid shear rate dependent. 49th Annual Meeting of the Orthopaedic Research Society; 2003; New Orleans, LA.
251. Knoth Tate ML. "Whither flows the fluid in bone?" An osteocyte's perspective. *J Biomech* 2003; 36(10):1409-24.
252. Nicoletta DP, Lankford J. Microstructural strain near osteocyte lacuna in cortical bone *in vitro*. *J Musculoskelet Neuronal Interact* 2002;2(3):261-3.
253. Martin RB. Toward a unifying theory of bone remodeling. *Bone* 2000;26(1):1-6.
254. Klein-Nulend J, van der Plas A, Semeins CM, Ajubi NE, Frangos JA, Nijweide PJ, et al. Sensitivity of osteocytes to biomechanical stress *in vitro*. *FASEB J* 1995;9(5):441.
255. Cowin SC, Moss-Salentijn L, Moss ML. Candidates for the mechanosensory system in bone. *J Biomech Eng* 1991;113(2):191-7.
256. Judex S, Gupta S, Rubin C. Regulation of mechanical signals in bone. *Orthod Craniofac Res* 2009;12(2):94-104.

257. Heino TJ, Hentunen TA, Vaananen HK. Conditioned medium from osteocytes stimulates the proliferation of bone marrow mesenchymal stem cells and their differentiation into osteoblasts. *Exp Cell Res* 2004;294(2):458-68.
258. Prendergast PJ. Mechanics applied to skeletal ontogeny and phylogeny. *Meccanica* 2002;37(4-5):317-34.
259. Luo Y. Bone mineral density averaged over a region of interest on femur is affected by age-related change of bone geometry. *Osteoporos Int* 2018;29(6):1419-25.
260. Martin TJ, Sims NA. Osteoclast-derived activity in the coupling of bone formation to resorption. *Trends Mol Med* 2005;11(2):76-81.
261. Seeman E. Periosteal bone formation - A neglected determinant of bone strength. *N Engl J Med* 2003;349(4):320-3.
262. Seeman E. Growth in bone mass and size--are racial and gender differences in bone mineral density more apparent than real? *J Clin Endocrinol Metab* 1998;83(5):1414-9.
263. Kukuljan S, Nowson CA, Sanders KM, Nicholson GC, Seibel MJ, Salmon J, et al. Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. *J Clin Endocrinol Metab* 2011;96(4):955-63.
264. Uusi-Rasi K, Kannus P, Cheng S, Sievanen H, Pasanen M, Heinonen A, et al. Effect of alendronate and exercise on bone and physical performance of postmenopausal women: A randomized controlled trial. *Bone* 2003;33(1):132-43.
265. Raab-Cullen D, Thiede M, Petersen D, Kimmel D, Recker R. Mechanical loading stimulates rapid changes in periosteal gene expression. *Calcif Tissue Int* 1994;55(6):473-8.
266. Beck BR, Snow CM. Bone health across the lifespan: Exercising our options. *Exerc Sport Sci Rev* 2003;31(3):117-22.
267. Cullen D, Smith R, Akhter M. Time course for bone formation with long-term external mechanical loading. *J Appl Physiol* 2000;88(6):1943-8.
268. Turner CH, Burr DB. Basic biomechanical measurements of bone: A tutorial. *Bone* 1993;14(4):595-608.
269. Horcajada M-N, Offord E. Naturally plant-derived compounds: Role in bone anabolism. *Curr Mol Pharmacol* 2012;5(2):205-18.
270. Nilsson M, Ohlsson C, Odén A, Mellström D, Lorentzon M. Increased physical activity is associated with enhanced development of peak bone mass in men: A five-year longitudinal study. *J Bone Miner Res* 2012;27(5):1206-14.
271. Huuskonen J, Väisänen S, Kröger H, Jurvelin J, Alhava E, Rauramaa R. Regular physical exercise and bone mineral density: a four-year controlled randomized trial in middle-aged men. The DNASCO study. *Osteoporos Int* 2001;12(5):349-55.
272. Duan Y, Wang XF, Evans A, Seeman E. Structural and biomechanical basis of racial and sex differences in vertebral fragility in Chinese and Caucasians. *Bone* 2005;36(6):987-98.
273. Wang XF, Duan Y, Beck TJ, Seeman E. Varying contributions of growth and ageing to racial and sex differences in femoral neck structure and strength in old age. *Bone* 2005;36(6):978-86.
274. Stegen S, Stockmans I, Moermans K, Thienpont B, Maxwell PH, Carmeliet P, et al. Osteocytic oxygen sensing controls bone mass through epigenetic regulation of sclerostin. *Nat Commun* 2018;9(1):2557.
275. Choksi P, Jepsen KJ, Clines GA. The challenges of diagnosing osteoporosis and the limitations of currently available tools. *Clinical diabetes and endocrinology* 2018;4(1):12.
276. Reider L, Beck T, Alley D, Miller R, Shardell M, Schumacher J, et al. Evaluating the relationship between muscle and bone modeling response in older adults. *Bone* 2016;90:152-8.
277. Santos L, Elliott-Sale KJ, Sale C. Exercise and bone health across the lifespan. *Biogerontology* 2017;18(6):931-46.
278. Laudermilk MJ, Manore MM, Thomson CA, Houtkooper LB, Farr JN, Going SB. Vitamin C and zinc intakes are related to bone macroarchitectural structure and strength in prepubescent girls. *Calcif Tissue Int* 2012;91(6):430-9.
279. Pitukcheewanont P, Safani D. Extremely low-level, short-term mechanical stimulation increases cancellous and cortical bone density and muscle mass of children with low bone density: A pilot study. *The Endocrinologist* 2006;16(3):128-32.
280. Hartman C, Hochberg Z, Shamir R. Osteoporosis in paediatrics. *Isr Med Assoc J* 2003;5(7):509-15.
281. Bonjour J-P, Theintz G, Buchs B, Slosman D, Rizzoli R. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. *J Clin Endocrinol Metab* 1991;73(3):555-63.
282. Ilich JZ, Kerstetter JE. Nutrition in bone health revisited: A story beyond calcium. *J Am Coll Nutr* 2000;19(6):715-37.
283. Ireland A, Rittweger J, Schonau E, Lamberg-Allardt C, Viikari-Juntura H. Time since onset of walking predicts tibial bone strength in early childhood. *Bone* 2014;68:76-84.
284. Warden SJ, Roosa SM. Physical activity completed when young has residual bone benefits at 94 years of age: A within subject controlled case study. *J Musculoskelet Neuronal Interact* 2014;14(2):239.
285. Pettersson U, Nilsson M, Sundh V, Mellström D, Lorentzon M. Physical activity is the strongest predictor of calcaneal peak bone mass in young Swedish men. *Osteoporos Int* 2010;21(3):447-55.
286. Janz KF, Gilmore JM, Burns TL, Levy SM, Torner JC, Willing MC, et al. Physical activity augments bone mineral accrual in young children: The Iowa Bone Development Study. *J Pediatr* 2006;148(6):793-9.
287. Ruff C. Growth in bone strength, body size, and muscle size in a juvenile longitudinal sample. *Bone*

- 2003;33(3):317-29.
288. MacKelvie KJ, Khan KM, McKay HA. Is there a critical period for bone response to weight-bearing exercise in children and adolescents? A systematic review. *Br J Sports Med* 2002;36(4):250-7.
 289. Modlesky CM, Lewis RD. Does exercise during growth have a long-term effect on bone health? *Exerc Sport Sci Rev* 2002;30(4):171-6.
 290. MacKelvie KJ, McKay HA, Khan KM, Crocker PR. A school-based exercise intervention augments bone mineral accrual in early pubertal girls. *J Pediatr* 2001;139(4):501-8.
 291. Ural A, Vashishth D. Interactions between microstructural and geometrical adaptation in human cortical bone. *J Orthop Res* 2006;24(7):1489-98.
 292. Neu CM, Rauch F, Manz F, Schoenau E. Modeling of cross-sectional bone size, mass and geometry at the proximal radius: A study of normal bone development using peripheral quantitative computed tomography. *Osteoporos Int* 2001;12(7):538-47.
 293. Burr D. Why bones bend but don't break. *J Musculoskelet Neuronal Interact* 2011;11(4):270-85.
 294. Heaney RP. The bone-remodeling transient: Implications for the interpretation of clinical studies of bone mass change. *J Bone Miner Res*. 1994;9(10):1515-23.
 295. Hillam RA, Skerry TM. Inhibition of bone resorption and stimulation of formation by mechanical loading of the modeling rat ulna *in vivo*. *J Bone Miner Res* 1995;10(5):683-9.
 296. Herman BC, Cardoso L, Majeska RJ, Jepsen KJ, Schaffler MB. Activation of bone remodeling after fatigue: differential response to linear microcracks and diffuse damage. *Bone* 2010;47(4):766-72.
 297. Li J, Mashiba T, Burr D. Bisphosphonate treatment suppresses not only stochastic remodeling but also the targeted repair of microdamage. *Calcif Tissue Int* 2001;69(5):281-6.
 298. Jilka RL. Biology of the basic multicellular unit and the pathophysiology of osteoporosis. *Med Pediatr Oncol* 2003;41(3):182-5.
 299. Lassen NE, Andersen TL, Pløen GG, Søre K, Hauge EM, Harving S, et al. Coupling of bone resorption and formation in real time: New knowledge gained from human haversian BMUs. *J Bone Miner Res* 2017;32(7):1395-405.
 300. Thiel A, Reumann MK, Boskey A, Wischmann J, von Eisenhart-Rothe R, Mayer-Kuckuk P. Osteoblast migration in vertebrate bone. *Biological Reviews* 2018;93(1):350-63.
 301. Clansey AC, Hanlon M, Wallace ES, Lake MJ. Effects of fatigue on running mechanics associated with tibial stress fracture risk. *Med Sci Sports Exerc* 2012;44(10):1917-23.
 302. Bloomfield SA. Disuse osteopenia. *Curr Osteoporos Rep* 2010;8:91-7.
 303. Sievänen H. Immobilization and bone structure in humans. *Arch Biochem Biophys* 2010;503(1):146-52.
 304. Bennell K, Matheson G, Meeuwisse W, Brukner P. Risk factors for stress fractures. *Sports Med* 1999;28(2):91-122.
 305. Khosla S. Pathogenesis of age-related bone loss in humans. *J Gerontol A Biol Sci Med Sci* 2013;68(10):1226-35.
 306. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Loading and skeletal development and maintenance. *J Osteoporos* 2011;2011:1-15.
 307. Lau RY-c, Guo X. A review on current osteoporosis research: With special focus on disuse bone loss. *J Osteoporos* 2011;2011:1-6.
 308. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, et al. A population-based assessment of rates of bone loss at multiple skeletal sites: Evidence for substantial trabecular bone loss in young adult women and men. *J Bone Miner Res* 2008;23(2):205-14.
 309. Cervinka T, Rittweger J, Hyttinen J, Felsenberg D, Sievänen H. Anatomical sector analysis of load-bearing tibial bone structure during 90-day bed rest and 1-year recovery. *Clin Physiol Funct Imaging* 2011;31(4):249-57.
 310. Landrigan MD, Li J, Turnbull TL, Burr DB, Niebur GL, Roeder RK. Contrast-enhanced micro-computed tomography of fatigue microdamage accumulation in human cortical bone. *Bone*. 2011;48(3):443-50.
 311. Macione J, Kavukcuoglu N, Nesbitt R, Mann A, Guzelsu N, Kotha S. Hierarchies of damage induced loss of mechanical properties in calcified bone after *in vivo* fatigue loading of rat ulnae. *J Mech Behav Biomed Mater*. 2011;4(6):841-8.
 312. Berg HE, Eiken O, Miklavcic L, Mekjavic IB. Hip, thigh and calf muscle atrophy and bone loss after 5-week bedrest inactivity. *Eur J Appl Physiol*. 2007;99(3):283-9.
 313. Danova N, Colopy S, Radtke C, Kalscheur V, Markel M, Vanderby Jr R, et al. Degradation of bone structural properties by accumulation and coalescence of microcracks. *Bone*. 2003;33(2):197-205.
 314. Ehrlich PJ, Lanyon LE. Mechanical strain and bone cell function: A review. *Osteoporos Int* 2002;13(9):688-700.
 315. LeBlanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM. Bone mineral loss and recovery after 17 weeks of bed rest. *J Bone Miner Res*. 1990;5(8):843-50.
 316. Bauer JJ, Snow CM. What is the prescription for healthy bones? *J Musculoskelet Neuronal Interact* 2003;3(4):352-5.
 317. Ellman R, Spatz J, Cloutier A, Palme R, Christiansen BA, Bouxsein ML. Partial reductions in mechanical loading yield proportional changes in bone density, bone architecture and muscle mass. *J Bone Miner Res* 2013;28(4):875-85.
 318. Gaudio A, Pennisi P, Bratengeier C, Torrisi V, Lindner B, Mangiafico RA, et al. Increased sclerostin serum levels associated with bone formation and resorption markers in patients with immobilization-induced bone loss. *J Clin Endocrinol Metab* 2010;95(5):2248-53.

319. Giangregorio L, Blimkie CJR. Skeletal adaptations to alterations in weight-bearing activity: A comparison of models of disuse osteoporosis. *Sports Med* 2002;32(7):459-76.
320. Gislason MK, Coupaud S, Sasagawa K, Tanabe Y, Purcell M, Allan DB, et al. Prediction of risk of fracture in the tibia due to altered bone mineral density distribution resulting from disuse: A finite element study. *Proc Inst Mech Eng* 2014;228(2):165-74.
321. Lloyd SA, Lang CH, Zhang Y, Paul EM, Laufenberg LJ, Lewis GS, et al. Interdependence of muscle atrophy and bone loss induced by mechanical unloading. *J Bone Miner Res* 2014;29(5):1118-30.
322. Torcasio A, Jähn K, Van Guyse M, Spaepen P, Tami AE, Sloten JV, et al. Trabecular bone adaptation to low-magnitude high-frequency loading at micro-gravity. *J Biomech* 2012;45:S531.
323. Wall BT, Dirks ML, Snijders T, Senden JMG, Dolmans J, van Loon LJ. Substantial skeletal muscle loss occurs during only 5 days of disuse. *Acta Physiol* 2014;210(3):600-11.
324. Klein-Nulend J, Bacabac RG, Bakker AD. Mechanical loading and how it affects bone cells: the role of the osteocyte cytoskeleton in maintaining our skeleton. *Eur Cell Mater* 2012;24:278-91.
325. Armbrrecht G, Belavý DL, Backström M, Beller G, Alexandre C, Rizzoli R, et al. Trabecular and cortical bone density and architecture in women after 60 days of bed rest using high-resolution pQCT: WISE 2005. *J Bone Miner Res* 2011;26(10):2399-410.
326. Rittweger J, Beller G, Armbrrecht G, Mulder E, Buehring B, Gast U, et al. Prevention of bone loss during 56 days of strict bed rest by side-alternating resistive vibration exercise. *Bone* 2010;46(1):137-47.
327. Rittweger J, Felsenberg D. Recovery of muscle atrophy and bone loss from 90 days bed rest: Results from a one-year follow-up. *Bone* 2008;44(2):214-24.
328. Rittweger J, Simunic B, Bilancio G, Gaspere De Santo N, Cirillo M, Biolo G, et al. Bone loss in the lower leg during 35 days of bed rest is predominantly from the cortical compartment. *Bone* 2009;44(4):612-8.
329. LeBlanc AD, Spector ER, Evans HJ, Sibonga JD. Skeletal responses to space flight and the bed rest analog: A review. *J Musculoskelet Neuronal Interact* 2007;7(1):33.
330. Rittweger J, Frost HM, Schiessl H, Ohshima H, Alkner B, Tesch P, et al. Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: Results from the LTBR study. *Bone* 2005;36(6):1019-29.
331. Baecker N, Tomic A, Mika C, Gotzmann A, Platen P, Gerzer R, et al. Bone resorption is induced on the second day of bed rest: results of a controlled crossover trial. *J Appl Physiol* 2003;95(3):977-82.
332. Klein-Nulend J, Bacabac R, Veldhuijzen J, Van Loon J. Microgravity and bone cell mechanosensitivity. *Adv Space Res* 2003;32(8):1551-9.
333. Shields RK, Dudley-Javoroski S, Boaldin KM, Corey TA, Fog DB, Ruen JM. Peripheral quantitative computed tomography: Measurement sensitivity in persons with and without spinal cord injury. *Arch Phys Med Rehabil* 2006;87(10):1376-81.
334. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. *J Bone Miner Res* 2004;19(6):1006-12.
335. Vico L, Collet P, Guignandon A, Lafage-Proust MH, Thomas T, Rehailia M, et al. Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. *Lancet* 2000;355(9215):1607-11.
336. Collet P, Uebelhart D, Vico L, Moro L, Hartmann D, Roth M, et al. Effects of 1- and 6-month spaceflight on bone mass and biochemistry in two humans. *Bone* 1997;20(6):547-51.
337. Del Puente A, Pappone N, Mandes MG, Mantova D, Scarpa R, Oriente P. Determinants of bone mineral density in immobilization: A study on hemiplegic patients. *Osteoporos Int* 1996;6(1):50-4.
338. Bettis T, Kim BJ, Hamrick MW. Impact of muscle atrophy on bone metabolism and bone strength: implications for muscle-bone crosstalk with aging and disuse. *Osteoporos Int* 2018;29(8):1713-20.
339. Einhorn TA. Bone Strength: The bottom line. *Calcif Tissue Int* 1992;51(5):333-9.
340. Nagaraja MP, Jo H. The role of mechanical stimulation in recovery of bone loss-high versus low magnitude and frequency of force. *Life* 2014;4(2):117-30.
341. Ju Y-I, Sone T, Okamoto T, Fukunaga M. Jump exercise during remobilization restores integrity of the trabecular architecture after tail suspension in young rats. *J Appl Physiol* 2008;104(6):1594-600.
342. Eser P, Schiessl H, Willnecker J. Bone loss and steady state after spinal cord injury: a cross-sectional study using pQCT. *J Musculoskelet Neuronal Interact* 2004;4(2):197-8.
343. Birkhold AI, Razi H, Duda GN, Weinkamer R, Checa S, Willie BM. The Periosteal Bone Surface is Less Mechano-Responsive than the Endocortical. *Sci Rep* 2016;6(1):23480.
344. Demontiero O, Vidal C, Duque G. Aging and bone loss: new insights for the clinician. *Ther Adv Musculoskelet Dis* 2012;4(2):61-76.
345. Dionyssiatis Y, Lyritis GP, Mavrogenis AF, Papagelopoulos PJ. Factors influencing bone loss in paraplegia. *Hippokratia* 2011;15(1):54-9.
346. Dionysiatis Y, Trovas G, Galanos A, P. R, Papaioannou N, Papagelopoulos P, et al. Bone loss and mechanical properties of tibia in spinal cord injured men. *J Musculoskelet Neuronal Interact*. 2007;7(1):62-8.
347. Jiang S-D, Dai L-Y, Jiang L-S. Osteoporosis after spinal cord injury. *Osteoporos Int* 2006;17(2):180-92.
348. Lisková M, Hert J. Reaction of bone to mechanical stimuli. 2. Periosteal and endosteal reaction of tibial

- diaphysis in rabbit to intermittent loading. *Folia Morphol (Praha)* 1971;19(3):301-17.
349. Mellon SJ, Tanner KE. Bone and its adaptation to mechanical loading: a review. *International Materials Reviews* 2012;57(5):235-55.
 350. Ruff C, Holt B, Trinkaus E. Who's afraid of the big bad Wolff?: "Wolff's law" and bone functional adaptation. *Am J Phys Anthropol* 2006;129(4):484-98.
 351. Rantalainen T, Duckham RL, Suominen H, Heinonen A, Alén M, Korhonen MT. Tibial and Fibular Mid-Shaft Bone Traits in Young and Older Sprinters and Non-Athletic Men. *Calcif Tissue Int* 2014;95(2):132-40.
 352. Cheng S, Sipilä S, Taaffe DR, Puolakka J, Suominen H. Change in bone mass distribution induced by hormone replacement therapy and high-impact physical exercise in post-menopausal women. *Bone* 2002;31(1):126-35.
 353. Lespessailles E, Hambli R, Ferrari S. Osteoporosis drug effects on cortical and trabecular bone microstructure: a review of HR-pQCT analyses. *BoneKEy Rep* 2016;5:836.
 354. Tsai JN, Uihlein AV, Burnett-Bowie S-AM, Neer RM, Zhu Y, Derrico N, et al. Comparative Effects of Teriparatide, Denosumab, and Combination Therapy on Peripheral Compartmental Bone Density, Microarchitecture, and Estimated Strength: the DATA-HRpQCT Study. *J Bone Miner Res* 2015;30(1):39-45.
 355. Zebaze RM, Libanati C, Austin M, Ghasem-Zadeh A, Hanley DA, Zanchetta JR, et al. Differing effects of denosumab and alendronate on cortical and trabecular bone. *Bone* 2014;59:173-9.
 356. Beck TJ, Ruff CB, Mourtada FA, Shaffer RA, Maxwell-Williams K, Kao GL, et al. Dual-energy X-ray absorptiometry derived structural geometry for stress fracture prediction in male U.S. Marine Corps recruits. *J Bone Miner Res* 1996;11(5):645.
 357. McCormick F, Nwachukwu BU, Provencher MT. Stress fractures in runners. *Clin Sports Med* 2012;31(2):291-306.
 358. Warden SJ, Burr DB, Brukner PD. Stress fractures: Pathophysiology, epidemiology, and risk factors. *Curr Osteoporos Rep* 2006;4(3):103-9.
 359. Jones BH, Thacker SB, Gilchrist J, Kimsey CD, Sosin DM. Prevention of lower extremity stress fractures in athletes and soldiers: a systematic review. *Epidemiol Rev* 2002;24(2):228-47.
 360. Tommasini SM, Nasser P, Jepsen KJ. Sexual dimorphism affects tibia size and shape but not tissue-level mechanical properties. *Bone* 2007;40(2):498-505.
 361. Milgrom C, Simkin A, Eldad A, Nyska M, Finestone A. Using bone's adaptation ability to lower the incidence of stress fractures. *Am J Sports Med* 2000; 28(2):245-51.
 362. Anliker E, Toigo M. Functional assessment of the muscle-bone unit in the lower leg. *J Musculoskelet Neuronal Interact* 2012;12(2):46-55.
 363. Ashe MC, Liu-Ambrose T, Khan KM, White N, McKay HA. Optimizing results from pQCT: reliability of operator-dependent pQCT variables in cadavers and humans with low bone mass. *J Clin Densitom* 2005;8(3):335.
 364. Lai YM, Qin L, Yeung HY, Lee KKH, Chan KM. Regional differences in trabecular BMD and micro-architecture of weight-bearing bone under habitual gait loading—A pQCT and microCT study in human cadavers. *Bone* 2005;37(2):274-82.
 365. Griffin LV, Gibeling JC, Martin RB, Gibson VA, Stover SM. The effects of testing methods on the flexural fatigue life of human cortical bone. *J Biomech*. 1999;32(1):105-9.
 366. Snyder SM, Schneider E. Estimation of mechanical properties of cortical bone by computed tomography. *J Orthop Res* 1991;9(3):422-31.
 367. Nazer RA, Lanovaz J, Kawallak C, Johnston JD, Kontulainen S. Direct *in vivo* strain measurements in human bone: A systematic literature review. *J Biomech* 2012;45:27-40.
 368. Lester ME, Urso ML, Evans RK, Pierce JR, Spiering BA, Maresh CM, et al. Influence of exercise mode and osteogenic index on bone biomarker responses during short-term physical training. *Bone* 2009;45(4):768-76.
 369. Popp AW, Buffat H, Eberli U, Lippuner K, Ernst M, Richards RG, et al. Microstructural parameters of bone evaluated using HR-pQCT correlate with the DXA-derived cortical index and the trabecular bone score in a cohort of randomly selected premenopausal women. *PLoS One* 2014;9(2):e88946.
 370. Wehrli FW, Song HK, Saha PK, Wright AC. Quantitative MRI for the assessment of bone structure and function. *NMR Biomed* 2006;19(7):731-64.
 371. Kang C, Paley M, Ordidge R, Speller R. *In vivo* MRI measurements of bone quality in the calcaneus: a comparison with DXA and ultrasound. *Osteoporos Int* 1999;9(1):65-74.
 372. Ferretti JL. Perspectives of pQCT technology associated to biomechanical studies in skeletal research employing rat models. *Bone*. 1995;17(4):S353-S64.
 373. Sheu Y, Zmuda JM, Boudreau RM, Petit MA, Ensrud KE, Bauer DC, et al. Bone strength measured by peripheral quantitative computed tomography and the risk of nonvertebral fractures: The osteoporotic fractures in men (MrOS) study. *J Bone Miner Res* 2011;26(1):63-71.
 374. Petit MA, Beck TJ, Kontulainen SA. Examining the developing bone: What do we measure and how do we do it? *J Musculoskelet Neuronal Interact* 2005;5(3):213-24.
 375. Cross TM, Smart RC, Thomson JE. Exposure to diagnostic ionizing radiation in sports medicine: assessing and monitoring the risk. *Clin J Sport Med* 2003;13(3):164-70.
 376. Nijs J, Westhovens R, Joly J, Cheng X, Borghs H, Dequeker J. Diagnostic sensitivity of peripheral quantitative computed tomography measurements at ultradistal and proximal radius in postmenopausal women. *Bone* 1998;22(6):659-64.
 377. Desforges JF, Johnston Jr CC, Slemenda CW, Melton III LJ. Clinical use of bone densitometry. *N Engl J Med*

- 1991;324(16):1105-9.
378. Rogers RS, Dawson AW, Wang Z, Thyfault JP, Hinton PS. Acute response of plasma markers of bone turnover to a single bout of resistance training or plyometrics. *J Appl Physiol* 2011;111:1353-60.
 379. Rantalainen T, Heinonen A, Linnamo V, Komi PV, Takala TES, Kainulainen H. Short-term bone biochemical response to a single bout of high-impact exercise. *J Sports Sci Med* 2009;8(4):553-9.
 380. Durkin JL, Dowling JJ, Andrews DM. The measurement of body segment inertial parameters using dual energy X-ray absorptiometry. *J Biomech* 2002;35(12):1575-80.
 381. Toombs RJ, Ducher G, Shepherd JA, Souza MJ. The impact of recent technological advances on the trueness and precision of DXA to assess body composition. *Obesity* 2012;20(1):30-9.
 382. Pietrobelli A, Wang Z, Formica C, Heymsfield SB. Dual-energy X-ray absorptiometry: fat estimation errors due to variation in soft tissue hydration. *Am J Physiol Endocrinol Metab* 1998;274(5):E808-E16.
 383. Cointy G, Capozza R, Negri A, Roldan E, Ferretti J. Biomechanical background for a noninvasive assessment of bone strength and muscle-bone interactions. *J Musculoskelet Neuronal Interact* 2004;4(1):1.
 384. Licata A. Bone density vs bone quality: What's a clinician to do? *Cleve Clin J Med* 2009;76(6):331-6.
 385. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: Scientific review. *JAMA* 2002;288(15):1889-97.
 386. Bilsborough JC, Greenway K, Opar D, Livingstone S, Cordy JT, Coutts AJ. The accuracy and precision of DXA for assessing body composition in team sport athletes. *J Sports Sci* 2014;20(1):1-8.
 387. Rothney MP, Martin FP, Xia Y, Beaumont M, Davis C, Ergun D, et al. Precision of GE Lunar iDXA for the measurement of total and regional body composition in nonobese adults. *J Clin Densitom* 2012;15(4):399-404.
 388. Santos DA, Silva AM, Matias CN, Fields DA, Heymsfield SB, Sardinha LB. Accuracy of DXA in estimating body composition changes in elite athletes using a four compartment model as the reference method. *Nutr Metab (Lond)* 2010;7(1):22-31.
 389. Hart NH, Nimphius S. Segmental musculoskeletal examinations using dual-energy X-Ray absorptiometry (DXA): Positioning and analysis considerations. *J Sports Sci Med* 2015.
 390. Burkhart TA, Arthurs KL, Andrews DM. Manual segmentation of DXA scan images results in reliable upper and lower extremity soft and rigid tissue mass estimates. *J Biomech* 2009;42(8):1138-42.
 391. Chen Z, Wang Z, Lohman T, Heymsfield SB, Outwater E, Nicholas JS, et al. Dual-energy X-ray absorptiometry is a valid tool for assessing skeletal muscle mass in older women. *J Nutr* 2007;137(12):2775-80.
 392. Stewart AD, Hannan J. Total and regional bone density in male runners, cyclists and controls. *Med Sci Sports Exerc* 2000;32(8):1373-7.
 393. De Lorenzo A, Andreoli A, Candeloro N. Within-subject variability in body composition using dual-energy X-ray absorptiometry. *Clin Physiol* 1997;17(4):383-8.
 394. Trevisan C, Gandolini GG, Sibilla P, Penotti M, Caraceni MP, Ortolani S. Bone mass measurement by DXA: influence of analysis procedures and interunit variation. *J Bone Miner Res* 1992;7(12):1373-82.
 395. Bianchi ML, Baim S, Bishop NJ, Gordon CM, Hans DB, Langman CB, et al. Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents. *Pediatr Nephrol* 2010;25(1):37-47.
 396. Suman VB, Subbalakshmi NK, Pai SR, Shaila MD. Risk factors associated with osteoporosis - A population based study using p-DXA technique. *Int J Sci Res* 2013;3(2):1-5.
 397. Gurlek AM, Bayraktar M, Ariyurek M. Inappropriate reference range for peak bone mineral density in dual-energy X-ray absorptiometry: implications for the interpretation of T-scores. *Osteoporos Int*. 2000;11(9):809-13.
 398. Chen Q, Bao N, Yao Q, Li Z-Y. Fractal dimension: A complementary diagnostic indicator of osteoporosis to bone mineral density. *Med Hypotheses*. 2018;116:136-8.
 399. Sievänen H, Koskue V, Rauhio A, Kannus P, Heinonen A, Vuori I. Peripheral quantitative computed tomography in human long bones: Evaluation of *in vitro* and *in vivo* precision. *J Bone Miner Res* 1998;13(5):871-82.
 400. Ammann P, Rizzoli R. Bone strength and its determinants. *Osteoporos Int*. 2003;14(S3):13-8.
 401. Kröger H, Vainio P, Nieminen J, Kotaniemi A. Comparison of different models for interpreting bone mineral density measurements using DXA and MRI technology. *Bone* 1995;17(2):157-9.
 402. Ho-Pham LT, Ho-Le TP, Mai LD, Do TM, Doan MC, Nguyen TV. Sex-difference in bone architecture and bone fragility in Vietnamese. *Sci Rep*. 2018;8(1):7707.
 403. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. *In vivo* assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 2005; 90(12):6508-15.
 404. Popp AW, Windolf M, Senn C, Tami A, Richards RG, Brianza S, et al. Prediction of bone strength at the distal tibia by HR-pQCT and DXA. *Bone* 2012;50(1):296-300.
 405. Di Iorgi N, Maruca K, Patti G, Mora S. Update on bone density measurements and their interpretation in children and adolescents. *Best Pract Res Clin Endocrinol Metab* 2018;32(4):477-98.
 406. Stagi S, Cavalli L, Cavalli T, De Martino M, Brandi ML. Peripheral quantitative computed tomography (pQCT) for the assessment of bone strength in most of bone affecting conditions in developmental age: A review. *Ital J Pediatr* 2016;42(1):88.

407. Louis O, Cattrysse E, Scafoglieri A, Luypaert R, Clarys JP, de Mey J. Accuracy of peripheral quantitative computed tomography and magnetic resonance imaging in assessing cortical bone cross-sectional area: a cadaver study. *J Comput Assist Tomogr* 2010;34(3):469-72.
408. Engelke K, Adams JE, Armbrrecht G, Augat P, Bogado CE, Bouxsein ML, et al. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: The 2007 ISCD official positions. *J Clin Densitom* 2008;11(1):123-62.
409. Jast J, Jasiuk I. Age-related changes in the 3D hierarchical structure of rat tibia cortical bone characterized by high-resolution micro-CT. *J Appl Physiol* 2013;114(7):923-33.
410. Willnecker J. XCT-3000 manual - Software version 6.20. Medizintechnik, Pforzheim, Germany: Stratec; 2011.
411. Burrows M, Cooper DML, Liu D, McKay HA. Bone and muscle parameters of the tibia: agreement between the XCT 2000 and XCT 3000 instruments. *J Clin Densitom* 2009;12(2):186.
412. Evans R, Negus C, Centi A, Spiering B, Kraemer W, Nindl B. Peripheral QCT sector analysis reveals early exercise-induced increases in tibial bone mineral density. *J Musculoskelet Neuronal Interact* 2012;12(3):155-64.
413. Kontulainen S, Liu D, Manske S, Jamieson M, Sievänen H, McKay H. Analyzing cortical bone cross-sectional geometry by peripheral QCT: comparison with bone histomorphometry. *J Clin Densitom* 2007;10(1):86-92.
414. Genant HK, Engelke K, Fuerst T, Gluer C-C, Grampp S, Harris ST, et al. Noninvasive assessment of bone mineral and structure: State of the art. *J Bone Miner Res* 1996;11(6).
415. Cramer JT, Palmer IJ, Ryan ED, Herda TJ, Bemben DA, Bemben MG, et al. Validity and reliability of a peripheral quantitative computed tomography scanner for measuring muscle cross-sectional area. *Med Sci Sports Exerc* 2007;39(5):S225-S6.
416. Sornay-Rendu E, Boutroy S, Duboeuf F, Chapurlat RD. Bone microarchitecture assessed by HR-pQCT as predictor of fracture risk in postmenopausal women: The OFELY Study. *J Bone Miner Res* 2017;32(6):1243-51.
417. Lala D, Cheung AM, Lynch CL, Inglis D, Gordon C, Tomlinson G, et al. Measuring apparent trabecular structure with pQCT: A comparison with HR-pQCT. *J Clin Densitom* 2014;17(1):47-53.
418. Lala D, Cheung AM, Gordon C, Giangregorio L. Comparison of cortical bone measurements between pQCT and HR-pQCT. *J Clin Densitom* 2012;15(3):275-81.
419. Bonaretti S, Majumdar S, Lang TF, Khosla S, Burghardt AJ. The comparability of HR-pQCT bone measurements is improved by scanning anatomically standardized regions. *Osteoporos Int* 2017;28(7):2115-28.
420. Rauch F, Schönau E. Peripheral quantitative computed tomography of the distal radius in young subjects - New reference data and interpretation of results. *J Musculoskelet Neuronal Interact* 2005;5(2):119-26.
421. Jaworski M, Graff K. Peripheral quantitative computed tomography of the distal and proximal forearm in children and adolescents: bone densities, cross-sectional sizes and soft tissues reference data. *J Musculoskelet Neuronal Interact* 2018;18(2):237-47.
422. Gabel L, Macdonald HM, Nettlefold LA, McKay HA. Sex-, ethnic-, and age-specific centile curves for pQCT- and HR-pQCT-derived measures of bone structure and strength in adolescents and young adults. *J Bone Miner Res* 2018;33(6):987-1000.
423. Amstrup AK, Jakobsen NFB, Moser E, Sikjaer T, Mosekilde L, Rejnmark L. Association between bone indices assessed by DXA, HR-pQCT and QCT scans in post-menopausal women. *J Bone Miner Metab* 2016;34(6):638-45.
424. Burt LA, Hanley DA, Boyd SK. Cross-sectional versus longitudinal change in a prospective HR-pQCT study. *J Bone Miner Res* 2017;32(7):1505-13.
425. Srivastava AK, Vliet EL, Baylink DJ, Lewiecki EM, Maricic M, Abdelmalek A, et al. Clinical use of serum and urine bone markers in the management of osteoporosis. *Curr Med Res Opin* 2005;21(7):1015-26.
426. Singer FR, Eyre DR. Using biochemical markers of bone turnover in clinical practice. *Cleve Clin J Med* 2008;75(10):739-50.
427. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan JJ. The use of biochemical markers of bone turnover in osteoporosis. *Osteoporos Int* 2000;11(18):S2-S17.
428. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, et al. Practical clinical application of biochemical markers of bone turnover: consensus of an expert panel. *J Clin Densitom* 1999;2(3):323-42.
429. Clouth A, Oremek GM. Value of procollagen type I aminoterminal propeptide in women with breast cancer with regard to metastases. *Patholog Res Int* 2011;2011.
430. Camozzi V, Tossi A, Simoni E, Pagani F, Francucci CM, Moro L. Role of biochemical markers of bone remodeling in clinical practice. *J Endocrinol Invest* 2007;30(6 Suppl):13.
431. Maïmoun L, Sultan C. Effects of physical activity on bone remodeling. *Metabolism* 2011;60(3):373-88.
432. Galliera E, Dogliotti G, Melegati G, Corsi Romanelli MM, Cabitza P, Banfi G. Bone remodelling biomarkers after whole body cryotherapy (WBC) in elite rugby players. *Injury* 2013;44(8):1117-21.
433. Allen MJ. Biochemical markers of bone metabolism in animals: Uses and limitations. *Vet Clin Pathol* 2003;32(3):101-13.
434. Risteli L, Risteli J. Biochemical markers of bone metabolism. *Ann Med* 1993;25(4):385-93.
435. Seibel MJ, Woitge HW. Basic principles and clinical applications of biochemical markers of bone metabolism: Biochemical and technical aspects. *J Clin Densitom* 1999;2(3):299-321.
436. Fujimura R, Ashizawa N, Watanabe M, Mukai N, Amagai H, Fukubayashi T, et al. Effect of resistance exercise training on bone formation and resorption in young male subjects assessed by biomarkers of bone metabolism. *J Bone Miner Res* 1997;12(4):656-62.