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

Yong Xie¹, Licheng Zhang¹, Qi Xiong², Yanpan Gao³, Wei Ge³ and Peifu Tang¹

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.

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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.⁴ 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.⁶ The abnormal remodeling status of bone with osteoporosis would deteriorate after bed bracing, which poses a disadvantage with respect to fracture healing and bone callus strength; furthermore, the refracture 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 patients⁴. 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

¹Department of Orthopedics, Chinese PLA General Hospital, Beijing, China; ²Department of Oncology, Chinese PLA General Hospital, Beijing, China and ³State Key Laboratory of Medical Molecular Biology and Department of Immunology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, China

Correspondence: Wei Ge (wei.ge@chem.ox.ac.uk) or Peifu Tang (pftang301@163.com)

These authors contributed equally: Yong Xie, Licheng Zhang, Qi Xiong

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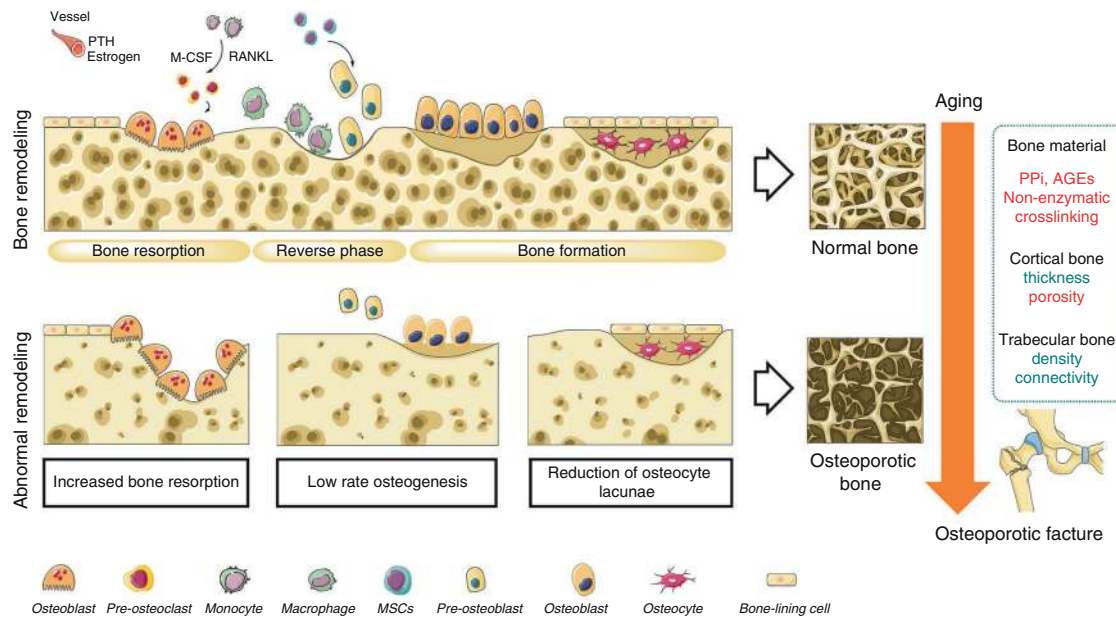


Fig. 1 Static and dynamic changes in osteoporotic bone. An osteoporotic fracture is the macroscopic result of microstructural alterations that change the response of bone to the applied load. The aging process in osteoporotic bone would lead to overaccumulation of PPi, AGEs, and nonenzymatic crosslinking 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, PPi inorganic pyrophosphate, AGEs advanced glycation end-products, MSCs mesenchymal stem cells. “Red” refers to upregulation; “Green” refers to downregulation

mineralization.¹³ 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%).¹⁴ The mechanical competence of cancellous bone is based largely on the BMD, while the stiffness of cortical bone is highly dependent on its porosity.^{3,15} 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.¹⁶ A large proportion (90%) of the organic matrix is composed of type I collagen, which undergoes numerous posttranslational modifications.¹⁷ Among them, enzymatic modifications positively affect the biomechanical stability of bone, while nonenzymatic crosslinking is associated with a deterioration in these properties.¹⁶ 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.¹⁸ 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.¹⁹ The cortical and trabecular bone both undergo lifelong remodeling coupled with bone resorption, which is mediated by osteoclasts following osteoblastic bone formation.²⁰ Osteoclasts are of hematopoietic stem cell (HSC) origin and share precursors with macrophages.²¹ 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.²¹ In contrast, osteoblasts are derived from mesenchymal stem cells (MSCs),²² and osteoblastic bone formation is separated from resorption by a reversal phase for several weeks.²³ Mature

osteoblasts then differentiate into osteocytes, which reside in small lacunae inside the calcified bone matrix.²⁴ The long dendritic extensions of osteocytes together with the cell bodies form the lacuno-canalicular 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.^{25,26} However, the normal regulation of bone remodeling could be interrupted as a consequence of skeletal senescence,^{27,28} which impact the integrity and biomechanical properties of both cortical and cancellous bones.²⁹ 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.³⁰ In addition, age-related loss of proteostasis and increased levels of oxidants result in the overaccumulation of inorganic pyrophosphate (PPi) or advanced glycation end-products (AGEs). During the development of osteoporosis, osteocyte numbers per unit of bone area are gradually reduced,³¹ resulting in decreased trabecular thickness and more intracortical porosity.³² These considerable changes in the matrix composition and structure cause deterioration of bone quality and compromise its resistance to mechanical loading.³³ Thus, osteoporotic fractures are the macroscopic result of microstructural alterations that increase the susceptibility of bone to the applied load³⁴ (Fig. 1).

OSTEOIMMUNOLOGY IN HEMATOMA AND INFLAMMATORY PHASES

Secondary fracture healing occurs after a fracture without rigid fixation. Under the influence of active loading, an external callus is initiated to bridge the fracture gap³⁵ in a three-stage process consisting of inflammation, repair, and remodeling.³⁶ The first two of these partially overlapping phases restore bone structure and

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 µm. 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 antigen⁵⁹ 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),⁶⁴ 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,⁴¹ 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 supports 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 acidosis.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,¹³ 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

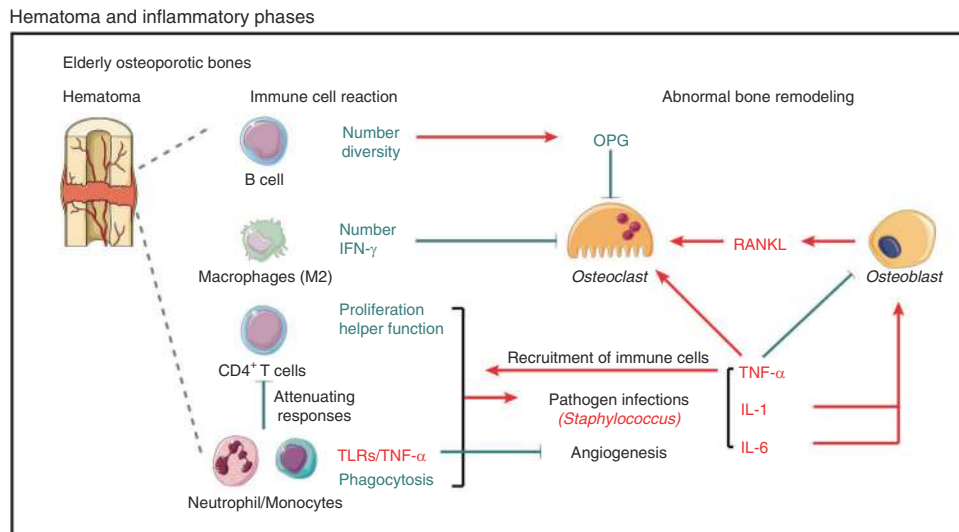


Fig. 2 Osteoimmunology in elderly osteoporotic bones. Hematoma and inflammatory phases are the immediate reactions to a fracture. The limited inflammatory response at the fracture site is essential to initiate repair processes and mobilize all the required factors involved in the early bridging of the fracture gap, especially in indirect bony unions without rigid fixation. 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 intra- or postoperative further fractures. OPG osteoprotegerin, IFN- γ interferon gamma, RANKL receptor activator of nuclear factor kappa-B ligand, TLRs toll-like receptors, TNF- α tumor necrosis factor alpha, IL-1 interleukin-1, IL-6 interleukin-6. “Red” refers to upregulation; “Green” refers to downregulation

of bone cells are ubiquitous sensors of mechanical forces capable of detecting alterations in the mechanical environment in the extracellular milieu.⁸⁹ 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.⁹⁰ Wnt signaling is also activated by cilia via the noncanonical pathway, resulting in β -catenin degradation.^{91,92} The role of canonical Wnt in the suppression of the SOST gene (sclerostin) has also been demonstrated.⁹³ 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.^{94,95} PGE2 and ATP are released via connexin hemichannels formed following extracellular signal-regulated kinase1/2 (ERK1/2)-induced transcription of connexin-43 (Cx43).^{96,97} Compressive/tensile forces impose hydraulic pressure in the lacunar-canalicular system,⁸⁹ which increases cellular deformation of osteocytes.⁹⁸ 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 fiber polymerization.⁹⁸ 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.⁹⁹ 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.¹⁰⁰

The morphological changes of osteocytes with aging have been reported to influence their mechanosensitivity and the response to loads.¹⁰¹ Changes in LCN volume due to the increased rate of osteocytic osteolysis with aging or trauma have been shown to affect local bone mechanosensation.¹⁰² 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.^{103,104} Furthermore, periosteal lining cell numbers and osteoblast life-span are reduced by an increased rate of apoptosis.¹⁰⁵ There is an age-related switch in macrophage differentiation from the anti-inflammatory (M2) phenotype.⁵³ 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.⁷ In osteoporotic fractures, the inevitable immobilization and stress shielding achieved by orthopedic surgery reduce the mechanical loading compared with that at normal sites.¹⁰⁶ The deficiency of stress loading on surface sensors of bone cells is accompanied by NF- κ B activation of osteoblasts and neighboring immune cells that promotes RANKL production to trigger osteoclastogenesis and bone resorption.^{107,108} This process results in the excess removal of bone mass,⁹³ 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.¹⁰⁹ Delayed ER expression was shown to be correlated with impaired callus formation capacity in the healing process.¹¹⁰ A study in humans suggested that mechanical interventions enhance periosteal modeling and bone strength in the young skeleton,¹¹¹ while the effects are markedly diminished in the elderly skeleton.^{111,112} 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 regeneration¹¹¹ (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.⁹³

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

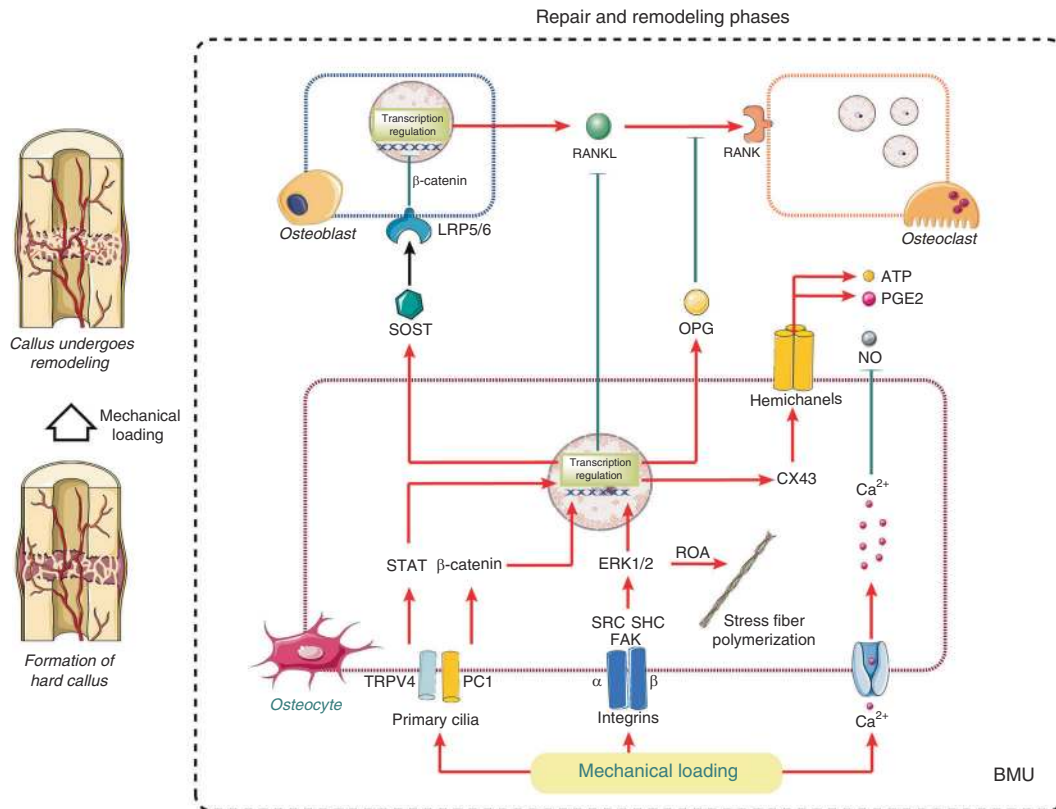


Fig. 3 Molecular basis of bone mechanosensation. The bone multicellular unit (BMU), which consists of osteocytes, osteoblasts, and osteoclasts, functions as a large mechanosensitive organ. Mechanical loading can be sensed by primary cilia, integrins, and Ca^{2+} channels on the surface of bone cells, 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

environment without excessive inflammation.³⁷ In these long-term phases, mechanics play a pivotal role, not only as the forces driving remodeling but also as the regulators that function to inhibit inflammation and abrogate the associated repression of growth factors and matrix synthesis.¹¹³ The traumatic signals caused by fracture and surgery initiate pro-inflammatory signaling cascades via activation of NF- κ B transcription factors.^{114,115} NF- κ B activation leads to the production of high levels of NO and superoxide that mediate both bone damage and matrix degradation.¹¹⁶ Mediators such as TNF- α , IL-1 β , and matrix metalloproteinases (MMPs) play key roles in the pathogenesis of inflammatory bone diseases and injuries.¹¹⁷ In IL-1 β -treated osteoblast-like cells, mechanical signals have been shown to rapidly (within 10 min) and dramatically inhibit NF- κ B nuclear translocation.¹¹⁸ The mechanism involves the inhibition of TNF receptor-associated factor 6 (TRAF6) phosphorylation and subsequent activation of the inhibitor of NF- κ B kinase (IKK) complex.¹¹⁹ This process prevents the proteasomal degradation of NF- κ B inhibitor alpha (I κ B α) and NF- κ B inhibitor beta (I κ B β) phosphorylation, which in turn inhibits nuclear translocation of NF- κ B and subsequent pro-inflammatory gene transcription.¹²⁰ In fact, mechanotransduction at low magnitudes is a potent anti-inflammatory signal¹²¹ that counters the NF- κ B signaling cascade.¹²² In vitro studies in osteoblasts have shown that the pro-inflammatory mediators suppressed by mechanical signals (tensile, compressive, and shear) include IL-1 β -induced NO, COX-2, PGE2, cytokines (IL-1 β and TNF- α), and

MMPs.¹²³ Simultaneously, mechanical signals upregulate the expression of growth factors, such as BMPs, OCN, and alkaline phosphatase (ALP), which are inhibited during inflammation.¹²⁴ 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.¹²⁵ 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.¹²⁶ Furthermore, in the presence of PGE2 signaling, osteocytes release NO in response to mechanical stimulation via cytoskeletal adaptation and mitogen-activated protein kinase (MAPK) pathways.¹²⁷ Additionally, mechanical loading increases ER- α expression at the fracture callus, which is beneficial for mechanical signal transduction and fracture repair.^{128,129} These data indicate that rigid fixation and adequate mechanical loading are a means of improving the immune environment that benefits bone healing¹³⁰ (Fig. 4).

MANAGEMENT OF HEMATOMA AND PERIOPERATIVE INFECTION

The most satisfactory bone healing depends on a good biological environment and appropriate mechanical loading for bone repair

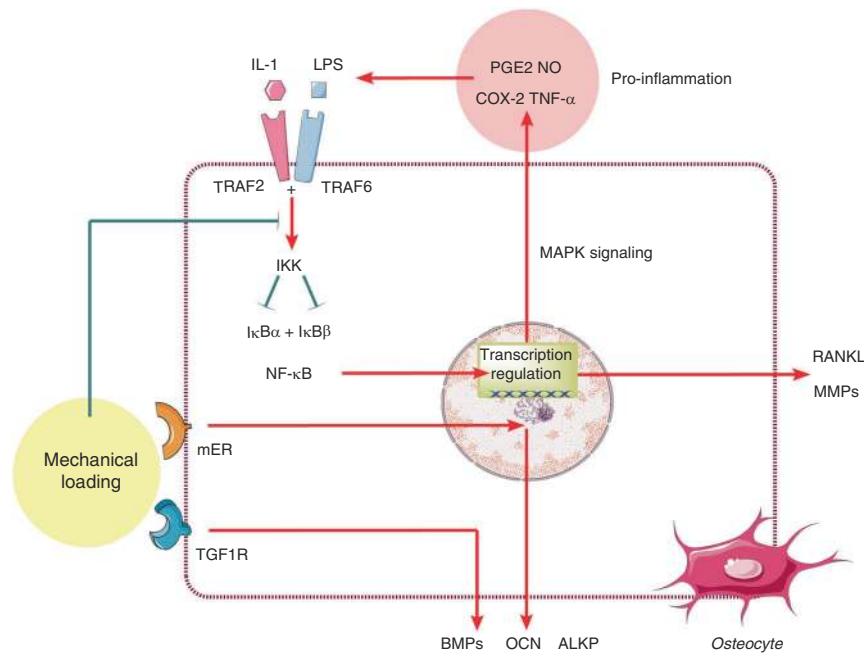


Fig. 4 Anti-inflammatory effects of mechanical loading. The mechanotransduction at low magnitudes is a potent signal to counter inflammation activated by the NF- κ B signaling cascade. IL-1 interleukin-1, LPS lipopolysaccharide, TRAF2 TNF receptor-associated factor 2, TRAF6 TNF receptor-associated factor 6, PGE2 prostaglandin E2, NO nitric oxide, COX-2 cyclooxygenase-2, TNF- α tumor necrosis factor alpha, IKK inhibitor of NF- κ B kinase, I κ B α NF- κ B inhibitor alpha, I κ B β NF- κ B inhibitor beta, BMPs bone morphogenetic proteins; OCN osteocalcin; ALKP alkaline phosphatase; RANKL receptor activator of nuclear factor kappa-B ligand, MAPK mitogen-activated protein kinase, MMPs matrix metalloproteinases. “Red” refers to upregulation; “Green” refers to downregulation

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 intervention³. 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 in fracture healing, especially in the inflammatory phase.^{42,131} However, there is still no consensus on hematoma management among surgeons. Grundnes and Reikeras reported that early removal of the hematoma (2–7 days) after fracture greatly prohibited bone healing in an animal fracture model.¹³² Other researchers, however, found that hematoma without normal fibrinolysis was an obstacle to cellular trafficking, which subsequently inhibited fracture healing by impeding macrophage accumulation.¹³³ Thus, in clinical practice, early hematoma in the fracture site should be preserved and induced to “mature”. Indeed, the use of fibrin biomaterials, including platelet-rich plasma (PRPs), platelet-rich fibrin (PRFs) and other treatments,¹³⁴ mimicking the structure of the natural hematoma, has demonstrated promising effects on the improvement of fracture healing. In addition, early-stage treatment with recombinant human platelet-derived growth factor-BB (rhPDGF-BB) could be beneficial for vascularization and angiogenesis in local sites,¹³⁵ which would promote the recruitment of progenitors and accelerate bone remodeling in fracture healing of the elderly.¹³⁶ In short, hematoma is a natural factor that enhances fracture healing and should be preserved in fracture sites, although thorough mechanisms are needed to be well investigated. Due to the decline of immune responses and pathogen clearance dysfunction in elderly patients with osteoporotic fractures, the prevention of perioperative infection through the use of adequate doses of antibiotics is important for maintaining a normal environment for initiating fracture

healing (Fig. 5). Consequently, in orthopedic surgery, antibiotics, such as antibiotic-augmented acrylic cements/beads are increasingly used in topical form.¹³⁷ However, the enhanced antibiotic treatment doses are thousands of times higher than those required to inhibit bacterial growth.¹³⁷ Current evidence suggests that this concentration is detrimental to abnormal bone remodeling as a result of negative effects on mitochondrial physiology.¹³⁷ Thus, local antibiotic vehicles must be designed to deliver sufficiently high concentrations to inhibit bacterial growth without affecting bone cell metabolism.¹³⁸

ANTI-INFLAMMATION AND 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 providing protection against bone loss. Studies have shown that healthy transgenic mice injected with anti-TNF- α repeatedly promote T cell responses to cognate peptide antigen.¹³⁹ In the clinical setting, anti-TNF- α (infliximab, Remicade) rapidly and remarkably restores the responses of T cells from rheumatoid arthritis (RA) patients.⁵⁶ Treatment with infliximab protects against bone loss and improves the formation/resorption marker ratio in this population, suggesting beneficial systemic and local bone effects.^{140,141} 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 TNF¹⁴² and IL-1¹⁴³ by somatic gene therapy¹⁴⁴ 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

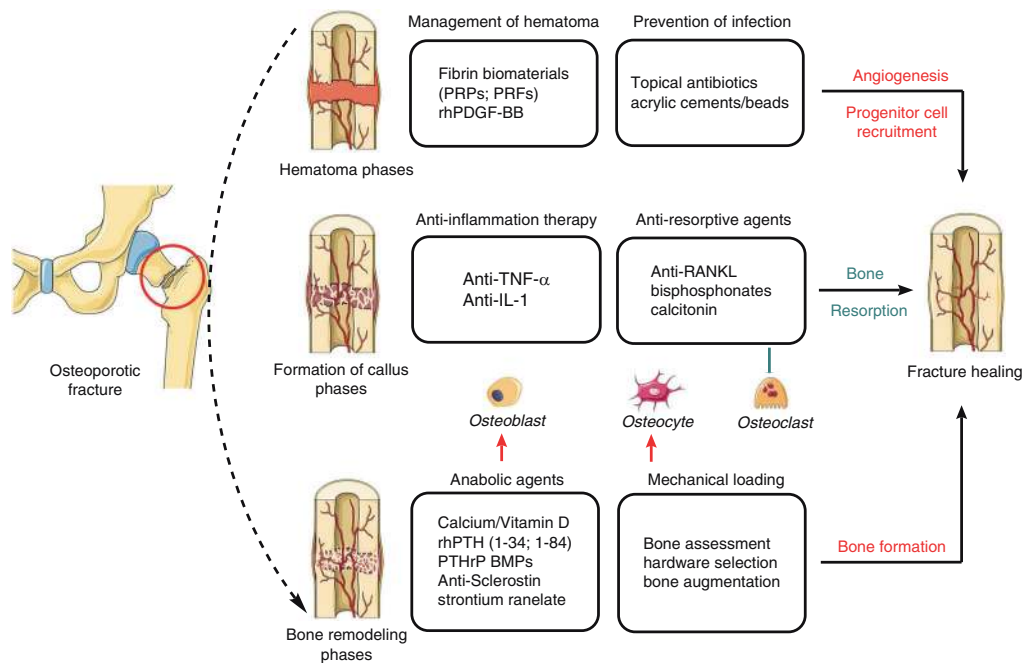


Fig. 5 Bench-to-bedside strategies for osteoporotic fracture. The most satisfactory bone healing depends on two pivotal factors: a good biological environment and appropriate mechanical loading for bone repair and homeostasis. Bench-to-bedside strategies, including management of hematomas and perioperative 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, PRFs 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

inflammation in addition to protection against bone loss. However, the risk of infection is increased in patients undergoing anti-inflammation treatment, suggesting that anti-inflammatory drugs should be discontinued for a period of time before surgery.¹⁴⁵ 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 aging-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.

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 $-2.5SD$ 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 ranelate 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 TGF β 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.^{162,163} These cements undergo interdigitation in porous bone³⁸ 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.¹⁶⁴ However, PMMA undergoes an exothermic reaction during the drying process, with the potential to initiate thermal bone necrosis.¹⁶⁵ In addition, PMMA is difficult to remove in cases of revision or infection without integrating into the bony architecture.¹⁶⁶ In contrast, the integration of tricalcium phosphate into the bone provides a potential scaffold for biological activity and cell growth in a demineralized bone matrix.¹⁶⁷ Allograft fibulas are used in bone with low BMD as tools for reduction as well as the provision of medial calcar support.¹⁶⁸ 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.^{169,170} However, current evidence is insufficient to support the benefit of

ultrasound and extracorporeal shockwave therapies (ECSW) for fracture healing in clinical practice¹⁷¹ (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.¹⁷² Both trabecular connectivity and cortical porosity significantly influence bone strength parameters, including stiffness to resist deformation and elasticity to absorb energy.¹⁷³ 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.¹⁷⁴ 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 Thickness and porosity of cortical bone	DXA 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 SMI BV/TV	DXA HR-pQCT μMRI	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 SMI BV/TV	DXA HR-pQCT	Medial malleolus fractures		185,198,199
Traditional plates	Compress the fracture fragments between bone implant interface to create fixation strength	BMD Bone stiffness and strength	DXA	Regular fractures	Decrease of the axial and torsional stiffness	190,200,201
Locking plate	Fixed-angle construct between screw and plate	BMD, TBS Proximal cortical thickness Failure load	DXA 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 Cortical thickness	DXA 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 SMI BV/TV BMSi	DXA 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	Comminution of tibial plateau fractures		190
Primary arthroplasty	Early mobilization and weight bearing	BMD, TBS Subchondral bone quality	DXA HR-pQCT DensiProbe	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.¹⁷⁵ The trabecular bone score (TBS) correlates positively with trabecular connectivity based on evaluation of the DXA image.¹⁷⁶ Combining TBS and BMD measurements provides an improved prediction of bone strength compared with BMD alone.^{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.¹⁷⁹ The DensiProbe can be a helpful tool for intraoperative assessment of mechanical peak torque in mechanical testing setups,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.¹⁸⁰ Cortical and cancellous screws are traditional designs, with the former having relatively narrower outer diameters and decreased thread pitch.¹⁸¹ In both cases, the fixation strength depends on the torque generated between the bone and thread that resists shear.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.¹⁸³ The changes in screw geometry that confer an advantage on cancellous screws are lost below a threshold BMD of 0.4 g-cm^{-3} .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).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.¹⁸⁶ Unstable and comminuted fracture patterns as well as early implant-bone fatigue in osteoporotic bones lead to implant loosening and fixation failure.³ Locking-plate technology provides a more advantageous biomechanical environment that facilitates the formation of a fixed angle between the plate and screw.¹⁸⁷ Despite the greater overall stability, locking plates may create an excessively rigid construct, which is predisposed to peri-implant fracture.¹⁸⁸ In proximal humeral fractures with low BMD, 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.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.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.¹⁹² Primary arthroplasty (total hip/knee/elbow 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.¹⁹³ 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).

CONCLUSION AND PERSPECTIVE

Low bone mass and compromised bone structure in osteoporotic fractures are undesirable for the reduction and rigid fixation, and the decreased regeneration and mechanosensation ability of osteoporotic bone also affect the healing. The initiation of supportive management, including anti-inflammatory drugs and sufficient application of antibiotics, is key for creating the proper environment for bone repair and homeostasis in patients with osteoporotic fractures. The adverse effects of insufficient mechanical loading in bone healing are critical factors that should be considered around the orthopedic procedure. Bench-to-bedside strategies for bone augmentation and hardware selection should be made according to further elucidation of the biomechanics and molecular mechanisms involved in bone repair. Multidisciplinary collaboration will facilitate the improvement of overall osteoporotic care and the reduction of secondary fracture incidence.

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ADDITIONAL INFORMATION

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