

2017

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This article was originally published as:

Hart, N. H., Nimphius, S., Rantalainen, T., Ireland, A., Siafarikas, A., & Newton, R. U. (2017). Mechanical basis of bone strength: Influence of bone material, bone structure and muscle action. *Journal of Musculoskeletal and Neuronal Interactions*, 17 (3), 114-139.

Original article available here:

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This article originally published in *Journal of Musculoskeletal and Neuronal Interactions* available at: <http://www.ismni.org/jmni/Archive.php?year=2017>

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Review Article

Mechanical basis of bone strength: influence of bone material, bone structure and muscle action

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Abstract

This review summarises current understanding of how bone is sculpted through adaptive processes, designed to meet the mechanical challenges it faces in everyday life and athletic pursuits, serving as an update for clinicians, researchers and physical therapists. Bone's ability to resist fracture under the large muscle and locomotory forces it experiences during movement and in falls or collisions is dependent on its established mechanical properties, determined by bone's complex and multidimensional material and structural organisation. At all levels, bone is highly adaptive to habitual loading, regulating its structure according to components of its loading regime and mechanical environment, inclusive of strain magnitude, rate, frequency, distribution and deformation mode. Indeed, the greatest forces habitually applied to bone arise from muscular contractions, and the past two decades have seen substantial advances in our understanding of how these forces shape bone throughout life. Herein, we also highlight the limitations of *in vivo* methods to assess and understand bone collagen, and bone mineral at the material or tissue level. The inability to easily measure or closely regulate applied strain in humans is identified, limiting the translation of animal studies to human populations, and our exploration of how components of mechanical loading regimes influence mechanoadaptation.

Keywords: Adaptation, Strain, Magnitude, Rate, Frequency, Load, Tolerance, Injury

Introduction

Skeletal fragility is directly related to mortality¹⁻³ and injury risk⁴⁻⁸, with lower bone strength increasing vulnerability to fracture. Given the incidence and severity of fractures can be minimised through causal prevention (i.e. falls, collision, overload) and/or through prophylactic or remedial intervention (i.e. mechanical, nutritional, pharmacological programs); a thorough understanding of bone strength and its mechanical behaviour under physical load is required.

Indeed, the skeleton critically underpins movement and is highly sensitive, responsive and adaptive to its mechanical environment⁹⁻¹⁵, thus knowledge of the interactions and interplay between bone material and bone structure to deliver bone strength, in addition to the synergy and neutrality of localised muscle mass to modify the behavioural mechanics of bone is of critical interest to clinicians, researchers and physical therapists.

Accrual of bone occurs most rapidly in teenage years¹⁶⁻¹⁸, culminating in the third decade of life to achieve peak bone mass, providing practitioners with a considerable opportunity [window of adaptation] to optimise bone accretion and skeletal robustness during maturation and early-stage development¹⁹⁻²¹. Beyond the evident ceiling of bone mass proliferation, bone strength is also increased through spatially relevant adaptations specific to geometrical rearrangement driven by the mechanical environment, in addition to bone health homeostasis driven by the stochastic and systemic endocrine environment through-out the lifespan (mediated

The authors have no conflict of interest.

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Edited by: F. Rauch
Accepted 19 May 2017



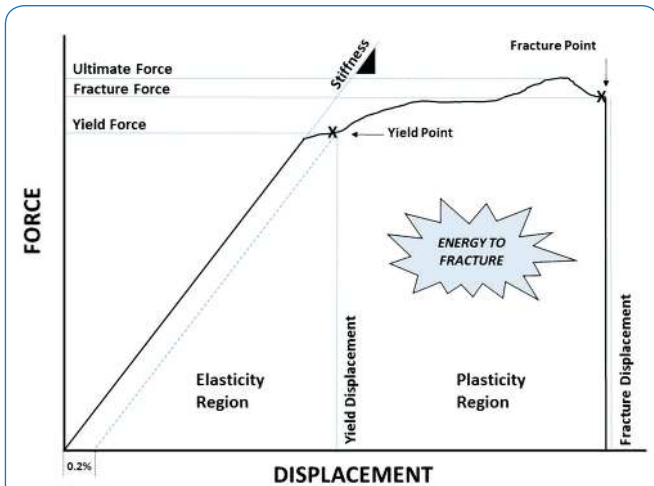


Figure 1. Stress-strain, force-deformation curve demonstrating elastic and plastic regions, and ultimate strength (adapted from 95,99-101).

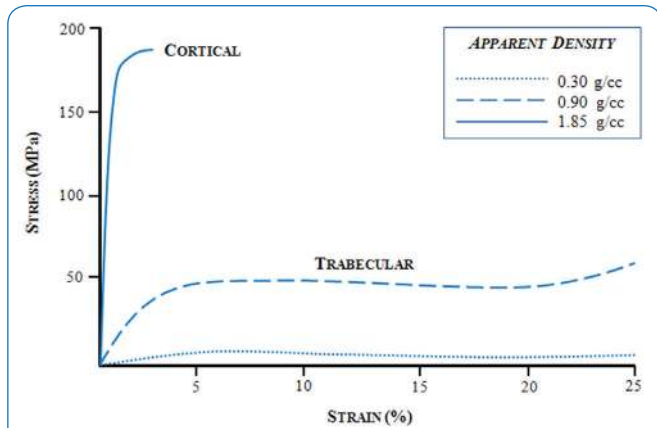


Figure 2. Stress-strain characteristics of macroscopic tissue (adapted from 95,118). Cortical bone is stiffer with a high resistance to stress and low resistance to strain [2% yield]. Trabecular bone is porous with a low resistance to stress and high resistance to strain [50% yield].

by mechanical inputs)^{17,22-25}. Bone is also hierarchically organised, where structures at macroscopic and microscopic levels co-exist at varying proportions through-out the body to manage (and adapt to) mechanical loads functionally. Bone strength is therefore a sophisticated and multifactorial proposition specific to the complex interplay of macroscopic tissue (trabecular and cortical), material properties (organic and inorganic) and structural properties (geometry and distribution); and is modulated by neighbouring muscle as a key osteogenic stimulant and modifier of mechanical behaviour²⁶⁻³⁶.

Our understanding of the mechanisms underpinning skeletal adaptation to the prevalent loading environment has developed over the last century, whereby the local cellular-level osteogenic responses, and signaling pathways are currently understood in great detail³⁷. These cellular-level responses intuitively lead into gross morphological adaptations, with Dual-energy X-ray Absorptiometry (DXA) based randomised controlled trials showing this to be true in healthy humans over the past several decades^{38,39}. Indeed, the meritorious work of Turner and colleagues⁴⁰⁻⁴² formalised preclinical, animal model experimentations into an osteogenic index formula, which represents the relationship between mechanical loading and corresponding osteogenic effect^{40,43-45}. However, these rules can only be applied in designing targeted interventions with full understanding of the intricate interplay between gross motor patterns (e.g. jumping or running) and the resulting site-specific skeletal loads⁴⁶⁻⁴⁹. Our ability to predict site-specific local loading has improved greatly with the emergence and maturation of 3-D musculoskeletal modeling for dynamic skeletal strains^{47,50,51}, and it has relatively recently become sufficiently advanced to enable exploration of site-specific dynamic skeletal loads in osteogenic exercises^{49,52-54}. In addition, the recent

development and application of an optimal segment tracking (OST) approach has further expanded our understanding of *in vivo* bone deformation^{54,55}. Indeed, recent advances in detailed site- and direction-specific analyses of bone material distribution in clinical populations (fracture cases^{56,57}), chronic conditions (aging⁵⁸⁻⁶⁰, paralysis⁶¹⁻⁶³, habitual activity^{10,12,64}), and following loading interventions (exercise⁶⁵, immobilisation⁶⁶), have established that site-specific skeletal adaptations can be captured and should be explored.

Therefore, this paper provides a thorough overview of the interplay between bone material, bone structure and muscle action to modulate and influence mechanical behaviour of bone. Through increased understanding, this information allows clinicians, researchers and physical therapists to comprehensively examine bone strength within the realm of present technology; identify potential sources of skeletal fragility in a range of populations specific to function and morphology; and investigate ways to produce systemic (stochastic) and/or targeted (deterministic) interventions to preserve or promote bone strength.

Mechanical load

Bone formation, regeneration and degradation processes are stimulated by mechanical strain as a result of applied mechanical stress in the form of muscular contraction, impact loading and gravitational forces^{31,41,67-73}. In particular, bone cells are responsive to local strains expressed in their precise vicinity by routine stresses supplied by activities of daily living^{42,68,73-81}; therefore, the determinants of bone adaptation in response to mechanical load involve all aspects of the strain environment, including strain magnitude, strain rate, strain frequency, strain distribution, number of loading cycles, and

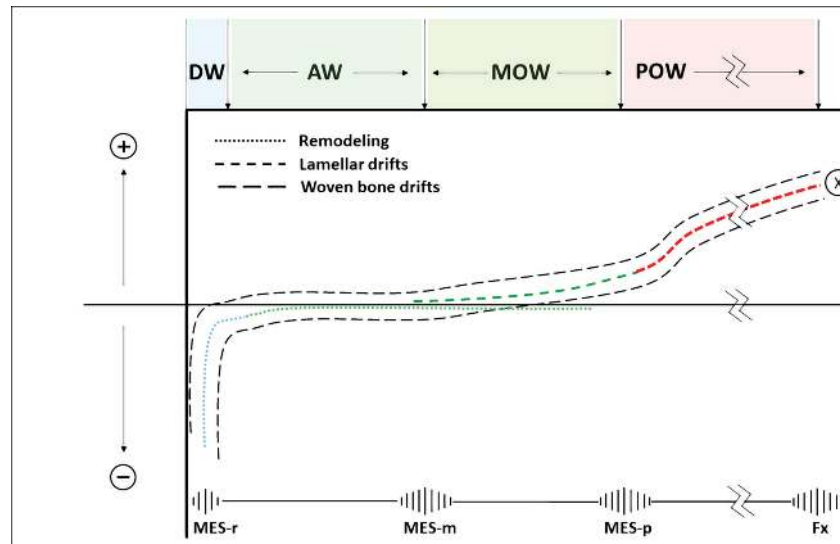


Figure 3. Mechanostat Theory: Modeling and remodeling effects on bone strength and mass. DW= disuse window; AW= adapted window; MOW = mild overload window; POW= pathologic overload window; MES= minimum effective strain (r= remodeling, m= modeling, p= microdamage), Fx= fracture strain (adapted from ^{69,127,131}).

rest-recovery periods^{31,40,41,51,70,71,73,78,82-85}. Specifically, all components of the strain environment are interlinked and interdependent, such that they collectively contribute to the osteogenic effect and potency of mechanical loading.

Stress - Strain

Bone receives stress (external force) which produces strain (structural deformation). In particular, applied forces generate stresses of varying intensities that produce strains of varying magnitudes and modes^{51,85-93}. Stress is a measure of load per unit of area, expressed in Newtons per square metre (N/m²) or Pascals (Pa); whereas strain is a measure of linear or shear deformation expressed as microstrain ($\mu\epsilon$), or as a percentage (%) of change in dimension^{92,94-96}. The interaction of stress and strain provides insight into the mechanical behaviour of material properties in bone when deforming under load^{36,51,85,86,89,94,97-100}.

Bones under strain exhibit two distinct behavioural characteristics either side of their yield point, noted as elastic and plastic regions on the stress-strain curve^{89,92,101-103}. In the elastic region, lower level strains beneath the yield point allow bone material to elastically store and return applied stress, thus escaping microdamage in the process^{97,103-106}. Conversely, in the plastic region, higher level strains above the yield point deform bone material beyond its point of resilience, consequently generating material damage, usually in the form of micro-cracks^{85,94,107-111}. Resilience explicitly refers to the capacity of bone to elastically store energy and thus resist microdamage, and is represented by the area under the elastic portion of the stress-strain cu

ve^{95,102,103,107,110,112,113}. Elasticity or stiffness of biomaterial (Young's modulus; $E = \Delta\epsilon/\Delta\sigma$) can considerably modify skeletal resilience in response to changes in the gradient of the stress-strain curve^{86,97,98,101,104,114-116}. Similarly, an adjustment in resilience can subsequently alter skeletal toughness, represented by the whole area [elastic and plastic regions] under the stress-strain curve^{94,96,98,102,103,105,112,113,117}, thus altering the total amount of energy absorbed by bone prior to failure.

Stress-strain characteristics differ between macroscopic tissues in response to their underlying microscopic architecture^{96,101,116-120}. Cortical bone is stiffer than trabecular bone, thus can withstand higher stress (~150 MPa) yet lower strain (~2%) prior to failure; whereas the porous nature of trabecular bone provides greater elasticity than cortical bone, thus withstands lower levels of stress (~50 MPa) yet much higher strain (~50%) prior to failure^{86,95,98,107,109,121}. However, variations in macroscopic composition through-out the skeleton; coupled with the interaction of different material properties producing different stress-strain characteristics; highlights a complex yet sophisticated relationship between physical load, material deformation and mechanical behaviour^{24,97,113,119-122}.

Strain magnitude

Magnitudes of strain received by bone from muscular contraction and gravitational load form the central thesis and most influential feature of bone adaptation^{69,77,84,123-125}. Conceptually referred to as "mechanostat" theory; a qualitatively described, dose-response continuum of strain

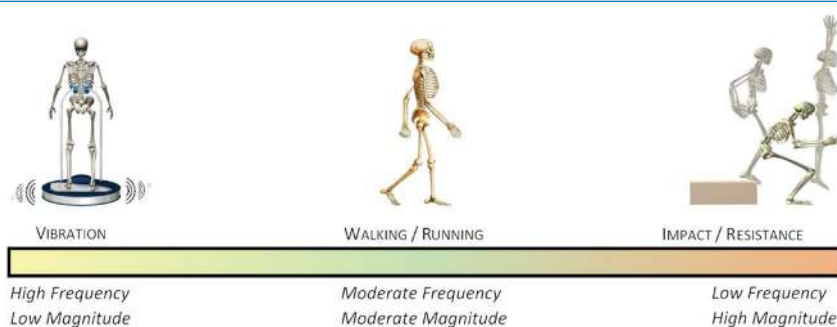


Figure 4. Osteogenic relationship between strain magnitude and strain frequency: Low magnitude, low frequency activities and high magnitude, high frequency activities may lead to maladaptation due to insufficient (resorptive) or excessive (stress reaction) stimuli.

magnitudes can elicit resorptive, regenerative or formative responses in bone^{40,69,91,126-128}. Functionally, the mechanostat serves to modify bone in order to meet mechanical demands; therefore to simply maintain bone mass, a minimum effective strain (MES) is required^{68,69,127,129-131}. If strain magnitude sits below the MES threshold, mechanical degradation occurs to eliminate unnecessary, excess mass; if strain magnitude exceeds the MES threshold, bone formation occurs to increase bone strength by adding mass and increasing cross-sectional area^{42,77,91,123,126-129}.

Strain magnitude is not the sole progenitor of, 'nor linearly related to bone adaptation, which highlights an inherent limitation of mechanostat theory in its current form^{68,76,132-134}. Biologically, strain is not sensed and transduced uniformly at the cellular level therefore mechanistically, bone adaptation responds to various combinations of different strain-related stimuli rather than a specific magnitude of strain itself^{76,77,126,128,129,133,134}. Strain frequency, strain rate and strain distribution are derivatives of strain magnitude, and have therefore been recognised as additional, important determinants of bone adaptation^{40,41,68,70,83}.

Strain frequency

Strain frequency represents the number of applied cycles-per-second to a given structure^{40,70,135}. The frequency of strain delivered to bone has been established as an influential and programmable determinant of osteogenesis^{82,136-140}. Specifically, increases in loading frequency adjust mechanostat thresholds downward; reducing the minimum effective strain required to stimulate osteogenesis, thus enabling strain-related bone formation to occur at lower relative strain magnitudes^{78,126,134,141}. This somewhat inverse relationship between strain frequency and strain magnitude highlights a potential volume-specific adjustable loading mechanism to provide osteogenic stimulus within appropriate, safe and variable strain environments^{40,78,135,141-143}.

Bone responds in a non-linear fashion to strain frequency, with osteogenic adaptations ceasing to intensify beyond a 10 Hz stimulus cycle due to signal saturation^{78,136,139,141}. Instead, osteogenic activity interacts with magnitude and

frequency loading schemes on a proposed continuum. For example, low magnitude, low frequency strains are likely to result in resorption due to insufficient stimuli; whereas high magnitude, high frequency strains are likely to result in stress reactions or structural failure due to excessive overload. Therefore high-magnitude, low frequency strains (e.g. impact exercise), low magnitude, high frequency strains (e.g. whole-body vibration), or variants of these end-points will optimally yield desirable, formative adaptations^{71,135,137,142,144,145}.

Strain rate & distribution

Strain rate and strain distribution represent the temporal and spatial characteristics of strain magnitude respectively^{70,78,93,134,144,146,147}. Specifically, strain rate refers to temporal change in strain magnitude within each strain cycle (microstrain per second; $\mu\epsilon/s$), thus measures the rapidity at which alternations in strain application occur^{70,132,148}; whereas strain distribution refers to spatial change in strain magnitude across a given volume of bone (microstrain per linear distance, $\Delta\mu\epsilon/d$), quantified circumferentially and longitudinally in each orthogonal axis^{70,83,149}. Given the teleological purpose of bone in humans, it seems logical that in order to induce osteogenic adaptation, strain should be supplied dynamically rather than statically^{41,45,138,150,151}; therefore variable and volatile strain environments involving these strain parameters should ideologically optimise anabolism in bone^{40,68,70,79,128}.

Human and animal models have directly and indirectly established strain rate as a key driver of osteogenesis independent of strain magnitude^{132,144,146,148,152-156}. In particular, adaptive modeling is closely and positively associated with strain rate, such that slowly applied dynamic strains yield minimal adaptations whereas rapidly applied dynamic strains yield significantly intensified adaptations^{41,45,144,153,157}. Similarly, strain location, direction and gradient also contribute to nonlinear outcomes of bone loading paradigms such that irregular and unusual distribution (spatial delivery) of strain is also positively influential to osteogenesis^{40,78,83,158}. Bone cells therefore optimally respond to the net-effect of loading activity that

is dominated by high strains (magnitude or frequency) changing at fast rates while presenting in unusual and unbalanced distributions^{40,68,77,112,132,134,147,156}. Recent work also suggests that strain modality is important, with torsional deformations key to both development and maintenance of bone strength^{159,160}.

Strain volume

Strain volume is the durational product of strain magnitude, rate and frequency for a given loading session, often aggregately quantified into a total number of daily loading cycles^{40,71,95,156}. Specifically, precise amounts of loading cycles at given magnitudes, rates or frequencies generate formative, preservative or resorptive responses in bone dependent upon the strain environment within each session and accumulative strain history within each day^{68,76,153}. While many combinations of strain magnitude, rate and frequency can interact to provide potent osteogenic stimuli; bone adaptation does not linearly respond to strain volume^{40,71,156}. In particular, increases in skeletal loading duration do not elicit proportional changes in bone mass formation; rather, bone responsiveness to mechanical load eventually declines, highlighting an evident suppression of mechanosensitivity^{153,161-169}.

Bone's rapid and acute desensitisation to anabolic stimulus in response to mechanical loading is governed by a law of diminishing returns, such that received load differs from perceived load^{156,162,167,170}. Remarkably small amounts of mechanical stimulation at effective strain thresholds are required to promote osteogenesis prior to a rapid reduction in cellular responsiveness^{40,161,167,171}. Specifically, ~95% of mechanosensitivity is dampened after only ~20 to 40 loading cycles at physiologic thresholds (~2000 $\mu\epsilon$ in compression), with almost no discernible osteogenic benefit established beyond ~100 loading cycles within equivalent strain environments, at which point strain volume becomes asymptotic^{153,170,172}. Indeed, the osteogenic relationship between strain volume and mechanosensitivity is fluid, such that a variety of effective strains along the magnitude-frequency continuum will adjust the number of loading cycles experienced prior to rapid sensory suppression. Nevertheless, the existence of a tangible saturation point beyond a given cyclical loading threshold has considerable implications for targeted mechanical loading programs^{40,130,164,166,171-173}.

Restoration of mechanosensitivity following previous loading bouts is necessary for bone cells to progressively transduce osteogenic stimuli during successive or future loading bouts^{163,166,171,174-176}. In order for resensitisation to occur, the provision of unloaded rest periods is required to afford bone with recovery time; the duration of which is proportionate to the nature of recent loading stimulus incurred^{40,162,174,175}. Akin to desensitisation, bone cell resensitisation also presents as a logarithmic function. Specifically, the restoration of mechanosensitivity is also initially rapid, until an inflection point is reached whereby only mild osteogenic improvements occur beyond it^{164,176}. In

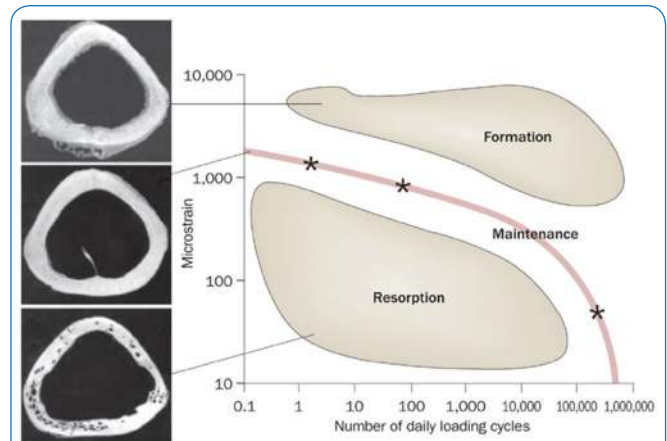


Figure 5. The relationship between daily loading cycles (magnitude, rate and frequency) and subsequent bone adaptation (reprinted with permission from ⁷¹). Bone is maintained (red line), formed (superior portion) or resorbed (inferior portion) using a variety of different strain environments.

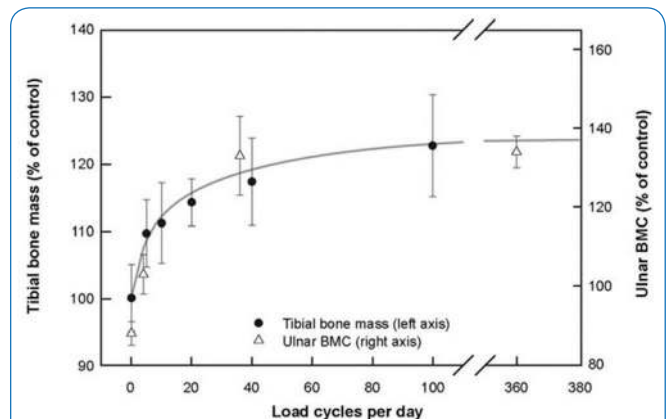


Figure 6. Bone mass of rats (•) and turkeys (Δ). Anabolic effect of mechanical loading saturates as the number of loading cycle's increases, with limited benefit above ~40 cycles per day (reprinted with permission from ¹⁵³).

particular, rest periods spanning ~15 seconds to ~4 hours increase bone formation outcomes by ~65% to 100%; whereas no significant advantage is evident beyond ~8 to 10 hours; and ~98% of mechanosensitivity restored ~24 hours post-loading event^{40,153,169}. Rest periods therefore enable an equivalent strain volume to be delivered across several discrete loading blocks; increasing anabolic potency and osteogenic outcomes through targeted mechanical loading schemes^{162,169,176-178}.

Cellular accommodation (mechanical acclimatisation) to frequent mechanical loading events creates prolonged

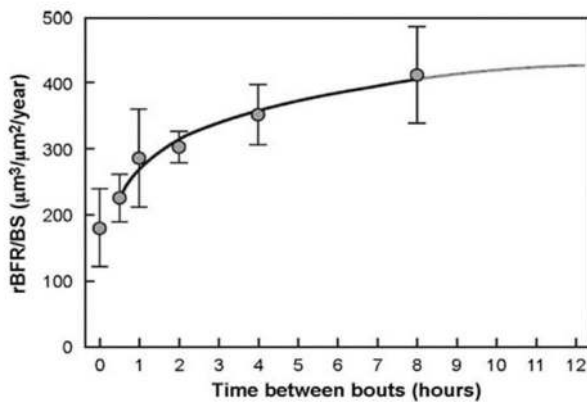


Figure 7. Bone formation (rBFR/BS) of rat tibia after applying loads in 4 bouts of 90-cycles every second day, with various rest provided between bouts; ~4 to 8 hours appears optimal (reprinted with permission from ¹⁶⁴).

cytoskeletal alterations in bone, resulting in longer-term mechanosensitive reductions to familiar strain environments^{40,42,143,168,170,179,180}. Acutely, loading cycles delivered in the first bout of activity provide the greatest opportunity to elicit the largest adaptations within a given session or day, as strain detection and bone adaptation is most responsive at this time^{161,165,166,169,171,178}. Chronically, this same principle applies; initial loading blocks within a sequential, long-term loading program also provide the greatest potential for osteogenic adaptation to occur, exemplified when comparing volume-matched regressive and progressive loading schemes^{40,42,130,181}. Akin to acute mechanosensitive suppression; chronic acclimatisation of bone can also be reversed with the provision of unloaded recovery blocks within a broader mechanical loading program^{163,168,182} thus the potency of initial stimulus appears to drive bone adaptation, rather than long-term accumulation of mechanical loads^{40,42,168,181,182}. Clinicians and physical therapists must therefore be cognisant of the temporal design and delivery of their prescribed, targeted mechanical loading programs.

Mechanical behaviour

Bone is structurally complex and hierarchically designed, with diverse arrangements and various layers of biomaterial working co-operatively to meet numerous paradoxical requirements^{36,183-188}. Specifically, the material (mechanical) and structural (geometrical) properties of bone implicitly determines its behaviour under mechanical load, dictating its performance under stress and strain to deliver mechanical stiffness and structural strength to the skeleton^{22,23,89,94,95,98,112,189}. Owing to its anisotropic and viscoelastic design, bones behave and respond uniquely to various loading modalities of differing magnitudes,

Table 1. Average anisotropic values of ultimate strength (compression, tension, shear), elastic modulus and Poisson's ratio in cortical bone (adapted from ^{95,203}).

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

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

directions, rates and frequencies^{95,97,114,116,119,122,190}. While this relationship between mechanical load and mechanical behaviour is multifactorial; bone strength and stiffness are greatest in the direction where loads are most commonly expressed^{23,69-71,85,86,90,102,191,192}.

Loading types

Bone exhibits distinct mechanical behaviours when loaded across orthogonal axes, as it structurally differs in concentration and arrangement between longitudinal and transverse planes^{51,97,102,112,185,187,193,194}. Consequently, bone strength and stiffness vary across the loading spectrum in an anisotropic and viscoelastic fashion, highlighting a context-specific tolerance to mechanical load^{101,122,185,190,195-202}.

Cortical bone is stronger and stiffer in compression than tension; under longitudinal loads than transverse or shear loads; and under higher strain rates than lower strain rates^{95,101,104,114,198,203-205}. By comparison, the mechanical behaviour of trabecular bone is less predictable and widely volatile, owing to its perforated, variable and less organised lamella arrangement and architectural connectivity^{24,36,101,116,121,206-209}.

Bone routinely withstands tensile (pulling; positive elongation), compressive (pushing; negative elongation) and shear strains^{97,194,210}. Although forces generating strain can act in isolation (uniaxial) or combination (biaxial or triaxial); at any given time bone will still experience all three forms of strain at various locations and magnitudes^{51,101,209,211-213}. The co-existence of linear and angular strains under uniaxial, biaxial and triaxial loading is represented by Poisson's effect; a ratio which describes the susceptibility of bone to deform transversely under given axial loads^{95,114,205}. Specifically, bone widens under compression and narrows under tension in accordance with its anisotropic and viscoelastic properties; the sum of which explains the ability and extent of bone to bend and twist under complex or strenuous loads^{102,114,190}.

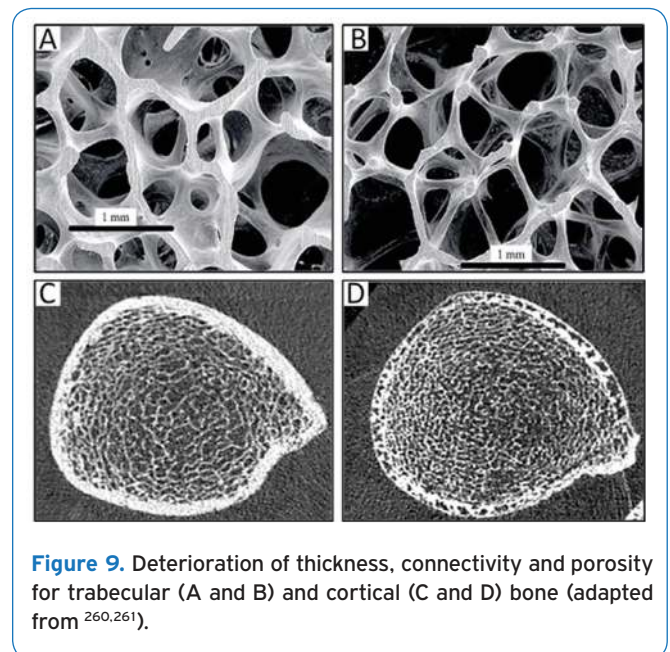
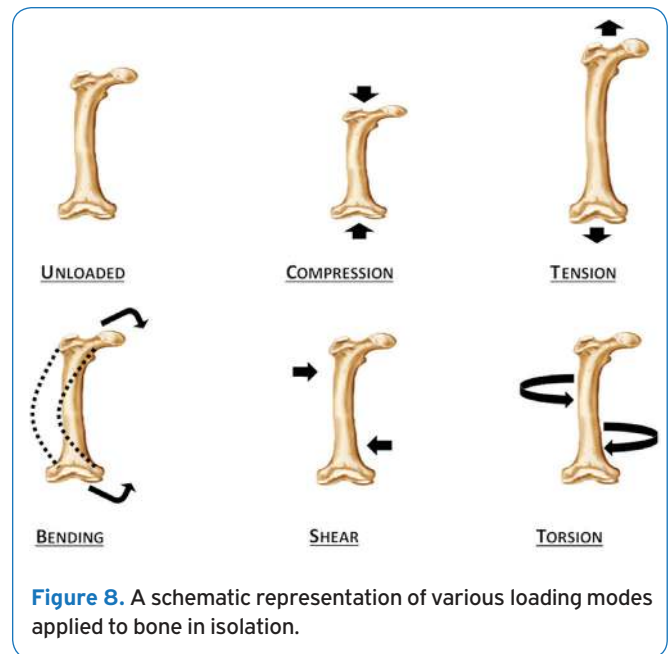
Bone therefore dynamically responds to forces and moments in various directions, translating compressive, tensile and shear strains into compression, tension, bending, shear and torsional mechanical outputs^{54,55,95,97,101,112,194,205}.

Material contribution

Bones are bi-phasic composite materials, with organic and inorganic components. The interplay between these materials and their relative composition considerably influences mechanical behaviour and bone strength, independent of geometry, when loaded under static, dynamic or fatiguing conditions^{36,94,187,189,214-218}. Specifically, the degree of mineralisation and porosity (i.e.: apparent density) ultimately determines the quality of bone material, and therefore how it responds to load^{58,187,189,214,219-223}; influencing its ability to resist deformation (stiffness), absorb stress (elasticity) and absorb energy (toughness) prior to failure (ultimate strength).

Mineralisation refers to the deposition and maturation of mineral content within bone through primary and secondary biomineral phases^{23,36,89,94,224,225}. Sequentially, newly deposited bone begins to rapidly mineralise within ~5 to 10 days of creation, generating ~60% of its total mineral content during primary mineralisation, prior to gradually advancing toward complete maturation and calcification during secondary mineralisation within ~30 months of initial deposition^{189,219,220,224,226-228}. This time-course of mineralisation occurs asynchronously and continuously at multiple sites across various regions of bone^{36,189,214,219,224,229,230}, thus mechanically, the degree to which immature and mature inorganic material (hydroxyapatite crystals) surrounds organic material (type 1 collagen) at any given time will ultimately determine the level of structural flexibility or stiffness conferred to bone, and therefore its mechanical competence^{23,86,89,184,191,218,222,226,231-234}.

Mechanical behaviour is not solely influenced by the degree of bone mineralisation, but also the quality of mineral within the bone matrix^{36,78,189,191,215,216}. Indeed, the degree of crystallinity is of behavioural interest as increases in crystal size, number and distribution during secondary mineralisation alter the elastic, plastic and viscoelastic properties of bone in favour of increased micro-hardness^{189,204,214,219,220,225,228,235-237}. If mineralisation and crystallinity are too high, bone may become excessively stiff and brittle, thus micro-crack initiation, propagation and coalescence may arise at reduced levels of deformation^{85,189,219,221,228,238,239}. If mineralisation and crystallinity are too low, bone may become fragile and weak; thus a presently undefined, yet evidently optimal ratio of organic-to-inorganic material exists in a U-shaped relationship with bone strength and mechanical competence^{23,36,183,224,226,228,240,241}. This arbitrary conundrum is confounded by the recognition that certain combinations of material properties can improve tolerance to one type of loading, whilst at the same time deleteriously affect another type of loading^{98,183,189,191,216,223}. Fortunately, mineralisation and crystallinity are closely linked, temporally aligned processes; metabolically regulated



and mechanically modulated to maintain homeostasis in the absence of pathology or ageing to meet functional requirements^{204,228,229,237}.

Porosity represents the prevalence, magnitude and distribution of pores within the bone matrix^{24,58,72,204,242,243}, which characteristically differs between macroscopic tissues. Porosity is a prominent and purposeful architectural feature of trabecular bone (~50 to 90% porous); while minimal in quantity and size within cortical bone (~5 to 10% porous)

under normal circumstances^{72,85,184,244}. The functional merit of porosity in trabecular and cortical bone is provided at the expense of strength, with small increases in porosity equating to disproportionately large decreases in bone mass and density^{24,36,114,189,245-247}; the major clinical feature of bone degeneration from ageing, disuse or disease^{58,114,248,249}. Trabecular bone is rapidly affected by increased porosity; resulting in progressively thinner, disconnected and separated trabeculae^{36,58,188,208,245,250-253}; similarly, the weakening of cortical bone is also predominated by increased porosity, resulting in loss of stiffness and reduced load tolerability^{58,85,114,204,244,247,254-257}. Consequently, microarchitectural deterioration of trabecular and cortical bone rapidly compromises mechanical integrity, accounting for ~90% and ~75% of strength loss during ageing respectively^{36,85,188,208,243,245,254,255,258}. Bone porosity should therefore be restricted, where possible, to only those cavities required for biological functions such as vascular supply, marrow storage, blood-cell production, biochemical signaling, transduction and remodelling processes^{24,58,189,249,257,259}.

Density is the product of mineralisation and porosity, expressed as mass per unit of volume^{187,262-265}. Specifically, the amount of mineral content per volume of bone (mineralisation), and its ratio of void volume to total volume (porosity) respectively combine to establish apparent bone mineral density^{263,264,266-268}; the relationship of which exemplifies trabecular and cortical performance under mechanical loads^{36,119,124,183,208,268,269}. Owing to their architectural and functional differences, components of trabecular and cortical density (surface-to-volume ratios) poorly correlate with each other ($r \approx 0.11$); yet co-operatively influence whole-bone behaviour and strength through separate genetic and environmental mechanisms, the interaction of which remains poorly understood^{36,266,270-272}. Genetically, ~60% of trabecular density and ~40% of cortical density is pre-determined^{271,273} with unique genomic expressions evident between microarchitectural components; including FMN2/GREM2, RANKL and WNT16 variants effecting trabeculae thickness and number, cortical porosity, and cortical thickness respectively^{271,274-277}. Synergistically, this provides scope for environmental mechanisms to separately and aggregately modulate bone density through physical, nutritional and pharmacological mechanisms.

Bone mineral density (BMD) is a frequently used surrogate measure of mechanical competence and bone strength in clinical and experimental contexts, expressed in areal (aBMD) and volumetric (vBMD) terms^{208,262,265,266,269,278}. Traditionally, areal BMD (mass per area; g/cm²) has featured as the central measure of bone quality to establish fracture risk; diagnose osteopenia and osteoporosis; or quantify interventional efficacy of preventative and remedial programs^{271,278-281}. However, aBMD is limited by its generality; incapable of measuring material volume, composition or structural design; explaining ~50 - 70% of variation in bone strength^{36,94,184,262,265,269,271,273,280,282,283}. Volumetric BMD (mass per volume; mg/cm³) has gained ascendancy in recent times, owing to its separation of cortical and trabecular

compartments; enabling a more refined analysis of tissue composition, adaptation and material contribution to bone strength^{24,187,266,269,280,284-287}. While this improves upon the limitations of aBMD, all measures of bone mineral density inherently neglect structural properties of bone (architecture, morphology, geometry), which substantially influences mechanical behaviour, and greatly contributes to bone strength and fatigue resistance^{22,23,89,191,280,288-291}. Although bone density provides valuable modifiable and measureable insights into bone quality; it is only one of several determinants of bone strength^{94,183,188,189,215,262,266,292,293}, and should therefore form part of a wider investigative framework which includes structural quantities.

Structural contribution

Bone has unique geometrical and morphological properties which specifically and functionally adapt to routine mechanical loads in order to enhance bone strength and stiffness in the absence of increased bone mass^{22,23,97,127,191,211,294,295}. Specifically, bone modifies its structure by adjusting its size (thickness and diameter), shape (contour and dimensions) and architecture (alignment and distribution) to increase cross-sectional area (CSA) and cross-sectional moment of inertia (CSMI) as mechanisms to improve load tolerability and fatigue resistance^{22,97,189,191,211,245,295-300}. In particular, compressive and tensile strength are proportional to CSA, while bending and torsional strength are exponential to CSMI, such that small amounts of material apposition can significantly improve structural strength^{23,193,250,259,300,301}. CSMI is additionally important as it has several bone strength derivatives, including polar moment of inertia (J); section modulus (Z); and bone strength index (BSI).

Cortex diameter and thickness (i.e. bone size) dramatically influences the mechanical integrity and behaviour of bone when loaded^{23,94,245,295,302-304}. Specifically, cortex expansion (increased cross-sectional area) advantageously positions material further from the neutral axis of long bones by concomitantly coordinating periosteal apposition with endosteal resorption^{191,259,298,305-307}. Mechanically, increases in external and internal diameter of long bone cortices powerfully increases resistance to stress and strain, distributing mechanical forces over a larger area while promoting lightness for efficient movement; accounting for ~55% of bone strength variation^{23,92,94,189,302,308}. In particular, bone strength is proportional to the fourth power of material distance from the neutral axis, such that a doubling in cortex diameter will yield eight-fold increments in mechanical resistance to bending and torsional loads; and modest increments in mechanical resistance to compressive loads; without concomitant changes to mass or density^{189,259,299}.

Cortex shape and architectural arrangements are also highly adaptive morphological components of bone^{69,259,292,294,295,309,310}. Specifically, bone mass asymmetrically and rotationally distributes around the cortex, predominating in areas of high stress, resulting in undulating periosteal and endosteal contours^{95,97,211,292,311-313}. Indeed,

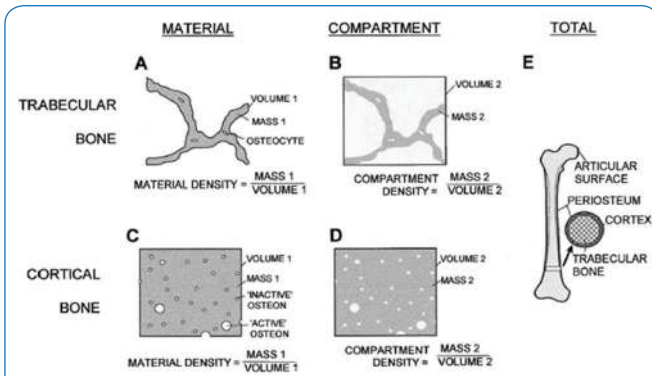


Figure 10. Definitions of mineral density at the material, compartment and whole-bone levels (reprinted with permission from ²⁸⁰). Mineralisation and porosity differ between trabecular (A and B) and cortical (C and D) regions. Mass is equal (grey areas); however volume differs (areas encased by black lines).

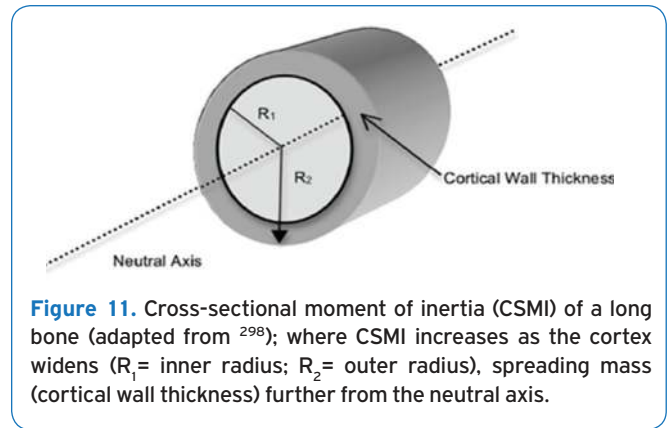


Figure 11. Cross-sectional moment of inertia (CSMI) of a long bone (adapted from ²⁹⁸); where CSMI increases as the cortex widens (R_1 = inner radius; R_2 = outer radius), spreading mass (cortical wall thickness) further from the neutral axis.

multi-planar bending and torsional forces lead to irregularly distributed increases in diameter and thickness; altering bone size and shape to increase CSA and CSMI; thereby maximising bone strength and stiffness^{193,250,259,298,300}. Additionally, cortical and trabecular microarchitecture (collagen fibre organisation) also spatially align in the direction of most commonly expressed stresses to resist customary loads^{24,36,69,102,188,292}. While these alterations may improve bone strength under common loading scenarios, irregular loading patterns may compromise mechanical competency in the absence of multi-directional, multi-modal and variable stimuli.

Bone size and shape established during ontogeny determines skeletal robustness or slenderness into adulthood, influencing the format of geometrical co-adaptations to mechanical load during maturation^{210,259,292,295,298,311-316}. Owing to their anthropometric differences (wide versus narrow cortices); material and structural traits of robust and slender bones co-adapt differently to withstand mechanical loads^{315,317-322}. Slender bones develop thicker cortices with higher mineral densities than robust bones; conferring additional stiffness at the expense of ductility and toughness in order to compensate for reduced CSA and CSMI dimensions^{318,320,322-327}. Consequently, slender bones exhibit greater susceptibility to damage accumulation (fragility and micro-crack coalescence), whereas robust bones exhibit greater resilience and resistance to fatigue or overload^{317,322,324,325,328}. Given the responsiveness of bone mass and radial growth to mechanical loading during ontogeny, it is highly recommended and opportune to maximise robustness within genetic limits where possible^{19,210,298,329-332}. Indeed, there is some evidence that the influence of mechanical loading on bone may predate birth³³³⁻³³⁶. However, the

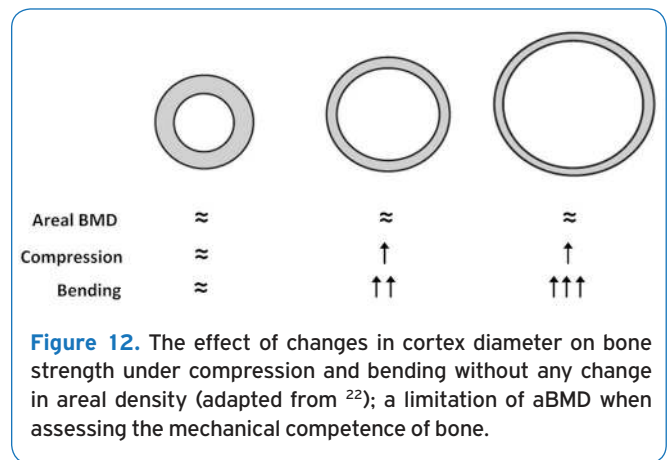


Figure 12. The effect of changes in cortex diameter on bone strength under compression and bending without any change in areal density (adapted from ²²); a limitation of aBMD when assessing the mechanical competence of bone.

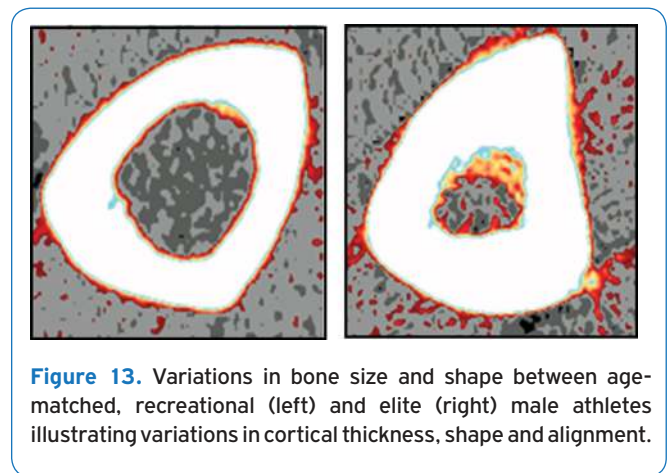


Figure 13. Variations in bone size and shape between age-matched, recreational (left) and elite (right) male athletes illustrating variations in cortical thickness, shape and alignment.

osteogenic potential of loading in older age appears diminished due to factors such as reduced muscular force and dampened mechanosensitivity³³⁷⁻³³⁹. Despite bone strength and stiffness increasing via geometrical means in adulthood³⁴⁰; robustness established during ontogeny remains protective through-out life^{20,21,292,305-307}.

Table 2. Myokines (peptides) secreted by muscle to influence bone, the mechanisms which stimulate release, and the bone metabolism outcomes.

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

Muscular contribution

Muscle and bone are inextricably linked by anatomical, mechanical, metabolic and pleiotropic functions^{26,28,29,341-348}. Anatomically, muscle transforms and mobilises skeletal segments into an interlinked system of levers via tendinous junctions^{184,343,344,349,350}. Mechanically, muscle exerts contractile forces onto the skeleton in order to effectuate movement, providing bone with its largest voluntary delivery of stimulus; superseding gravitational loads^{26,342,349-354}. Metabolically, endocrine-paracrine cross-talk between muscle and bone releases secretory factors capable of modulating each other (muscle to bone; bone to muscle), nearby tissues, and distant organs^{26-29,341,343,355-358}. Pleiotropically, muscle and bone share several phenotypic traits, responsive to the same genetic influences and pathways, which if altered, cooperatively contribute to the development of sarcopenia and osteopenia simultaneously, and may explain co-adaptive anabolic and catabolic responses to present or absent mechanical stimulus^{341,344,359-362}.

Adaptation of muscle and bone are interdependent; such that alterations in muscle size, density and strength are temporally linked and positively correlated with alterations in bone size, density and strength^{341,342,346,351,363-365}. Specifically, when immobilised; muscle cross-sectional area, volume and strength significantly reduces after ~5 to 7 days; whereas bone thickness, volume and strength significantly reduces after ~14 to 21 days^{345,346,366-372}. Conversely, when mechanically loaded; muscle cross-sectional area, length and strength significantly increases after ~20 days; whereas bone diameter, thickness and volume significantly increases after ~40 to 80 days^{126,373-377}. The time-course of adaptation is such that genomic and metabolic alterations occur rapidly and precede morphological adaptations; changes in muscle precede changes in bone (~3:1 to 4:1); and losses of muscle-bone occur more rapidly than accrual (~3:1 to 4:1); thus

exercise-induced long-term gains are rapidly reversed and gradually recovered^{346,367,371,378-382}.

Muscle is a potent osteogenic stimulant, routinely exerting contractile force onto the skeleton; the frequency, rate, magnitude and distribution of which provides bone with its primary delivery of mechanical load^{342,343,352,383-387}. Muscle therefore asserts synergistic dominance over bone, such that bone growth or loss is subservient to muscle hypertrophy or atrophy^{345-347,388-392}. In this regard, muscle and bone are stoichiometric, co-adapting together in response to anabolic or catabolic stimuli; highlighting the importance of muscle size and strength as trainable features to enhance and protect bone size and strength^{85,102,341,343,347,363,383,393}. Beyond its osteogenic capabilities, muscle also acts to mechanically alter the distribution of stress applied to bone, utilising short mechanical levers (1:2 to 1:10) to counteract and neutralise tensile forces through partially or wholly equivalent compressive forces as a mechanism to minimise bending moments^{95,102,342,383,394,395}. In particular, volatile forces transmitted through impact loading and agonist muscle contraction create uneven compressive forces onto bone, generating ipsilateral bending moments and contralateral tensile forces; thus antagonist muscle activity serves to actively neutralise tensile forces while evenly distributing compressive forces across the cortex, owing to long-bones superior strength under axial compression^{97,342,396-399}.

Endocrine-paracrine secretomes hold important implications for muscle-bone biology, providing new opportunities to utilise muscle as a targeted mechanism to cross-regulate and modulate bone. Specifically, molecular cross-talk may independently mediate muscle and bone, separate to mechanical inputs, through secretory factors known as myokines^{28,29,343,356,357,400-403}. Myokines (muscle-derived peptides) influence the local activity of neighbouring bone via endocrine-paracrine mechanisms at the muscle-bone interface; an area where muscle fibre inserts

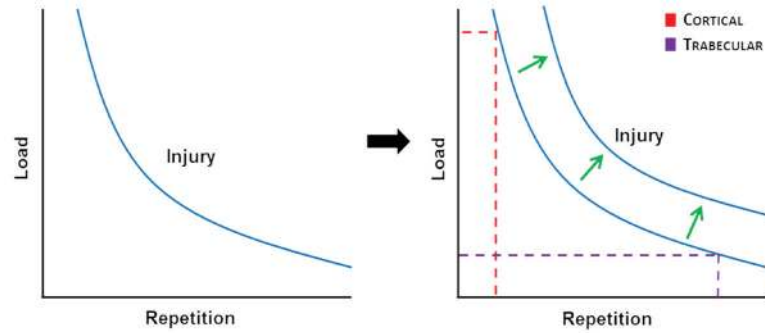


Figure 14. Fatigue curve (adapted from ⁹⁵): The relationship between load, repetition and injury onset (left), with cortical bone and trabecular bone stress-strain properties super-imposed (right). A positive shift in the fatigue-curve demonstrates the benefit of increasing bone strength; a more resilient bone able to handle more stress prior to strain.

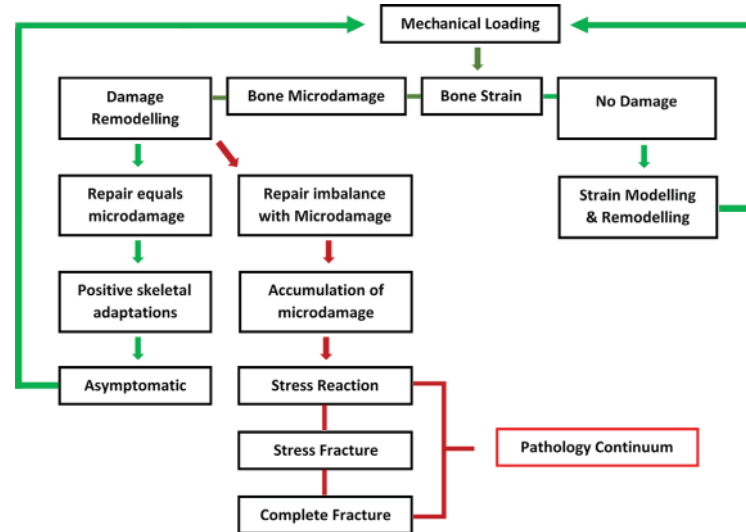


Figure 15. A pathophysiological overview of overuse and fatigue fractures (adapted from ^{416,417}).

directly into the periosteum, thus excluding tendinous and aponeurotic attachments^{26,28,400,404,405}. The direct insertion of muscle fibre into bone promotes localised bone formation and reparation activity owing to its collateral delivery of blood and rich supply of secreted trophic factors to the skeleton^{27,29,401,403,406,407}. In particular, healthy and active muscle tissue positioned alongside and onto the periosteum directly stimulates bone formation without mechanical stimulation; similarly, muscle damage or trauma also delays and impairs bone healing^{32,33,393,406,408,409}. As a result, the generation, preservation and reparation of bone is interlinked with the health and activity of surrounding muscle, such that cross-regulation has the potential to optimise anabolic and catabolic processes during growth, development, ageing and musculoskeletal rehabilitation^{26,27,356,400,403}.

Muscle-derived secretomes influence bone metabolism in

a variety of ways, with several growth factors and cytokines importantly linked to bone quality, including interleukin (IL-6, IL-7, IL-15), insulin growth-like factor (IGF-1), fibroblast growth factor (FGF-2), bone morphogenic protein (BMP-1), osteonectin (SPARC), matrix metalloproteinase (MMP-2), transforming growth factor (TGF- β 1) and myostatin (GDF-8); exerting anabolic or catabolic effects onto bone in response to physical activity, resistance exercise, muscle damage or trauma^{28,29,341,343,344,359,362,401,402,405,410}. Conversely, bone-derived secretomes are also capable of influencing muscle metabolism, with recent evidence implicating prostaglandin E2 (PGE2) and undercarboxylated osteocalcin (ucOC) as potential regulators of muscle mass, function and regeneration^{341,357,411,412}. Indeed, endocrine-paracrine cross-talk coupled with mechanical load presents a new and emerging paradigm, whereby muscle and bone

closely interact and cross-regulate each other throughout all stages of the lifecycle; highlighting the importance of translational and integrated examinations of muscle and bone biology with growth, development, ageing, exercise and disease^{27,29,356,403,404,413}.

Loading tolerance

Bone mass, material and structure interact with muscle to determine the resultant mechanical behaviour and load tolerability of bone to a given loading environment^{22,24,36,85,89,94,95,102,183,189,342}. Specifically, the interplay between loading magnitude and repetition generates a level of musculoskeletal fatigue and structural vulnerability which, in the absence of suitable rest and recovery, will eventuate in traumatic or overuse injury⁴¹⁴⁻⁴¹⁷. The generally inverse relationship between magnitude and repetition describes the causal relationship between mechanical loading and skeletal fatigue on a continuum of high magnitude, low repetition to low magnitude, high repetition loads until structural failure^{95,118,414,416}. To generate and accumulate microdamage, bone must endure strain applications of ~1500 to 10,000 $\mu\epsilon$; the precise magnitude of which is commensurate with resultant microdamage incurred^{95,416-418}.

Load tolerance and fatigue resistance can be enhanced by increasing bone strength through trainable and modifiable mechanisms; favourably shifting the fatigue curve to the right. Owing to specific material and structural adaptations, stronger and robust bones tolerate higher levels of stress prior to damaging strains, such that equivalent loading environments are less stressful and accumulate less damage than equally loaded weaker or slender bones, subsequently producing less overall skeletal fatigue^{85,202,320,322,323,325,419-421}. Paradoxically, anabolic stimulus required to strengthen bone (long-term) temporarily generates structural vulnerability through acute musculoskeletal fatigue (short-term), implicating muscle fatigue as a covariate to bone fatigue. Specifically, movement quality and efficiency becomes compromised as muscle fatigues^{397-399,422-425}, resulting in an altered gait; reduced shock absorption; irregular loading; and abnormal stress distribution, such that higher rates and magnitudes of force undesirably transmit direct to the skeleton^{399,424-429}. In the absence of recovery following strenuous activity, accumulative bone fatigue; microdamage; and eventual bone failure eventuates, highlighting the importance of inserting rest periods within mechanical loading programs designed to promote growth or prevent injury^{85,416,430-436}.

Future directions and conclusion

Bone is a sophisticated and finely tuned biomaterial; the importance of which cannot be over-stated, as it forms the functional framework for human movement and is directly associated with injury incidence, quality of life and mortality. While bone has been the focus of research for centuries, our

comprehensive understanding of the multidimensional and multifactorial components of bone strength and its mechanical behaviour remains elusive, particularly when translating evidence from animal models to humans. This information is vitally important to the clinician or physical therapist and a necessary focus of researchers, as it can be used to inform: 1) screening processes and procedures for quality examinations of musculoskeletal health status in healthy, athletic or diseased-state populations; 2) preventative efficacy of mechanical, nutritional or pharmacological programs designed to strengthen musculoskeletal tissues and protect from skeletal injury or fracture; and, 3) remedial efficacy of equivalent programs to rehabilitate individuals across the life-span following a skeletal injury or fracture.

Despite advancements in technology and improvements in knowledge through research and clinical practice, numerous limitations remain that require solutions or further investigation. Firstly, bone comprises of material that extends beyond its mineralised mass (inorganic component), however due to current quantitative limitations, mineralised tissue remains the primary measure of bone strength, and the key surrogate for skeletal health and mechanical performance under load. Meanwhile collagen (the organic component of bone) remains almost entirely neglected in clinical investigations, beyond the equivocal use of systemic biomarkers which have limited applicability at present. Indeed, the anisotropic and viscoelastic properties of bone highlight the obvious role of organic material as a key driver of skeletal strength, ductility and toughness, which requires further exploration in healthy and diseased states, as well as fracture aetiology and reparation. Secondly, highly utilised clinical densitometric assessments of mineral mass cannot yet capture important microstructural components such as the prevalence or severity of microdamage (i.e. individual or coalesced microcracks), or the degree of mineralisation and crystallinity in-vivo which may further inform evolving changes in mechanical integrity of a given skeletal site. Thirdly, while microarchitectural deterioration rapidly leads to fragility, high-resolution imaging devices which can measure features such as trabecular thickness, connectivity and number; cortical porosity and volume fraction remain scarce and are yet to gain ascendancy in clinical and research settings due to their infancy in development and high associated costs.

Lastly, the ability to accurately estimate or directly quantify site-specific internally distributed mechanical loads within humans remains complicated, invasive and equivocal. As a result, available evidence of the multifarious effects of various mechanical loading modalities and programming variables (volume, intensity, frequency, distributions, rest and recovery) remains in its infancy in humans with very few explorations in the literature. Therefore, further work to identify region-specific adaptations using a range of loading models under various loading conditions in human subjects, where strain patterns are known and can be tightly controlled, would permit first understanding in humans of factors known to influence bone adaptation in animal models.

This will allow researchers and practitioners to explore the dose-response of mechanical loads subsequent to bone adaptation outcomes in a refined manner.

Key points:

1. Bone material and bone structure co-operatively confer strength to the skeleton, with neither morphologic characteristic considered a suitable surrogate measure in isolation. Clinicians, researchers and physical therapists wishing to screen, monitor or develop bone strength and its mechanical integrity should quantify and examine material and structural components of skeletal tissue at macroscopic levels if achievable.
2. Muscle plays a vital role in developing bone strength, providing mechanical protection, and preserving or repairing skeletal tissue. As muscle and bone co-adapt and exquisitely interact, clinicians, researchers and physical therapists should concomitantly measure muscle and bone when screening, monitoring or examining skeletal health or potential fracture risk, and when developing prophylactic or remedial interventional programs.
3. Collagen (organic material of bone) remains severely neglected in clinical examinations despite its clear role in mechanical behaviour and skeletal integrity (i.e. anisotropy and viscoelasticity). Future research should aim to establish the ability to examine collagen quality in bone health assessments in-vivo. Clinicians and researchers should also consider ways to promote collagen health in populations at risk of fracture.

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