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Review Article

Biological basis of bone strength: anatomy, physiology and measurement

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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 toughness[1-4]. In particular, bone structure, size and strength are reliant upon and responsive to the routine physiological and mechanical demands placed upon it[5-12]. 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 immobilisation[13-17]. 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 mass[18-24]. 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 capabilities[29-35]. 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

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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 injury[50-57].

Despite the complex and multidimensional relationship between various loading schemes and bone mechanical properties (beyond the scope of this review, and published earlier[12]), bone strength and stiffness are greatest in the direction by which loads are most commonly expressed[13,44,49,58]. The prevaling 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 mechanotransduction[59-62]. 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 strength[63-65]. 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 interventions[68]. 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 strength[12] 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 loads[73-78]. 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 stuctural 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 re-modelling 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 torsion[142-146]. 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 compression[153-155]. 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 canaliculated 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, supresses BMP-2 and calcium absorption.	Inhibits Formation Stimulates Resorption
Ghrelin	Gut-derived peptide hormone; secretagogue of growth hormone; modulates energy homeostasis.	Stimulates Formation Inhibits Resorption
Leptin	Adipocyte peptide hormone; proportional to fat stores; modulates energy homeostasis.	Inhibits Formation Stimulates Resorption
Thyroxin (T_3 and T_4)	Tyrosine-based hormones produced by thyroid gland; regulates energy metabolism through thyroid stimulation hormone (TSH) activity.	Stimulates Formation Stimulates Resorption Net Effect: Homeostatic
ACTH	Peptide hormone secreted from the anterior pituitary; stimulates cortisol production; dose- dependent proliferation of osteoblast activity.	Stimulates Formation Stimulates Resorption Net Effect: Homeostatic
Oxytocin	Peptide hormone secreted from the posterior pituitary; modulated by estrogen; autocrine- paracrine osteoblast regulator of formation.	Stimulates Formation Stimulates Resorption Net Effect: Homeostatic
Gonadal Regulators		
Androgens	Sex steroid secreted from testes (men) and adrenals (men and women); also converts to estrogen; acts in presence of hGH.	Stimulates Formation
Estrogen	Synthesised from androgens in ovaries (women) and extra-glandular tissue (men and women); dominant role in bone metabolism.	Permits Formation Inhibits Resorption
Calcitropic Regulators		
PTH	Polypeptide secreted by parathyroid gland, tightly controls calcium and phosphate; acts to maintain bone mineral homeostasis.	Stimulates Formation Stimulates Resorption Net Effect: Formation
Calcitonin	Secreted by thyroid gland when plasma calcium is elevated; lowers plasma calcium; deposits into bone; relatively weak in comparison to PTH.	Stimulates Formation Inhibits Resorption
Vitamin D_3	Activated in the liver and kidney; essential for intestinal absorption of calcium and phosphate; deficiency results in bone demineralisation.	Permits Formation Stimulates Resorption

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

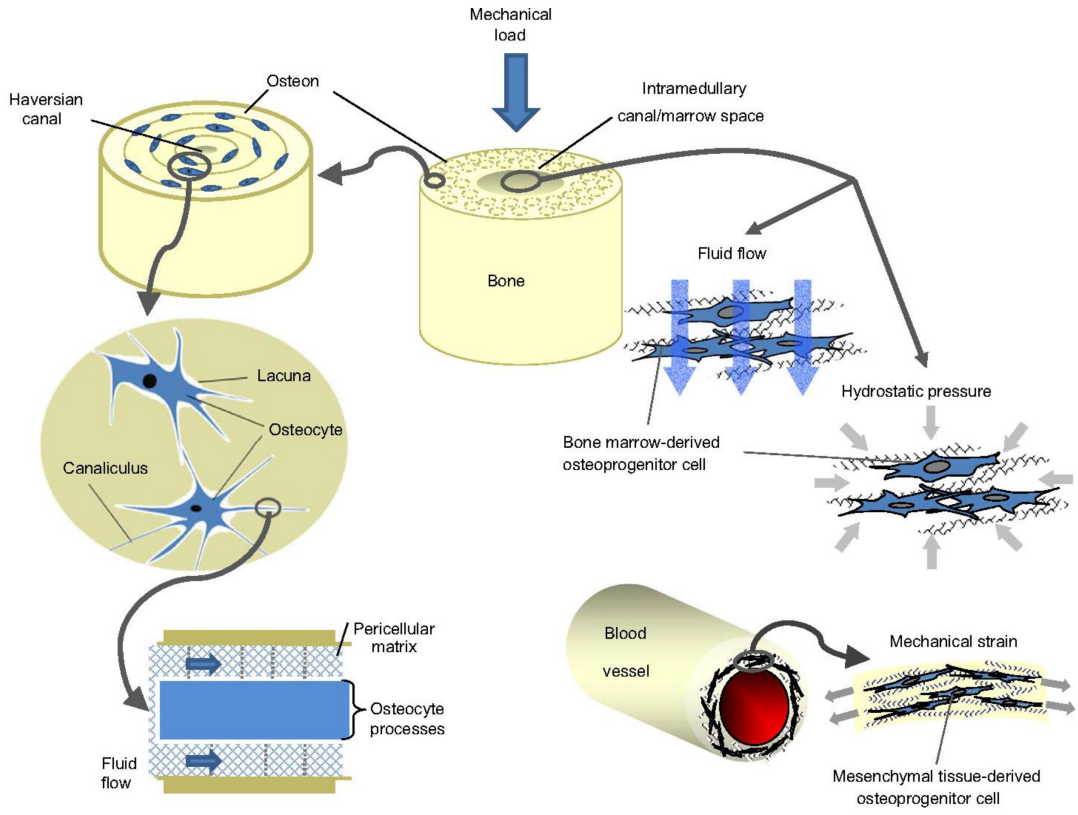

Figure 1. Mechanotransduction (adapted from [14,15]): illustrating the hierarchical structure of bone and the organizational structure of osteocytes within (left); and the mechanically induced fluid flow from hydrostatic pressure and osteoprogenitors through which biochemical signals proliferate (right).

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

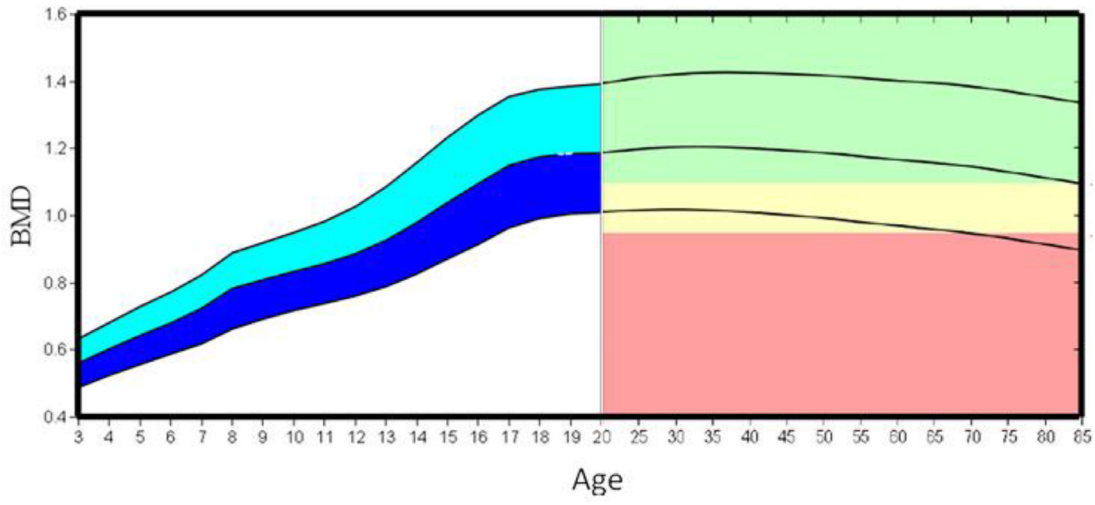

Figure 2. Bone mineral density accrual, maintenance and loss through-out the life-span as indication of bone mass alterations; with approximately 50–60% of total adult bone mass gained during adolescent years preceding peak bone mass and skeletal maturity at ~30 years of age. Bone mass deteriorates gradually 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 review[12]. 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 mass[269-271]. 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[73,82,97,257,262,267,272-27]7. 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

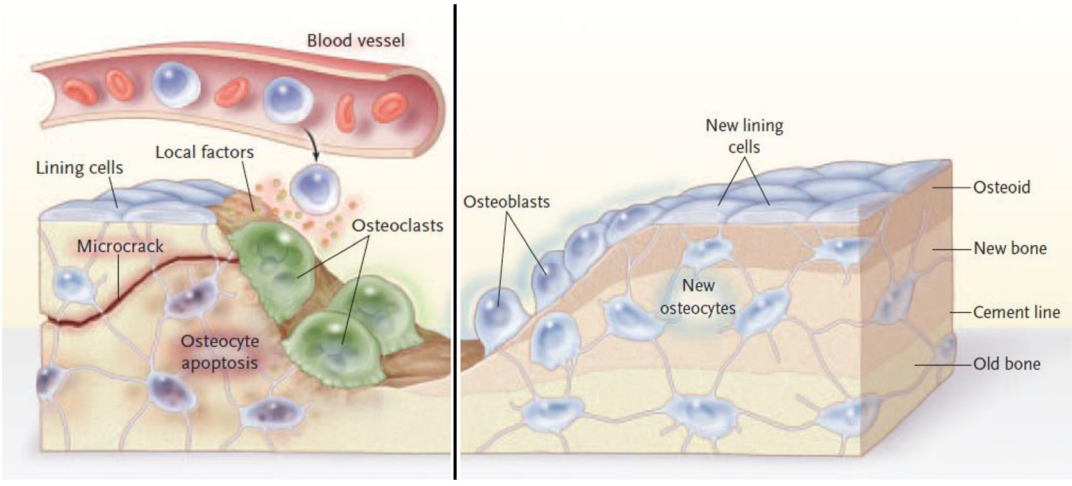

Figure 3. A graphical representation of the remodelling cycle (adapted from [24]). Bone resorption (left) is stimulated by a micro-crack which severs canaliculi channels between osteocytes leading to osteocytic apoptosis. Lining cells and osteocytes release signals attracting cells from blood and marrow 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 [96,109110,123]).

• Lifespan of BMU: **~6-9 months**
• Duration of remodelling: **~4-6 months**
• Speed of remodelling: **~25 µm/day**
• Bone volume replaced by a single BMU: **~0.025 mm^3**
• Lifespan of osteoclasts: **~2 weeks**
• Lifespan of osteoblasts (active): **~3 months**
• Interval between successive remodelling events at the same location: **~2-5 years.**
• Rate of turnover of whole skeleton: **~10% per year** [a]
[a] 10% per year approximation assumes 4% turnover per year of cortical bone (75% of the skeleton), and 28% turnover per year of trabecular bone (25% of the skeleton): Calculated as [0.75 x 4] + [0.25 x 28] = 10%; BMU = basic multicellular unit.

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 paralyisis 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 surfaces[348-350], 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 systemtically (stochastically) through-out bone material[353-355]. Taken together, while cellular proceses are tighly 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].

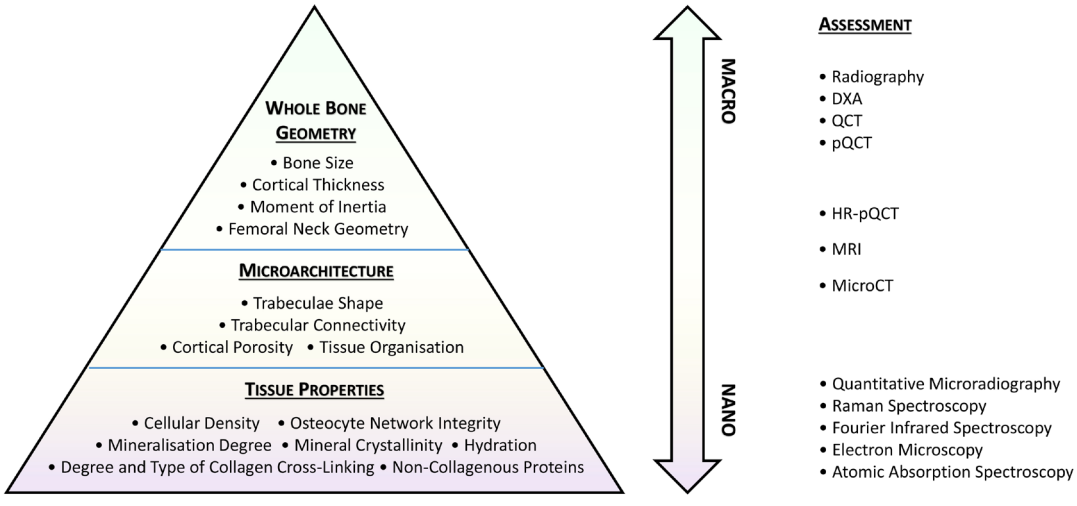

Figure 4. Material and structural determinants of bone strength or fragility (left) with associated technologies required to examine bone properties (right); along the macroscopic, microscopic and nanoscopic continuum [top to bottom], (adapted from [1]).

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 environments[372-377], often supported by the collection of biochemical markers through serological and urianalytical 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 manner[380-382]. Importantly, DXA quantifies areal bone mineral density (aBMD) and its derivatives (bone area and bone mineral content) in order to examine bone quality[383-385], 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 urianalytical 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
Deoxypiridoline	DPD / D-PYR	Serum & Urine	Resorption
Carboxyterminal Crosslink, Procollagen I	ITCP	Serum	Resorption
Carboxyterminal Crosslink, Type I Collagen	CTx	Urine	Resorption
Aminoterminal Cross-link, Type I Collagen	NTx	Urine	Resorption
Tartrate-resistant Acid Phosphate	TRAP5	Serum	Resorption
Parathyroid Hormone	PTH	Serum	Turnover Rate
Note: Information adapted from [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 fat[409-411]. 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 mass[410-414]. 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 values[423]. 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 ascendency 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 urianalytical provisions of biochemical markers provide clinicians with a useful methodology to examine physiological alterations in bone metabolism, specifically the prevalence of formative and resorptive activity within the skeleton[425-428]. 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 resportion 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 paper[12]). In terms of the gross bone morpohology, it bears repeating that responses to mechanical loads are site-sepcific. 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 limiations 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 densometric 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, densiometric 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 review[12]), 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.

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