Bench-to-bedside strategies for osteoporotic fracture: From osteoimmunology to mechanosensation

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Osteoporosis is characterized by a decrease in bone mass and strength, rendering people prone to osteoporotic fractures caused by low-energy forces. The primary treatment strategy for osteoporotic fractures is surgery; however, the compromised and comminuted bones in osteoporotic fracture sites are not conducive to optimum reduction and rigid fixation. In addition, these patients always exhibit accompanying aging-related disorders, including high inflammatory status, decreased mechanical loading and abnormal skeletal metabolism, which are disadvantages for fracture healing around sites that have undergone orthopedic procedures. Since the incidence of osteoporosis is expected to increase worldwide, orthopedic surgeons should pay more attention to comprehensive strategies for improving the poor prognosis of osteoporotic fractures. Herein, we highlight the molecular basis of osteoimmunology and bone mechanosensation in different healing phases of elderly osteoporotic fractures, guiding perioperative management to alleviate the unfavorable effects of insufficient mechanical loading, high inflammatory levels and pathogen infection. The well-informed pharmacologic and surgical intervention, including treatment with anti-inflammatory drugs and sufficient application of antibiotics, as well as bench-to-bedside strategies for bone augmentation and hardware selection, should be made according to a comprehensive understanding of bone biomechanical properties in addition to the remodeling status of osteoporotic bones, which is necessary for creating proper biological and mechanical environments for bone union and remodeling. Multidisciplinary collaboration will facilitate the improvement of overall osteoporotic care and reduction of secondary fracture incidence.

Bone Research (2019) 7:25; https://doi.org/10.1038/s41413-019-0066-7

INTRODUCTION
The major characteristic of osteoporosis is a decrease in bone mass and quality,¹ rendering people prone to osteoporotic fracture (fragility fracture) caused by low-energy trauma.² Osteoporosis is a prevailing skeletal disease of the elderly; nearly 200 million osteoporotic patients are diagnosed annually, and almost 9 million osteoporotic fractures occur worldwide.³ Surgery is the primary treatment strategy for osteoporotic fracture; however, poor prognoses are presented due to the combination of biological and surgical factors.³ The common sites of osteoporotic bones are usually compromised and comminuted, which makes it hard to achieve an optimum reduction and stable fixation.³,⁵ Osteoporotic fractures occur mostly in elderly patients, who exhibit underlying, unfavorable systemic conditions that are prone to complications.⁵ The abnormal remodeling status of bone with osteoporosis would deteriorate after bed braking, which poses a disadvantage with respect to fracture healing and bone callus strength; furthermore, the re-fracture risk following surgery increases significantly.⁷ In terms of the complexity of treatment and poor prognosis, the annual facility-related hospital cost of osteoporotic fractures is the highest (up to $5.1 billion), followed by that of myocardial infarction and stroke.⁸

Although the results of the clinical studies remain controversial, the majority have demonstrated that decreased callus area (20%–40%) and bone mineral density (BMD) occur in the fracture sites of elderly osteoporotic patients⁶. Studies have indicated that the delayed or nonunion of osteoporotic fractures is implicated in the scarce capacity of bone regeneration with aging.⁹,¹⁰ Additionally, the bone properties of such patients are quite different from those of normal individuals and are manifested in the decrease of bone mechanics and mechanosensation, as well as the abnormal bone metabolism caused by immune disorders.¹¹ To improve the current unsatisfactory status of osteoporotic fracture treatment, we must first gain an in-depth understanding of the mechanism of fracture healing in elderly patients with osteoporosis. Herein, we highlight the pivotal roles of mechanical loading and osteoimmunology in aging-related osteoporotic fractures, guiding the intervention in osteoporotic fracture patients combined with an optimal treatment strategy for improving the overall standard of care and reducing the incidence of secondary fracture.

STATIC AND DYNAMIC CHANGES IN OSTEOPOROTIC BONE
Bone is a unique tissue due to its elasticity and strength that permits deformation under a certain level of loading stress before failing.¹² The strength of bone is mainly dependent on the distribution and density of the inorganic matrix

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Received: 1 November 2018 Revised: 20 June 2019 Accepted: 21 June 2019
Published online: 15 August 2019
mineralization. Cortical bone consisting of dense and well-organized lamellae has higher strength but a lower capacity to withstand a load that exceeds the elastic deformation range compared with that of trabecular bone, which is composed of unparallel lamellar units with variable porosity (50%–90%). The mechanical competence of cancellous bone is based largely on the BMD, while the stiffness of cortical bone is highly dependent on its porosity. In contrast to calcified matrix mineralization, the organic matrix (e.g., collagen and noncollagenous proteins) is thought to control bone ductility and its capacity to withstand an impact without cracking. A large proportion (90%) of the organic matrix is composed of type I collagen, which undergoes numerous posttranslational modifications. Among them, enzymatic modifications positively affect the biomechanical stability of bone, while nonenzymatic crosslinking is associated with a deterioration in these properties. Noncollagenous proteins, including osteopontin (OPN) and osteocalcin (OCN), account for 10% of the organic matrix and limit crack energy through the control of hydroxyapatite size and orientation. Whereas bone material properties provide only a static snapshot of bone quality, the abilities of self-regeneration and remodeling provide a dynamic profile of bone health. The cortical and trabecular bone both undergo lifelong remodeling coupled with bone resorption, which is mediated by osteoclasts following osteoblastic bone formation. Osteoclasts are of hematopoietic stem cell (HSC) origin and share precursors with macrophages. In the presence of macrophage colony-stimulating factor (M-CSF), osteoclast precursors differentiate to preosteoclasts by the binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to its cognate receptor, receptor activator of nuclear factor kappa-B (RANK). These mononuclear preosteoclasts then fuse to form multinuclear bone-resorbing osteoclasts. In contrast, osteoblasts are derived from mesenchymal stem cells (MSCs), and osteoblastic bone formation is separated from resorption by a reversal phase for several weeks. Mature osteoblasts then differentiate into osteocytes, which reside in small lacunae inside the calcified bone matrix. The long dendritic extensions of osteocytes together with the cell bodies form the lacuno-canaliculal network (LCN), which allows direct signal transduction. The speed of mineral accumulation in the bone remodeling cycle is also affected by numerous endocrine factors, such as parathyroid hormone (PTH) and estrogen, which are supplied by the bone vascular systems. However, the normal regulation of bone remodeling could be interrupted as a consequence of skeletal senescence, which impact the integrity and biomechanical properties of both cortical and cancellous bones. The abnormal bone remodeling shifts toward bone resorption, which is either due to excessive activation of osteoclasts or to a low capacity of bone regeneration. In addition, age-related loss of proteostasis and increased levels of oxidants result in the overaccumulation of inorganic pyrophosphate (Pi), AGEs advanced glycation end-products, MSCs mesenchymal stem cells. “Red” refers to upregulation; “Green” refers to downregulation.

**Fig. 1** Static and dynamic changes in osteoporotic bone. An osteoporotic fracture is the macroscopic result of microstructural alterations that change the response of bone to the applied load. The aging process in osteoporotic bone would lead to overaccumulation of Pi, AGEs, and nonenzymatic crosslinking of collagen, which disturb the normal organization of bone material. With the increase of bone resorption and low rate osteogenesis, the osteocyte lacunae reduction leads to decreased trabecular thickness and more porous cortical bone. PTH parathyroid hormone, M-CSF macrophage colony-stimulating factor, RANKL receptor activator of nuclear factor kappa-B ligand, Pi inorganic pyrophosphate, AGEs advanced glycation end-products, MSCs mesenchymal stem cells. “Red” refers to upregulation; “Green” refers to downregulation.
continuity over a period of 3 months to allow full weight bearing. The last phase involves gradual remodeling of bone to withstand the usual strains of daily life.37 In contrast, primary fracture healing without formation of a periosteal callus usually requires direct contact of compact bone or rigid surgical intervention that makes the fracture gap <200 m. However, elderly osteoporotic bones, such as metaphyseal sites, which are highly susceptible to bone degradation, make it difficult to maintain anatomical reduction and rigid fixation using traditional screws due to inadequate insertional torque.38 In this situation, the healing process will be more like indirect bony union with the response of loading and inflammation, forming a periosteal callus bridging the fracture gap. The specific osteoimmunology and mechanosensation status of patients with osteoporotic fractures affect these healing phases in different manners.39

Bone fracture induces immediate inflammation and bleeding around bone extremities and within the medulla, where a template is formed for callus formation, called a hematoma.40 Around the hematoma sites, inflammatory cells, such as macrophages/monocytes or B/T cells, are activated to release inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) into the systemic circulation.41 These cytokines are responsible for the initiation of immune and inflammatory responses,42 including enhancement of blood flow and vessel permeability, as well as the recruitment of immune cells for pathogen clearance.43 The limited inflammatory response is required to initiate the repair cascade and mobilize all the required factors involved in the early bridging of the fracture gap, especially in indirect bony unions without rigid fixation.44 The interactions between the skeletal system and immune function, comprising osteoimmunology, in osteoporotic fractures are altered with age.45 It has been reported that an age-associated decline in the absolute numbers of human B cell precursors in bone marrow46 leads to a significant decrease in the number of mature human B cells.47,48 Compared with young adults, the B cell repertoire is less diverse in elderly individuals.49 As to T cells, studies exhibit reductions of proliferation and helper function in CD4+ T cells that recruit neutrophils and macrophages to infected sites of elderly individuals.50 Consistent with this finding, the impaired neutrophil51/monocytes52-mediated phagocytosis also showed an age-dependent reduction.53 In contrast, the expression of Toll-like receptors (TLRs), a group of pattern recognition receptors (PRRs) that trigger pro-inflammatory responses,54 is increased in monocytes and dendritic cells in elderly people, accompanied by increased production of IL-1 and TNF-α.55 In vitro and in vivo studies have shown that persistent tumor necrosis factor (TNF) expression impairs cell-mediated immune responses and Th2 differentiation from naïve T cells.56-58 Moreover, constant stimulation by TNF-α elevates the threshold for T cell activation via the T-cell receptor (TCR), attenuating T cell responses to antigens59 and negatively affecting angiogenesis during fracture healing.60 Thus, the early immune responses and pathogen clearance of aged patients with osteoporotic fractures would be impaired or delayed due to the insufficient acquired immunity and dysfunction of the innate immune system.61 Furthermore, pathogen infections induce host inflammation and contribute to local bone loss. The most frequent pathogen identified in bone infection is Staphylococcus.62 Staphylococcus aureus protein A induces the production of inflammatory cytokines, such as TNF-α,63 IL-6, interleukin-1 alpha (IL-1α),64 interleukin-1 beta (IL-1β),65 and neutrophil-attracting chemokines in local tissues. On the one hand, short-term (24 h) upregulated cytokines, such as TNF-α are essential for local recruitment of neutrophils,66 macrophages, and T cells for pathogen clearance.65,66 However, the long-term presence of these cytokines, especially TNF-α, IL-1, and IL-6, activates CD4+ T cells, promoting RANKL expression by osteoblasts67 and synergizing directly with RANK to amplify osteoclastogenesis68 and bone resorption.69

In general, high levels of pro-inflammatory cytokines, either in the circulation or local tissues, are found in the aged population.70 Serum IL-1, IL-6, and/or TNF-α levels have been shown to be upregulated in elderly patients with bone loss,70 supporting the hypothesis of increased inflammation with aging.71 In fact, TNF-α promotes bone resorption by both directly inducing osteoclast differentiation72 and inhibiting osteoblast differentiation and function.73,74 IL-1 drives osteoclast differentiation via a RANKL/RANK-independent mechanism.75 IL-6 indirectly plays a positive role in osteoclast differentiation by binding IL-6 receptors expressed on osteoblastic cells to induce RANKL expression.76 Neutrophils stimulate osteoclastogenesis by upregulating cell surface RANKL expression under TLR stimulation77 or by inducing osteoblast retraction.78 Interferon gamma (IFN-γ), secreted by anti-inflammatory macrophages (M2), inhibits osteoclast differentiation via rapid degradation of TRAF6.79 However, macrophage polarization shows a shift toward macrophages (M1) that promote inflammatory cytokines as a consequence of aging.80 In contrast, mature B cells are important regulators of a decoy receptor for RANKL, osteoprotegerin (OPG). In total, 40% of the OPG in bone marrow is produced by mature B cells alone.81 The increased bone resorption and low levels of bone marrow OPG were demonstrated in B cell-deficient mice; this defect can be normalized by the transplantation of B cells. As a result of the decreased number of mature human B cells, the supply of OPG is low in patients with osteoporosis. Thus, current evidence shows that the high RANKL/OPG ratio caused by aging-related inflammation and the lack of mature B cells is associated with the hyperactivation of osteoclastogenesis and aggravation of bone resorption in elderly patients with bone loss, which increases the incidence of further intraoperative or postoperative fractures (Fig. 2). Moreover, Nagae et al. concluded that overactivation of osteoclasts plays an important role in chronic pain after osteoporotic fracture by creating acidity.82 Hyper osteoclast activity may lead to pathological modifications of bone sensory nerve fibers, with an overexpression of acid-sensitive pain receptors, which contributes to generating and maintaining pain in osteoporosis.83

**MOLECULAR BASIS OF BONE MECHANOSENSATION**

Primary fracture healing occurs when the fracture site achieves rigid anatomical and mechanical fixation. Under these conditions, a soft callus enveloping the bone extremities subsequently calcifies to a peripheral solid callus by intramembranous ossification.35 However, in elderly osteoporotic bones, the healing process will be more like indirect bony union by forming a periosteal callus bridging the fracture gap, since it is usually difficult for the compromised bones to maintain enough stress stimulation.84 Among the bone multicellular units (BMUs), which consist of various cells involved in bone remodeling, the osteocytes embedded in the matrix function as major mechanosensitive cells.85 Substantial evidence indicates that the mechanosensation of osteocytes is mediated by signaling molecules, such as Wnts, bone morphogenetic proteins (BMPs), nitric oxide (NO), and prostaglandin E2 (PGE2) in response to mechanical stimulation.86 Furthermore, altered enzyme activity and RNA synthesis have been reported in osteoclasts after mechanical loading of intact bone, which further supports the mechanosensory role of osteocytes in bone.87 Thus, adequate mechanical loading and mechanotransduction are pivotal factors in the repair and remodeling phase of fracture healing.

Mechanical forces, including fluid flow as well as compressive/tensile forces in the LCN,88 induce cell-level physical signals of shear stress, electric/streaming potentials, and substrate strain by acting on cell surface sensors and within the signaling pathways.88 To date, evidence strongly suggests that integrins on the surface
of bone cells are ubiquitous sensors of mechanical forces capable of detecting alterations in the mechanical environment in the extracellular milieu. Shear strain is detected by primary cilia via polycystin 1 (PC1) and transient receptor potential cation channel subfamily V member 4 (TRPV4), which activate signal transducer and activator of transcription (STAT) signals to induce ion flux. Wnt signaling is also activated by cilia via the noncanonical pathway, resulting in β-catenin degradation. The role of canonical Wnt in the suppression of the SOST gene (sclerostin) has also been demonstrated. Furthermore, fluid shear stress can activate voltage-sensitive calcium channels on the plasma membrane, leading to influx of Ca\(^{2+}\), which induces PGE2 synthesis via ATP and inhibits NO generation as a second messenger. PGE2 and ATP are released by connexin hemichannels formed following extracellular signal-regulated kinase1/2 (ERK1/2)-induced transcription of connexin-43 (Cx43). Compressive/tensile forces impose hydraulic pressure in the lacunar-canonical system, which increases cellular deformation of osteocytes. The substrate strain at the membrane can be sensed by integrins that transmit force to the cell cytoskeleton via ERK, proto-oncogene tyrosine-protein kinase Src (SRC) and replication origin activator (ROA) to induce stress loading on surface sensors. The cell nucleus plays crucial roles in response to cellular mechanotransduction. Transcriptional regulation in the cell nucleus converts incoming mechanoresponsive signals into biological signaling and even directly responds to cellular deformation. These intracellular signaling pathways converge to modulate osteogenic transcription factors in addition to regulators of growth factors and matrix proteins required for osteogenesis. Evidence suggests that mechanical signals induce OPG and suppress RANKL to inhibit osteoclast differentiation.

The morphological changes of osteocytes with aging have been reported to influence their mechanosensitivity and the response to loads. Changes in LCN volume due to the increased rate of osteocytic osteolysis with aging or trauma have been shown to affect local bone mechanosensation. Additionally, age-related changes in periosteal modeling arise from cell function/signaling deficits combined with increased marrow adiposity leading to a reduced pool of osteoblast progenitors. Furthermore, peristomal lining cell numbers and osteoblast life-span are reduced by an increased rate of apoptosis. There is an age-related switch in macrophage differentiation from the anti-inflammatory (M2) phenotype that mediates tissue repair to the inflammatory (M1) phenotype. As a consequence of the decline in the secretion of anti-inflammatory and osteogenic cytokines, the bone regeneration capability could be impaired in the process of remodeling osteoporotic fractures. In osteoporotic fractures, the inevitable immobilization and stress shielding achieved by orthopedic surgery reduce the mechanical loading compared with that at normal sites. The deficiency of stress loading on surface sensors of bone cells is accompanied by NF-κB activation of osteoblasts and neighboring immune cells that promotes RANKL production to trigger osteoclastogenesis and bone resorption. This process results in the excess removal of bone mass, which therefore leads to a coarse trabecular pattern and thinning of cortical bone. Estrogen controls the adaptation of osteoblasts and osteocytes to mechanical loads via binding to the estrogen receptor (ER) or activation of TGF1 receptors. Delayed ER expression was shown to be correlated with impaired callus formation capacity in the healing process. A study in humans suggested that mechanical interventions enhance periosteal modeling and bone strength in the young skeleton, while the effects are markedly diminished in the elderly skeleton. In vitro studies indicate that the age-related increase in osteocyte degradation and reduction in the basal level of mechanosensation significantly affect second messenger signaling to modulate bone regeneration (Fig. 3). An optimal strategy for improving the treatment of osteoporotic fractures must address both biological and mechanical issues based on the molecular mechanisms of mechanical loading in fracture healing.

**ANTI-INFLAMMATORY EFFECTS OF MECHANICAL LOADING**

After the fracture gap has been bridged by a callus, the woven bone is slowly replaced with lamellar bone structures. Balanced resorption and formation of new bone require a normal
In the NF-κB signaling cascade, mediators such as TNF-α and superoxide that mediate bone damage and matrix degradation lead to the production of high levels of NO and inflammatory mediators suppressed by inflammatory suppressors and abrogate the associated repression of inflammatory signal that counters the NF-κB signaling cascade. In vitro studies in osteoblasts have shown that the pro-inflammatory mediators suppressed by mechanical signals (tensile, compressive, and shear) include IL-1β-induced NO, COX-2, PGE2, cytokines (IL-1β and TNF-α), and MMPs. Simultaneously, mechanical signals upregulate the expression of growth factors, such as BMPs, OCN, and PGE2 and alkaline phosphatase (ALKP), which are inhibited during inflammation. Several anti-inflammatory cytokines (IL-10) and tissue inhibitors of metalloproteinases (TIMPs) that are inhibited during inflammation are upregulated by mechanical signals. For instance, IL-10 and TIMP-II synthesized by low magnitudes of mechanical signals can suppress inflammation and matrix breakdown in osteoblast and osteoblast-like cells. In contrast, exogenous PGE2 was demonstrated to function as an intercellular messenger for enhancement of the mechanosensitivity of bone to loading forces both in vitro and in vivo. Furthermore, in the presence of PGE2 signaling, osteocytes release NO in response to mechanical stimulation via redox-sensitive mechanisms and mitogen-activated protein kinase (MAPK) pathways. Additionally, mechanical loading increases ERα expression at the fracture callus, which is beneficial for mechanical signal transduction and fracture repair. These data indicate that rigid fixation and adequate mechanical loading are means of improving the immune environment that benefits bone healing.

**Fig. 3 Molecular basis of bone mechanosensory.** The bone multicellular unit (BMU), which consists of osteocytes, osteoblasts, and osteoclasts, functions as a large mechanosensitive organ. Mechanical loading can be sensed by primary cilia, integrins, and Ca^2+ channels on the surface of bone cells, then transcribed in the nucleus with inhibition of RANKL production and promotion of sclerostin and OPG. LRP5/6, low-density lipoprotein receptor-related protein 5/6; SOST sclerostin, RANKL receptor activator of nuclear factor kappa-B ligand, RANK receptor activator of nuclear factor kappa-B, OPG osteoprotegerin, ATP adenosine triphosphate, PGE2 prostaglandin E2, NO nitric oxide, CX43 connexin-43, STAT signal transducer and activator of transcription, ERK1/2 extracellular signal-regulated kinase1/2, ROA replication origin activator, TRPV4 transient receptor potential cation channel subfamily V member 4, PC1 polycystin 1, SRC proto-oncogene tyrosine-protein kinase Src, SHC Shc-transforming protein, FAK focal adhesion kinase, BMU bone multicellular unit. "Red" refers to upregulation; "Green" refers to downregulation.

**MANAGEMENT OF HEMATOMA AND PERIOPERATIVE INFECTION**

The most satisfactory bone healing depends on a good biological environment and appropriate mechanical loading for bone repair.
and remodeling. Orthopedic surgeons are encouraged to familiarize themselves with the molecular basis of skeletal senescence, mechanical loading and osteoimmunology in osteoporotic fractures, which is critical for determining an appropriate surgical technique or nonsurgical intervention. In terms of the decrease in early immune responses and pathogen clearance in aged patients with osteoporotic fractures, special preoperative management is required to achieve a better local healing environment. Previous studies have revealed the osteoimmunological role of hematoma with osteoporotic fractures, special preoperative management is required to inhibit bacterial growth. Current evidence suggests that this concentration is detrimental to abnormal bone remodeling as a result of negative effects on mitochondrial physiology. Thus, local antibiotic vehicles must be designed to deliver sufficiently high concentrations to inhibit bacterial growth without affecting bone cell metabolism.

ANTI-INFLAMMATORY REGULATION OF BONE REMODELING
Increased RANKL/OPG ratios caused by aging-related inflammation are associated with hyperactivation of osteoclastogenesis and exacerbation of bone resorption in elderly patients, leading to subsequent impairment of bone healing and inflammatory pain. Anti-inflammation therapy is a potential strategy that may benefit aging-related osteoporotic fracture by reducing inflammation and protecting against bone loss. Studies have shown that healthy transgenic mice injected with anti-TNF-α repeatedly promote T cell responses to cognate peptide antigen. In the clinical setting, anti-TNF-α (infliximab, Remicade) rapidly and remarkably restores the responses of T cells from rheumatoid arthritis (RA) patients. Treatment with infliximab protects against bone loss and improves the formation/resorption marker ratio in this population, suggesting beneficial systemic and local bone effects. Although anti-inflammatory therapies have not been used clinically to treat osteoporosis, they have shown good promise in mouse models. Indeed, pharmacological or genetic ablation of TNF and IL-1 by somatic gene therapy has been used effectively to prevent ovariectomy-induced bone loss in mice. Thus, anti-inflammation therapy is a potential strategy that may benefit osteoporosis patients because of reduced...
inhibitor, can significantly reduce the high RANKL/OPG ratio in the inflammation phase and facilitate bone healing, suggesting that anti-inflammatory drugs should be discontinued for a period of time before surgery.143 Because chronic inflammation affects bone healing, the anti-inflammatory drug should be reused in osteoporotic fracture after an acute immune response to alleviate inflammation-induced bone loss.

The recent development of anti-resorptive agents (e.g., bisphosphonates, RANKL inhibitor) represents a significant advance in therapeutic options for improving bone quality and metabolism.146 Bisphosphonates are commonly used in osteoporosis to prevent and reduce pain by modifying osteoclast activity.147 Following an osteoporotic fracture, early intervention with anti-resorptive drugs after surgery would not affect fracture union.148 However, bisphosphonate-dependent repair processes become progressively dominant in the late phases, suggesting that continuous administration of alendronate causes delayed healing in mechanically compromised situations.149 Denosumab, a RANKL inhibitor, can significantly reduce the high RANKL/OPG ratio in the inflammatory and repair phases of fracture healing with age-related osteoporosis150 and has been identified as an efficacious osteoporosis treatment option with low rates of adverse events.151 Calcitonin effectively relieves bone pain and can reduce bone loss in osteoporotic fractures, although short-term (3 months) use is recommended.152,153 In summary, reducing the frequency of postoperative syndromes in patients with osteoporosis requires not only regulation of the immune response but also balanced bone resorption and osteogenesis (Fig. 5). Studies have demonstrated that anti-inflammation therapy combined with a bone resorption blocking drug154 reverses systemic bone loss,155 while the timing and extent of immune intervention require further clinical exploration.

**Fig. 5** Bench-to-bedside strategies for osteoporotic fracture. The most satisfactory bone healing depends on two pivotal factors: a good biological environment and appropriate mechanical loading for bone repair and homeostasis. Bench-to-bedside strategies, including management of hematomas and perioperative infections, anti-inflammation and regulation of bone resorption, and rigid fixation and mechanical loading enhancement would benefit the creation of the proper environment for fracture healing of osteoporotic bones. PRPs platelet-rich plasma, PRF, platelet-rich fibrin, rhPDGF-BB recombinant human platelet-derived growth factor-BB, TNF-α tumor necrosis factor alpha, IL-1 interleukin-1, RANKL receptor activator of nuclear factor kappa-B ligand, rhPTH recombinant human parathyroid hormone, PTHrP parathyroid hormone-related protein, BMPs bone morphogenetic proteins. “Red” refers to upregulation; “Green” refers to downregulation

**STRATEGIES FOR MECHANICAL LOADING ENHANCEMENT AND RIGID FIXATION**

The biochemical responses of osteocytes to mechanical loads are mediated by signals induced via a variety of mechanosensitive proteins, such as primary cilia, integrins, and activated ion channels.156 However, it is as yet unclear how osteocytes perceive and differentiate responses to two drastically opposite magnitudes of mechanical signals, that is, those of physiological magnitudes that initiate regenerative responses and of traumatic signals that initiate bone damage and resorption.87 Appropriate use of bone formation promoters (e.g., calcium/vitamin D), mainly for osteoblasts and osteocytes, helps to further enhance the mechanical induction and repair of bone structure. Patients over 65 years old with BMD less than –2.5 SD or postmenopausal women with multiple osteoporotic vertebral fractures or hip fractures who have not responded to bisphosphonate therapy should be switched to the available anabolic agents,7,131 including recombinant human parathyroid hormone (rhPTH, [1–34] [1–84]) and parathyroid hormone-related protein (PTHrP).30 Strontium ranelate is now considered effective in enhancing the biomechanical properties of bone for resistance fragility fractures. Strontium ranelate increases bone formation and decreases bone resorption, thereby rebalancing bone remodeling, which is conducive to new bone formation.157 Numerous studies have shown that strontium ranelates functions in improvement in all parameters related to bone quality and strength.158 The sclerostin monoclonal antibody, such as romosozumab, has been shown to lead to gains in hip BMD.159 In addition, BMPs, which belong to transforming growth factor-beta (TGF-β) family members,160 lead to synergistic induction of downstream TGFβ signaling for osteogenesis combined with physical microenvironment.161 Tricalcium phosphate and polymethylmethacrylate (PMMA) are usually employed to augment bone cement and increase the stability of implant fixation in
osteoporotic bone. These cements undergo interdigitation in porous bone to increase the surface area of contact and provide additional resistance against the screw threads. PMMA has also been used for the delivery of drugs, such as antibiotics, via bone cements. However, PMMA undergoes an exothermic reaction during the drying process, with the potential to initiate thermal bone necrosis. In addition, PMMA is difficult to remove in cases of revision or infection without integrating into the bony matrix. Allograft fibulas are used in bone with low BMD as tools for reduction as well as the provision of medial calcar support. As mechanical stimulation is a potent anti-inflammatory signal, sufficient postsurgery mechanical loading interventions, including physical therapy and rehabilitation, are helpful for building a supportive mechanical and biological environment around the local fracture sites for bone healing. Low intensity vibration (LIV) improves bone quality by activating cells responsible for bone remodeling and biasing the differentiation of mesenchymal and HSC progenitors toward osteoblastogenesis. However, current evidence is insufficient to support the benefit of ultrasound and extracorporeal shockwave therapies (ECSW) for fracture healing in clinical practice (Fig. 5). Mechanical bone strength is vital for the stable anchorage of hardware required for fracture repair. Due to the impaired bone strength and complicated immunology environment in elderly individuals with osteoporosis, more suitable implants with better mechanical characteristics are required to improve aging-related osteoporotic fracture healing. Measurement of the thickness and porosity of cortical bone prior to surgery is important in guiding hardware selection for the repair of osteoporotic fractures. Thus, it is of great importance to identify parameters for evaluating bone quality (Fig. 5). Only 60% of the variation in bone densitometry was measured by dual-energy X-ray absorptiometry (DXA) because it is hard to recognize differences in both trabecular and cortical bone geometrical macrostructure. Both trabecular connectivity and cortical porosity significantly influence bone strength parameters, including stiffness to resist deformation and elasticity to absorb energy. To determine a better intervention, state-of-the-art clinical imaging techniques will help in measuring bone structural parameters, instead of focusing on BMD alone. Evaluation of the grayscale intensity map of DXA imaging can provide more precise information for bone structural parameters.

**Table 1. Clinical options in osteoporotic fractures**

| Clinical options          | Characteristic                                      | Index        | Methods     | Fracture site and pattern               | Disadvantage in osteoporotic bone                                | Ref.            |
|---------------------------|-----------------------------------------------------|--------------|-------------|-----------------------------------------|------------------------------------------------------------------|-----------------|
| Cortical bone screws      | Narrow outer diameters and decreased thread pitch compared to cancellous bone screw | BMD, TBS     | DXA: HR-pQCT, QCT | Femoral heads, Femoral neck fractures | 50% reduction of the holding strength per 1 mm decrease of cortical thickness | 175, 194, 195   |
| Cancellous bone screw     | Reach the plateau torque level prior to contact of all the screw threads | BMD, TBS     | DXA: HR-pQCT, QCT | Femoral metaphysis, Distal radius, Femoral heads | Reduction of thread-bone interface that produces torque | 183, 184, 196, 197 |
| Bicortical lag screw      | Potential improvement of thread purchase            | BMD, TBS     | DXA: HR-pQCT, QCT | Medial malleolus fractures              |                                                                  | 185, 198, 199   |
| Traditional plates        | Compress the fracture fragments between bone implant interface to create fixation strength | BMD, TBS     | DXA: HR-pQCT, QCT | Regular fractures                       | Decrease of the axial and torsional stiffness                   | 190, 200, 201   |
| Locking plate             | Fixed-angle construct between screw and plate       | BMD, TBS     | DXA: HR-pQCT, QCT | Proximal humerus fractures              | Reduction of callus formation without micromotion across the fracture site; Loss of fixation and screw cut-out | 5, 187, 188, 198, 202 |
| Intramedullary nail       | Preserving the soft tissues around fracture site     | BMD, TBS     | DXA: HR-pQCT, QCT | Proximal humerus fractures              | A larger-diameter nail is required to achieve a diaphyseal fit and stability | 191, 203   |
| Bone augmentation         | Increase surface area; PMMA carries osteogenic and antibiotic drugs; Tricalcium phosphate and Allograft fibulas act more as a scaffold | BMD, TBS, BMSi | DXA: HR-pQCT, QCT | Femoral neck fractures, Spine fractures, Comminuted proximal humerus fractures | Damage surrounding soft tissues or initiate thermal bone necrosis; Difficult to remove | 38, 162, 164, 196, 204, 205 |
| External fixation         | Lower fixation failure rates                        | BMD, TBS     | DXA: HR-pQCT, QCT | Commination of tibial plateau fractures |                                                                  | 190   |
| Primary arthroplasty      | Early mobilization and weight bearing                | BMD, TBS     | DXA: HR-pQCT, QCT | Acute acetabular fractures, Displaced intra-articular fractures of the tibial plateau |                                                                  | 193   |

BMD: bone mineral density, DXA: dual-energy X-ray absorptiometry, QCT: quantitative computed tomography, HR-pQCT: high-resolution peripheral QCT, μMRI: micromagnetic resonance imaging, TBS: trabecular bone score, BMSi: bone material strength index, PMMA: polymethylmethacrylate, SMI: structure model index, BV/TV: bone volume fraction.
Compared with BMD measurement.\textsuperscript{175} The trabecular bone score (TBS) correlates positively with trabecular connectivity based on evaluation of the DXA image.\textsuperscript{176} Combining TBS and BMD measurements provides an improved prediction of bone strength compared with BMD alone.\textsuperscript{177,178} Evaluations of structural, material, and mechanical properties based on bone biopsy specimens provide a reliable assessment of local bone characteristics, which are vital independent determinants of bone strength.\textsuperscript{179} The DensiProbe can be a helpful tool for intraoperative assessment of mechanical peak torque in mechanical testing setups,\textsuperscript{180} providing information that can be valuable in choosing implants. Furthermore, this approach does not increase the risk to the patient or increase the surgeon’s workload since the central peg hole can be used for the next procedure.\textsuperscript{180} Cortical and cancellous screws are traditional designs, with the former having relatively narrower outer diameters and decreased thread pitch.\textsuperscript{181} In both cases, the fixation strength depends on the torque generated between the bone and thread that resists shear.\textsuperscript{182} During insertion of a cancellous bone screw into the osteoporotic bone, the torque reaches the plateau prior to the contact of all the screw threads.\textsuperscript{183} The changes in screw geometry that confer an advantage on cancellous screws are lost below a threshold BMD of 0.4 g·cm\textsuperscript{-3}.\textsuperscript{184} The plateau torque (T Plateau), which is an efficient predictor of insertion failure at the femoral head, is significantly dependent on aspects of the bone microarchitecture, such as the structure model index (SMI) and bone volume fraction (BV/TV).\textsuperscript{185} Previous studies suggest that a more plate-like bone structure, a higher BV/TV, and a higher surface-to-volume ratio provide a structural environment that favors cutting of the screw threads into the bone, resulting in an increased T Plateau.\textsuperscript{186} Unstable and comminuted fracture patterns as well as early implant-bone fatigue in osteoporotic bones lead to implant loosening and fixation failure.\textsuperscript{3} Locking-plate technology provides a more advantageous biomechanical environment that facilitates the formation of a fixed angle between the plate and screw.\textsuperscript{187} Despite the greater overall stability, locking plates may create an excessively rigid construct, which is predisposed to peri-implant fracture.\textsuperscript{188} In proximal humeral fractures with low BMD,\textsuperscript{189} computed tomography (CT) assessments suggest that locking plates do not reduce the rate of mechanical failure. In elderly patients with low BMD, tibial plateau fracture is associated with increased comminution and compromised fixation, suggesting that external fixation might be a more effective option than dual plating.\textsuperscript{190} An intramedullary nail (IMN) is a load-sharing device with the advantage of promoting secondary bone healing while preserving the surrounding soft tissues and minimizing fracture-induced hematomas.\textsuperscript{191} The loss of interlocking screw fixation can be mitigated through a number of strategies, including the application of washers and interlocking screws in multiple planes. However, cortical thinning of osteoporotic bone increases the intramedullary canal diameter, and a larger-diameter nail is required to achieve a diaphyseal fit and stability. Therefore, an early quantitative computed tomography (QCT) assessment of the cortical thickness is critical in using IMN in osteoporotic fractures. Intra-articular and complex fractures in patients with osteoporosis pose unique challenges for surgeons. These patients have inadequate subchondral bone quality to allow for anatomic reductions, and the stability of the implant is difficult to maintain after the reintroduction of weight-bearing and increased range of motion.\textsuperscript{192} Primary arthroplasty (total hip/knee/shoulder arthroplasty) has been adopted to obtain adequate weight-bearing and early mobilization, which has a superior prognosis compared to internal fixation in acute acetabular fractures, displaced intra-articular tibial plateau fractures and complex distal humeral fractures.\textsuperscript{93} Despite the advent of locked anatomic plates, a majority of experts recommend arthroplasty in the context of poor bone quality and small fracture fragments (Table 1).
19. Qi, Z., Liu, W. & Lu, J. The mechanisms underlying the beneficial effects of exercise on bone remodeling: roles of bone-derived cytokines and microRNAs. Prog. Biophys. Mol. Biol. 122, 131–139 (2016).

20. Katsimpi, P. The biology of normal bone remodelling. Eur. J. Cancer Care 26, https://doi.org/10.1111/ecc.12740 (2017).

21. Boyce, B. F., Rosenberg, E., de Papp, A. E. & Duong, L. T. The osteoclast, bone resorption, and treatment of metabolic bone disease. Eur. J. Clin. Investig. 42, 1332–1341 (2012).

22. Li, C., Williams, B. O., Cao, X. & Wan, M. LRP6 in mesenchymal stem cells is required for bone formation during bone remodeling and bone repair. Bone Res. 2, 14006 (2014).

23. Delaisse, J. M. The reversal phase of the bone-remodeling cycle: cellular prerequisites for coupling resorption and formation. Bone. 39, 561 (2014).

24. Lai, X. et al. The dependences of osteocytte network on bone compartment, age, and disease. Bone Res. 3, 15009 (2015).

25. Hajdúdiáskis, D. J. & Androulakis, I. I. Bone remodeling. Ann. New Y. Acad. Sci. 1092, 385–396 (2006).

26. Watson, E. C. & Adams, R. H. Biology of bone: the vasculature of the skeletal system. Cold Spring Harbor Perspect. Med. 8, a031559 (2018).

27. Dick, D. L. & Watts, N. B. Postmenopausal osteoporosis. Curr. Opin. Endocrinol. Diab. Obes. 20, 501–509 (2013).

28. Duque, G. & Troen, B. R. Understanding the mechanisms of senile osteoporosis: new facts for a major geriatric syndrome. J. Am. Geriatr. Soc. 56, 935–941 (2008).

29. Marie, P. J. Bone cell senescence: mechanisms and perspectives. J. Bone Miner. Res. 29, 1311–1321 (2014).

30. Black, D. M. & Rosen, C. J. Clinical practice. Postmenopausal osteoporosis. N Engl. J. Med. 374, 254–262 (2016).

31. Yamashita, S. Role of advanced glycation end products (AGEs) in osteoporosis in diabetes. Curr. Drug Targets 12, 2096–2102 (2011).

32. Chen, H., Zhou, X., Fujita, H., Onozuka, M. & Kubo, K. Y. Age-related changes in trabecular and cortic bone microarchitecture. Int. J. Endocrinol. 2013, 213234 (2013).

33. Osterhoff, G. et al. Bone mechanical properties and changes with osteoporosis. Injury 47(Suppl. 2), S11–S20 (2016).

34. Silva, M. J. Biomechanics of osteoporotic fractures. Injury 38(Suppl. 3), S69–S76 (2007).

35. Mansell, R. & Einhorn, T. A. The biology of fracture healing. Injury 42, 551–555 (2011).

36. Einhorn, T. A. & Gerstenfeld, L. C. Fracture healing: mechanisms and interventions. Nat. Rev. Rheumatol. 11, 45–54 (2015).

37. Claes, L., Recknagel, S. & Ignatius, A. Fracture healing under healthy and inflammatory conditions. Nat. Rev. Rheumatol. 8, 133–143 (2012).

38. Rotherberg, D. L. & Lee, M. A. Internal fixation of osteoporotic fractures. Curr. Osteoporos. Rep. 13, 16–21 (2015).

39. Lu, C. et al. Cellular basis for age-related changes in fracture repair. J. Orthop. Res. 23, 1300–1307 (2005).

40. Ozaki, A., Tsunoda, M., Kinoshita, S. & Saura, R. Role of fracture hemotama and periosteum during fracture healing in rats: interaction of fracture hemotama and the periosteum in the initial step of the healing process. J. Orthop. Sci. 5, 64–70 (2000).

41. Chan, J. K. et al. Low-dose TNF augments fracture healing in normal and osteoporotic bone by up-regulating the innate immune response. EBMB Mol. Med. 7, 547–561 (2015).

42. Timlin, M. et al. Fracture hemotama is a potent proinflammatory mediator of neutrophil function. J. Trauma 58, 1223–1229 (2005).

43. Gibson, E., Lu, L. & Goodman, S. B. Aging, inflammation, stem cells, and bone healing. Stem Cell Res. Ther. 7, 44 (2016).

44. Briot, K., Geusens, P., Em Bulthuijts, L., Lems, W. F. & Roux, C. Inflammatory diseases and bone fragility. Osteoporos. Int. 28, 3301–3314 (2017).

45. Weng, N. J. Aging of the immune system: how much can the adaptive immune system adapt? Immunology 24, 495–499 (2006).

46. McKenna, R. W., Washington, L. T., Aquino, D. B., Picker, L. J. & Kroft, S. H. Immunophenotypic analysis of hematogones (B-lymphocyte precursors) in 662 consecutive bone marrow specimens by 4-color flow cytometry. Blood 98, 2498–2507 (2001).

47. Frasca, D. et al. Aging down-regulates the transcription factor E2A, activation-induced cytokine deafamine, and Ig class switch in human B cells. J. Immunol. 180, 5283–5290 (2008).

48. Gohng, Y. et al. CD27+ (memory) B cell decrease and apoptosis-resistant CD27− (naive) B cell increase in aged humans: implications for age-related peripheral B cell developmental disturbances. Int. Immunol. 17, 383–390 (2005).

49. Wekslcr, M. E., Goodhardt, M. & Szabo, P. The effect of age on B cell development and humoral immunity. Springer. Immunom. 14, 35–52 (2002).

50. Swain, S., Clise-Dwyer, K. & Haynes, L. Homeostasis and the age-associated defect of CD4 T cells. Semin. Immunol. 17, 370–377 (2005).
101. Temiyasathit, S. & Jacobs, C. R. Osteocyte primary cilium and its role in bone.

102. Goggin, P. M., Zygalakis, K. C., Oreffo, R. O. & Schneider, P. High-resolution 3D imaging of osteocytes and computational modelling in mechanobiology: the influence of the mechanical environment on bone healing. Front. Physiol. 3, 678 (2016).

103. Plotkin, L. I., Bellido, T. Osteocytic signalling pathways as therapeutic targets for bone fragility. Nat. Rev. Endocrinol. 12, 593–605 (2016).

104. Liu, H. et al. Osteoporogenin/osteostaglogenesis inhibitory factor decreases human prostate cancer burden in human adult bone implanted into nudeose diabetic/severe combined immunodeficient mice. Cancer Res. 63, 2096–2102 (2003).

105. Catalano, A. et al. Pain in osteoporosis from pathophysiology to therapeutic approach. Drugs Aging 34, 755–765 (2017).

106. Manolagas, S. C. The quest for osteoporosis mechanisms and rational therapies: novel players in mechanotransduction. Trends Cell Biol. 17, 1162–1179 (2007).

107. Plotkin, L. I. & Bellido, T. Osteocytic calcium signals encode strain magnitude and loading of bone. Ann. New Y. Acad. Sci. 1192, 410–421 (2010).

108. Tu, X. et al. Osteocytes mediate the anabolic actions of canonical Wnt/beta-catenin signaling in bone. Proc. Natl Acad. Sci. USA 112, E478–E486 (2015).

109. Ngyuen, A. M. & Jacobs, C. R. Emerging role of primary cilia as mechanosensors in osteocytes. Bone 54, 196–204 (2013).

110. Yavropoulou, M. P. & Yovos, J. G. The molecular basis of bone mechanotransduction. J. Musculoskelet. Neuron. Interact. 16, 221–236 (2016).

111. Ranade, S. S., Syeda, R. & Patapoutian, A. Mechanically activated ion channels. Neuron 78, 1162–1179 (2015).

112. Plotkin, L. I. & Bellido, T. Osteocytes mediate the anabolic actions of canonical Wnt/beta-catenin signaling in bone. Proc. Natl Acad. Sci. USA 112, E478–E486 (2015).

113. Lewis, K. J. et al. Osteocyte primary cilium and its role in bone mechanotransduction. Ann. New Y. Acad. Sci. 1192, 422–428 (2010).

114. Goggin, P. M., Zygalakis, K. C., Oreffo, R. O. & Schneider, P. High-resolution 3D imaging of osteocytes and computational modelling in mechanobiology: insights on bone development, ageing, health and disease. Eur. Cells Mater. 31, 264–295 (2016).

115. Devlin, M. J., Aguirre, J. I. et al. A novel ligand-independent function of the estrogen receptor mediated by mechanical strain. J. Bone Miner. Res. 30, 141–147 (2015).

116. Fedorchak, G. R., Kaminski, A. & Lammertding, J. Cellular mechanosensing: get¬ting to the nucleus of it all. Trends Cell Biol. 17, 33–42 (2011).

117. Lewis, K. J. et al. Osteocyte calcium signals encode strain magnitude and loading in vivo. Proc. Natl Acad. Sci. USA 114, 11775–11780 (2017).

118. Xu, H. et al. Connexin 43 channels are essential for normal bone structure and osteocyte viability. J. Bone Miner. Res. 30, 436–448 (2015).

119. Plotkin, L. I., Speach, T. L. & Donahue, H. J. Cx43 and mechanotransduction at adhesion sites. J. Cell Sci. 112, 1313–1321 (1999).

120. Novack, D. V. Role of NF-kappaB in the skeleton. Ann. Biomed. Eng. 33, 1962–1970 (2005).

121. Novack, D. V. Role of NF-kappaB in the skeleton. Cell Res. 21, 169–182 (2011).

122. Yu, H. S., Kim, J. J., Kim, H. W., Lewis, M. P. & Wall, I. Impact of mechanical stretch on the cell behaviors of bone and surrounding tissues. J. Tissue Eng. 7, 2041731415618342 (2016).

123. Pires, B. R. S., Silva, R., Ferreira, G. M. & Abdelhay, E. NF-kappaB: two sides of the same coin. Genes 9, 63 (2018).

124. Wang, L. et al. Involvement of p38MAPK/NF-kappaB signaling pathways in osteoblasts differentiation in response to mechanical stretch. Ann. Biomed. Eng. 40, 1884–1894 (2012).

125. Wang, L. et al. Involvement of BMP5/Smad signaling pathway in mechanical response in osteoblasts. Cell. Physiol. Biochem.: Int. J. Exp. Cell Physiol. Biochem. Pharmacol. 26, 1093–1102 (2010).

126. Long, P., Hu, J., Piesco, N., Buckley, M. & Agarwal, S. Low magnitude of tensile strain inhibits IL-1-beta-dependent induction of pro-inflammatory cytokines and induces synthesis of IL-10 in human periodontal ligament cells in vitro. J. Dent. Res. 80, 1416–1420 (2001).

127. Sauerwirg, M. et al. Effect of COX-2 inhibition on tendon-to-bone healing and PGE2 concentration after anterior cruciate ligament reconstruction. Eur. J. Med. Res. 23, 1 (2018).

128. Thorsen, K., Kristoﬀersson, A. O., Lerner, U. H. & Lorentzon, R. P. In situ microdialysis in bone tissue. Stimulation of prostaglandin E2 release by weight-bearing mechanical loading. J. Clin. Invest. 98, 2446–2449 (1996).

129. Cheung, W. H., Miclau, T., Chow, S. K., Yang, F. F. & Alt, V. Fracture healing in osteoporotic bone. Injury 47(Suppl. 2), S21–S26 (2016).

130. Thomas, M. & Puleo, D. Infection, inflammation, and bone regeneration: a paradoxical relationship. J. Dent. Res. 90, 1052–1061 (2011).

131. Peichl, P., Holzer, L. A., Maier, R. & Holzer, G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J. Bone Jt. Surg. Am. Vol. 93, 1583–1587 (2011).

132. Grundnes, O. & Reikeras, O. The role of hematoma and periosteal sealing for fracture healing in rats. Acta Orthop. Scand. 64, 47–49 (1993).

133. Juhaszova, M. et al. Fibrinolysis is essential for fracture repair and prevention of heterotopic ossification. J. Clin. Investig. 115, 3723 (2005).

134. Antoci, V. Jr., Adams, C. S., Hickok, N. J., Shapiro, I. M. & Parvizi, J. Antibiotics for local delivery systems cause skeletal cell toxicity in vitro. Clin. Orthop. Relat. Res. 462, 200–206 (2007).
119. Schumacher, A. & Grave, B. Proximal humerus fractures: evaluation and man-
agement in the elderly patient. Geriatr. Orthop. Surg. Rehabil. 9, 21514585177550516 (2018).
120. Chan, M. E., Uzer, G. & Rubin, C. T. The potential benefits and inherent risks of
vibration as a non-drug therapy for the prevention and treatment of osteo-
porosis. Curr. Osteoporos. Rep. 11, 36–44 (2013).
121. Nagoya, M. & Jo, H. The role of mechanical stimulation in recovery of bone
loss-high versus low magnitude and frequency of force. Life 8, 117–130
(2014).
122. Griffin, X. L., Parsons, N., Costa, M. L. & Metcalfe, D. Ultrasound and shockwave
therapy for acute fractures in adults. Cochrane Database Syst. Rev. Cd008579,
https://doi.org/10.1002/14651858.CD008579.pub3 (2014).
123. Miller, P. D. The history of bone densitometry. Bone 104, 4–6 (2017).
124. Seeman, E. Pathogenesis of bone fragility in women and men. Lancet 359,
1841–1850 (2002).
125. de Bakker, C. M. J., Tseng, W. J., Li, Y., Zhao, H. & Liu, X. S. Clinical evaluation of
bone strength and fracture risk. Curr. Osteoporos. Rep. 15, 32–42 (2017).
126. Silva, B. C. et al. Trabecular bone score (TBS)—a novel method to evaluate bone
microarchitectural texture in patients with primary hyperparathyroidism. J. Clin.
Endocrinol. Metab. 98, 1963–1970 (2013).
127. Harvey, N. C. et al. Trabecular bone score (TBS) as a complementary approach
for osteoporosis evaluation in clinical practice. Bone 78, 216–224
(2015).
128. Shevroja, E. et al. Use of trabecular bone score (TBS) as a complementary
approach to dual-energy X-ray absorptiometry (DXA) for fracture risk assess-
ment in clinical practice. J. Clin. Densitom. 20, 334–345 (2017).
129. Iki, M. et al. Trabecular bone score may improve FRAX(R) prediction accuracy for
major osteoporotic fractures in elderly Japanese men: the Fujisawa-kyo Osteo-
porosis Risk in Men (FORMEN) Cohort Study. Osteoporos. Int. 26, 1841–1848
(2015).
130. Brandi, M. L. Microarchitecture, the key to bone quality. Rheumatology 48(Suppl.
4), iv3–iv8 (2009).
131. Eckert, J. A., Jaeger, S., Klotz, M. C., Schwarze, M. & Bitsch, R. G. Can intro-
peroperative measurement of bone quality help in decision making for cementless
unipartamental knee arthroplasty? Knee 25, 609–618 (2016).
132. Seebeck, J. et al. Effect of cortical thickness and cancellous bone density on
the holding strength of internal fixator screws. J. Orthop. Surg. 22, 1237–1242
(2014).
133. Shea, T. M. et al. Designs and techniques that improve the pullout strength of
pedicle screws in osteoporotic vertebrae: current status. BioMed Res. Int. 2014,
748393 (2014).
134. Wang, T., Boone, C., Behn, A. W., Ledesma, J. B. & Bishop, J. A. Cancellous screws
are biomechanically superior to cortical screws in metaphyseal bone. Orthope-
dics 39, e828–e832 (2016).
135. Cornell, C. N. Internal fracture fixation in patients with osteoporosis. J. Am. Acad.
Orthop. Surg. 11, 109–119 (2003).
136. Ab-Lazid, R., Perilli, E., Ryan, M. K., Costi, J. J. & Reynolds, K. J. Does cancellous
screw insertion torque depend on bone mineral density and/or micro-
architecture? J. Biomech. 47, 347–353 (2014).
137. Karim, L. & Vashishth, D. Role of trabecular microarchitecture in the formation,
accumulation, and morphology of microdamage in human cancellous bone. J.
Orthop. Surg. 29, 1739–1744 (2011).
138. Greive, R. M. & Archdeacon, M. T. Locking plate technology: current concepts. J.
Knee Surg. 20, 50–55 (2007).
139. Miranda, M. A. Locking plate technology and its role in osteoporotic fractures.
Injury 38(Suppl. 3), 533–539 (2007).
140. Nargessi, F. et al. Influence of local bone density on the outcome of one
hundred and fifty proximal humeral fractures treated with a locking plate. J.
Bone Jt. Surg. Am. Vol. 96, 1026–1032 (2014).
141. Johansson, N. A., Litrenta, J., Zampini, J. M., Kleinbart, F. & Goldman, H. M. Surgical
treatment options in patients with impaired bone quality. Clin. Orthop. Relat.
Res. 465, 2237–2247 (2011).
142. Ro, K., Hungebuhrer, R., Wohl, D. & Grass, R. Improved intramedullary nail
interlocking in osteoporotic bone. J. Orthop. Trauma 15, 192–196 (2001).
143. McKee, M. D. et al. A multicenter, prospective, randomized, controlled trial of
open reduction-internal fixation versus total elbow arthroplasty for displaced
infra-articular distal humeral fractures in elderly patients. J. Shoulder Elb. Surg.
18, 3–12 (2009).
144. Borai, S., Ragdale, M., Achor, T., Zelcic, S. & Aspinro, D. E. Open reduction
internal fixation and primary total hip arthroplasty of selected acetabular frac-
tures. J. Orthop. Trauma 23, 243–248 (2009).
145. Golinhahn, J., Suhn, N., Golinhahn, S., Blauth, M. & Hanson, B. Influence of
osteoporosis on fracture fixation—a systematic literature review. Osteoporos.
Int. 19, 761–772 (2008).
195. Seebeck, J., Goldhahn, J., Morlock, M. M. & Schneider, E. Mechanical behavior of screws in normal and osteoporotic bone. Osteoporos. Int. 16(Suppl. 2), S107–S111 (2005).
196. McAndrew, C. M. et al. Local bone quality measurements correlates with maximum screw torque at the femoral diaphysis. Clin. Biomech. 52, 95–99 (2018).
197. Parkinson, I. H. & Fazzalari, N. L. Whole bone geometry and bone quality in distal forearm fracture. J. Orthop. Trauma 22, 559–565 (2008).
198. Cornell, C. N. & Ayalon, O. Evidence for success with locking plates for fragility fractures. HSS J. 7, 164–169 (2011).
199. Ricci, W. M., Tometta, P. & Borrelli, J. Jr. Lag screw fixation of medial malleolar fractures: a biomechanical, radiographic, and clinical comparison of unicortical partially threaded lag screws and bicortical fully threaded lag screws. J. Orthop. trauma 26, 602–606 (2012).
200. Egol, K. A., Kubiak, E. N., Fulkerson, E., Kummer, F. J. & Koval, K. Biomechanics of locked plates and screws. J. Orthop. trauma 18, 488–493 (2004).
201. Babhulkar, S. Unstable trochanteric fractures: Issues and avoiding pitfalls. Injury 48, 803–818 (2017).
202. Oheim, R., Schinke, T., Amling, M. & Pogoda, P. Can we induce osteoporosis in animals comparable to the human situation? Injury 47(Suppl. 1), S3-S9 (2016).
203. Sproul, R. C., Iyengar, J. J., Devic, Z. & Feeley, B. T. A systematic review of locking plate fixation of proximal humerus fractures. Injury 42, 408–413 (2011).

204. Mellibovsky, L. et al. Bone tissue properties measurement by reference point indentation in glucocorticoid-induced osteoporosis. J. Bone Miner. Res. 30, 1651–1656 (2015).
205. Sanchez-Riera, L. et al. Osteoporosis and fragility fractures. Best Pract. Res. Clin. Rheumatol. 24, 793–810 (2010).