

Please cite the Published Version

Hart, NH, Nimphius, S, Rantalainen, T, Ireland, AD, Siafarakis, A and Newton, RU (2017) Mechanical basis of bone strength: influence of bone material, bone structure and muscle action. The Journal of Musculoskeletal and Neuronal Interactions, 17 (3). pp. 114-139. ISSN 1108-7161

Publisher: International Society of Musculoskeletal and Neuronal Interactions

Version: Published Version

Downloaded from: https://e-space.mmu.ac.uk/619454/

Usage rights: Creative Commons: Attribution-Noncommercial-Share Alike

Additional Information: This is an Open Access article published in The Journal of Musculoskeletal and Neuronal Interactions, published by International Society of Musculoskeletal and Neuronal Interactions, copyright The Author(s).

Enquiries:

If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines)



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

N.H. Hart^{1,2}, S. Nimphius^{2,3}, T. Rantalainen^{2,4}, A. Ireland⁵, A. Siafarikas^{2,6,7,8}, R.U. Newton¹

¹Exercise Medicine Research Institute, Edith Cowan University, Perth, W.A., Australia; ²Western Australian Bone Research Collaboration, Perth, W.A., Australia; ³Centre for Exercise and Sport Science Research, Edith Cowan University, Perth, W.A., Australia; ⁴School of Exercise and Nutrition Sciences, Deakin University, Melbourne, VIC, Australia; ⁵School of Healthcare Science, Manchester Metropolitan University, Manchester, United Kingdom; ⁶Department of Endocrinology, Princess Margaret Hospital, Perth, W.A., Australia; ⁷School of Paediatrics and Child Health, University of Western Australia, Perth, W.A., Australia; ⁸Institute of Health Research, University of Notre Dame Australia, Perth, W.A., Australia

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.

Edited by: F. Rauch Accepted 19 May 2017



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.

Corresponding author: Dr. Hart, Nicolas, Building 21, Room 222, 270 Joondalup Drive, JOONDALUP, Perth, Western Australia, Australia, 6027 E-mail: n.hart@ecu.edu.au



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 cellularlevel 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



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].

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



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 (µɛ), 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

(Young's modulus; $E=\Delta E/\Delta \sigma$) 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

rve^{95,102,103,107,110,112,113}. Elasticity or stiffness of biomaterial

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 crosssectional 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 cyclesper-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. wholebody 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; μ E/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, $\Delta\mu E/d$), 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 guantified 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 μ E 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 magnitudefrequency 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; \sim 4 to 8 hours appears optimal (reprinted with permission from ¹⁶⁴).

cytoskeletal alterations in bone, resulting in longerterm 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) lonaitudinally.		

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 deposition189,219,220,224,226-228. This timecourse 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 whichimmatureandmatureinorganicmaterial(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 guality 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-hardne ss^{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



Figure 8. A schematic representation of various loading modes applied to bone in isolation.



Figure 9. Deterioration of thickness, connectivity and porosity for trabecular (A and B) and cortical (C and D) bone (adapted from ^{260,261}).

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 circumstances72,85,184,244. 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 tolerability^{58,85,114,204,244,247,254-257} load 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 pervolume 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 lo ads^{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 wholebone 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 predetermined^{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 streng th^{36,94,184,262,265,269,271,273,280,282,283}. Volumetric BMD (mass per volume; mg/cm³) has gained ascendency in recent times, owing to its separation of cortical and trabecular compartments; enabling a more refined analysis of tissue composition, adaptation and material contribution to bone strength^{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 load co-adaptations to mechanical 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 agematched, 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}.

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

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

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 musclebone 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 (musclederived peptides) influence the local activity of neighbouring bone via endocrine-paracrine mechanisms at the musclebone 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.



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

6, IL-7, IL-15), insulin growth-like factor (IGF-1), fibroblast growth factor (FGF-2), bone morphogenic protein (BMP-1), osteonectin (SPARC), matrix metalloproteinase (MMP-2), transforming growth factor (TGF-β1) and myostatin (GDF-8); exerting anabolic or catabolic effects onto bone in response to physical activity, resistance exercise, muscle damage or trauma^{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, endocrineparacrine cross-talk coupled with mechanical load presents a new and emerging paradigm, whereby muscle and bone

a variety of ways, with several growth factors and cytokines

importantly linked to bone quality, including interleukin (IL-

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 μ E; 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 iniurv^{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 ascendency 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:

- 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.

References

- Pasco JA, Mohebbi M, Holloway KL, Brennan-Olsen SL, Hyde NK, Kotowicz MA. Musculoskeletal decline and mortality: prospective data from the Geelong Osteoporosis Study. J Cachexia Sarcopenia Muscle 2016.
- Ray R, Clement ND, Aitken SA, McQueen MM, Court-Brown CM, Ralston SH. High mortality in younger patients with major osteoporotic fractures. Osteoporos Int 2017;28(3):1047-52.
- Milte R, Crotty M. Musculoskeletal health, frailty and functional decline. Best Pract Res Clin Rheumatol 2014;28(3):395-410.
- Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. J Bone Miner Res 1997;12(1):6-15.
- Hart NH, Nimphius S, Weber J, Dobbin M, Newton RU. Lower body bone mass characteristics of elite, subelite and amateur Australian Footballers. J Aust Str Cond 2013;21(1):50-3.
- Uchiyama S, Ikegami S, Kamimura M, Moriya H, Akahane T, Nonaka K, et al. Bone strength, skeletal muscle area, and biochemical markers associated with bone metabolism in patients with fragility distal radius fracture. J Osteopor Phys Act 2016;4(1):167.

- 7. Bennell KL, Malcolm SA, Thomas SA, Wark JD, Brukner PD. The incidence and distribution of stress fractures in competitive track and field athletes. Amer J Sports Med 1996;24(2):2011-7.
- 8. Finestone A, Milgrom C. How stress fracture incidence was lowered in the Israeli army: a 25-year struggle. Med Sci Sports Exerc 2008;40(11):S623-S9.
- 9. Bach-Gansmo FL, Wittig NK, Bruel A, Thomsen JS, Birkedal H. Immobilization and long-term recovery results in large changes in bone structure and strength but no corresponding alterations of osteocyte lacunar properties. Bone 2016;91:139-47.
- Hart NH, Nimphius S, Weber J, Spiteri T, Rantalainen T, Dobbin M, et al. Musculoskeletal asymmetry in football athletes: a product of limb function over time. Med Sci Sports Exerc 2016;48(7):1379-87.
- Nikander R, Kannus P, Rantalainen T, Uusi-Rasi K, Heinonen A, Sievänen H. Cross-sectional geometry of weight-bearing tibia in female athletes subjected to different exercise loadings. Osteoporos Int 2010; 21(10):1687-94.
- Rantalainen T, Duckham RL, Suominen H, Heinonen A, Alen M, Korhonen MT. Tibial and Fibular mid-shaft bone traits in young and older sprinters and nonathletic men. Calc Tissue Int 2014;05(2):132-40.
- 13. Turner C. Skeletal adaptation to mechanical loading. Clin Rev Bone Miner Metab 2007;5(4):181-94.
- 14. Yavropoulou MP, Yovos JG. The molecular basis of bone mechanotransduction. J Musculoskelet Neuronal Interact 2016;16(3):221-36.
- 15. Schulte FA, Ruffoni D, Lambers FM, Christen D, Webster DJ, Kuhn G, et al. Local mechanical stimuli regulate bone formation and resorption in mice at the tissue level. PLoS One 2013;8(4):e62172.
- 16. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during pubertal growth spurt. Bone 2004;34(5):771-5.
- Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systemic review and implementation recommendations. Osteoporos Int 2016;27(4):1281-386.
- Baird J, Kurshid MA, Kim M, Harvey N, Dennison E, Cooper C. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. Osteoporosis Int 2011;22(5):1323-34.
- Ireland A, Rittweger J, Schonau E, Lamberg-Allardt C, Vijakainen H. Time since onset of walking predicts tibial bone strength in early childhood. Bone 2014;68:76-84.
- Ireland A, Sayers A, Deree KC, Emond A, Tobias JH. Motor competence in early childhood is positively associated with bone strength in late adolescence. J Bone Miner Res 2016;31(5):1089-98.
- 21. Ireland A, Muthuri S, Rittweger J, Adams JE, Ward KA, Kuh D, et al. Later age at onset of independent

walking is associated with lower bone strength at fracture-prone sites in older men. J Bone Miner Res 2017;32(xx):1-9.

- 22. Bouxsein ML, Karasik D. Bone geometry and skeletal fragility. Curr Osteoporos Rep 2006;4(2):49-56.
- Martin RM, Correa PHS. Bone Quality and Osteoporosis Therapy. Arq Bras Endocrinol Metab 2010;54(2):186-99.
- 24. Seeman E. Age-and menopause-related bone loss compromise cortical and trabecular microstructure. J Gerontol Series A: Biol Sci Med Sci 2013:glt071.
- Ural A, Vashishth D. Interactions between microstructural and geometrical adaptation in human cortical bone. J Orthopaed Res 2006;24(7):1489-98.
- DiGirolamo DJ, Kiel DP, Esser KA. Bone and skeletal muscle: Neighbours with close ties. J Bone Miner Res 2013;28(7):1509-18.
- Girgis CM, Mokbel N, DiGirolamo DJ. Therapies for Musculoskeletal Disease: Can we treat two birds with one stone? Curr Osteoporos Rep. 2014;12(2):142-53.
- 28. Hamrick MW. A role for myokines in muscle-bone interactions. Exerc Sport Sci Rev 2011;39(1):43.
- 29. Hamrick MW. The skeletal muscle secretome: an emerging player in muscle-bone crosstalk. BoneKEy Rep 2012;1(4).
- Hamrick MW, McGee-Lawrence ME, Frechette DM. Fatty infiltration of skeletal muscle: mechanisms and comparisons with vone marrow adiposity. Frontiers in Endocrinol 2016;7(Article 69):1-7.
- Kohrt WM, Barry DW, Schwartz RS. Muscle forces or gravity: what predominates mechanical loading on bone? Med Sci Sports Exerc 2009;41(11):2050.
- Liu R, Birke O, Morse A, Peacock L, Mikulec K, Little DG, et al. Myogenic progenitors contribute to open but not closed fracture repair. BMC Musculoskelet Disord 2011;12(1):288-97.
- Liu R, Schindeler A, Little DG. The potential role of muscle in bone repair. J Musculoskelet Neuronal Interact 2010;10(1):71-6.
- Regan JN, Trivedi T, Guise TA, Waning DL. The role of TGFβ in bone-muscle crosstalk. Curr Osteoporos Rep 2017;15(1):18-23.
- Giangregorio L, El-Kotob R. Exercise, muscle, and the applied load-bone strength balance. Osteoporos Int 2017;28:21-33.
- 36. Fonseca H, Moreira-Goncalves D, Coriolano HJ, Duarte JA. Bone quality: the determinants of bone strength and fragility. Sports Med 2014;44(1):37-53.
- Knapik DM, Perera P, Nam J, Blazek AD, Rath B, Leblebicioglu B, et al. Mechanosignaling in one heath, trauma and inflammation. Antioxid Redox Signal 2014; 20(6):970-85.
- Heinonen A, Kannus P, Sievänen H, Oja P, Pasanen M, Rinne M, et al. Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. The Lancet 1996; 348(9038):1343-7.

- Heinonen A, Oja P, Sievänen H, Pasanen M, Vuori I. Effect of two training regimens on bone mineral density in healthy perimenopausal women: a randomized controlled trial. J Bone Miner Res 1998;13(3):483-90.
- 40. Robling AG, Castillo AB, Turner CH. Biomechanical and molecular regulation of bone remodeling. Annu Rev Biomed Eng 2006;8:455-98.
- 41. Turner C. Three rules for bone adaptation to mechanical stimuli. Bone 1998;23(5):399-407.
- 42. Turner CH, Pavalko FM. Mechanotransduction and functional response of the skeleton to physical stress: The mechanisms and mechanics of bone adaptation. J Orthopaed Sci 1998;3(6):346-55.
- 43. Erickson CR, Vukovich MD. Osteogenic index and changes in bone markers during a jump training program: a pilot study. Med Sci Sports Exerc 2010; 42(8):1485-92.
- 44. Lester ME, Urso ML, Evans RK, et al. Influence of exercise mode and osteogenic index on bone biomarker responses during short-term physical training. Bone 2009;45(4):768-76.
- Turner CH, Robling AG. Designing exercise regimens to increase bone strength. Exerc Sport Sci Rev 2003; 31(1):45-50.
- 46. Fuchs RK, Kersh ME, Carballido-Gamio J, Thompson WR, Keyak JH, Warden SJ. Physical activity for strengthening fracture prone regions of the proximal femur. Curr Osteoporos Rep 2017;15:43-52.
- 47. Al Nazer R, Klodowski A, Rantalainen T, Heinonen A, Sievänen H, Mikkola A. Analysis of dynamic strains in tibia during human locomotion based on flexible multibody approach integrated with magnetic resonance imaging technique. Multibody Syst Dyn 2008;20(4):287-306.
- 48. Kelley S, Hopkinson G, Strike S, Luo J, Lee R. An Accelerometry-Based Approach to Assess Loading Intensity of Physical Activity on Bone. Res Q Exerc Sport 2014;85(2):245-50.
- 49. Martelli S, Kersh ME, Schache AG, Pandy MG. Strain energy in the femoral neck during exercise. Journal of biomechanics 2014;47(8):1784-91.
- 50. Al Nazer R, Lanovaz J, Kawalilak C, Johnston J, Kontulainen S. Direct *in vivo* strain measurements in human bone - a systematic literature review. J Biomech 2012;45(1):27-40.
- 51. Yang P, Bruggemann G, Rittweger J. What do we currently know from *in vivo* bone strain measurements in humans. J Musculoskelet Neuronal Interact 2011;11(1):8-20.
- Martelli S, Kersh ME, Pandy MG. Sensitivity of femoral strain calculations to anatomical scaling errors in musculoskeletal models of movement. J Biomech 2015;48(13):3606-15.
- 53. Roriz P, Carvalho L, Frazao O, Santos JL, Simoes JA. Roriz P, Carvalho L, Frazão O, Santos JL, Simões JA. From conventional sensors to fibre optic sensors for strain and force measurements in biomechanics

applications: A review. J Biomech 2014;47(6):1251-61.

- 54. Yang PF, Sanno M, Ganse B, Koy T, Bruggemann GP, MUller LP, et al. Torsion and antero-posterior bending in the *in vivo* human tibia loading regimes during walking and running. PLoS One 2014;9(4):e94525.
- 55. Yang PF, Kriechbaumer A, Albracht K, Sanno M, et al. On the relationship between tibia torsional deformation and regional muscle contractions in habitual human exercises *in vivo*. J Biomech 2015;48(3):456-64.
- Poole KES, Treece GM, Mayhew PM, Vaculik J, Dungl P, Horak M, et al. Cortical Thickness Mapping to Identify Focal Osteoporosis in Patients with Hip Fracture. PLoS One 2012;7(6):e38466.
- 57. Poole KES, Treece GM, Gee AH, Brown JP, McClung MR, Wang A, et al. Denosumab Rapidly Increases Cortical Bone in Key Locations of the Femur: A 3D Bone Mapping Study in Women With Osteoporosis. J Bone Mineral Res 2015;30(1):46-54.
- 58. Zebaze R, Ghasem-Zadeh A, Bohte A, Luliano-Burns S, Mirams M, Price RI, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: A cross-sectional study. The Lancet 2010;375(9727):1729-36.
- 59. Sornay-Rendu E, Boutroy S, Duboeuf F, Chapurlat RD. Bone Microarchitecture Assessed by HR-pQCT as Predictor of Fracture Risk in Postmenopausal Women: The OFELY Study. J Bone Mineral Res 2017.
- Mirzaali MJ, Schwiedrzik JJ, Thaiwichai S, Best JP, Michler J, Zysset PK, et al. Mechanical properties of cortical bone and their relationships with age, gender, composition and microindentation properties in the elderly. Bone 2016;93:196-211.
- Ireland A, Capozza RF, Cointry GR, Nocciolino L, Ferretti JL, Rittweger J. Meagre effect of disuse on the human fibula are not explained by bone size or geometry. Osteoporos Int 2017;28:633-41.
- 62. Giangregorio LM, Gibbs JC, Craven BC. Measuring muscle and bone in individuals with neurologic impairment: lessons learned about participant selection and pQCT scan acquisition and analysis. Osteoporos Int 2016;27(8):2433-46.
- 63. Eser P, Frotzler A, Zehnder Y, Wick L, Knecht H, Denoth J, et al. Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals. Bone 2004;34(5):869-80.
- 64. Rantalainen T, Weeks BJ, Nogueria RC, Beck BR. Effects of bone-specific physical activity, gender and maturity on tibial cross-sectional bone material distribution: a cross-sectional pQCT comparison of children and young adults aged 5-29 years. Bone 2015;72:101-8.
- 65. Allison SJ, Poole KES, Treece GM, Gee AH, Tonkin C, Rennie WJ, et al. The Influence of High-Impact Exercise on Cortical and Trabecular Bone Mineral Content and 3D Distribution Across the Proximal Femur in Older Men: A Randomized Controlled Unilateral Intervention. J Bone Mineral Res 2015;30(9):1709-16.
- 66. Cervinka T, Sievänen H, Hyttinen J, Rittweger J. Bone

loss patterns in cortical, subcortical, and trabecular compartments during simulated microgravity. J Appl Physiol 2014;117:80-8.

- 67. Bergmann P, Body JJ, Boonen S, et al. Loading and skeletal development and maintenance. Journal of osteoporosis 2011;2011:1-15.
- Ehrlich P, Lanyon L. Mechanical strain and bone cell function: a review. Osteoporos Int 2002;13(9):688-700.
- 69. Frost HM. A 2003 update of bone physiology and Wolff's Law for clinicians. Angle Orthodontist 2004; 74(1):3-15.
- Judex S, Gupta S, Rubin C. Regulation of mechanical signals in bone. Orthod Craniofac Res 2009;12(2):94-104.
- 71. Ozcivici E, Luu YK, Adler B, Qin Y-X, Rubin J, Judex S, et al. Mechanical signals as anabolic agents in bone. Nat Rev Rheumatol 2010;6(1):50-9.
- 72. Sikavitsas VI, Temenoff JS, Mikos AG. Biomaterials and bone mechanotransduction. Biomaterials 2001; 22(19):2581-93.
- 73. Skerry TM. One mechanostat or many? Modifications of the site-specific response of bone to mechanical loading by nature and nurture. J Musculoskelet Neuronal Interact 2006;6(2):122-7.
- 74. Chen J-H, Liu C, You L, Simmons CA. Boning up on Wolff's Law: mechanical regulation of the cells that make and maintain bone. J Biomech 2010;43(1):108-18.
- 75. Ellman R, Spatz J, Cloutier A, Palme R, Christiansen BA, Bouxsein ML. Partial reductions in mechanical loading yield proportional changes in bone density, bone architecture and muscle mass. J Bone Miner Res 2013;28(4):875-85.
- Fritton SP, McLeod KJ, Rubin CT. Quantifying the strain history of bone: Spatial uniformity and self-similarity of low-magnitude strains. J Biomech 2000;33(3):317-25.
- 77. Hsieh Y-F, Robling AG, Ambrosius WT, Burr DB, Turner CH. Mechanical loading of diaphyseal bone *in vivo*: the strain threshold for an osteogenic response varies with location. J Bone Mineral Res 2001;16(12):2291-7.
- Reis J, Capela e Silva F, Queiroga M, Lucena S, Potes J. Bone mechanotransduction: A review. J Biomed Bioeng 2011;2(1):37-44.
- 79. Rubin CT, McLeod KJ, Bain SD. Functional strains and cortical bone adaptation: epigenetic assurance of skeletal integrity. J Biomech 1990;23:43-54.
- Ruff C, Holt B, Trinkaus E. Who's afraid of the big bad Wolff?: "Wolff's Law" and bone functional adaptation. Amer J Phys Anthropol 2006;129(4):484-98.
- 81. Currey JD. The structure and mechanics of bone. J Mater Sci 2012;47(1):41-54.
- Amidzic O, Riehle HJ, Fehr T, Wienbruch C, Elbert T. Pattern of focal γ-bursts in chess players. Nature. 2001;412(6847):603-.
- 83. Gross TS, Edwards JL, McLeod KJ, Rubin CT. Strain gradients correlate with sites of periosteal bone formation. J Bone Mineral Res 1997;12(6):982-8.

- 84. Mosley JR, March BM, Lynch J, Lanyon LE. Strain magnitude related changes in whole bone architecture in growing rats. Bone 1997;20(3):191-8.
- 85. Burr D. Why bones bend but don't break. J Musculoskelet Neuronal Interact 2011;11(4):270-85.
- 86. Currey JD. How well are bones designed to resist fracture? J Bone Mineral Res 2003;18(4):591-8.
- Duncan RL, Turner CH. Mechanotransduction and the functional response of bone to mechanical strain. Calcif Tissue Int 1995;57(5):344-58.
- Forwood M, Turner C. Skeletal adaptations to mechanical usage: results from tibial loading studies in rats. Bone 1995;17(4):S197-S205.
- 89. Friedman AW. Important determinants of bone strength: beyond bone mineral density. J Clin Rheumatol 2006;12(2):70-7.
- 90. Huiskes R. If bone is the answer, then what is the question? J Anat 2000;197(02):145-56.
- Turner CH. Homeostatic control of bone structure: an application of feedback theory. Bone 1991; 12(3):203-17.
- 92. TurnerCH,BurrDB.Basicbiomechanicalmeasurements of bone: A tutorial. Bone 1993;14(4):565-608.
- Turner CH, Robling AG. Mechanisms by which exercise improves bone strength. J Bone Miner Metab 2005; 23(1):16-22.
- 94. Ammann P, Rizzoli R. Bone strength and its determinants. Osteoporos Int 2003;14(3):13-8.
- Nordin M, Frankel VH. Basic biomechanics of the musculoskeletal system. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2012.
- Wang X, Puram S. The toughness of cortical bone and its relationship with age. Ann Biomed Eng 2004; 32(1):123-35.
- 97. Pearson OM, Lieberman DE. The aging of Wolff's "law": ontogeny and responses to mechanical loading in cortical bone. Amer J Phys Anthropol 2004; 125(S39):63-99.
- Weiner S, Wagner HD. The material bone: Structuremechanical function relations. Ann Rev Mater Sci 1998;28(1):271-98.
- Cole JH, van der Meulen MC. Whole bone mechanics and bone quality. Clin Orthop Relat Res 2011; 469(8):2139-49.
- 100. Jepsen KJ, Silva MJ, Vashishth D, Guo XE, van der Meulen MCH. Establishing biomechanical mechanisms in mouse models: Practical guidelines for systemically evaluating phenotypic changes in the diaphyses of long bones. J Bone Mineral Res 2015;30:951-66.
- Beaupied H, Lespessailles E, Benhamou C-L. Evaluation of macrostructural bone biomechanics. Joint Bone Spine 2007;74(3):233-9.
- 102. Cardinale M, Newton R, Nosaka K. Strength and conditioning: biological principles and practical applications: John Wiley & Sons; 2011.
- 103. Einhorn TA. Bone Strength: The bottom line. Calcif Tissue Int 1992;51(5):333-9.

- 104. Bayraktar HH, Morgan EF, Niebur GL, Morris GE, Wong EK, Keaveny TM. Comparison of the elastic and yield properties of human femoral trabecular and cortical bone tissue. J Biomech 2004;37(1):27-35.
- 105. Burstein AH, Currey JD, Frankel VH, Reilly T. The ultimate properties of bone tissue: the effects of yielding. J Biomech 1972;5(1):35-42.
- 106. Burstein AH, Zika JM, Heiple KG, Klein L. Contribution of collagen and mineral to elastic-plastic properties of bone. J Bone Joint Surg 1975;57(7):956-61.
- 107. Currey JD. The mechanical adaptations of bones. Princeton: Princeton University Press; 1984.
- 108. Kulin RM, Jiang F, Vecchio KS. Loading rate effects on the< i> R</i>-curve behavior of cortical bone. Acta Biomat 2011;7(2):724-32.
- 109. Carter DR, Spengler DM. Mechanical properties and composition of cortical bone. Clin Orthop Relat Res 1978;135:192-217.
- 110. Schaffler M. Role of bone turnover in microdamage. Osteoporos Int 2003;14:73-80.
- 111. Zimmerman EA, Gludovatz B, Schaible E, Busse B, Ritchie RO. Fracture resistance of human cortical bone across multiple length-scales at physiological strain rates. Biomaterials 2014;35(21):5472-81.
- 112. RussoCR. The effects of exercise on bone. Basic concepts and implications for the prevention of fractures. Clin Cases Miner Bone Metab 2009;6(3):223-8.
- 113. Hayes WC, Gerhart TN. Biomechanics of bone: applications for assessment of bone strength. J Bone Miner Res 1985;3:259-94.
- 114. Dong XN, Guo XE. The dependence of transversely isotropic elasticity of human femoral cortical bone porosity. J Biomech 2004;37(8):1281-7.
- 115. Keller TS, Mao Z, Spengler DM. Young's modulus, bending strength, and tissue physical properties of human compact bone. J Orthop Res 1990;8(4):592-603.
- 116. Zysset PK. A review of morphology elasticity relationships in human trabecular bone: theories and experiments. J Biomech 2003;36(10):1469-85.
- 117. Yeni YN, Fyhrie DP. A rate-dependent microcrackbridging model that can explain the strain rate dependency of cortical bone apparent yield strength. J Biomech 2003;36(9):1343-53.
- Keaveny TM, Hayes WC. Mechanical properties of cortical and trabecular bone. Bone Mechanics Handbooks. 1st ed. Boca Raton, FL: CRC Press; 1993. p. 285-344.
- 119. Main RP, Lynch ME, van der Meulen MCH. Load induced changes in bone stiffness and cancellous and cortical bone mass following tibial compression diminish with age in female mice. J Exp Biol 2014;217(10):1775-83.
- 120. Szabo ME, Zekontye J, Katsamenis OL, Taylor M, Thurner PJ. Similar damage initiation but different failure behaviour in trabecular and cortical bone tissue. J Mechanical Behav Biomed Mater 2011;4(8):1787-96.
- 121. Kopperdahl DL, Keaveny TM. Yield strain behavior of

trabecular bone. J Biomech 1998;31(7):601-8.

- Buechner P, Lakes R. Size effects in the elasticity and viscoelasticity of bone. Biomech Model Mechanobiol 2003;1(4):295-301.
- 123. Frost HM. A determinant of bone architecture: the minimum effective strain. Clin Orthop Relat Res 1983; 175:286-92.
- Turner CH, Forwood M, Rho JY, Yoshikawa T. Mechanical loading thresholds for lamellar and woven bone formation. J Bone Mineral Res 1994;9(1):87-97.
- Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int 1985; 37(4):411-7.
- 126. Cullen D, Smith R, Akhter M. Time course for bone formation with long-term external mechanical loading. J Appl Physiol 2000;88(6):1943-8.
- 127. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A Discov Mol Cell Evol Biol 2003;275(2):1081-101.
- 128. Sugiyama T, Meakin LB, Browne WJ, Galea GL, Price JS, Lanyon LE. Bones' adaptive response to mechanical loading is essentially linear between the low strains associated with disuse and the high strains associated with the lamellar/woven bone transition. J Bone Miner Res 2012;27(8):1784-93.
- 129. Sugiyama T, Yamaguchi A, Kawai S. Effects of skeletal loading on bone mass and compensation mechanism in bone: a new insight into the "mechanostat" theory. J Bone Miner Metab 2002;20(4):196-200.
- 130. Umemura Y, Baylink DJ, Wergedal JE, Mohan S, Srivastava AK. A time course of bone response to jump exercise in C57BL/6J mice. J Bone Miner Metab 2002;20(4):209-15.
- Frost HM. Why do marathon runners have less bone than weight lifters? A vital-biomechanical view and explanation. Bone 1997;20(3):183-9.
- 132. Turner CH, Takano Y, Owan I. Aging changes mechanical loading thresholds for bone formation in rats. J Bone Miner Res 1995;10(10):1544-9.
- 133. Wallace IJ, Demes B, Mongle C, Pearson OM, Polk JD, Lieberman DE. Exercise-Induced Bone Formation Is Poorly Linked to Local Strain Magnitude in the Sheep Tibia. PloS one 2014;9(6):e99108.
- 134. Judex S, Boyd S, Qin YX, Turner S, Ye K, Muller R, et al. Adaptations of trabecular bone to low magnitude vibrations result in more uniform stress and strain under load. Ann Biomed Eng 2003;31(1):12-20.
- Tanaka SM, Alam IM, Turner CH. Stochastic resonance in osteogenic response to mechanical loading. FASEB J 2003;17(2):313-4.
- 136. Judex S, Lei X, Han D, Rubin C. Low-magnitude mechanical signals that stimulate bone formation in the ovariectomized rat are dependent on the applied frequency but not on the strain magnitude. J Biomech 2007;40(6):1333-9.
- Rubin C, Turner A, Mallinckrodt C, Jerome C, McLeod K, Bain S. Mechanical strain, induced noninvasively in the high-frequency domain, is anabolic to cancellous bone,

but not cortical bone. Bone 2002;30(3):445-52.

- 138. Turner C, Robling A. Exercises for improving bone strength. Br J Sports Med 2005;39(4):188-9.
- 139. Warden S, Turner C. Mechanotransduction in the cortical bone is most efficient at loading frequencies of 5-10 Hz. Bone. 2004;34(2):261-70.
- 140. Rubin CT, McLeod KJ. Promotion of bony ingrowth by frequency-specific, low-amplitude mechanical strain. Clin Orthop Relat Res 1994;298:165-74.
- Hsieh Y-F, Turner CH. Effects of loading frequency on mechanically induced bone formation. J Bone Miner Res 2001;16(5):918-24.
- 142. Bacabac RG, Smit TH, Mullender MG, Dijcks SJ, Van Loon JJ, Klein-Nulend J, editors. Fluid shear stressinduced activation of bone cells is rate dependent and requires an initial stress kick. 50th Meeting of the Orthopaedic Research Society 2004; Anaheim, CA.
- Rubin CT, Judex S, Hadjiargyrou M. Skeletal adaptation to mechanical stimuli in the absence of formation or resorption of bone. J Musculoskelet Neuronal Interact 2002;2(3):264-7.
- 144. Judex S, Zernicke RF. High-impact exercise and growing bone: relation between high strain rates and enhanced bone formation. J Appl Physiol 2000;88(6):2183-91.
- 145. Ward K, Alsop C, Caulton J, Rubin C, Adams J, Mughal Z. Low magnitude mechanical loading is osteogenic in children with disabling conditions. J Bone Miner Res 2004;19(3):360-9.
- 146. Mosley J, Lanyon L. Strain rate as a controlling influence on adaptive modeling in response to dynamic loading of the ulna in growing male rats. Bone 1998;23(4):313-8.
- 147. Turner CH, Anne V, Pipadarti R. A uniform strain criterion for trabecular bone adaptation? J Biom 1997;30(6):555-63.
- 148. LaMothe JM, Hamilton NH, Zernicke RF. Strain rate influences periosteal adaptation in mature bone. Med Eng Phys. 2005;27(4):277-84.
- 149. Judex S, Gross TS, Zernicke RF. Strain gradients correlate with sites of exercise-induced bone-forming surfaces in the adult skeleton. J Bone Miner Res 1997;12(10):1737-45.
- 150. Lanyon LE, Rubin CT. Static vs dynamic loads as an influence on bone remodelling. J Biomech 1984; 17(12):897-905.
- 151. Robling AG, Duijvelaar KM, Geevers JV, Ohashi N, Turner CH. Modulation of appositional and longitudinal bone growth in the rat ulna by applied static and dynamic force. Bone 2001;29(2):105-13.
- 152. Bacabac RG, Smit TH, Mullender MG, Van Loon JJ, Klein-Nulend J. Initial stress-kick is required for fluid shear stress-induced rate dependent activation of bone cells. Ann Biomed Eng 2005;33(1):104-10.
- 153. Burr D, Robling AG, Turner CH. Effects of biomechanical stress on bones in animals. Bone 2002;30(5):781-6.
- 154. Ferretti J, Cointry G, Capozza R, Capiglioni R, Chiappe M. Analysis of biomechanical effects on bone and on the muscle-bone interactions in small animal models.

J Musculoskelet Neuronal Interact 2001;1(3):263-74.

- O'Connor JA, Lanyon LE, MacFie H. The influence of strain rate on adaptive bone remodelling. J Biomech 1982;15(10):767-81.
- 156. Qin YX, Rubin CT, McLeod KJ. Nonlinear dependence of loading intensity and cycle number in the maintenance of bone mass and morphology. J Orthop Res 1998; 16(4):482-9.
- Robling AG, Burr DB, Turner CH. Skeletal loading in animals. J Musculoskelet Neuronal Interact 2001; 1(3):249-62.
- 158. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am 1984; 66(3):397-402.
- 159. Mittag U, Kriechbaumer A, Bartsch M, Rittweger J. Form follows function: a computational simulation exercise on bone shape forming and conservation. J Musculoskelet Neuronal Interact 2015;15(2):215-26.
- 160. Rubin CT, Gross TS, Qin YX, Fritton SP, Guilak F, McLeod KJ. Differentiation of the bone-tissue remodeling response to axial and torsional loading in the turkey ulna. J Bone Joint Surg Am 1996;78:1523-33.
- Donahue T, Haut T, Yellowley C, Donahue H, Jacobs C. Mechanosensitivity of bone cells to oscillating fluid flow induced shear stress may be modulated by chemotransport. J Biomech 2003;36(9):1363-71.
- 162. Gross TS, Poliachik SL, Ausk BJ, Sanford DA, Becker BA, Srinivasan S. Why rest stimulates bone formation: a hypothesis based on complex adaptive phenomenon. Exerc Sport Sci Rev 2004;32(1):9.
- 163. Raab-Cullen D, Akhter M, Kimmel D, Recker R. Bone response to alternate-day mechanical loading of the rat tibia. J Bone Miner Res 1994;9(2):203-11.
- 164. Robling AG, Burr DB, Turner CH. Recovery periods restore mechanosensitivity to dynamically loaded bone. J Exp Biol 2001;204(19):3389-99.
- 165. Robling AG, Hinant FM, Burr DB, Turner CH. Improved bone structure and strength after long-term mechanical loading is greatest if loading is separated into short bouts. J Bone Miner Res 2002;17(8):1545-54.
- 166. Robling AG, Hinant FM, Burr DB, Turner CH. Shorter, more frequent mechanical loading sessions enhance bone mass. Med Sci Sports Exerc 2002;34(2):196-202.
- Robling AG, Turner CH. Mechanotransduction in bone: genetic effects on mechanosensitivity in mice. Bone 2002;31(5):562-9.
- 168. Saxon L, Robling A, Alam I, Turner C. Mechanosensitivity of the rat skeleton decreases after a long period of loading, but is improved with time off. Bone 2005; 36(3):454-64.
- 169. Srinivasan S, Weimer DA, Agans SC, Bain SD, Gross TS. Low-Magnitude Mechanical Loading Becomes Osteogenic When Rest Is Inserted Between Each Load Cycle. J Bone Miner Res 2002;17(9):1613-20.
- 170. Wu Q, Sample SJ, Baker TA, Thomas CF, Behan M, Muir P. Mechanical loading of a long bone induces plasticity

in sensory input to the central nervous system. Neurosci Lett 2009;463(3):254-7.

- 171. Umemura Y, Sogo N, Honda A. Effects of intervals between jumps or bouts on osteogenic response to loading. J Appl Physiol 2002;93(4):1345-8.
- 172. Umemura Y, Ishiko T, Yamauchi T, Kurono M, Mashiko S. Five jumps per day increase bone mass and breaking force in rats. J Bone Miner Res 1997;12(9):1480-5.
- 173. Umemura Y, Ishiko T, Tsujimoto H, Miura H, Mokushi N, Suzuki H. Effects of jump training on bone hypertrophy in young and old rats. Int J Sports Med 1995;16(06):364-7.
- 174. Srinivasan S, Agans SC, King KA, Moy NY, Poliachik SL, Gross TS. Enabling bone formation in the aged skeleton via rest-inserted mechanical loading. Bone 2003;33(6):946-55.
- 175. Gross TS, Srinivasan S. Building bone mass through exercise: could less be more? Br J Sports Med 2006;40(1):2-3.
- 176. Robling AG, Burr DB, Turner CH. Partitioning a daily mechanical stimulus into discrete loading bouts improves the osteogenic response to loading. J Bone Miner Res 2000;15(8):1596-602.
- 177. Batra NN, Li YJ, Yellowley CE, You L, Malone AM, Kim CH, et al. Effects of short-term recovery periods on fluid-induced signaling in osteoblastic cells. J Biomech 2005;38(9):1909-17.
- Poliachik SL, Agans SC, King KA, Gross TS, Srinivasan S. Rest alleviates tissue saturation due to repetitive mechanical loading. J Bone Miner Res 2003;18:S73.
- 179. Fyhrie DP, Schaffler MB. The adaptation of bone apparent density to applied load. J Biomech 1995;28(2):135-46.
- Turner C. Toward a mathematical description of bone biology: the principle of cellular accommodation. Calcif Tissue Int 1999;65(6):466-71.
- Schriefer JL, Warden SJ, Saxon LK, Robling AG, Turner CH. Cellular accommodation and the response of bone to mechanical loading. J Biomech 2005; 38(9):1838-45.
- 182. Srinivasan S, Ausk BJ, Poliachik SL, Warner SE, Richardson TS, Gross TS. Rest-inserted loading rapidly amplifies the response of bone to small increases in strain and load cycles. J Appl Physiol 2007; 10(2):1945-52.
- 183. Brandi ML. Microarchitecture, the key to bone quality. Rheumatol 2009;48(suppl 4):iv3-iv8.
- Clarke B. Normal bone anatomy and physiology. Clin J Am Soc Nephrol 2008;3(Supplement 3):S131-S9.
- Doblaré M, Garcia JM. Anisotropic bone remodelling model based on a continuum damage-repair theory. J Biomech 2002;35(1):1-17.
- Hammer A. The paradox of Wolff's theories. Ir J Med Sci 2014:1-10.
- Rho J-Y, Kuhn-Spearing L, Zioupos P. Mechanical properties and the hierarchical structure of bone. Med Eng Phys. 1998;20(2):92-102.

- 188. Seeman E, Delmas PD. Bone quality the material and structural basis of bone strength and fragility. New Eng J Med 2006;354(21):2250-61.
- 189. Davison KS, Siminoski K, Adachi J, et al. Bone strength: the whole is greater than the sum of its parts. Semin Arthritis Rheu 2006;36(1):22-31.
- 190. Garner E, Lakes R, Lee T, Swan C, Brand R. Viscoelastic dissipation in compact bone: implications for stress-induced fluid flow in bone. J Biomech Eng 2000;122(2):166-72.
- Seeman E. Bone Quality: The material and structural basis of bone strength. J Bone Miner Metab 2008; 26(1):1-8.
- 192. Wolff J. Das Gesetz der Transformation der Knochen. Berlin: A. Hirchwild; 1892.
- Lieberman DE, Polk JD, Demes B. Predicting long bone loading from cross-sectional geometry. Amer J Phys Anthropol 2004;123(2):156-71.
- 194. Lynch ME, Main RP, Xu Q, Schmicker TL, Schaffler MB, Wright TM, et al. Tibial compression is anabolic in the adult mouse skeleton despite reduced responsiveness with ageing. Bone 2011;49(3):439-46.
- 195. Cowin SC, Sadegh AM, Luo GM. An evolutionary Wolff's Law for trabecular architecture. J Biomech Eng 1992; 114(1):129-36.
- 196. Guedes RM, Simoes JA, Morais JL. Viscoelastic behaviour and failure of bovine cancellous bone under constant strain rate. J Biomech 2006;39(1):49-60.
- 197. Iyo T, Maki Y, Sasaki N, Nakata M. Anisotropic viscoelastic properties of cortical bone. J Biomech 2004;37(9):1433-7.
- 198. Li S, Demirci E, Silberschmidt VV. Variability and anisotropy of mechanical behavior of cortical bone in tension and compression. J Mech Behav Biomed Mater 2013;21:109-20.
- 199. Muller R, Ruegsegger P. Analysis of mechanical properties of cancellous bone under conditions of simulated bone atrophy. J Biomech 1996; 29(8):1053-60.
- Sasaki N, Enyo A. Viscoelastic properties of bone as a function of water content. J Biomech 1995;7(809-815).
- Terrier A, Rakotomanana RL, Ramaniraka AN, Leyvraz PF. Adaptation models of anisotropic bone. Comp Methods Biomech Biomed Eng 1997;1(1):47-59.
- 202. Yamashita J, Li X, Furman BR, Rawls HR, Wang X, Agrawal C. Collagen and bone viscoelasticity: a dynamic mechanical analysis. J Biomed Mater Res 2002;63(1):31-6.
- Reilly DT, Burnstein AH. The elastic and ultimate properties of compact bone tissue. J Biomech 1975; 8(6):393-405.
- 204. Augat P, Schorlemmer S. The role of cortical bone and its microstructure in bone strength. Age and Ageing 2006;35(suppl 2):ii27-ii31.
- 205. Shahar R, Zaslansky P, Barak M, Friesem A, Currey J, Weiner S. Anisotropic Poisson's ratio and compression

modulus of cortical bone determined by speckle interferometry. J Biomech 2007;40(2):252-64.

- 206. Gong H, Zhu D, Gao J, Lv L, Zhang X. An adaptation model for trabecular bone at different mechanical levels. Biomed Eng Online 2010;9:32-49.
- Jacobs CR. The mechanobiology of cancellous bone structural adaptation. J Rehab Res Dev 2000; 37(2):209-16.
- 208. Mosekilde L, Ebbesen E, Tornvig L, Thomsen J. Trabecular bone structure and strength-remodelling and repair. J Musculoskelet Neuronal Interact 2000; 1(1):25-30.
- 209. Lai YM, Qin L, Yeung HY, Lee KK, Chan KM. Regional differences in trabecular BMD and micro-architecture of weight-bearing bone under habitual gait loading a pQCT and microCT study in human cadavers. Bone 2005;37(2):274-82.
- 210. Carter DR, Beaupre GS. Skeletal Function and Form: Mechanbiology of skeletal development, ageing and regeneration: Cambridge University Press; 2007.
- 211. Lai YM, Qin L, Hung VWY, Chan KM. Regional differences in cortical bone mineral density in the weight-bearing long bone shaft a pQCT study. Bone 2005;36(3):465-71.
- 212. Milgrom C, Finestone A, Simkin A, et al. *In vivo* strain measurements to evaluate the strengthening potential of exercises on the tibial bone. J Bone Joint Surg 2000a;82(4):591-4.
- 213. Hazenberg JG, Freeley M, Ellis F, Lee TC, Taylor D. Microdamage: a cell transducing mechanism based on ruptured osteocyte processes. J Biomech 2005; 39(11):2096-103.
- 214. Boivin G, Bala Y, Doublier A, Farlay D, Ste-Marie L, Meunier P, et al. The role of mineralization and organic matrix in the microhardness of bone tissue from controls and osteoporotic patients. Bone 2008;43(3):532-8.
- 215. Liu XS, Zhang XH, Sekhon KK, et al. High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. J Bone Miner Res 2010; 25(4):746-56.
- 216. Peterlik H, Roschger P, Klaushofer K, Fratzl P. From brittle to ductile fracture of bone. Nat Mater 2005;5(1):52-5.
- 217. van der Meulen MCH, Jepsen KJ, Mikic B. Understanding bone strength: Size isn't everything. Bone 2001;29(2):101-4.
- Wang T, Feng Z. Dynamic mechanical properties of cortical bone: The effect of mineral content. Mater Lett 2005;59(18):2277-80.
- 219. Bala Y, Farlay D, Boivin G. Bone mineralization: from tissue to crystal in normal and pathological contexts. Osteoporos Int 2013;24(8):2153-66.
- 220. Bala Y, Farlay D, Delmas PD, Meunier PJ, Boivin G. Time sequence of secondary mineralization and microhardness in cortical and cancellous bone from

ewes. Bone 2010;46(4):1204-12.

- 221. Boskey A. Bone mineral crystal size. Osteoporosis International 2003b;14(5):16-21.
- 222. Currey JD. The many adaptations of bone. J Biomech 2003;36(10):1487-95.
- 223. Su X, Sun K, Cui FZ, Landis WJ. Organization of apetite crystals in human woven bone. Bone 2003;32(2):150-62.
- 224. Boivin G, Meunier PJ. Changes in bone remodeling rate influence the degree of mineralization of bone. Connect Tissue Res 2002a;43(2-3):535-7.
- 225. Golub EE. Role of matrix vesicles in biomineralization. Biochim Biophys Acta 2009;1790(12):1592-8.
- 226. Boivin G, Meunier PJ. The degree of mineralization of bone tissue measured by computerized quantitative contact microradiography. Calcif Tissue Int 2002b; 70(6):503-11.
- 227. Boskey A. Biomineralization: An overview. Connect Tissue Res 2003a;44(1):5-9.
- 228. Boskey A. Bone composition: relationship to bone fragility and antiosteoporotic drug effects. BoneKEy Reports 2013;2(447):1-11.
- Sapir-Koren R, Livshits G. Bone mineralization and regulation of phosphate homeostasis. IBMS BoneKEy 2011;8(6):286-300.
- 230. Roschger P, Gupta HS, Berzlanovich A, Ittner G, Dempster DW, Fratzl P, et al. Constant mineralization density distribution in cancellous human bone. Bone 2003;32(3):316-23.
- 231. Allen MR, Burr DB. Three years of Alendronate treatment results in similar levels of vertebral microdamage as after one year of treatment. J Bone Miner Res 2007;22(11):1759-65.
- 232. Follet H, Boivin G, Rumelhart C, Meunier PJ. The degree of mineralization is a determinant of bone trength: a study on human calcanei. Bone 2004;34(5):783-9.
- 233. Fratzl P, Gupta HS, Paschalis EP, Roschger P. Structure and mechanical quality of the collagenmineral, nano-composite in bone. J Mater Chem 2004;14(14):2115-23.
- 234. Bouxsein ML. Bone quality: where do we go from here? Osteoporos Int 2003;14(5):118-27.
- 235. Farlay D, Panczer G, Rey C, Delmas PD, Boivin G. Mineral maturity and crystallinity index are distinct characteristics of bone mineral. J Bone Miner Metab 2010;28(4):433-45.
- 236. Golub EE. Biomineralization and matrix vesicles in biology and pathology. Semin Immunopathol 2011;33(5):409-17.
- 237. Yerramshetty JS, Akkus O. The associations between mineral crystallinity and the mechanical properties of human cortical bone. Bone 2008;42(3):476-482.
- 238. Burr DB. Microdamage and Bone Strength. Osteoporos Int 2003;14:67-72.
- 239. Currey JD. Physical characteristics affecting the tensile failure properties of compact bone. J Biomech 1990;23(8):837-44.

- 240. Boivin G, Meunier PJ. The mineralization of bone tissue: A forgotten dimension in osteoporosis research. Osteoporos Int 2003;14(3):19-24.
- 241. Weinstein RS. True strength. J Bone Miner Res 2000;15(4):621-5.
- 242. Wang X, Ni Q. Determination of cortical bone porosity and pore size distribution using a low field pulsed NMR approach. J Orthop Res 2003;21(2):312-9.
- Currey JD. The effect of porosity and mineral content on the Young's modulus of elasticity of compact bone. J Biomech. 1988;21(2):131-9.
- 244. Doblaré M, Garcia J, Gómez M. Modelling bone tissue fracture and healing: a review. Eng Fract Mech 2004;71(13):1809-40.
- 245. Turner CH. Biomechanics of bone: Determinants of skeletal fragility and bone quality. Osteoporos Int 2002;13(2):97-104.
- 246. van der Linden JC, Homminga J, Verhaar JA, Weinans H. Mechanical consequences of bone loss in cancellous bone. J Bone Miner Res 2001;16(3):457-65.
- 247. Schaffler MB, Burr DB. Stiffness of compact bone: effects of porosity and density. J Biomech 1988;21(1):13-6.
- 248. Lau RYC, Guo X. A review on current osteoporosis research: with special focus on disuse bone loss. J Osteoporos 2011:1-6.
- 249. Giusti A, Bianchi G. Treatment of primary osteoporosis in men. Clin Interv Aging 2014;10:105-15.
- 250. Siu WS, Qin L, Leung KS. pQCT bone strength index may serve as a better predictor than bone mineral density for long bone breaking strength. J Bone Miner Metab 2003;21(5):316-22.
- 251. Fields AJ, Keaveny TM. Trabecular architecture and vertebral fragility in osteoporosis. Curr Osteoporos Rep 2012;10(2):132-40.
- 252. Fields AJ, Lee GL, Liu XS, Jekir MG, Guo E, Keaveny TM. Influence of vertical trabeculae on the compressive strength of the human vertebra. J Bone Miner Res 2011;26(2):263-9.
- 253. Laib A, Kumer JL, Majumdar S, Lane NE. The temporal changes of trabecular architecture in ovariectomized rats assessed by MicroCT. Osteoporos Int 2001;12(11).
- 254. McCalden R, McGeough J, Barker M, Court-Brown C. Age-related changes in the tensile properties of cortical bone. J Bone Joint Surg Am 1993;75(8):1193-205.
- 255. Riggs BL, Melton LJ, Robb RA, et al. A Population-Based Assessment of Rates of Bone Loss at Multiple Skeletal Sites: Evidence for Substantial Trabecular Bone Loss in Young Adult Women and Men. J Bone Miner Res 2008;23(2):205-14.
- 256. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res 2010; 25(8):1886-94.
- 257. Sevostianov I, Kachanov M. Impact of the porous microstructure on the overall elastic properties of the

osteonal cortical bone. J Biomech 2000;33(7):881-8.

- 258. McCALDEN RW, McGEOUGH JA. Age-Related Changes in the Compressive Strength of Cancellous Bone. The Relative Importance of Changes in Density and Trabecular Architecture*. J Bone Joint Surg 1997;79(3):421-7.
- 259. Capozza RF, Rittweger J, Reina PS, Mortarino P, Nocciolino LM, Feldman S, et al. pQCT-assessed relationships between diaphyseal design and cortical bone mass and density in the tibiae of healthy sedentary and trained men and women. J Musculoskelet Neuronal Interact 2013;13(2):195-205.
- Link TM. The Founder's Lecture 2009: Advances in imaging of osteoporosis and osteoarthritis. Skeletal Radiol 2011;39(10):943-55.
- Launey ME, Beuhler MJ, Ritchie RO. On the mechanistic origins of toughness in bone. Ann Rev Mater Res 2010;40:25-53.
- 262. Cointry G, Capozza R, Negri A, Roldan E, Ferretti J. Biomechanical background for a noninvasive assessment of bone strength and muscle-bone interactions. J Musculoskelet Neuronal Interact 2004;4(1):1.
- Rauch F, Schoenau E. Changes in bone density during childhood and adolescence: an approach based on bone's biological organization. J Bone Miner Res 2001;16(4):597-604.
- 264. Seeman E. Growth in bone mass and size--are racial and gender differences in bone mineral density more apparent than real? J Clin Endocrinol Metab 1998;83(5):1414-9.
- 265. Wehrli FW, Song HK, Saha PK, Wright AC. Quantitative MRI for the assessment of bone structure and function. NMR Biomed 2006;19(7):731-64.
- 266. Järvinen TL, Sievänen H, Jokihaara J, Einhorn TA. Revival of bone strength: the bottom line. J Bone Miner Res 2005;20(5):717-20.
- 267. Macdonald H, Nishiyama K, Hanley D, Boyd S. Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. Osteoporos Int 2011;22(1):357-62.
- 268. MacDonald HM, Nishiyama KK, Kang J, Hanley DA, Boyd SK. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: A population-based HR-pQCT study. J Bone Miner Res 2011;26(1):50-62.
- 269. Petit M, Beck T, Kontulainen S. Examining the developing bone: what do we measure and how do we do it? J Musculoskelet Neuronal Interact 2005;5(3):213.
- 270. Kajimura D, Hinoi E, Ferron M, Kode A, Riley KJ, Zhou B, et al. Genetic determination of the cellular basis of the sympathetic regulation of bone mass accrual. J Exp Med 2011;208(4):841-51.
- 271. Paternoster L, Lorentzon M, Lehtimäki T, Eriksson J, Kähönen M, Raitakari O, et al. Genetic determinants of trabecular and cortical volumetric bone mineral

densities and bone microstructure. PLoS Genet 2013; 9(2):e1003247.

- 272. Paternoster L, Lorentzon M, Vandenput L, Karlsson MK, Ljunggren O, Kindmark A, et al. Genome-wide association meta-analysis of cortical bone mineral density unravels allelic heterogeneity at the RANKL locus and potential pleiotropic effects of bone. PLoS Genet 2010;6(11):e1001217.
- 273. Havill LM, Mahaney MC, Binkley T, Specker BL. Effects of genes, sex, age, and activity on BMC, bone size, and areal and volumetric BMD. J Bone Miner Res 2007;22(5):737-46.
- 274. Estrada K, Styrkarsdottir U, Evangelou E, Hsu YH, Duncan EL, Ntzani EE, et al. Genome-wide metaanalysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet 2012;44(5):491-501.
- 275. Rivadeneira F, Styrkarsdottir U, Estrada K, Halldorsson BV, Hsu YH, Richards B, et al. Twenty bone-mineraldensity loci identified by large-scale meta-analysis of genome-wide association studies. Nat Genet 2009;41(11):1199-206.
- 276. Zheng H-F, Tobias JH, Duncan E, Evans DM, Eriksson J, Paternoster L, et al. WNT16 influences bone mineral density, cortical bone thickness, bone strength, and osteoporotic fracture risk. PLoS Genet 2012;8(7):e1002745.
- 277. Richards JB, Rivadeneira F, Inouye M, et al. Bone mineral density, osteoporosis, and osteoporotic fractures: a genomic-wide association study. Lancet 2008;371(9623):1505-12.
- 278. Licata A. Bone density vs bone quality: What'sa clinician to do? Clev Clin J Med 2009;76(6):331-6.
- Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. JAMA 2002; 288(15):1889-97.
- 280. Rauch F, Schonau E. Peripheral quantitative computed tomography of the distal radius in young subjectsnew reference data and interpretation of results. J Musculoskelet Neuronal Interact 2005;5(2):119.
- Wilkin TJ. Changing perceptions in osteoporosis. Br Med J 1999;318:862-3.
- 282. Nicks KM, Amin S, Atkinson EJ, Riggs BL, Melton LJ, Khosla S. Relationship of age to bone microstructure independent of areal bone mineral density. J Bone Miner Res 2012;27(3):637-44.
- 283. Toombs RJ, Ducher G, Shepherd JA, Souza MJ. The impact of recent technological advances on the trueness and precision of DXA to assess body composition. Obesity 2012;20(1):30-9.
- 284. Lala D, Cheung AM, Gordon C, Giangregorio L. Comparison of cortical bone measurements between pQCT and HR-pQCT. J Clin Densitom 2012; 15(3):275-81.
- 285. Lala D, Cheung AM, Lynch CL, Inglis D, Gordon C, Tomlinson G, et al. Measuring Apparent Trabecular Structure With pQCT: A Comparison With HR-pQCT. J

Clin Densitom 2014;17(1):47-53.

- 286. Sheu Y, Zmuda JM, Boudreau RM, Petit MA, Ensrud KE, Bauer DC, et al. Bone strength measured by peripheral quantitative computed tomography and the risk of nonvertebral fractures: the osteoporotic fractures in men (MrOS) study. J Bone Miner Res 2011;26:63-71.
- 287. Sievänen H, Koskue V, Rauhio A, Kannus P, Heinonen A, Vuori I. Peripheral quantitative computed tomography in human long bones: evaluation of *in vitro* and *in vivo* precision. J Bone Miner Res 1998;13(5):871-82.
- 288. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. The J Clin Endocrinol Metab 2005; 90(12):6508-15.
- 289. Popp AW, Buffat H, Eberli U, Lippuner K, Ernst M, Richards RG, et al. Microstructural Parameters of Bone Evaluated Using HR-pQCT Correlate with the DXA-Derived Cortical Index and the Trabecular Bone Score in a Cohort of Randomly Selected Premenopausal Women. PloS One 2014;9(2):e88946.
- 290. Popp AW, Windolf M, Senn C, et al. Prediction of bone strength at the distal tibia by HR-pQCT and DXA. Bone 2012;50:296-300.
- 291. Seeman E. Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? Bone 2007;41(3):308-17.
- 292. Abel R, Macho GA. Ontogenetic changes in the internal and external morphology of the ilium in modern humans. J Anat 2011;218(3):324-34.
- 293. Engelke K, Adams JE, Armbrecht G, Augat P, Bogado CE, Bouxsein ML, et al. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions. J Clin Densitom 2008;11(1):123-62.
- 294. Daly RM, Petit MA. Optimizing Bone Mass and Strength: The role of physical activity and nutrition during growth. New York, USA: Karger: Med Sport Sci; 2007.
- 295. Fan Y, Fan Y, Li Z, Loan M, Lv C, Bo Z. Optimal principle of bone structure. PLoS One 2011;6(12):1-7.
- 296. Lochmuller EM, Groll O, Kuhn V, Eckstein F. Mechanical strength of the proximal femur as predicted from geometric and densitometric bone properties at the lower limb versus the distal radius. Bone 2002; 30(1):207-16.
- 297. Lochmuller EM, Lill CA, Kuhn V, Schneider E, Eckstein F. Radius bone strength in bending, compression and falling and its correlation with clinical densitometry at multiple sites. J Bone Miner Res 2002;17(9):1629-38.
- 298. Modlesky CM, Lewis RD. Does exercise during growth have a long-term effect on bone health? Exerc Sport Sci Rev 2002;30(4):171-6.
- 299. Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. Proceedings of a sattelite symposium held on the occasion of the EULAR Congress, Paris, France, June 13, 2008. Rheumatol

2008;47(Suppl. 4):iv2-iv8.

- 300. Jepsen KJ, Davy DT. Comparison of damage accumulation measures in human cortical bone. J Biomech 1997;30(9):891-4.
- McCabe F, Zhou LJ, Steele CR, Marcus R. Noninvasive assessment of ulnar bending stiffness in women. J Bone Miner Res 1991;6(1):53-9.
- 302. Ammann P, Rizzoli R, Meyer JM, Bonjour JP. Bone density and shape as determinants of strength in IGF-I and/or pamidronate-treated overiectomized rats. Osteoporos Int 1996;6(3):219-27.
- 303. Ejersted C, Andreassen T, Oxlund H, Jørgensen P, Bak B, Häggblad J, et al. Human parathyroid hormone (1-34) and (1-84) increase the mechanical strength and thickness of cortical bone in rats. J Bone Miner Res 1993;8(9):1097-101.
- 304. Oxlund H, Ejersted C, Andreassen TT, Torring O, Nilsson MH. Parathyroid hormone (1-34) and (1-84) stimulate cortical bone formation both from periosteum and endosteum. Calcif Tissue Int 1993;53(6):394-9.
- 305. Nilsson N, Sundh D, Ohlsson C, Karlsson M, Mellstrom D, Lorentzon M. Exercise during growth and young adulthood is independently asociated with cortical bone size and strength in Swedish men. J Bone Miner Res 2014;29(8):1795.
- 306. Warden SJ, Roosa SM. Physical activity completed when young has residual bone benefits at 94 years of age: A with-in subject controlled case study. J Musculoskelet Neuronal Interact 2014;14(2):239.
- 307. Warden SJ, Roosa SM, Kersh ME, Hurd AL, Fleisig GS, Pandy MG, et al. Physical activity when young provides lifelong benefits to cortical bone size and strength in men. Proc Natl Acad Sci 2014;111(14):5337-42.
- 308. Beck TJ, Oreskovic TL, Stone KL, Ruff CB, Ensrud K, Nevitt MC, et al. Structural adaptation to changing skeletal load in the progression toward hip fragility: The study of osteoporotic fractures. J Bone Miner Res 2001;16(6):1108-19.
- 309. Cheng S, Toivanen JA, Suominen H, Toivanen JT, Timonen J. Estimation of structural and geometrical properties of cortical bone by computerized tomography in 78-year-old women. J Bone Miner Res 1995;10(1):139-48.
- 310. Yeni Y, Brown C, Wang Z, Norman T. The influence of bone morphology on fracture toughness of the human femur and tibia. Bone 1997;21(5):453-9.
- Bass SL. The structural adaptations of cortical bone to loading during different stages of maturation. J Musculoskelet Neuronal Interact. 2003;3(4):345-7.
- 312. Bertram JEA, Biewener AA. Bone curvature: Sacrificing strength for load predictability? J Theor Biol 1988;131(1):75-92.
- 313. Goldman HM, McFarlin SC, Cooper DM, Thomas CD, Clement JG. Ontogenetic patterning of cortical bone microstructure and geometry at the human mid-shaft femur. Anat Rec (Hoboken) 2009;292(1):48-64.
- 314. Bass SL, Saxon L, Daly R, Turner CH, Robling AG,

Seeman E, et al. The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. J Bone Miner Res 2002;17(12):2274-80.

- 315. Jepsen KJ. Functional interactions among morphologic and tissue quality traits define bone quality. Clin Orthop Relat Res 2011;469(8):2150-9.
- Greene DA, Naughton DA. Adaptive skeletal responses to mechanical loading during adolescence. Sports Med 2006;36(9):723-32.
- 317. Jepsen KJ, Evans RK, Negus CH, Gagnier JJ, Centi A, Erlich T, et al. Variation in tibial functionality and fracture susceptibility among healthy, young adults arises from the acquisition of bioogically distinct sets of traits. J Bone Miner Res 2013;28(6):1290-300.
- 318. Jepsen KJ, Hu B, Tommasini SM, Courtland HW, Price CT, Terranova CJ, et al. Genetic randomization reveals functional relationships between morpholgic and tissue-quality traits that contribute to bone strength and fragility. Mammalian Genome 2007; 18(6-7):492-507.
- 319. Milgrom C, Gildadi M, Simkin A, Rand N, Kedem R, Kashtan H, et al. The area moment of inertia of the tibia: A risk factor for stress fractures. J Biomech 1989;22(11):1243-8.
- 320. Tommasini SM, Nasser P, Hu B, Jepsen KJ. Biological Co-Adaptation of Morphological and Composition Traits Contributes to Mechanical Functionality and Skeletal Fragility. J Bone Miner Res 2008;23(2):236-46.
- 321. Tommasini SM, Nasser P, Jepsen KJ. Sexual dimorphism affects tibia size and shape but not tissue-level mechanical properties. Bone 2007;40(2):498-505.
- 322. Tommasini SM, Nasser P, Schaffler MB, Jepsen KJ. Relationship between bone morphology and bone quality in male tibias: implications for stress fracture risk. J Bone Miner Res 2005;20(8):1372-80.
- 323. Beck TJ, Ruff CB, Mourtada FA, Shaffer RA, Maxwell-Williams K, Kao GL, et al. Dual-energy X-ray absorptiometry derived structural geometry for stress fracture prediction in male US Marine Corps recruits. J Bone Miner Res 1996;11(5):645-53.
- 324. Beck TJ, Ruff CB, Schaffer RA, Betsinger K, Trone DW, Brodine SK. Stress fracture in military recruits: Gender differences in muscle and bone susceptibility factors. Bone 2000;27(3):437-44.
- 325. Franklyn M, Oakes B, Field B, Wells P, Morgan D. Section modulus is the optimum geometric predictor for stress fractures and medial tibial stress syndrome in both male and female athletes. Amer J Sports Med 2008;36(6):1179-89.
- 326. Jepsen KJ, Centi A, Duarte GF, Galloway K, Goldman H, Hampson N, et al. Biological constraints that limit compensation of a common skeletal trait variant lead to inequivalent of tibial function among healthy young adults. J Bone Miner Res 2011;26(12):2872-85.
- 327. Wallace IJ, Tommasini SM, Judex S, Garland T, Demes B. Genetic variations and physical activity as

determinants of bone morphology: An experimental approach using a mouse model. Am J Phys Anthropol 2012;148(1):24-35.

- 328. Warden SJ, Hurst JA, Sanders MS, Turner CH, Burr DB, Li J. Bone adaptation to a mechanical loading program significantly increases skeletal fatigue resistance. J Bone Miner Res 2005;20(5):809-16.
- 329. Beck BR, Snow CM. Bone health across the lifespan - exercising our options. Exerc Sport Sci Rev 2003; 31(3):117-22.
- 330. Janz KF, Gilmore JM, Burns TL, Levy SM, Torner JC, Willing MC, et al. Physical activity augments bone mineral accrual in young children: The Iowa Bone Development study. J Pediatr 2006;148(6):793-9.
- 331. MacKelvie K, Khan K, McKay H. Is there a critical period for bone response to weight-bearing exercise in children and adolescents? A systematic review. Br J Sports Med 2002;36(4):250-7.
- 332. Nikander R, Sievänen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: A systematic review and meta-analysis for optimising bone strength throughout life. BMC Med 2010;8(1):47.
- 333. Giorgi M, Carriero A, Shefelbine SJ, Nowlan NC. Effects of normal and abnormal loading conditions on morphogenesis of the prenatal hip joint: application to hip dysplasia. J Biomech 2015;48(12):3390-7.
- 334. Pollard AS, Charlton BG, Hutchinson JR, Gustafsson T, McGonnell IM, Timmons JA, et al. Lmb proportions show developmental plasticity in response to embryo movement. Sci Rep 2017;7(41926).
- 335. Pollard AS, McGonnell IM, Pitsillides AA. Mechanoadaptation of developing limbs: shaking a leg. J Anat 2014;224(6):615-23.
- 336. Rodriguez JI, Garcia-Alix A, Palacios J, Paniagua R. Changes in the long bones due to fetal immobility caused by neuromuscular disease. A radiographic and histological study. J Bone Joint Surg Am 1988; 70(7):1052-60.
- 337. Ireland A, Maden-Wilkinson T, Ganse B, Degens H, Rittweger J. Effects of age and starting age upon side asymmetry in the arms of veteran tennis players: a cross-sectional study. Osteoporos Int 2014; 25(4):1389-400.
- 338. Kontulainen S, Sievanen H, Kannus P, Pasanen M, Vuori I. Effect of long-term impact-loading on mass, size, and estimated strength of humerus and radius of female racquet-sports players: a perhipheral quantitative computed tomography study between young and older starters and controls. J Bone Miner Res 2003;18(2):352-9.
- 339. Rubin CT, Bain SD, McLeod KJ. Suppression of the osteogenic response in the aging skeleton. Calcif Tissue Int 1992;50(4):306-13.
- 340. Lauretani F, Bandinelli S, Griswold ME, Maggio M, Semba R, Guralnik JM, et al. Longitudinal Changes in BMD and Bone Geometry in a Population-Based Study.

J Bone Miner Res 2008;23(3):400-8.

- 341. Cianferotti L, Brandi ML. Muscle-bone interactions: basic and clinical aspects. Endocrine 2014;45(2):165-77.
- 342. Ireland A, Rittweger J, Degens H. The influence of muscular action on bone strength via exercise. Clin Rev Bone Miner Metab 2014;12:93-102.
- 343. Kaji H. Interaction between Muscle and Bone. J Bone Metab 2014;21(1):29-40.
- 344. Karasik D, Cohen-Zinder M. The genetic pleiotropy of musculoskeletal aging. Front Physiol 2012;3:1-24.
- 345. LeBlanc AD, Spector ER, Evans HJ, Sibonga JD. Skeletal responses to space flight and the best rest analog: A review. J Musculoskelet Neuronal Interact 2007;7(1):33.
- 346. Lloyd SA, Lang CH, Zhang Y, Paul EM, Laufenberg LJ, Lewis GS, et al. Interdependence of Muscle Atrophy and Bone Loss Induced by Mechanical Unloading. J Bone Miner Res 2014;29(5):1118-30.
- 347. Qin Y, Lam H, Ferreri S, Rubin C. Dynamic skeletal muscle stimulation and its potential in bone adaptation. J Musculoskelet Neuronal Interact 2010;10(1):12-24.
- 348. Schoenau E. From mechanostat theory to development of the" Functional Muscle-Bone-Unit". J Musculoskelet Neuronal Interact 2005;5(3):232.
- 349. Anliker E, Toigo M. Functional assessment of the muscle-bone unit in the lower leg. J Musculoskelet Neuronal Interact 2012;12(2):46-55.
- 350. Rabischong P. Comprehensive Anatomy of Motor Functions. Switzerland: Springer International; 2014.
- Rittweger J, Beller G, Ehrig J, Jung C, Koch U, Ramolla J, et al. Bone-muscle strength indices for the human lower leg. Bone 2000;27(2):319-26.
- 352. Schiessl H, Frost H, Jee W. Estrogen and bone-muscle strength and mass relationships. Bone 1998;22(1):1-6.
- 353. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res 2002;17(6):1095-101.
- 354. Schoenau E, Werhahn E, Schiedermaier U, Mokow E, Schiessl H, Scheidhauer K, et al. Influence of muscle strength on bone strength during childhood and adolescence. Horm Res Paediatr 1996;45(Suppl 1): 63-6.
- 355. Hadjidakis DJ, Androulakis II. Bone remodeling. Ann NY Acad Sci 2006;1092(1):385-96.
- 356. Jähn K, Lara-Castillo N, Brotto L, Mo C, Johnson M, Brotto M, et al. Skeletal muscle secreted factors prevent glucocorticoid-induced osteocyte apoptosis through activation of B-Catenin. Eur Cells Mater 2012;24:197.
- 357. Mo C, Romero-Suarez S, Bonewald L, Johnson M, Brotto M. Prostaglandin E2: from clinical applications to its potential role in bone-muscle crosstalk and myogenic differentiation. Recent Pat Biotechnol 2012; 6(3):223.
- 358. Takeda S, Karsenty G. Central control of bone

formation. J Bone Miner Metab 2001;19(3):195-8.

- 359. Baud'huin M, Solban N, Cornwall-Brady M, Sako D, Kawamoto Y, Liharska K, et al. A soluble bone morphogenetic protein type IA receptor increases bone mass and bone strength. Proc Natl Acad Sci 2012;109(30):12207-12.
- 360. Mikkola TM, Sipila S, Rantanen T, Sievanen H, Suominen H, Tiainen K, et al. Muscle cross-sectional area and structural bone strength share genetic and environmental effects in older women. J Bone Miner Res 2009;24(2):338-45.
- 361. Gupta M, Cheung CL, Hsu YH, Demissie S, Cupples LA, Kiel DP, et al. Identification of homogenous genetic architecture of multiple genetically correlated traits by block clustering of genome-wide associations. J Bone Miner Res 2011;26(6):1261-71.
- Karasik D, Kiel DP. Evidence for pleiotropic factors in genetics of the musculoskeletal system. Bone 2010; 46(5):1226-37.
- 363. Rantalainen T, Heinonen A, Komi P, Linnamo V. Neuromuscular performance and bone structural characteristics in young healthy men and women. Eur J Appl Physiol 2008;102(2):215-22.
- 364. Szulc P, Seeman E, Duboeuf F, Sornay-Rendu E, Delmas PD. Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. J Bone Miner Res 2006;21(12):1856-63.
- 365. Roland M, Hanson AM, Cannon CM, Stodieck LS, Ferguson VL. Exercise prevention of unloadinginduced bone and muscle loss in adult mice. Biomed Sci Instrum 2005;41:128-34.
- 366. Berg HE, Eiken O, Miklavcic L, Mekjavic IB. Hip, thigh and calf muscle atrophy and bone loss after 5-week bedrest inactivity. Eur J Appl Physiol. 2007;99(3):283-9.
- 367. Giangregorio L, Blimkie CJ. Skeletal adaptations to alterations in weight-bearing activity. Sports Med 2002;32(7):459-76.
- 368. Sibonga JD, Evans HJ, Sung HG, Spector ER, Lang TF, OGanov VS, et al. Recovery of spaceflight-induced bone loss: Bone mineral density after long-duration missions as fitted with an exponential function. Bone 2007;41(6):973-8.
- 369. Wall BT, Dirks ML, Snijders T, Senden JM, Dolmans J, Loon L. Substantial skeletal muscle loss occurs during only 5 days of disuse. Acta Physiol 2014;210(3):600-11.
- 370. Orwoll ES, Adler RA, Armin S, Binkley N, Lewiecki EM, Petak SM, et al. Skeletal health in long-duration astronauts: nature, assessment, and management recommendations from the NASA Bone Summit. J Bone Miner Res 2013;28(6):1243-55.
- 371. Baecker N, Tomic A, Mika C, Gotzmann A, Platen P, Gerzer R, et al. Bone resorption is induced on the second day of bed rest: results of a controlled crossover trial. J Appl Physiol 2003;95(3):977-82.
- 372. Carvalho A, Louzada M, Riso N. Hindlimb unloading

producing effects on bone biomechanical properties in mature male rats. Braz J Morphol Sci 2007; 24(3):175-9.

- 373. Abe T, DeHoyos DV, Pollock ML, Garzarella L. Time course for strength and muscle thickness changes following upper and lower body resistance training in men and women. Eur J Appl Physiol 2000; 81(3):174-80.
- 374. Abe T, Yasuda T, Midorikawa T, Sato Y, Kearns C, Inoue K, et al. Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily" KAATSU" resistance training. Int J KAATSU Train Res 2005;1(1):6-12.
- 375. DeFreitas JM, Beck TW, Stock MS, Dillon MA, Kasishke II PR. An examination of the time course of traininginduced skeletal muscle hypertrophy. Eur J Appl Physiol 2011;111(11):2785-90.
- 376. Evans R, Negus C, Centi A, Spiering B, Kraemer W, Nindl B. Peripheral QCT sector analysis reveals early exercise-induced increases in tibial bone mineral density. J Musculoskelet Neuronal Interact 2012;12(3):155-64.
- 377. Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. J Appl Physiol 2007;102(1):368-73.
- 378. Armbrecht G, Belavý DL, Backström M, Beller G, Alexandre C, Rizzoli R, et al. Trabecular and cortical bone density and architecture in women after 60 days of bed rest using high-resolution pQCT: WISE 2005. J Bone Miner Res 2011;26(10):2399-410.
- 379. Goodship AE, Cunningham JL, Oganov V, Darling J, Miles AW, Owen GW. Bone loss during long term space flight is prevented by the application of a short term impulsive mechanical stimulus. Acta Astronaut 1998;43(3-6):65-75.
- 380. Nagaraja MP, Jo H. The Role of Mechanical Stimulation in Recovery of Bone Loss - High versus Low Magnitude and Frequency of Force. Life 2014;4(2):117-30.
- Rittweger J, Felsenberg D. Recovery of muscle atrophy and bone loss from 90 days bed rest: results from a one-year follow-up. Bone 2009;44(2):214-24.
- 382. Cervinka T, Rittweger J, Hytinnen J, Felsenberg D, Sievanen H. Anatomical sector analysis of loadbearing tibial bone structure during 90-day bed rest and 1-year recovery. Clin Physiol Funct Imaging 2011;31(4):249-57.
- 383. Avin KG, Bloomfield SA, Gross TS, Warden SJ. Biomechanical aspects of the muscle-bone interaction. Curr Osteoporos Rep 2014:1-8.
- 384. Colletti LA, Edwards J, Gordon L, Shary J, Bell NH. The effects of muscle-building exercise on bone mineral density of the radius, spine, and hip in young men. Calcif Tissue Int 1989;45(1):12-4.
- 385. El Hage RP, Courteix D, Benhamou C-L, Jacob C, Jaffré
 C. Relative importance of lean and fat mass on bone mineral density in a group of adolescent girls and boys.

Eur J Appl Physiol 2009;105(5):759-64.

- 386. Talla R, Galea M, Lythgo N, Angeli T, Eser P. Contralateral comparison of bone geometry, BMD and muscle function in the lower leg and forearm after stroke. J Musculoskelet Neuronal Interact 2011;11(4):306-13.
- 387. Travison TG, Araujo AB, Esche GR, Beck TJ, McKinlay JB. Lean mass and not fat mass is associated with male proximal femur strength. J Bone Miner Res 2008;23(2):189-98.
- 388. Bitsakos C, Kerner J, Fisher I, Amis AA. The effect of muscle loading on the simulation of bone remodelling in the proximal femur. J Biomech 2005;38(1):133-9.
- 389. Burr DB. Muscle Strength, Bone Mass, and Age-Related Bone Loss. J Bone Miner Res 1997;12(10):1547-51.
- 390. Ferretti JL, Cointry GR, Capozza RF, Frost HM. Bone mass, bone strength, muscle-bone interactions, osteopenias and osteoporoses. Mech Ageing Dev 2003;124(3):269-79.
- 391. Jackowski SA, Faulkner RA, Farthing JP, Kontulainen SA, Beck TJ, Baxter-Jones AD. Peak lean tissue mass accrual precedes changes in bone strength indices at the proximal femur during the pubertal growth spurt. Bone 2009;44(6):1186-90.
- 392. Laddu D, Farr J, Lee V, Blew R, Stump C, Houtkooper L, et al. Muscle density predicts changes in bone density and strength: a prospective study in girls. J Musculoskelet Neuronal Interact 2014;14(2):195.
- 393. Khalid M, Brannigan A, Burke T. Calf muscle wasting after tibial shaft fracture. Br J Sports Med 2006;40(6):552-3.
- 394. Martin RB, Burr DB, Sharkey NA. Skeletal tissue mechanics. New York, USA: Springer; 1998.
- 395. Pamukoff DN, Blackburn JT. Comparison of plantarflexor musculotendinous stiffness, geometry and architecture in male runners with and without a history of tibial stress fracture. J Appl Biomech 2015;31:41-7.
- 396. Duda GN, Heller M, Albinger J, Schulz O, Schneider E, Claes L. Influence of muscle forces on femoral strain distribution. J Biomech 1998;31(9):841-6.
- 397. Milgrom C, Radeva-Petrova DR, et al. The effect of muscle fatigue on *in vivo* tibial strains. J Biomech 2007;40(4):845-50.
- 398. Verbitsky O, Mizrahi J, Voloshin A, Treiger J, Isakov E. Shock transmission and fatigue in human running. J Appl Biomech 1998;14(300-311).
- 399. Yoshikawa T, Mori S, Santiesteban A, Sun T, Hafstad E, Chen J, et al. The effects of muscle fatigue on bone strain. J Exp Biol 1994;188(1):217-33.
- 400. LeBrasseur NK, Achenbach SJ, Melton LJ, Amin S, Khosla S. Skeletal muscle mass is associated with bone geometry and microstructure and serum insulin-like growth factor binding protein-2 levels in adult women and men. J Bone Miner Res 2012;27(10):2159-69.
- 401. Hamrick MW, McNeil PL, Patterson SL. Role of muscle-derived growth factors in bone formation. J Musculoskelet Neuronal Interact 2010;10(1):64-70.

- 402. Pedersen BK, Edward F. Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. J Appl Physiol 2009;107(4):1006-14.
- 403. Walsh K. Adipokines, myokines and cardiovascular disease. Circulation J 2009;73(1):13-8.
- 404. DiGirolamo DJ, Clemens TL, Kousteni S. The skeleton as an endocrine organ. Nat Rev Rheumatol 2012;8(11):674-83.
- 405. Pedersen BK. Muscles and their myokines. J Exp Biol 2011;214(2):337-46.
- 406. Utvag SE, Iversen KB, Grundes O, Reikeras O. Poor muscle coverage delays fracture healing in rats. Acta Orthop 2002;73(4):471-4.
- 407. Vogt PM, Boorboor P, Vaske B, Topsakal E, Schneider E, Meuehlberger T. Significant angiogenic potential is present in the microenvironment of muscle flaps in humans. J Reconstr Microsurg 2005;21(8):517-23.
- 408. Harry LE, Sandison A, Paleolog EM, Hansen U, Pearse MF, Nanchalal J. Comparison of the healing of open tibial fractures covered with either muscle or fasciocutaneous tissue in a murine model. J Orthop Res 2008;26(9):1238-44.
- 409. Gopal S, Majumder S, Batchelor AG, KNight SL, De Boer P, Smith RM. Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. J Bone Joint Surg Br 2000;82(7):959-66.
- 410. Kitase Y, Barragan L, Qing H, Kondoh S, Jiang JX, Johnson ML, et al. Mechanical induction of PGE2 in osteocytes blocks glucocorticoid-induced apoptosis through both the B-catenin and PKA pathways. J Bone Miner Res 2010;25(12):2657-68.
- 411. Ducy P. The role of osteocalcin in the endocrine crosstalk between bone remodelling and energy metabolism. Diabetologia 2011;54(6):1291-7.
- 412. Levinger I, Scott D, Nicholson GC, Stuart AL, Duque G, McCorquodale T, et al. Undercarboxylated osteocalcin, muscle strength and indices of bone health in older women. Bone 2014;64:8-12.
- 413. Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr 2006;84(3):475-82.
- 414. Gargac JA, Turnbull TL, Roeder RK, Neibur GL. A probabilistic damage model based on direct 3-D correlation of strain to damage formation following fatigue loading of rat femora. J Mech Behav Biomed Mater 2014;30:234-43.
- 415. Murgia C. Overuse, Tissue Fatigue and Injuries. J Dance Med Sci 2013;17(3):92-100.
- 416. Warden SJ, Burr DB, Brukner PD. Stress fractures: pathophysiology, epidemiology, and risk factors. Curr Osteoporos Rep 2006;4(3):103-9.
- 417. Warden SJ, Davis IS, Fredericson M. Management and prevention of bone stress injuries in longdistance runners. J Orthop Sports Phys Ther 2014; 44(10):749-65.
- 418. Chen JC, Beaupre GS, Carter DR. An approach to quantifying bone overloading and hypertrophy with application to multiple experimental studies. Bone 2010;46(2):322-9.
- 419. Newsham-West RJ, Lyons B, Milburn PD. Regional

bone geometry of the tibia in triathletes and stress reactions - An observational study. J Sci Med Sport 2014;17(2):150-4.

- 420. Popp KL, Hughes JM, Smock AJ, Novotny SA, Stovitz SD, Koehler SM, et al. Bone geometry, strength, and muscle size in runners with a history of stress fracture. Med Sci Sports Exerc 2009;41(12):2145-50.
- 421. Schnackenburg KE, Macdonald HM, Ferber R, Wiley JP, Boyd SK. Bone quality and muscle strength in female athletes with lower limb stress fractures. Med Sci Sports Exerc 2011;43(11):2110-9.
- 422. Clansey AC, Hanlon M, Wallace ES, Lake MJ. Effects of fatigue on running mechanics associated with tibial stress fracture risk. Med Sci Sports Exerc 2012; 44(10):1917-23.
- 423. Coventry E, O'Connor KM, Hart BA, Earl JE, Ebersole KT. The effect of lower extremity fatigue on shock attenuation during single-leg landing. Clin Biomech 2006;21(10):1090-7.
- 424. Mizrahi J, Verbitsky O, Isakov E, Daily D. Effect of fatigue on leg kinematics and impact acceleration in long distance running. Hum Movement Sci 2000; 19(2):139-51.
- 425. Fyhrie DP, Milgrom C, Hoshaw SJ, Simkin A, Dar S, Drumb D, et al. Effect of fatiguing exercise on longitudinal bone strain as related to stress fracture in humans. Ann Biomed Eng 1998;26(4):660-5.
- 426. Mizrahi J, Verbitsky O, Isakov E. Fatigue-related loading imbalance on the shank in running: A possible factor in stress fractures. Ann Biomed Eng 2000;28(4):463-9.
- 427. Mizrahi J, Verbitsky O, Isakov E. Shock accelerations and attentution in downhill and level running. Clin Biomech 2000;15(1):15-20.
- 428. Mizrahi J, Verbitsky O, Isakov E. Fatigue-induced changes in decline running. Clinical Biomechanics 2001;16(3):207-12.
- 429. Christina KA, White SC, Gilchrist LA. Effect of localized muscle fatigue on vertical ground reaction forces and ankle joint motion during running. Hum Movement Sci 2001;20(3):257-76.
- 430. Bennell K, Matheson G, Meeuwisse W, Brukner P. Risk factors for stress fractures. Sports Med 1999; 28(2):91-122.
- 431. Corrarino JE. Stress fractures in runners. Nurse Pract 2012;37(6):18-28.
- 432. Harrast MA, Colonno D. Stress fractures in runners. Clinics in sports medicine 2010;29(3):399-416.
- 433. Herman BC, Cardoso L, Majeska RJ, Jepsen KJ, Schaffler MB. Activation of bone remodeling after fatigue: differential response to linear microcracks and diffuse damage. Bone 2010;47(4):766-72.
- 434. McCormick F, Nwachukwu BU, Provencher MT. Stress fractures in runners. Clin Sports Med 2012; 31(2):291-306.
- 435. Reshef N, Guelich DR. Medial tibial stress syndrome. Clin Sports Med 2012;31(2):273-90.
- 436. Taylor D, Hazenberg JG, Lee TC. Living with cracks: damage and repair in human bone. Nat Mater 2007; 6(4):263-8.