



Fracture Healing

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2.1 Introduction

Musculoskeletal injury is one of the leading causes of disability and dysfunction worldwide. In the USA alone, the burden of fracture care in an aging population is projected to exceed \$25 billion in costs [1–3]. Achieving fracture union is paramount to patient recovery, return to activity, and quality of life following injury. While the majority of fractures will heal uneventfully, a small but significant number will demonstrate impaired healing [4]. When fractures fail to heal, they place a substantial burden on the patient and on the healthcare system [5–7]. Brinker and O'Connor [5] showed that fracture nonunion is more burdensome than many chronic medical conditions, including chronic obstructive pulmonary disease and congestive heart failure.

Fracture healing is a complex, highly orchestrated regenerative process to restore skeletal integrity. The response following injury involves tightly coordinated temporal and spatial interactions among cytokines, growth factors, progenitor cells, and adjacent tissues. The intricacy of fracture healing incorporates multiple pathways and interdependent processes; disruption

in key steps can delay or terminate healing altogether.

The causative factors underlying nonunion are often multifactorial. Injury patterns, patient factors, and even interventions all have substantial implications toward successful repair. A thorough understanding of the normal healing process, and where it goes awry, is essential to the diagnostic and therapeutic approach in treating nonunions.

The purpose of this chapter is to provide the conceptual framework for understanding fracture healing and its modulating factors in the context of nonunion management. The first part discusses the physiology of fracture healing—its biology, mechanics, and assessment. The second part focuses on modulators of healing—patient-related factors, comorbidities, injury patterns, surgical intervention, and biologic augmentation—that may promote or impair fracture union.

2.2 Physiology of Fracture Healing

Despite its complexity, fracture healing is driven by fundamental principles. Fractures all require a viable pool of progenitor cells, an osteoconductive scaffold (extracellular matrix), signaling molecules and their receptors, a vascular supply, and a suitable mechanical milieu to heal. Failure in one or more of these domains impairs successful healing [8–12]. The ability to achieve fracture healing hinges on the interdependency between the mechanics and the biology at the

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fracture site. The mechanical environment dictates the biologic response to skeletal injury, and there must be sufficient stability to promote bony healing. As healing progresses, extracellular matrix is laid across the fracture site, which lends further mechanical support to the fracture.

2.2.1 Biology of Fracture Healing

The healing response depends on the temporal and spatial interactions among four main tissue types: cortical bone, bone marrow, periosteum, and surrounding soft tissue. Ossification, the process of bone tissue formation both in normal development and in skeletal injury, is a key process in fracture healing. Endochondral ossification utilizes a cartilage scaffold to form bone, whereas intramembranous ossification forms bone without a cartilage scaffold.

There are two main pathways of fracture healing: *direct healing* and *indirect healing*. Direct, or primary, healing allows for direct remodeling of lamellar bone. It involves only intramembranous ossification in the formation of bone. Indirect, or secondary, healing relies on forming a cartilage callus scaffold, through which bone forms and remodels into its mature lamellar structure. Whether a fracture heals by direct or indirect means is determined early by its biologic and physical environment [13, 14]. Initial stability influences the inflammatory response following injury and can thus influence the mode of repair. Rigid stability follows a direct healing pathway, whereas relative stability leads to indirect healing. Additionally, as with most biologic phenomenon, fracture healing represents a spectrum with varying degrees of direct and indirect healing happening simultaneously, depending on the anatomical location and the mechanical environment.

2.2.1.1 Direct Fracture Healing

Direct or primary healing regenerates lamellar bone across the fracture without a cartilage scaffold. To do so, several conditions must exist. First, the cortical bone must be anatomically reduced and apposed. Second, the fragments

must be rigidly fixed, allowing minimal interfragmentary strain ($<5\%$) [15–19]. Gaps must be small, less than 1 mm [17]. Because these conditions usually do not occur naturally, direct healing is primarily achieved by operative fixation [9]. These fixation methods include compression plating, lag screw fixation (Fig. 2.1), and multiplanar external fixation. Failure to meet the above conditions can impair the healing process. Achieving rigid stability in the setting of comminution or a large fracture gap prohibits callus formation across the fracture site. Failing to respect the biology around the fracture site through extensive dissection and excessive soft tissue stripping likewise discourages healing (Fig. 2.2).

Contact healing occurs in the absence of gapping, where cortices are directly apposed. “Cutting cones” lay down new osteons longitudinally across the fracture site. Osteoclasts form the tip of the cone, resorb injured bone, and create new Haversian canals (Fig. 2.3) [8]. New blood vessels, branching from endosteal and periosteal circulation, penetrate the canals and deliver osteoblastic precursors. Osteoblasts form the end of the cutting cone unit, laying down new bone that will eventually mature into its lamellar structure (Fig. 2.4) [8, 9, 13]. There is limited contribution from the surrounding periosteum and soft tissues.

Gap healing occurs with small gaps less than 0.8–1 mm under similar rigid conditions. Unlike in contact healing, hematoma initially fills the gap. It is quickly replaced with woven bone in the first 1–2 weeks. Woven bone is then replaced by lamellar repair bone, though this interposed bone is oriented perpendicular to the long bone axis. While stronger than cartilage, this bone bridge is biomechanically weaker at its interface with the normal bone due to its orthogonal orientation. At 6–8 weeks, the repair bone undergoes secondary remodeling. Cutting cones from the neighboring cortices traverse and replace the repaired bone to reconstitute the canalicular system, recreate the longitudinal lamellar structure, and ultimately restore skeletal integrity. No cartilaginous callus is formed [9, 20].



Fig. 2.1 Primary healing with absolute stability. The patient is a 26-year-old woman who was struck by a motor vehicle and sustained a Grade III open right distal tibia fracture. **a** Injury radiographs. **b, c** Initial irrigation and debridement of the fracture site, spanning external fixation, and lag screw fixation. **d, e** Definitive fixation

with lag screw fixation, neutralization plate. **f, g** 3-month follow-up, showing progressive healing of tibia without callus formation and healing of fibula with callus. **h, i** 1-year follow-up showing complete healing of tibia and fibula

2.2.1.2 Indirect Fracture Healing

Indirect fracture healing regenerates bone through a cartilage callus scaffold (Fig. 2.5) [13]. It still requires a relatively stable environment, but it does not require rigid stability or

anatomical reduction. Rather, micromotion, to an extent, stimulates the healing response. Indirect healing is the predominant mechanism in most fractures treated by nonoperative means. It is also achieved by interventions that allow for relative

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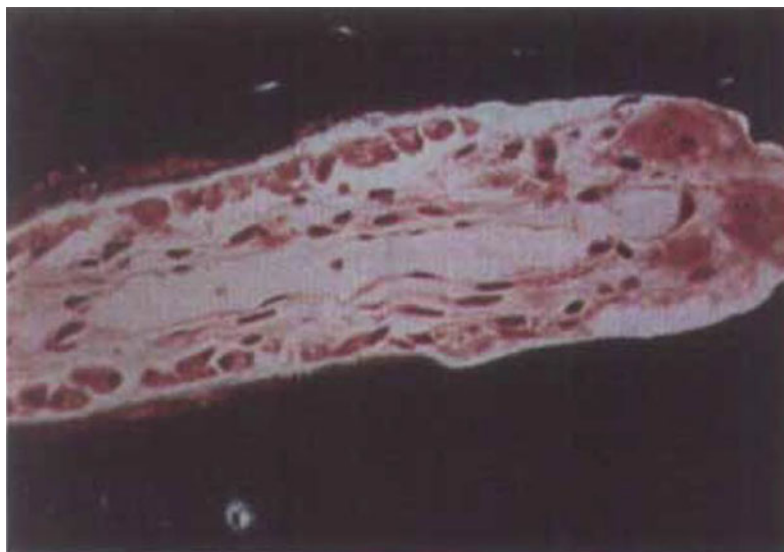


Fig. 2.2 Impaired healing with absolute stability. The patient is a 41-year-old man who sustained an open right distal tibia fracture that was initially treated with open reduction internal fixation at an outside facility. **a, b** 6-month postoperative radiographs demonstrate

persistent fracture lines with little evidence of healing as well as hardware failure, consistent with nonunion. **c, d** Nonunion repair with removal of hardware and intramedullary nailing. **e, f** 6-month postoperative radiographs with healing of fracture



Fig. 2.3 Cutting cones. Low power photomicrograph of a “cutting cone” in direct bone healing and remodeling. Multinucleated osteoclasts (*right*) form the leading edge of the cone, followed by osteoblasts (*left*) forming new bone. From Einhorn [8], with permission



stability. These include intramedullary nailing of long bone fractures (Fig. 2.6), external fixation (Fig. 2.7), bridge plating (Fig. 2.8), and splinting, bracing, or casting.

Three fundamental phases of indirect healing have been described [21]: inflammatory, reparative, and remodeling. Trauma initiates the acute inflammatory phase, and, through the release of mediators, cytokines, and growth factors, recruits progenitor cells responsible for initiating repair. In the reparative phase, progenitor cells lay down cartilaginous and bony callus, facilitate neoangiogenesis, and replace callus with woven bone. The remodeling phase replaces the woven bone with a mature lamellar bone structure.

Inflammatory Phase

Injury disrupts skeletal architecture, blood vessels, periosteum, and adjacent soft tissue. The response to injury initiates the inflammatory phase, characterized by the release of cytokines and chemoattractants that together initiate healing and recruit progenitor cells.

Following injury, hematoma occupies the fracture site. Fracture hematoma serves two key functions. It provides a physical scaffold for subsequent occupation by progenitor cells,

granulation tissue, and ultimately callus. Furthermore, the hematoma itself contains progenitor cells, cytokines, and growth factors that directly participate in the healing process [22, 23]. Recent studies have identified higher levels of factors and signaling molecules in fracture hematoma. These include macrophage colony-stimulating factor (M-CSF), transforming growth factor-beta (TGF- β), and interleukins (IL), all of which have important roles in stimulating fracture healing (Table 2.1) [24–27].

The initial inflammatory response occurs immediately after injury and lasts several days. The response is marked by infiltration of macrophages, platelets, polymorphonuclear leukocytes, and lymphocytes into the fracture site. These secrete proinflammatory cytokines including interleukins (IL-1, IL-6), platelet-derived growth factor (PDGF), and tumor necrosis factor-alpha (TNF- α). These factors recruit other inflammatory cells, promote angiogenesis, recruit progenitor stem cells, and induce their differentiation.

Reparative Phase

The reparative phase is characterized by the deposition of extracellular matrix across the fracture site. It involves a tightly regulated

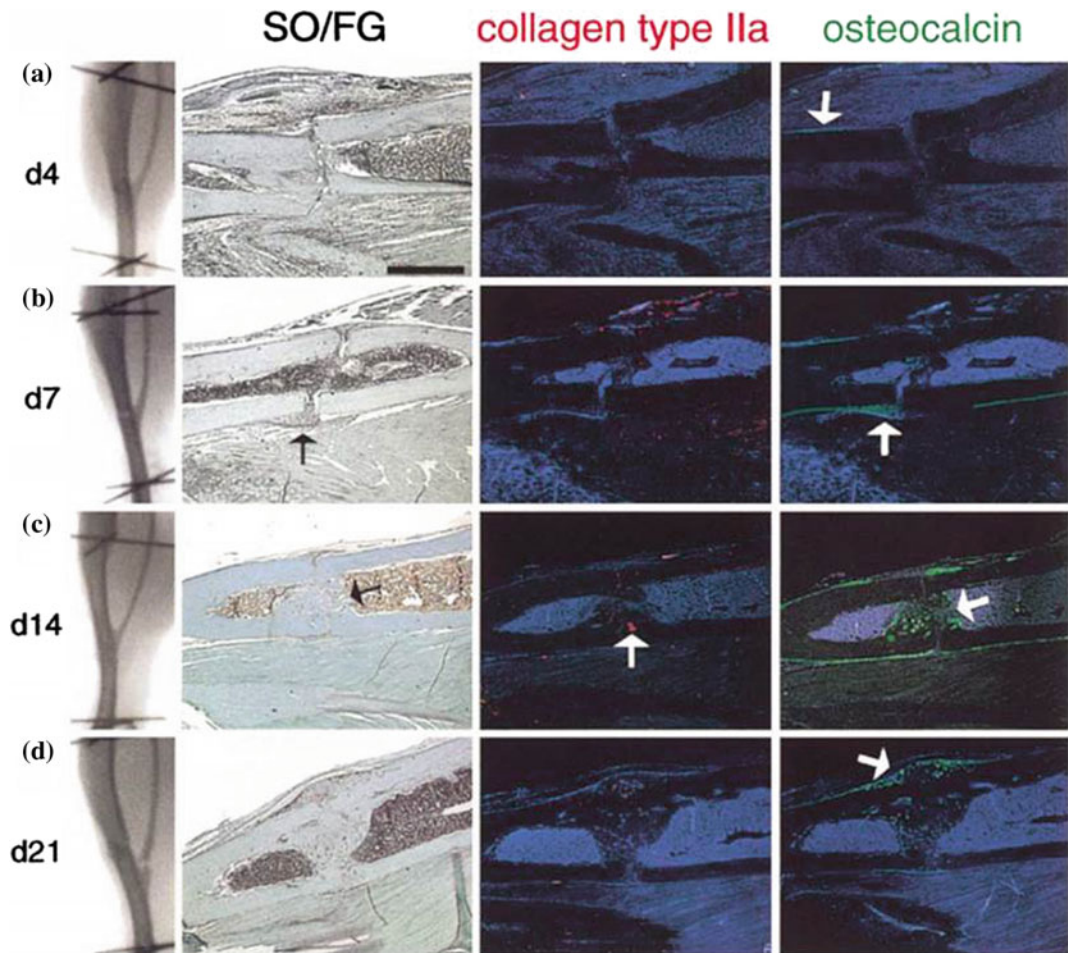


Fig. 2.4 Healing of stabilized fracture. Progressive healing of a stabilized tibia fracture in a mouse model demonstrates no callus formation on serial radiographs (day 4 through day 21) or on histological staining. In the

presence of new bone formation (green), there is minimal staining for collagen type IIa expression (red), a marker of chondrogenesis. (SO/FG Safranin O/Fast Green stain). From Thompson et al. [13], with permission

sequence of events that ultimately stabilizes the fracture site with bridging bone. Following the inflammatory phase, this phase begins with the recruitment of mesenchymal stem cells. These progenitors differentiate into osteogenic and chondrogenic cell lines, which produce soft cartilaginous callus as a scaffold for bone healing. Vascular ingrowth prompts the maturation of the fracture callus; the soft callus undergoes mineralization, resorption, and ultimately replacement by hard callus. The end result provides a stable bridge of bone across the fracture site.

Recruitment of Mesenchymal Stem Cells

The recruitment of MSCs is an essential component of fracture healing. MSCs reside throughout the body, including the periosteum, bone marrow, trabecular bone, muscle, and systemic circulation [28]. Periosteal- and bone marrow-derived MSCs were traditionally thought to be the primary sources of progenitor cells in early fracture repair [29]. However, current data suggests that other sources of MSCs, namely from muscle and systemic circulation, may also

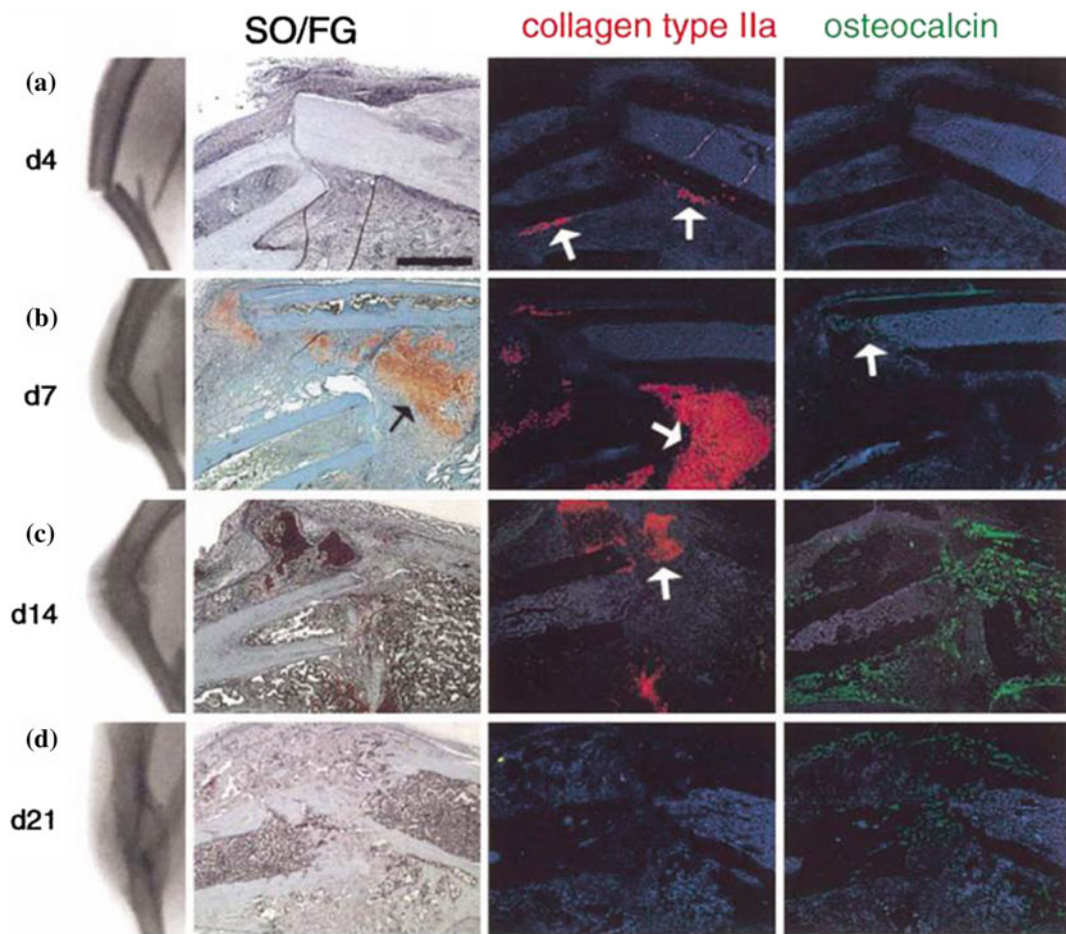


Fig. 2.5 Healing in unstabilized fractures. In contrast to stabilized fractures, progressive healing of a stabilized tibia fracture in a mouse model demonstrates abundant callus formation on serial radiographs and on histological staining. Safranin O/Fast Green staining demonstrates abundant collagen type IIa expression (red), consistent with robust chondrogenesis. From Thompson et al. [13], with permission

contribute to the progenitor cell population [28, 30].

Inflammation at the time of injury releases a number of chemokines, growth factors, and signals to recruit MSCs and other inflammatory cells. In the early phase, TNF- α , IL-1, and IL-6 play key roles in chemotaxis, mesenchymal stem cell (MSC) recruitment, and osteogenic and chondrogenic differentiation [14]. Peak levels of IL-1 and IL-6 are reached within the first 24 h, and then decline precipitously after 72 h. IL-1 and IL-6 contribute to chemotaxis of other inflammatory cells and of MSCs and promote angiogenesis via vascular endothelial growth

factor (VEGF) production [31]. TNF- α and IL-6 promote recruitment and differentiation of muscle-derived stromal cells. TNA- α , at low concentrations, also stimulates chondrogenic and osteogenic differentiation [32–34] (see Table 2.1). In vivo injection of TNF- α accelerates fracture healing and callus mineralization [32]. Conversely, the absence of TNF- α signaling appears to delay both chondrogenic differentiation and endochondral resorption [14, 24, 34].

Emerging evidence has also supported the role of stromal cell-derived factor (SDF-1) in skeletal repair. SDF-1 is a potent chemoattractant



Fig. 2.6 Secondary healing with intramedullary device. The patient is a 23-year-old man who was struck by a motor vehicle at high speed and sustained right tibial and fibular shaft fractures with associated compartment syndrome. **a, b** Initial injury radiographs. **c, d** Immediate postoperative radiographs following tibia intramedullary nailing. **e, f** 2-month follow-up, demonstrate callus

formation. **g, h** 9-month follow-up, with progressive callus formation and bone bridging across the tibial fracture. There is some callus at the fibula fracture ends, but no bone bridging across the fracture site. **i, j** 3-year follow-up, with complete healing of tibial fracture, and nonunion of fibular fracture

expressed at sites of injury to recruit MSCs from both circulating and local sources. Kitaori demonstrated that SDF-1 expression is

upregulated in periosteum at the fracture site and recruits MSCs that participated in the healing process. Additionally, blocking the function of

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Fig. 2.7 Secondary healing with external fixator. The patient is a 51-year-old man who was struck by a vehicle and sustained a Schatzker VI left tibial plateau fracture. **a, b** Initial injury radiographs. **c, d** Definitive treatment with

spanning external fixation. **e, f** 10-week follow-up, with interval removal of external fixator and cast application. There is bridging bone and progressive healing across the fracture site



◀ **Fig. 2.8** Secondary healing with bridge plating. The patient is a 62-year-old man who was involved in a motorcycle crash. He sustained a Grade I open left tibia fracture. **a, b** Initial injury radiographs. **c, d** Initial management consisted of external fixation, followed by bridge plating across the fracture. **e, f** 17-month follow-up after bridge plating, demonstrating bone healing across fracture site

Formation of Soft Cartilaginous Callus

By this time, the fracture hematoma has been converted to granulation tissue, containing inflammatory cytokines and growth factors that stimulate MSC differentiation, proliferation, and production of extracellular matrix. The formation of cartilaginous callus marks the initial attempts at achieving fracture union. The result is a calcified cartilaginous bridge that both provides stability and creates a template for further remodeling.

SDF-1 significantly reduced bone formation, indicating SDF-1 has a crucial role in fracture healing [35].

Table 2.1 Cytokines and their roles in fracture healing

Cytokine	Effect
IL-1	Stimulates chemotaxis of inflammatory cells, MSCs Promotes VEGF production and angiogenesis
IL-6	Stimulates chemotaxis of inflammatory cells, MSCs Promotes VEGF production and angiogenesis
PDGF	Released by platelets and inflammatory cells Stimulates chemotaxis of inflammatory cells and osteoblasts
TNF- α	Recruits MSCs during inflammatory phase Regulates chondrocyte apoptosis, resorption of cartilage callus Regulates bone remodeling, osteoclastogenesis Stimulates chondrogenic and osteogenic differentiation
FGF	Promote differentiation of fibroblasts, chondrocytes, myocytes, and osteoblasts
TGF- β	Stimulates chemotaxis and proliferation of MSCs Stimulates proliferation of chondrogenic and osteogenic cells Induces production of extracellular matrix
MMP	Degrades chondral and osseous extracellular matrix
VEGF	Mediates neoangiogenesis
angiopoietin	Regulates formation of larger vessels and branching of collateral branches from existing vessels
BMP	Promote osteoblast differentiation and osteogenesis Upregulates extracellular matrix production Stimulate VEGF production
M-CSF	Secreted by osteoblasts to induce osteoclast differentiation and proliferation Upregulates RANK expression
OPG	Inhibits osteoclast differentiation and activation Inhibits osteoclast-mediated resorption
RANKL	Stimulates osteoclastogenesis, osteoclast activation through its receptor RANK
Sclerostin	BMP antagonist

IL interleukin; PDGF platelet-derived growth factor; TNF- α tumor necrosis factor-alpha; FGF fibroblast growth factor; TGF- β transforming growth factor-beta; MMP matrix metalloproteinase; VEGF vascular endothelial growth factor; BMP bone morphogenetic protein; OPG osteoprotegerin; RANK receptor-activated NF- κ B; RANKL receptor-activated NF- κ B ligand. From Tsiridis et al. [24] with permission



Cartilaginous callus formation is driven by growth factors, chondrocytes, fibroblasts, and mechanical stimulation across the fracture site. TGF- β and IGF-1 play primary roles in this stage of chondrogenesis and endochondral bone formation, stimulating the recruitment, proliferation, and differentiation of MSCs. BMPs also promote chondrogenesis. Several days after fracture, chondrocytes derived from MSCs proliferate and synthesize collagen. Starting from the periosteum and the fractured ends, chondrogenesis progresses by appositional replacement of adjacent granulation tissue with cartilage matrix [29]. Fibroblasts produce fibrous tissue in areas with limited cartilage production. Micromotion across the fracture stimulates callus formation, and increased callus formation provides more mechanical stability to the fracture. When sufficient callus and stability have been attained, roughly 2 weeks after fracture, chondrocytes undergo hypertrophic differentiation. Proliferation ceases. Collagen synthesis is downregulated. Hypertrophic chondrocytes release vesicular stores containing calcium, proteases, and phosphatases into the surrounding matrix. As the collagen matrix is degraded, released phosphate ions bind with calcium to promote cartilage calcification. These calcium and phosphate deposits become the nidus for hydroxyapatite crystal formation [8].

At the same time, intramembranous ossification occurs in areas of low strain, beneath the periosteum, and directly adjacent to the fractured cortices. Within 24 h following injury, MSCs from the bone marrow differentiate into osteoblastic phenotypes. Proliferation and differentiation peak at day 7–10. Woven bone is formed in these regions without a cartilage scaffold.

Revascularization and Angiogenesis

Fracture healing begins in a relatively hypoxic environment; injury to vessels, periosteum, and soft tissue compromises local blood supply [22]. Early cartilage callus can form in this hypoxic environment. However, as healing progresses, subsequent callus remodeling and

bone formation require adequate oxygen delivery. Failure to do so leads to delayed healing. Revascularization is thus critical for progressive healing and bone formation [9, 11, 12, 36–38].

Two main molecular pathways regulate this process: an angiopoietin-dependent pathway and a VEGF-dependent pathway. Angiopoietins promote formation of larger vessels and collateral vessels off existing vessels. VEGF promotes endothelial cell differentiation, proliferation, and neoangiogenesis, and it mediates the principal vascularization pathway [11, 24].

Inflammatory cytokines from early fracture healing, particularly TNF- α , induce expression of angiopoietin, allowing for early vascular ingrowth from existing periosteal vessels [9, 33]. However, the primary vascularization process is driven by VEGF. Following calcification of cartilage callus, osteoblasts and hypertrophic chondrocytes housed in callus express high levels of VEGF, stimulating neoangiogenesis into the avascular chondral matrix [36, 38, 39]. Concurrently, matrix metalloproteinases (MMPs) degrade calcified cartilage to facilitate ingrowth of new vessels [40].

Hard Callus Formation

With the onset of neoangiogenesis, the next event is characterized by the transition from soft callus to hard callus: the removal of calcified cartilage and its replacement with woven bone matrix. This process is mediated by MMPs, BMPs, osteoclasts, chondroclasts, and osteoblasts [36, 40, 41].

Osteoclasts have historically been considered the key cell type in soft callus resorption. However, more recent evidence suggests that resorption is nonspecific and mediated by multiple cell lines, including osteoclasts and chondroclasts alike, and by MMP expression [40, 41]. This has been supported by findings that impaired osteoclast function does not necessarily impair healing. In an osteoclast-deficient osteopetrosis mouse model, there was no difference in callus remodeling or union rates compared with control mice [42].



Cartilage callus is removed and subsequently replaced by woven bone. Mature osteoblasts secrete osteoid, a combination of type I collagen, osteocalcin, and chondroitin sulfate. Collagen fibrils are randomly oriented, producing an irregular structure known as woven bone [41].

Remodeling Phase

While woven bone provides more biomechanical stability than fibrous tissue and soft callus, its irregular and disordered structure is mechanically inferior to native cortical bone. Further remodeling is required to restore structural integrity. The final phase of fracture healing converts irregular woven bone into structured lamellar bone. The process encompasses both catabolic and anabolic mechanisms, regulated by the coordinated relationship between osteoblasts and osteoclasts. Whereas the earlier phases take place over the course of days to weeks, this final phase spans months to years after injury [9].

Remodeling is characterized by woven bone resorption followed by lamellar bone formation. Osteoclasts are multinucleated polarized cells that attach to mineralized surfaces. At sites of attachment, osteoclasts form ruffled borders, effectively increasing surface area through which lysosomal enzymes and hydrogen ions are secreted. Enzymes degrade the organic collagen components, while the acidic milieu demineralizes the bone matrix. The erosive pits left by the osteoclasts are termed “Howship’s lacuna.” Following resorption, osteoblasts form new bone within these lacunae. This process progresses along the length of hard callus, layer upon layer, replacing woven bone with lamellar bone [43, 44].

Activation and regulation of remodeling depends on intimate coupling between osteoblasts and osteoclasts. Osteoblasts initiate remodeling by producing factors to stimulate osteoclastogenesis and osteoclast function. The principle cytokines secreted by osteoblasts are M-CSF, receptor-activated $\text{NF-}\kappa\text{B}$ ligand (RANKL), and osteoprotegerin (OPG). M-CSF and RANKL are essential for osteoclast formation. Osteoblasts express RANKL on their cell membranes, whereas mononuclear osteoclast

progenitors express the complementary receptor, RANK. Upon contact, RANKL interacts with RANK to induce fusion of osteoclast progenitors and thus produce mature multinucleated osteoclasts. Alternatively, osteoblasts can also secrete OPG, which acts as a decoy by binding RANK and consequently disrupts RANKL–RANK interactions. By modulating RANKL and OPG expression, osteoblasts can tightly regulate osteoclast activation. Osteoblasts express and secrete M-CSF, which induces osteoclast precursor proliferation and differentiation. Additionally, M-CSF upregulates the expression of RANK on osteoclast precursors [43–45].

Metaphyseal Fracture Healing

The principles underlying fracture healing have largely been based on diaphyseal models. By comparison, the existing literature for metaphyseal healing is limited. Metaphyseal bone differs from diaphyseal bone in anatomy and biologic activity. Periosteum is thicker around the metaphysis. Blood supply is richer to the metaphysis [12]. Additionally, metaphyseal bone has a larger active bone surface area with consequently higher bone turnover rates [46].

Diaphyseal bone healing hinges on the interrelationship between biomechanics and biology. Early in the healing process, the mechanical environment determines the biologic response, whether healing will proceed by direct or indirect means. In stable situations, healing proceeds directly to osteogenesis. In unstable conditions, healing begins with chondrogenesis. The same holds true for metaphyseal healing. Under rigidly stable conditions, newly formed bone bridges the fracture gap with minimal chondrogenic tissue, similar to direct healing. Under more flexible conditions, bone intermixed with islands of chondrogenic tissue forms across the gap, analogous secondary healing. Interestingly, both situations do not generate a significant amount of external callus [47]. Whereas progenitor cells need to be recruited in diaphyseal healing, the metaphysis houses a large reservoir of precursor cells, obviating the need for a large periosteal reaction and MSC recruitment [48].



2.2.2 Biomechanics of Fracture Healing

The relationship between mechanics and biology is well established in skeletal physiology. Wolff's law stipulates that bone structurally adapts to its loading conditions. Likewise, biomechanics plays a central role in skeletal repair. Following injury, the mechanical environment influences the biologic healing response. This response in turn attempts to restore skeletal integrity. Understanding how biomechanical factors affect healing is therefore fundamental to fracture treatment. The existing body of literature has identified three mechanical parameters that impact fracture healing: interfragmentary strain, gap size, and hydrostatic pressure. The degree to which these parameters affect healing, and the timing at which they are applied, will be discussed in this section.

2.2.2.1 Interfragmentary Strain

Perren's strain theory proposes that "a tissue cannot be produced under strain conditions which exceed the elongation at rupture of the given tissue element" [16]. Thus, bone can only form in low strain environments, while fibrous tissue can form in high strain environments. In stable fractures, a low strain environment allows for primary osteogenesis across the fracture gap. However, in unstable fractures, high strains preclude direct bone formation. Instead, precursor tissues must first bridge the gap, providing adequate mechanical stability for osteogenesis to ultimately occur. Such is the case with endochondral bone formation. Cartilage callus first bridges the gap and provides provisional stability across the fracture. When sufficient stability has been attained, the cartilage callus can then undergo calcification, and woven bone can replace the chondral matrix. If strain is still too high, more callus is produced, increasing its diameter and effectively increasing its strength. If strain still remains too high, bone bridging may not occur and a fibrous nonunion may develop instead.

The relationship between strain and tissue differentiation correlates with both

histomorphometric and finite element analyses [15, 49, 50]. In models of indirect healing, intramembranous bone formation occurs at the periosteum and directly adjacent to the cortex, areas characterized by low strain. Cartilaginous callus developed between the fractured ends, in areas of high strain. Increasing the mechanical stress and strain, by early loading or delayed stabilization, impairs bone bridging and delayed healing across the fracture [51, 52]. Histological analysis in these animal models of delayed stabilization demonstrated higher proportions of cartilage and fibrous tissue in the fracture site compared to fractures that were stabilized early (Fig. 2.9) [53]. Similarly, Augat demonstrated in a sheep model that higher gap sizes and higher strains led to lower amounts of bone formation and higher proportions of connective tissue and fibrocartilage formation across the fracture (Fig. 2.10) [49].

2.2.2.2 Fracture Gap

While the strain theory accounts for some of the clinical observations seen in fracture healing, further work has shown that strain is not the only determinant of tissue differentiation. Fracture gap is as important, if not more important, than strain. Augat et al. and Claes et al. examined the effects of increasing gap size (1, 2, and 6 mm) and different strains (7 vs. 31%) on bone healing and mechanical strength. Augat demonstrated in a sheep model that higher gap sizes and higher strains led to lower amounts of bone formation and higher proportions of connective tissue and fibrocartilage formation across the fracture (Fig. 2.10) [49]. Increasing gap correlated with less bone formation. Cases in which bone failed to bridge the fracture gap were only observed for gaps >2 mm. Regardless of interfragmentary strain, gaps of 6 mm never healed. Strain played a more subtle role. While there was no difference in mechanical properties between strain groups, those that experienced higher strain (31%) had higher cartilage and fibrous tissue content, and lower bone content [49, 50]. Additionally, hydrostatic pressure and local stress play a role in tissue differentiation.

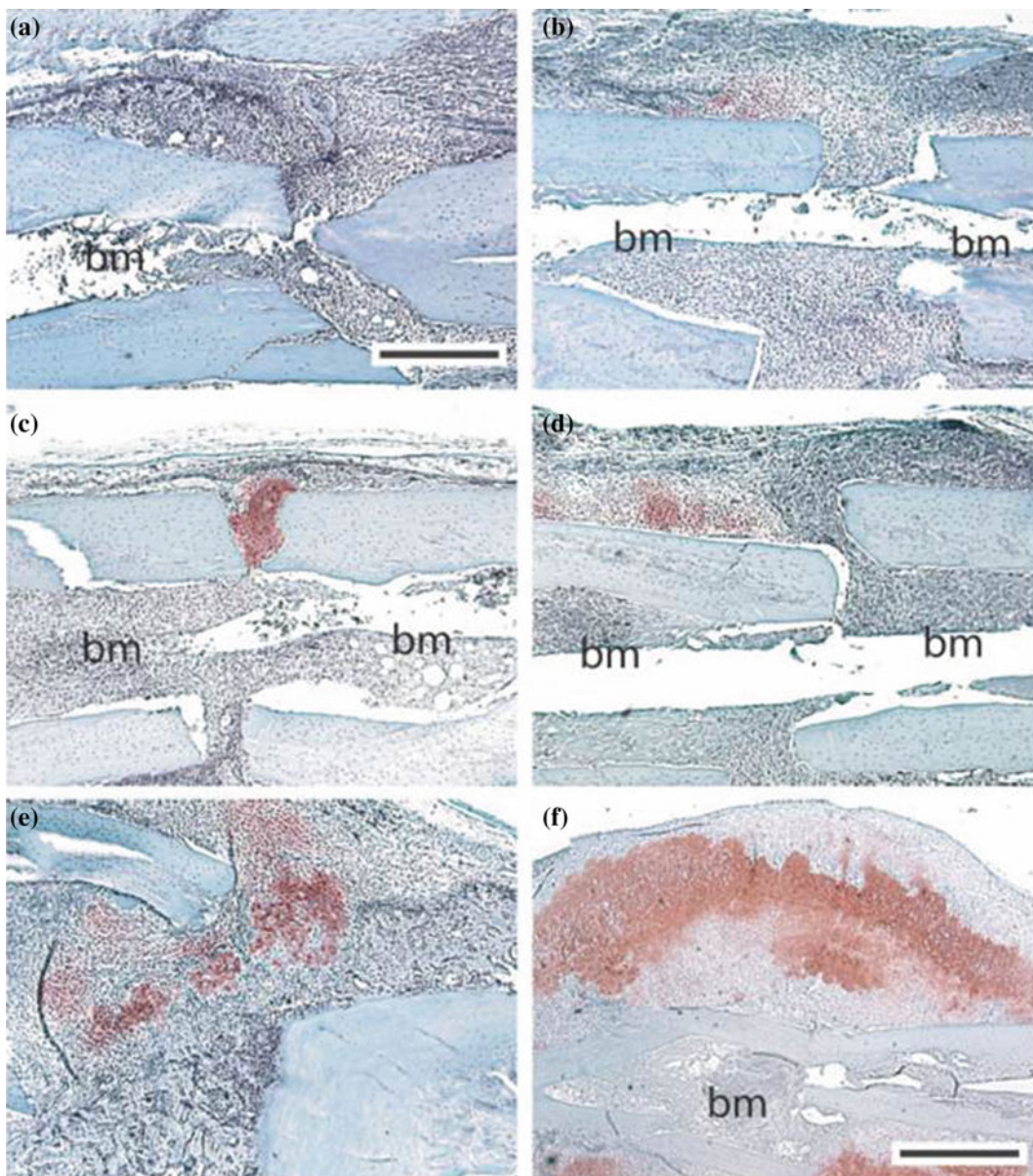


Fig. 2.9 Histological findings in impaired healing. Nonstabilized fractures (e) demonstrate increased cartilage formation compared to stabilized fractures (d). From Miclau et al. [53] with permission

2.2.2.3 Timing in Fracture Healing

Fracture healing involves a complex temporal and spatial sequence of events. The timing at which mechanical stimulation is introduced appears to affect the outcomes of skeletal repair. The initial mechanical environment is an early determinant of tissue differentiation and of

healing outcome [14]. Immediate and early full weight bearing in a sheep model has been shown to delay healing, demonstrating lower bone content compared to delayed weight bearing [51]. Others have likewise shown that early or immediate mechanical loading led to decreased bone formation and inferior mechanical

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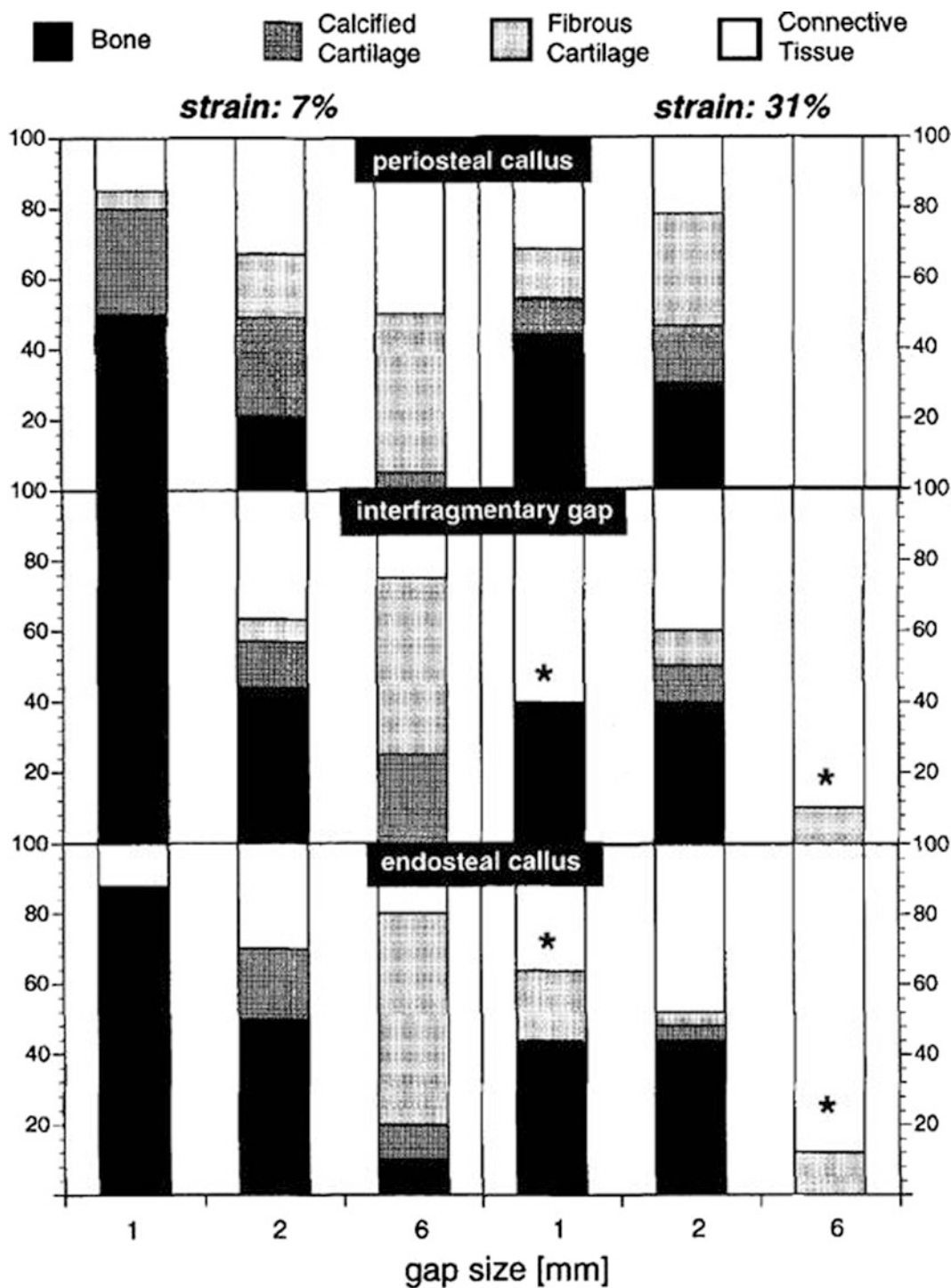


Fig. 2.10 Influence of fracture gap size and strain on tissue differentiation. Tissue differentiation as a function of fracture gap size and strain. With higher gaps and strains, there is an increasing proportion of connective

tissue and fibrocartilage at the fracture site and within the callus. Conversely, low strains and gaps had higher amounts of bone formation. From Augat et al. [49], with permission

properties [52, 54]. These same studies also showed that delayed loading led to higher proportions of bone formation and improved biomechanical properties. Miclau et al. showed that delayed stabilization for even 24 h in mice led to higher cartilage callus formation and lower bone content compared to those who had immediate stabilization [53]. Taken together, these findings demonstrate that timing of mechanical loading impacts fracture healing. When loading occurs prematurely or exceeds tolerable amounts, it can disrupt early healing and have deleterious effects. However, with callus providing some inherent stability across the fracture site, loading is better tolerated and may stimulate further callus formation and bony healing.

2.2.3 Assessment of Fracture Healing

The accurate assessment of fracture union is often a difficult undertaking, but nonetheless fundamental to clinical practice and research. Nonunions can be a source of significant disability, and its early diagnosis and treatment is paramount to improving patients' quality of life and return to function [55]. The definition of nonunion provided by the United States Food and Drug Administration (FDA) requires a minimum of at least nine months to elapse since the initial injury and no signs of healing for the final three months. Yet, there are no standardized methods of assessing fracture union, and there still remains considerable variability among clinicians and researchers alike [56, 57]. However, advances in imaging techniques, improved knowledge about the biology and biomechanics

of fracture healing, and new scoring systems are refining our ability to assess fracture healing.

2.2.3.1 Clinical Criteria

Physical examination and clinical evaluation remain the cornerstone of fracture healing assessment. Weight bearing status has been shown to correlate with fracture tissue stiffness [58], though the clinicians' ability to assess stiffness is not reliable [59]. Weight bearing without pain is the most commonly endorsed factor, used in over half of all published studies to assess healing [57]. Pain at the fracture site and tenderness to palpation are also important signs in assessing healing. Conversely, the lack of weight bearing is considered the most important clinical criteria for impaired healing.

2.2.3.2 Radiologic Scores

The Radiographic Union Score for Hip (RUSH) and the Radiographic Union Score for Tibia (RUST) were developed to provide standardized, reliable radiographic measures of fracture healing [60–63]. These scoring systems evaluate healing on the basis of cortical bridging and fracture line visibility on AP and lateral views (Table 2.2; Figs. 2.11 and 2.12). Both RUST and RUSH have high interobserver agreement, with intraclass correlation coefficients of 0.86 and 0.85, respectively. Compared to subjective assessment, these scores increase reliability and agreement among clinicians in assessing radiographic progression of fracture healing [62–65].

The lack of consensus in the orthopedic community limits the ability to establish consistent criteria to define union. Most practices use a combination of clinical and radiographic criteria to assess fracture healing. Additionally, several serologic markers of bone metabolism and

Table 2.2 Calculation of RUST and RUSH scores

Score per cortex	Callus	Fracture line
1	Absent	Visible
2	Present	Visible
3	Present	Invisible

The RUST and RUSH scores are based on radiographic findings on AP and lateral projections. Each cortex is scored according to the presence of callus and visibility of fracture line, with a maximum score of 12 for 4 cortices



cytokines, including TGF- β , have been identified as candidate biomarkers for tracking healing progression [8, 66]. Tools to measure mechanical properties in healing bone are also being developed. As our understanding of fracture healing continues to evolve, so too will our ability to gauge the healing process.

2.3 Modulation of Fracture Healing

2.3.1 Comorbidities

2.3.1.1 Aging

Aging has profound effects on bone health, modeling, and repair. Bone mass declines with advancing age, owing in part to hormonal changes, limited physical activity, and altered biologic responses. Additionally, elderly patients have a higher prevalence of comorbidities and take more medications, some of which may directly impact bone healing.

Animal studies have demonstrated decreased fracture healing capacity with increasing age [67]. Compared to adults, juveniles exhibit faster healing rates and remodeling potential [68]. In murine models, juveniles had more robust periosteal responses, higher chondrocytic and osteoblastic differentiation, and faster healing rates [67]. Additionally, juveniles mounted a larger angiogenic response, illustrated by higher VEGF, HIF-1 α , and MMP expression [69]. In contrast, adults had relative delays in endochondral ossification, decreased periosteal thickness, and decreased chondrogenic potential in the periosteum [46]. Furthermore, skeletal maturity brought on a sharp drop in regenerative potential [67]. Additionally, elderly mice demonstrated decreased angiogenic potential [69]. In a murine model of senile osteoporosis, bone marrow-derived MSCs had increased adipogenic and decreased osteogenic differentiation. Despite these abnormalities, the process of fracture healing was unchanged [70].

How aging affects fracture healing after skeletal maturity remains controversial, and the clinical evidence has thus far been limited and inconclusive. D'Ippolito et al. [71] demonstrated lower numbers

Fig. 2.11 Radiographic union score for hip (RUSH) ► fracture healing assessment, Assignment of RUSH in a patient who sustained a left intertrochanteric fracture. **a**, **b** Immediate postoperative radiographs, with a RUSH = 4. **c**, **d** 6-week follow-up radiographs, with a RUSH = 8, demonstrating callus on the anteroposterior view and lateral views, though the fracture lines are still visible

of MSCs with osteogenic potential in adult human vertebrae. In contrast, Stenderup et al. [72] found no age-related decrement in the number of osteogenic stem cells from iliac crest marrow. The effects of age on fracture healing in humans, independent of other associated variables such as metabolic bone diseases, require further investigation.

2.3.1.2 Metabolic Bone Disease

Osteoporosis

Osteoporosis is the most common metabolic bone disease, affecting over 200 million people worldwide [73]. Unlike normal age-related changes, osteoporosis is a metabolic disease characterized by decreased bone mass, decreased mineral content, increased porosity, and compromised microarchitecture. On a cellular level, the balance between anabolic and catabolic processes is unhinged to favor net bone resorption. Clinically, the weakened architecture predisposes to fragility fractures. Almost half of women with osteoporosis will sustain at least one fragility fracture in their lifetime [73].

Osteoporotic fractures are challenging to treat. Appropriate management requires an appreciation of how osteoporosis affects bone health, bone quality, and healing. As most clinical studies have focused on medical management and fracture prevention, there is limited data on how osteoporosis influences fracture healing in humans. More recently, Nikolaou et al. assessed the effect of osteoporosis on healing time in patients with femoral shaft fractures following intramedullary nailing. The elderly group of patients with radiologic evidence of osteoporosis had delayed healing compared to a younger cohort (19.4 weeks versus 16.2 weeks, respectively), though this difference is probably not clinically significant [74].

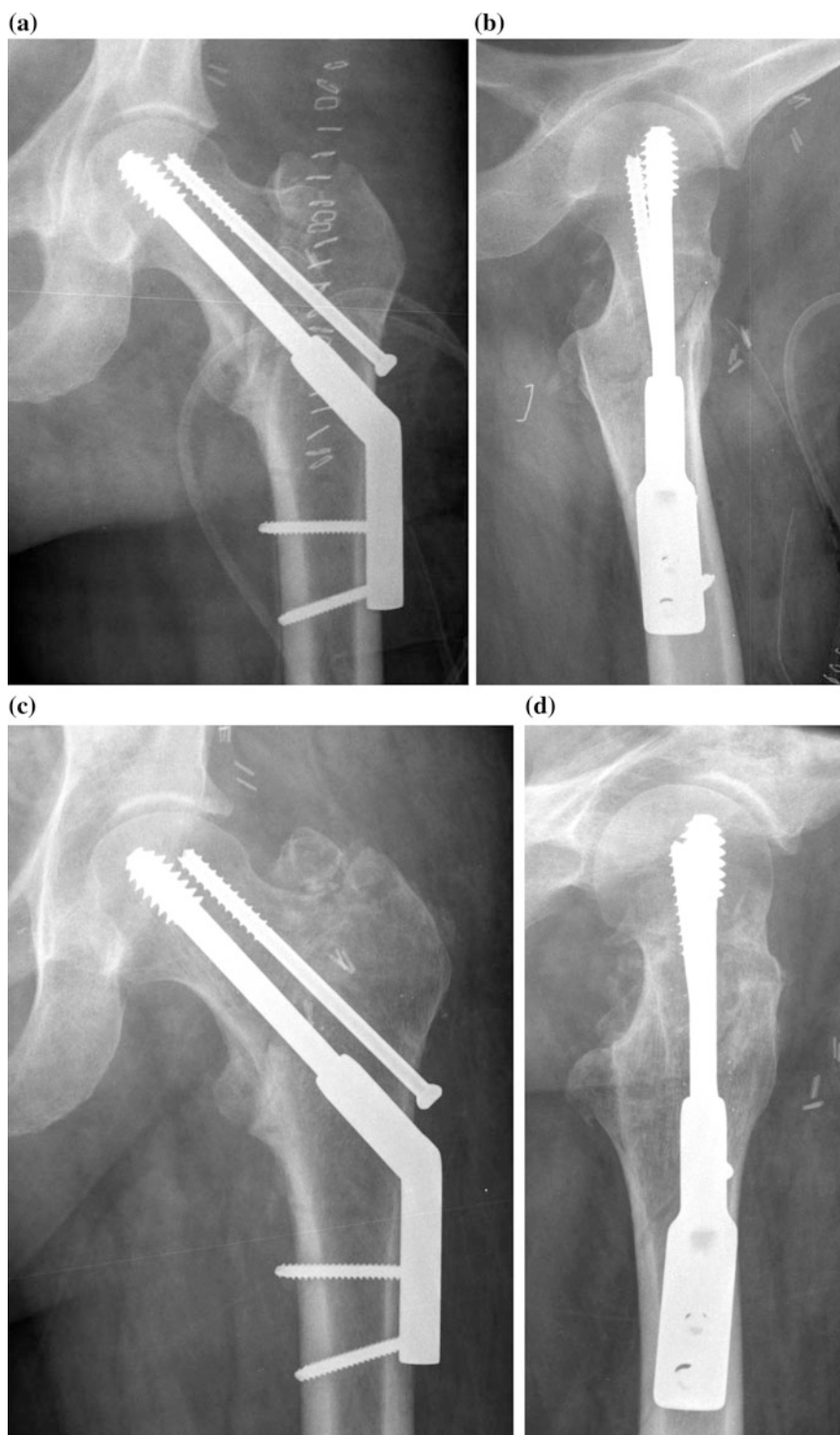
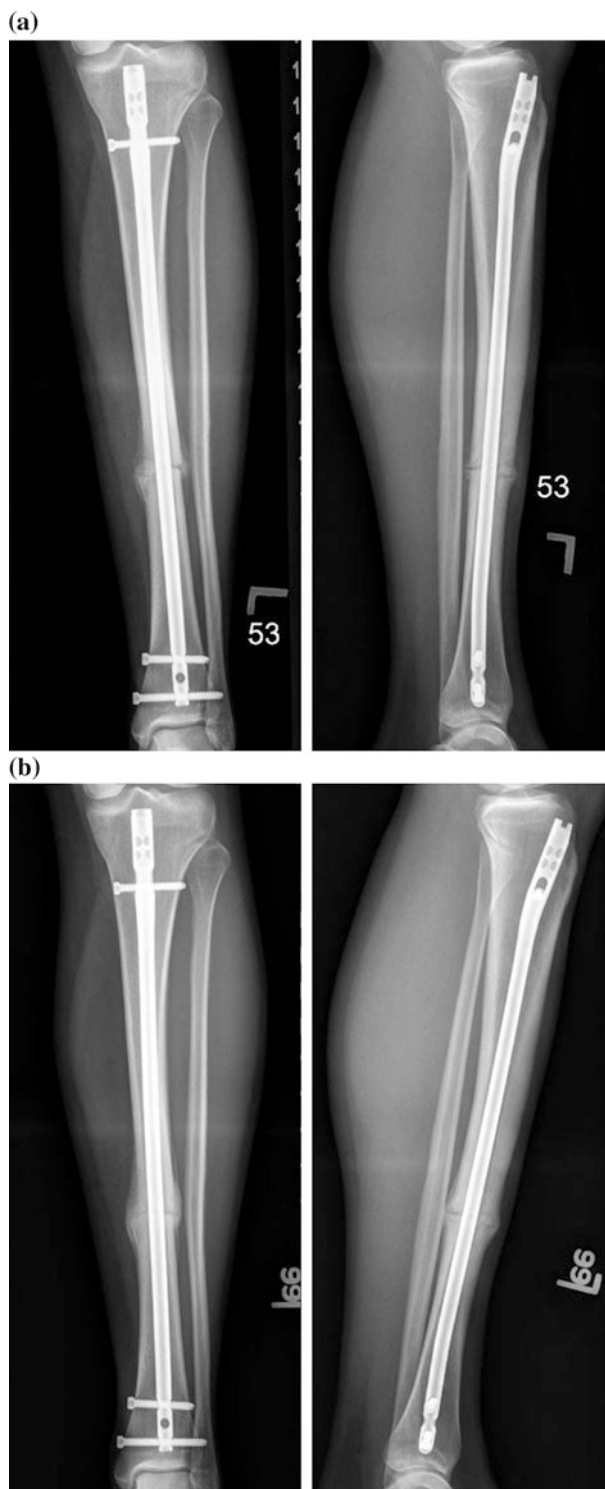


Fig. 2.12 Radiographic union score for tibia (RUST) fracture healing assessment. Assignment of RUST in a patient with distal tibial shaft fracture at 3 months. **a** At 4 weeks, there is healing callus along the medial, lateral, and anterior cortices, but fracture lines are visible. RUST score = 8. **b** At 10 weeks, there is bridging callus and no fracture line at the anterior and medial cortices. Fracture lines are still visible posteriorly and laterally. RUST score = 10





Animal studies have shown that osteoporosis impairs fracture healing. In an ovariectomized rat osteoporosis model, Namkung-Matthai et al. [75] demonstrated early failure in the repair process with a 40% reduction in callus size, and decreased bone mineral density and strength. Walsh et al. [76] demonstrated delayed healing and decreased tensile and bending strength in estrogen-deficient rats. Lill et al. likewise demonstrated decreased bending stiffness and delayed healing in their osteoporotic sheep model. However, final strength at the end of healing was not different from healthy sheep [77].

To what degree osteoporosis impairs fracture healing remains unclear. While the healing potential is present in patients with osteoporosis, it may not be as robust. Furthermore, concomitant comorbidities such as vitamin D deficiency or other disorders of calcium homeostasis in these patients may also impair the healing response.

2.3.1.3 Endocrine Disorders

Hyperparathyroidism, thyroid disorders, and hypogonadism have also been shown to impair fracture healing [78, 79]. In patients with unexplained nonunions, Brinker et al. found a high prevalence of these metabolic and endocrine disorders that had previously been unrecognized. The mechanisms by which these impede the healing process are still undetermined. However, medical management of the underlying abnormality, in conjunction with surgical fixation, successfully treats the majority of cases [78]. While routine screening is not indicated in the acute setting, impaired healing in otherwise appropriately treated fractures warrants further evaluation for metabolic abnormalities.

Diabetes Mellitus

Diabetes mellitus poses significant challenges to fracture management through impairment of healing, protective sensation, and host immunity. These effects are mediated by incompetent microcirculation, and in severe cases, they may also be associated with peripheral vascular disease. Delayed fracture healing in diabetic patients

has been well documented. Early observations by Cozen showed significantly delayed fracture healing and nonunions in a series of diabetic patients [80]. Healing time in nondisplaced fractures was prolonged by 87% in non-neuropathic diabetic patients compared to nondiabetic patients [81].

Diabetes is a chronic inflammatory disorder; type I is an autoimmune disorder against insulin-producing islet of Langerhans beta cells, while type II is associated with obesity-related inflammation. Acute inflammation plays a pivotal role in early fracture healing in recruiting skeletal progenitors to the site of injury. However, these events are tightly regulated; inflammatory cytokine levels are active within the first 72 h after injury, and at specific points in the healing cascade. Continued inflammation and continued cytokine expression, left unchecked, can halt the progression of bone remodeling and fracture healing [82, 83].

Recent evidence from animal studies suggests that uncontrolled diabetes may directly impact callus formation, chondrocyte survival, and osteoclast activity. Hyperglycemia upregulates the expression of proinflammatory factors, such as TNF- α and VEGF [82]. Upregulation of TNF- α stimulates chondrocyte apoptosis. Additionally, diabetes is associated with premature resorption of the cartilaginous callus and increased osteoclastogenesis. Impaired matrix synthesis, chondrocyte dysfunction, and premature resorption all decrease callus formation. These mechanisms may explain its weaker biomechanical strength in diabetic fracture healing [83–86].

Glycemic control should be the cornerstone of fracture management in diabetic patients. It has repeatedly been shown to reduce or prevent the aforementioned issues with bone healing [87]. Successful fracture healing in these patients often requires prolonged immobilization and weight bearing precautions [80]. Soft tissue management is also paramount, particularly in those with peripheral neuropathy. Surgical interventions



likewise should respect soft tissue coverage; aggressive dissection and inattentiveness to soft tissue handling may further compromise the already tenuous blood supply in diabetic patients [81, 85, 88].

2.3.2 Habits

2.3.2.1 Smoking

Smoking is well known to impair fracture healing. In multiple clinical trials, smoking has consistently been associated with nonunion, pseudarthrosis, and delayed healing. In the Lower Extremity Assessment Project (LEAP), smokers, both former and active, were 32 and 37% more likely to develop nonunion, respectively. Smokers also required longer healing times [89, 90]. For midshaft clavicle fractures, smoking was the strongest risk factor for nonunion [91]. Among distal tibia fractures treated with two-ring hybrid external fixators, smoking delayed union by 10 weeks [92]. Additionally, smoking has been associated with higher complication, reoperation, and infection rates [89, 93].

Cigarette smoke contains hundreds of chemicals and gases, among them nicotine, carbon monoxide, and carcinogens. Carbon monoxide impairs oxygen delivery, creating a hypoxic environment for tissues. Nicotine induces vasoconstriction, likewise impairing oxygen delivery to tissues. Recent studies have found a bimodal dose-dependent effect of nicotine on osteoblasts. At high concentrations, nicotine had an inhibitory effect on osteoblast proliferation and differentiation, but at lower doses, it actually stimulated osteoblast activity [94]. While considered the addictive constituent in cigarettes, the role of nicotine in impaired fracture healing has undergone re-evaluation [95, 96]. Tobacco extract without nicotine reduced the mechanical strength in healing femoral fractures compared to nicotine alone [96]. The negative effects of smoking toward fracture healing are likely due to other constituents in cigarette smoke rather than

from nicotine itself. These studies suggest that nicotine replacement may be safe and would reduce exposure to inhaled CO and other chemicals that may pose more physiologic harm.

2.3.2.2 Alcohol Consumption

Alcoholism and binge drinking are well-documented risk factors for traumatic injuries, disrupted bone metabolism, and impaired fracture healing. Not only does alcohol abuse confer higher fracture risk [97], but it also prolongs healing times. Nyquist et al. [98] showed that alcohol abusers with transverse tibia fractures required longer healing times than nonalcoholic patients. Alcoholic patients have lower bone mineral density and abnormal bone turnover markers consistent with defective bone formation and osteoblast dysfunction [99, 100]. Furthermore, alcoholism is frequently paired with smoking and malnutrition, which may further compromise bone health and bone repair [101].

Alcohol exposure predominantly affects early repair and bone formation [102–104]. In vitro osteoblast cultures demonstrate decreased proliferation and osteoid synthesis when exposed to ethanol. Additionally, rodent models have demonstrated decreased mechanical properties in fracture repair tissue following alcoholic ingestion [103]. In ethanol-fed rats, there was absence of mineralized callus on radiographs while in ethanol-free controls there was complete healing [105]. Recent evidence demonstrates that production of inflammatory cytokines, including IL-1 and TNF- α , increased oxidative stress, and impaired Wnt signaling may mediate these effects [104].

Just as acute ingestion can lead to impaired healing, abstinence can lead reversal of its effects [102, 103]. Laitinen et al. [99] found that bone formation markers improved to near control levels after two weeks of abstinence. More recent evidence also suggests a role for antioxidant treatment with N-acetylcysteine in reversing the negative healing effects of alcohol consumption [106].



2.3.3 Medications

2.3.3.1 Nonsteroidal Anti-inflammatory Drugs

Inflammation is critical in fracture healing. As part of the inflammatory cascade, cyclooxygenase (COX) converts arachidonic acid into prostaglandins [107, 108]. Downstream, prostaglandin E₂ (PGE₂) stimulates bone metabolism, bone formation, and maintenance [108, 109]. Deficient PGE₂ signaling conversely leads to osteopenia and impaired bone healing [110]. Additionally, COX-2 is essential to fracture healing, mediating repair through osteogenesis. COX-2 knockout mice fail to form mineralized matrix during endochondral ossification, where COX-1 knockout mice display no disruption in healing [111].

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effect by interfering with prostaglandin production and COX function. NSAIDs have long been used as prophylaxis for heterotopic ossification, and human studies suggest adverse effects of NSAIDs on fracture repair. However, these clinical studies are all level III-IV data, have been retrospective, and have produced conflicting results [107, 108, 112, 113]. Giannoudis et al. correlated NSAID use > 4 weeks with higher rates of nonunion in femoral shaft fractures treated with intramedullary nailing. Even short-term use demonstrated delayed union [112]. However, this study was largely limited by its retrospective nature and lack of controls; whether true causality exists cannot be extrapolated from these results.

In animal studies, NSAIDs do appear to negatively affect skeletal repair [107, 108, 111, 114]. The earliest of these studies demonstrated that indomethacin treatment not only reduced the mechanical properties of rat femora during fracture healing, but also created fibrous tissue rather than callus between fractured ends [114]. Subsequent studies have also shown that the use of both nonselective and COX-2 selective NSAIDs decreases bone formation and cortical bridging, prolongs healing times, and increases rates of nonunion [111, 115]. These effects do appear to be both time and dose dependent [14, 107, 108,

115, 116]. Aspirin, at doses equivalent to 325 mg, similarly delayed fracture healing, though smaller doses did not demonstrate any radiographic or mechanical differences compared with controls [116].

The importance of COX-2 and prostaglandins in fracture healing has been clearly established. While the mounting evidence in animal studies supports the effect of NSAIDs in suppressing fracture healing, translation of these effects to human subjects remains less convincing. As such, there is currently inadequate clinical evidence to prohibit their routine use in acute fracture care. NSAIDs remain an important feature in the development of a multimodal, opiate-sparing approach to postinjury and postsurgical pain regimen, and further clinical work is paramount in understanding its effects in orthopedic patients.

2.3.3.2 Bisphosphonates

Bisphosphonates are a mainstay of antiresorptive osteoporosis treatment. This class of drugs acts by inhibiting osteoclast-mediated resorption, improving bone mass and mineralization. However, there have been concerns about the hypothetical risk that bisphosphonates may impair bone healing. The reparative process relies on osteoclast-mediated remodeling of hard callus into woven bone and woven bone into mature lamellar bone.

Clinical studies have reported mixed results. In a retrospective review of humeral fractures, Solomon reported a higher nonunion rate with bisphosphonate use in the postfracture period. However, the conclusions of this study should be tempered with its limitations, including the rare occurrence of fractures (0.4%) and its retrospective design [117]. Rozental et al. explored the effect of bisphosphonate use on distal radius fracture healing time. Patients treated with bisphosphonates had slightly longer healing times (55 days versus 49 days), but this difference, while statistically significant, was not considered clinically significant [118]. More recently, Gong similarly investigated the impact of bisphosphonate treatment on healing in distal radius fractures after surgical fixation. There was no

difference in time to union, or in radiographic or clinical outcomes [119]. In a randomized, double-blind, placebo-controlled trial using zoledronic acid after hip fracture, Lyles et al. did not find any evidence of delayed healing. Furthermore, if administered within 90 days after surgical fixation, zoledronic acid improved survival and reduced the incidence of new clinical fractures [120].

Thus far, animal studies have been largely reassuring and have not demonstrated a detrimental effect of bisphosphonates on fracture healing. Rather, animals treated with bisphosphonates had increased callus formation and mineralization. Others have demonstrated some evidence of delay in callus remodeling and resorption, though there was no long-term impact on healing [121–124].

The short-term results of bisphosphonate use postfracture are encouraging. Clinical and basic science studies have not shown major differences in healing with bisphosphonate use. However, its long-term effects remain unclear. Furthermore, the emergence of atypical femur fractures associated with long-term bisphosphonate use has raised safety concerns (Fig. 2.13) [125]. These fractures have a reported prolonged healing course [126, 127]. As these fractures occur in the subtrochanteric region, an area subject to high stress and prone to malunion, it is difficult to ascertain whether these healing issues are a result of the fracture or a result of the drug effect. Additionally, while true causality has yet to be determined, the FDA has proposed offering a drug holiday for certain lower risk patients, though concrete guidelines

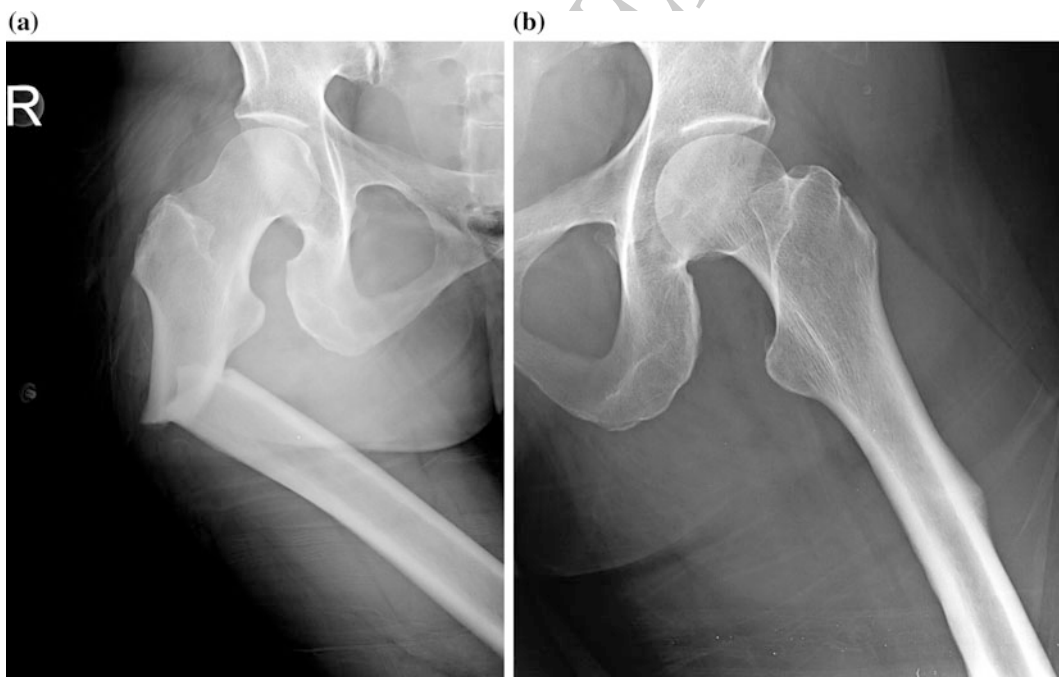


Fig. 2.13 Atypical femur fracture related to bisphosphonate use. The patient is a 43-year-old woman with a history of metastatic breast cancer status postlumpectomy and hormone therapy. She had a long history of bisphosphonate use. A recent positron emission tomography scan did not demonstrate any bony metastases. She

sustained a low-energy right femur subtrochanteric oblique fracture after twisting that leg, consistent with an atypical femur fracture. **a** Imaging of the contralateral leg demonstrated stress reaction in the subtrochanteric region, concerning for an impending pathologic fracture **(b)**



defining appropriate candidates have not been established [128].

2.3.3.3 Parathyroid Hormone Analogs

Parathyroid hormone regulates serum calcium homeostasis via intestinal absorption, renal secretion, and bone metabolism. In the skeletal system, PTH binds to and stimulates osteoblasts to form new bone. Continuous PTH stimulation increases RANKL expression and decreases OPG expression, increasing osteoclast formation and catabolic function. However, intermittent PTH exposure preferentially stimulates anabolic osteoblast activity [124, 129].

Teriparatide, the biologically active 1–34 fragment of recombinant human PTH, is the first anabolic medication approved for osteoporosis [124], and its applications in fracture care are currently being investigated [130]. Animal studies in both rodent and simian models support PTH's role in enhancing fracture healing. In rodent models, PTH appears to accelerate healing during chondrogenesis. PTH treatment elevates chondrogenic gene expression, cell recruitment, and differentiation, while osteogenic gene expression was not significantly increased. Additionally, PTH stimulates earlier chondrocyte hypertrophy and maturation of cartilage callus [131, 132]. Andreassen demonstrated increased fracture site strength and improved bone mineral content with PTH administration in a dose-dependent manner [133, 134]. Similarly, in monkeys, higher dose PTH treatment had smaller callus sizes, consistent with accelerated remodeling of callus to lamellar bone [135].

Early clinical results, while limited, have also been encouraging. In a prospective, randomized control trial, placebo, 20 µg teriparatide or 40 µg teriparatide was administered following distal radius fracture. Interestingly, median time to cortical bridging was significantly shorter in the 20 µg group (7.4 weeks) compared to both placebo (9.1 weeks) and 40 µg (8.8 weeks) groups [136]. In a prospective clinical trial of pelvic fractures using CT to evaluate fracture union, PTH treatment decreased healing time to 7.8 weeks, compared to 12.6 weeks for controls. Additionally, PTH-treated patients had better

functional scores, with lower pain scores and faster “Timed Up and Go” testing compared to untreated patients [137].

2.4 Conclusion

In conclusion, fracture healing is a highly complex temporally and spatially coordinated process to restore mechanical integrity to bone following trauma. Appropriate management of both acute fractures and nonunions requires a comprehensive understanding of the principles that govern healing. This includes the biologic factors, the mechanical factors, and their interdependence. Previous work has concentrated on optimizing the mechanical environment for healing to occur, driving new innovations in implant design and function. More recently, the focus has shifted toward optimizing the biologic environment. The goal of fracture care is to achieve union in order to restore patients' functionality and livelihood. To this end, our treatment strategies in fracture care will continue to evolve in stride with our growing understanding of fracture healing as well as its impact on patient-important outcomes such as health related quality of life and function.

References

1. Spiegel DA, Gosselin RA, Coughlin RR, Joshupura M, Browner BD, Dormans JP. The burden of musculoskeletal injury in low and middle-income countries: challenges and opportunities. *J Bone Joint Surg Am*. 2008;90(4):915–23.
2. United States Bone and Joint Initiative. Injuries. The burden of musculoskeletal diseases in the United States (BMUS), 3rd ed. Rosemont, IL; 2014. Available at <http://www.boneandjointburden.org>. Accessed 31 Aug 2015.
3. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res*. 2007;22(3):465–75.
4. Tzioupis C, Giannoudis PV. Prevalence of long-bone non-unions. *Injury*. 2007;38(Suppl 2): S3–9. *Erratum in Injury*. 2007;38(10):1224.
5. Brinker M, O'Connor DP. The incidence of fractures and dislocations referred for orthopaedic



- services in a capitated population. *J Bone Joint Surg.* 2004;86-A(2):290–7.
6. Dahabreh Z, Dimitriou R, Giannoudis PV. Health economics: a cost analysis of treatment of persistent fracture non-unions using bone morphogenetic protein-7. *Injury.* 2007;38(3):371–7.
7. Kanakaris NK, Giannoudis PV. The health economics of the treatment of long-bone non-unions. *Injury.* 2007;38(Suppl):S77–84.
8. Einhorn TA. The cell and molecular biology of fracture healing. *Clin Orthop Relat Res.* 1998;355 (Suppl):S7–21.
9. Marsell R, Einhorn TA. The biology fracture healing. *Injury.* 2011;42(6):551–5.
10. Giannoudis PV, Einhorn TA, Marsh D. Fracture healing: the diamond concept. *Injury.* 2007;38(3 Suppl):S3–6.
11. Hankenson KD, Dishowitz M, Gray C, Schenker M. Angiogenesis in bone regeneration. *Injury.* 2011;42(6):556–61.
12. Rhinelander FW. Tibial blood supply in relation to fracture healing. *Clin Orthop Relat Res.* 1974;105:34–81.
13. Thompson Z, Miclau T, Hu D, Helms JA. A model for intramembranous ossification during fracture healing. *J Orthop Res.* 2002;20(5):1091–8.
14. Pape HC, Marcucio R, Humphrey C, Colnot C, Knobe M, Harvey EJ. Trauma-induced inflammation and fracture healing. *J Orthop Trauma.* 2010;24 (9):522–5.
15. Claes LE, Heigele CA. Magnitudes of local stress and strain along bony surfaces predict the course and type of fracture healing. *J Biomech.* 1999;32 (3):255–66.
16. Perren SM. Evolution of the internal fixation of long bone fractures. *J Bone Joint Surg Br.* 2002;84 (8):1093–10.
17. Rahn BA, Gallinaro P, Baltensperger A, Perren SM. Primary bone healing. An experimental study in the rabbit. *J Bone Joint Surg.* 1971;53(4):783–6.
18. Schenck R, Willenegger H. On the histological picture of so-called primary healing of pressure osteosynthesis in experimental osteotomies in the dog. *Experientia.* 1963;19:593–5. [article in German].
19. Perren SM. Physical and biological aspects of fracture healing with special reference to internal fixation. *Clin Orthop Relat Res.* 1979;138:175–96.
20. Shapiro F. Cortical bone repair: the relationship of the lacunar-canalicular system and intercellular gap junctions to the repair process. *J Bone Joint Surg.* 1988;70(7):1067–81.
21. Cruess RL, Dumont J. Fracture healing. *Can J Surg.* 1975;18(5):403–13.
22. Kolar P, Schmidt-Bleed K, Schell H, Gaber T, Toben D, Schmidmaier G, et al. The early fracture hematoma and its potential role in fracture healing. *Tissue Eng Part B Rev.* 2010;16(4):427–34.
23. Oe K, Miwa M, Sakai Y, Lee SY, Kuroda R, Kurosaka M. An in vitro study demonstrating that haematomas found at the site of human fractures contain progenitor cells with multilineage capacity. *J Bone Joint Surg Br.* 2007;89(1):133–8.
24. Tsiridis E, Upadhyay N, Giannoudis P. Molecular aspects of fracture healing: which are the important molecules? *Injury.* 2007;38(Suppl 1):S11–25.
25. Sarahrudi K, Thomas A, Albrecht C, Aharinejad S. Strongly enhanced levels of sclerostin during human fracture healing. *J Orthop Res.* 2012;30 (10):1549–55.
26. Sarahrudi K, Thomas A, Mousavi M, Kaiser G, Kottstorfe J, Kecht M, et al. Elevated transforming growth factor-beta 1 (TGF- β 1) levels in human fracture healing. *Injury.* 2011;42(8):833–7.
27. Sarahrudi K, Mousavi M, Thomas A, Eipeldauer S, Vecsei C, Pietschmann P, Aharinejad S. Elevated levels of macrophage colony-stimulating factor in human fracture healing. *J Orthop Res.* 2010;28 (5):671–6.
28. Bielby R, Jones E, McGonagle. The role of mesenchymal stem cells in maintenance and repair of bone. *Injury.* 38(Suppl 1):S26–32.
29. Malizos KN, Paptheodorou. The healing potential of the periosteum. *Injury.* 2005;36(Suppl 3):S13–9.
30. Shah K, Majeed Z, Jonason J, O’Keefe RJ. The role of muscle in bone repair: the cells, signals, and tissue responses to injury. *Curr Osteoporos Rep.* 2013;11(2):130–5.
31. Yang X, Ricciardi BG, Hernandez-Soria A, Shi Y, Pleshko Camacho N, Bostrom MP. Callus mineralization and maturation are delayed during fracture healing in interleukin-6 knockout mice. *Bone.* 2007;41(6):928–36.
32. Glass GE, Chan JK, Freidin A, Feldmann M, Horwood NJ, Nanchahal J. TNF-alpha promotes fracture repair by augmenting the recruitment and differentiation of muscle-derived stromal cells. *Proc Nat Acad Sci U S A.* 2011;108(4):1585–90.
33. Lehmann W, Edgar CM, Wang K, Cho TJ, Barnes GL, Kakar S, et al. Tumor necrosis factor alpha (TNF-A) coordinately regulates the expression of specific matrix metalloproteinases (MMPs) and angiogenic factors during fracture healing. *Bone.* 2005;36:300–10.
34. Gerstenfeld LC, Cho TJ, Kon T, Aizawa T, Tsay A, Fitch J, et al. Impaired fracture healing in the absence of TNF-alpha signaling: the role of TNF-alpha in endochondral cartilage resorption. *J Bone Miner Res.* 2003;18(9):1584–92.
35. Kitaori T, Ito H, Schwarz EM, Tsutsumi R, Yoshitomi H, Oishi S, et al. Stromal cell-derived factor 1/CXCR4 signaling is critical for the recruitment of mesenchymal stem cells to the fracture site during skeletal repair in a mouse model. *Arthritis Rheum.* 2009;60(3):813–23.
36. Schindeler A, McDonald MM, Bokko P, Little DG. Bone remodeling during fracture repair: the cellular picture. *Semin Cell Dev Biology.* 2008;19(5): 459–66.



37. Lu C, Saless N, Wang X, Sinha A, Decker S, Kazakia G, et al. The role of oxygen during fracture healing. *Bone*. 2013;52(1):220–9.
38. Keramaris NC, Calori GM, Nikolaou VS, Schemitsch EH, Giannoudis PV. Fracture vascularity and bone healing: a systematic review of the role of VEGF. *Injury*. 2008;39(Suppl 2):S45–57.
39. Gerber HP, Vu TH, Ryan AM, Kowalski J, Werb Z, Ferrara N. VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nat Med*. 1999;5(6):623–8.
40. Behonick DJ, Xing Z, Lieu S, Buckley JM, Lotz JC, Marcucio RS, et al. Role of matrix metalloproteinase 13 in both endochondral and intramembranous ossification during skeletal regeneration. *PLoS ONE*. 2007;2(11):e1150.
41. Shapiro F. Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. *Eur Cell Mater*. 2008;15:53–76.
42. Flick LM, Weaver JM, Ulrich-Vinther M, Abuzahab F, Zhang X, Dougall WC, et al. Effects of receptor activator of NF κ B (RANK) signaling blockade on fracture healing. *J Orthop Res*. 2003;21(4):676–84.
43. Raisz LG. Physiology and pathophysiology of bone remodeling. *Clin Chem*. 1999;45(8 Pt 2):1353–8.
44. Sims NA, Gooi JH. Bone remodeling: multiple cellular interactions required for coupling of bone formation and resorption. *Semin Cell Dev Biol*. 2008;19(5):444–51.
45. Teitelbaum SL. Bone resorption by osteoclasts. *Science*. 2000;289(5484):1504–8. (Review).
46. Fan W, Crawford R, Xiao Y. Structural and cellular differences between metaphyseal and diaphyseal periosteum in different aged rats. *Bone*. 2008;42(1):81–9.
47. Uthoff HK, Rahn BA. Healing patterns of metaphyseal fractures. *Clin Orthop Relat Res*. 1981;160:295–303.
48. Claes L, Reusch M, Göckelmann M, Ohnmacht M, Wehner T, Amling M, et al. Metaphyseal fracture healing follows similar biomechanical rules as diaphyseal healing. *J Orthop Res*. 2011;29(3):425–32.
49. Augat P, Margevicius K, Simon J, Wolf S, Suger G, Claes L. Local tissue properties in bone healing: influence of size and stability of the osteotomy gap. *J Orthop Res*. 1998;16(4):475–81.
50. Claes LE, Heigele CA, Neidlinger-Wilke C, Kaspar D, Seidl W, Margevicius KJ, Augat P. Effects of mechanical factors on the fracture healing process. *Clin Orthop Relat Res*. 1998;(355 Suppl):S132–47.
51. Augat P, Merk J, Ignatius A, Margevicius K, Bauer G, Rosenbaum D, Claes L. Early full weightbearing with flexible fixation delays fracture healing. *Clin Orthop Relat Res*. 1996;328:194–202.
52. Willie BM, Blakytyn R, Glockelmann M, Ignatius A, Claes L. Temporal variation in fixation stiffness affects healing by differential cartilage formation in a rat osteotomy model. *Clin Orthop Relat Res*. 2011;469(11):3094–101.
53. Miclau T, Lu C, Thompson Z, Choi P, Puttitz C, Marcucio R, Helms JA. Effects of delayed stabilization on fracture healing. *J Orthop Res*. 2007;25(12):1552–8.
54. Weaver AS, Su YP, Begun DL, Miller JD, Alford AI, Goldstein SA. The effects of axial displacement on fracture callus morphology and MSC homing depend in the timing of application. *Bone*. 2010;47(1):41–8.
55. Brinker MR, Hanus BD, Sen M, O'Connor DP. The devastating effects of tibial nonunion on health-related quality of life. *J Bone Joint Surg Am*. 2013;95(24):2170–6.
56. Bhandari M, Fong K, Sprague S, Williams D, Petrisor B. Variability in the definition and perceived causes of delayed unions and nonunions: a cross-sectional, multinational survey of orthopaedic surgeons. *J Bone Joint Surg Am*. 2012;94(15):e1091–6.
57. Corrales LA, Morshed S, Bhandari M, Miclau T 3rd. Variability in the assessment of fracture-healing in orthopaedic trauma studies. *J Bone Joint Surg Am*. 2008;90(9):1862–8.
58. Joslin CC, Eastaugh-Waring SJ, Hardy JR, Cunningham JL. Weight bearing after tibial fracture as a guide to healing. *Clin Biomech (Bristol, Avon)*. 2008;23(3):329–33.
59. Webb J, Herling G, Gardner T, Kenwright J, Simpson AH. Manual assessment of fracture stiffness. *Injury*. 1996;27(5):319–20.
60. Whelan DB, Bhandari M, Stephen D, Kreder H, McKee MD, Zdero R, Schemitsch EH. Development of the radiographic union score for tibial fractures for the assessment of tibial fracture healing after intramedullary fixation. *J Trauma*. 2010;68(3):629–32.
61. Kooistra BW, Dijkman BG, Busse JW, Sprague S, Schemitsch EH, Bhandari M. The radiographic union scale in tibial fractures: reliability and validity. *J Orthop Trauma*. 2010;24(Suppl 1):S81–6.
62. Bhandari M, Chiavaras M, Ayeni O, Chakraverty R, Parasu N, Choudur H, et al. Assessment Group for Radiographic Evaluation and Evidence (AGREE) Study Group (AGREE Investigators Writing Committee). Assessment of radiographic fracture healing in patients with operatively treated femoral neck fractures. *J Orthop Trauma*. 2013;27(9):e213–9.
63. Bhandari M, Chiavaras MM, Parasu N, Choudur H, Ayeni O, Chakraverty R, et al. Radiographic union score for hip substantially improves agreement between surgeons and radiologists. *BMC Musculoskelet Disord*. 2013;14:70.
64. McClelland D, Thomas PB, Bancroft G, Moorcroft CI. Fracture healing assessment comparing stiffness measurements using radiographs. *Clin Orthop Relat Res*. 2006;457:214–9.



65. Davis BJ, Roberts PJ, Moorcroft CI, Brown MF, Thomas PB, Wade RH. Reliability of radiographs in defining union of internally fixed fractures. *Injury*. 2004;35(6):557–61.
66. Cox G, Einhorn TA, Tzioupis C, Giannoudis PV. Bone-turnover markers in fracture healing. *J Bone Joint Surg Br*. 2010;92(3):329–34.
67. Lu C, Miclau T, Hu D, Hansen E, Tsui K, Puttlitz C, Marcucio RS. Cellular basis for age-related changes in fracture repair. *J Orthop Res*. 2005;23(6):1300–7.
68. Desai BJ, Meyer MH, Porter S, Kellam JF, Meyer RA Jr. The effect of age on gene expression in adult and juvenile rats following femoral fracture. *J Orthop Trauma*. 2003;17(10):689–98.
69. Lu C, Sapozhnikova A, Hu D, Miclau T, Marcucio RS. Effect of age on vascularization during fracture repair. *J Orthop Res*. 2008;26(10):1384–9.
70. Egermann M, Heil P, Tami A, Ito K, Janicki P, Von Rechenberg B, et al. Influence of defective bone marrow osteogenesis on fracture repair in an experimental model of senile osteoporosis. *J Orthop Res*. 2009;28(6):798–804.
71. D'Ippolito G, Schiller PC, Ricordi C, Roos BA, Howard GA. Age-related osteogenic potential of mesenchymal stromal stem cells from human vertebral bone marrow. *J Bone Miner Res*. 1999;14(7):1115–22.
72. Stenderup K, Justesen J, Eriksen EF, Rattan S, Kassem M. Number and proliferative capacity of osteogenic stem cells are maintained during aging and in patients with osteoporosis. *J Bone Miner Res*. 2001;16(6):1120–9.
73. International Osteoporosis Foundation. Epidemiology. <http://www.iofbonehealth.org/epidemiology>. Accessed 27 Aug 2015.
74. Nikolaou VS, Efsthathopoulos N, Kontakis G, Kanakaris NK, Giannoudis PV. The influence of osteoporosis in femoral fracture healing time. *Injury*. 2009;40(6):663–8.
75. Namkung-Matthai H, Appleyard R, Jansen J, Hao Lin J, Maastricht S, Swain M, et al. Osteoporosis influences the early period of fracture healing in a rat osteoporotic model. *Bone*. 2001;28(1):80–6.
76. Walsh WR, Sherman P, Howlett CR, Sonnabend DH, Ehrlich MG. Fracture healing in a rat osteopenia model. *Clin Orthop Relat Res*. 1997;342:218–27.
77. Lill CA, Hessel J, Schlegel U, Eckhardt C, Goldhahn J, Schneider E. Biomechanical evaluation of healing in a non-critical defect in a large animal model of osteoporosis. *J Orthop Res*. 2003;21(5):836–42.
78. Brinker MR, O'Connor DP, Monla YT, Earthman TP. Metabolic and endocrine abnormalities in patients with nonunions. *J Orthop Trauma*. 2007;21(8):557–70.
79. Lancourt JE, Hochberg F. Delayed fracture healing in primary hyperparathyroidism. *Clin Orthop Rel Res*. 1977;124:214–8.
80. Cozen L. Does diabetes delay fracture healing? *Clin Orthop Relat Res*. 1972;82:134–40.
81. Loder R. The influence of diabetes mellitus on the healing of closed fractures. *Clin Orthop*. 1988;232:210–6.
82. Albowi J, Tian C, Siqueira MF, Kayal RA, McKenzie E, Behl Y, et al. Chemokine expression is upregulated in chondrocytes in diabetic fracture healing. *Bone*. 2013;53(1):294–300.
83. Kayal RA, Siqueira M, Alblowi J, McLean J, Krothapalli N, Faibish D, et al. TNF-alpha mediates diabetes-enhanced chondrocyte apoptosis during fracture healing and stimulates chondrocyte apoptosis through FOXO1. *J Bone Miner Res*. 2010;25(7):1604–15.
84. Kayal RA, Tsatsas D, Bauer MA, Allen B, Al-Sebaei MO, Kakar S, et al. Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoclast activity. *J Bone Miner Res*. 2014;29(4):560–8.
85. Kagel EM, Einhorn TA. Alterations of fracture healing in the diabetic condition. *Iowa Orthop J*. 1967;16:147–52.
86. Follak N, Klötting I, Merk H. Influence of diabetic metabolic state on fracture healing in spontaneously diabetic rats. *Diabetes Metab Res Rev*. 2005;21(3):288–96.
87. Gandhi A, Beam HA, O'Connor JP, Parsons JR, Lin SS. The effects of local insulin delivery on diabetic fracture healing. *Bone*. 2005;37(4):482–90.
88. Chaudhary SB, Liporace FA, Gandhi A, Donley BG, Pinzur MS, Lin SS. Complications of ankle fracture in patients with diabetes. *J Am Acad Orthop Surg*. 2008;16(3):159–70.
89. Castillo RC, Bosse MJ, MacKenzie EJ, Patterson BM; LEAP Study Group. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. *J Orthop Trauma*. 2005;19(3):151–7.
90. Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. *Injury*. 2001;32(1):61–5.
91. Murray IR, Foster CJ, Robinson CM. Risk factors for nonunion after nonoperative treatment of displaced midshaft fractures of the clavicle. *J Bone Joint Surg Am*. 2013;95(13):1153–8.
92. Ristiniemi J, Flinkkila T, Hyvonen P, Lakovaara M, Pakarinen H, Biancari F, Jalovaara P. Two-ring hybrid external fixation of distal tibial fractures: a review of 47 cases. *J Trauma*. 2007;62(1):174–83.
93. Govender S, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, et al. BMP-2 Evaluation in Surgery for Tibial trauma (BESTT) Study Group. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am*. 2002;84-A(12):2123–34.



94. Shen Y, Liu HX, Ying XZ, Yang SZ, Nie PF, Cheng SW, et al. Dose-dependent effects of nicotine on proliferation and differentiation of human bone marrow stromal cells and the antagonistic action of vitamin C. *J Cell Biochem.* 2013;114(8):1720–8.
95. Lee JJ, Patel R, Biermann S, Dougherty PJ. The musculoskeletal effects of cigarette smoking. *J Bone Joint Surg Am.* 2013;95(9):850–9.
96. Skott M, Andreassen TT, Ulrich-Vinther M, Chen X, Keyler DE, LeSage MG, et al. Tobacco extract but not nicotine impairs the mechanical strength of fracture healing in rats. *J Orthop Res.* 2006;24(7):1472–9.
97. Kristensson H, Lunden A, Nilsson BE. Fracture incidence and diagnostic roentgen in alcoholics. *Acta Orthop Scan.* 1980;51(2):205–7.
98. Nyquist F, Berglund M, Nilsson BE, Obrant KJ. Nature and healing of tibial shaft fractures in alcohol abusers. *Alcohol.* 1997;32(1):91–5.
99. Laitinen K, Lamberg-Allardt C, Tunninen R, Harkonen M, Valimski M. Bone mineral density and abstention-induced changes in bone and mineral metabolism in noncirrhotic male alcoholics. *Am J Med.* 1992;93(6):642–50.
100. Diamond T, Stiel D, Lunzer M, Wilkinson M, Posen S. Ethanol reduces bone formation and may cause osteoporosis. *Am J Med.* 1989;86(3):282–8.
101. Hillers VN, Massey LK. Interrelationships of moderate and high alcohol consumption with diet and health status. *Am J Clin Nutr.* 1985;41(2):356–62.
102. Chakkalakal DA. Alcohol-induced bone loss and deficient bone repair. *Alc Clin Exper Res.* 2005;29(12):2077–90.
103. Chakkalakal DA, Novak JR, Fritz ED, Mollner TJ, McVicker DL, Garvin KL, et al. Inhibition of bone repair in a rat model for chronic and excessive alcohol consumption. *Alcohol.* 2005;36(3):1–14.
104. Jung MK, Callaci JJ, Lauing KL, Otis JS, Radek KA, Jones MK, Kovacs EJ. Alcohol exposure and mechanisms of tissue injury and repair. *Alcohol Clin Exp Res.* 2011;35(3):392–9.
105. Janicke-Lorenz J, Lorenz R. Alcoholism and fracture healing, a radiological study in the rat. *Arch Orthop Trauma Surg.* 1984;103(4):286–9.
106. Volkmer DL, Sears B, Lauing KL, Nauer RK, Roper PM, Yong S, et al. Antioxidant therapy attenuates deficient bone fracture repair associated with binge alcohol exposure. *J Orthop Trauma.* 2011;25(8):516–21.
107. Kurmis AP, Kurmis TP, O'Brien JX, Dalén T. The effect of nonsteroidal anti-inflammatory drug administration on acute phase fracture-healing: a review. *J Bone Joint Surg Am.* 2012;94(9):815–23.
108. Abdul-Hadi O, Parvizi J, Austin MA, Viscusi E, Einhorn T. Nonsteroidal anti-inflammatory drugs in orthopaedics. *J Bone Joint Surg Am.* 2009;91(8):2019–27.
109. Jee WS, Ma YF. The in vivo anabolic actions of prostaglandins in bone. *Bone.* 1997;21(4):297–304.
110. Li M, Healy DR, Li Y, Simmons HA, Crawford DT, Ke HZ, et al. Osteopenia and impaired fracture healing in aged EP4 receptor knockout mice. *Bone.* 2005;37(1):46–54.
111. Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. *J Bone Miner Res.* 2002;17(6):963–76.
112. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis: the influence of reaming and non-steroidal anti-inflammatory drugs. *J Bone Joint Surg Br.* 2000;82(5):655–8.
113. Dahners LE, Mullis BH. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. *J Am Acad Orthop Surg.* 2004;12(3):139–43.
114. Ro J, Sudmann E, Marton PF. Effect of indomethacin on fracture healing in rats. *Acta Orthop Scand.* 1976;47(6):588–99.
115. Gerstenfeld LC, Thiede M, Seibert K, Mielke C, Phippard D, Svagr B, et al. Differential inhibition of fracture healing by non-selective cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs. *J Orthop Res.* 2003;21(4):670–5.
116. Lack WD, Fredericks D, Petersen E, Donovan M, George M, Nepola J, et al. Effect of aspirin on bone healing in a rabbit ulnar osteotomy model. *J Bone Joint Surg Am.* 2013;95(6):488–96.
117. Solomon HM, Mogun H, Schneeweiss S. The relation between bisphosphonate use and non-union of fractures of the humerus in older adults. *Osteoporos Int.* 2009;20(6):895–901.
118. Rozental TD, Vazquez MA, Chacko AT, Ayogu N, Boussein ML. Comparison of radiographic fracture healing in the distal radius for patients on and off bisphosphonate therapy. *J Hand Surg Am.* 2009;34(4):595–602.
119. Gong HS, Song CH, Lee YH, Thee SH, Lee HJ, Baek GH. Early initiation of bisphosphonate does not affect healing and outcomes of volar plate fixation of osteoporotic distal radial fractures. *J Bone Joint Surg Am.* 2012;94(19):1729–36.
120. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. HORIZON recurrent fracture trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* 2007;357(18):1799–809.
121. Li J, Mori S, Kaji Y, Mashiba T, Kawanishi J, Norimatsu H. Effect of bisphosphonate (incadronate) on fracture healing of long bones in rats. *J Bone Miner Res.* 1999;14:969–79.
122. McDonald MM, Dulai S, Godfrey C, Amanat N, Sztynka T, Little DG. Bolus or weekly zoledronic acid administration does not delay endochondral fracture repair but weekly dosing enhances delays in hard callus remodeling. *Bone.* 2008;43(4):653–62.
123. Saito M, Shiraishi A, Ito M, Sakai S, Kayakawa N, Mihara M, Marumo K. Comparison of effects of alfacalcidol and alendronate on mechanical



- properties and bone collagen cross-links of callus in the fracture repair rat model. *Bone*. 2010;46(4):1170–9.
124. Jørgensen NR, Schwarz P. Effects of anti-osteoporosis medications on fracture healing. *Curr Osteoporos Rep*. 2011;9(3):149–55.
125. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab*. 2005;90(3):1294–301.
126. Egol KA, Park JH, Rosenberg ZS, Peck V, Tejwani NC. Healing delayed but generally reliable after bisphosphonate-associated complete femur fractures treated with IM nails. *Clin Orthop Relat Res*. 2014;472(9):2728–34.
127. Weil YA, Rivkin G, Safran O, Liebergall M, Foldes AJ. The outcome of surgically treated femur fractures associated with long-term bisphosphonate use. *J Trauma*. 2011;71(1):186–90.
128. Diab DL, Watts NB. Bisphosphonate drug holiday: who, when and how long. *Ther Adv Musculoskelet Dis*. 2013;5(3):107–11.
129. Ellegaard M, Jorgensen NR, Schwarz P. Parathyroid hormone and bone healing. *Calcif Tissue Int*. 2010;87(1):1–13.
130. Goldhahn J, Feron JM, Kanis J, Papapoulos A, Reginster JY, Rizzoli R, et al. Implications for fracture healing of current and new osteoporosis treatments: an ESCEO consensus paper. *Calcif Tissue Int*. 2012;90(5):343–53.
131. Kakar S, Einhorn TA, Vora S, Miara LJ, Hon G, Wigner NA, et al. Enhanced chondrogenesis and Wnt signaling in PTH-treated fractures. *J Bone Miner Res*. 2007;22(12):1903–12.
132. Holzer G, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA. Parathyroid hormone enhances fracture healing. A preliminary report. *Clin Orthop Relat Res*. 1999;366:258–63.
133. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1–34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res*. 1999;14(6):960–8.
134. Andreassen TT, Willick GE, Morley P, Whitfield JF. Treatment with parathyroid hormone hpth(1–34), hpth(1–31), and monocyclic hpth(1–31) enhances fracture strength and callus amount after withdrawal fracture strength and callus mechanical quality continue to increase. *Calcif Tissue Int*. 2004;74(4):351–6.
135. Manabe T, Mori S, Mashiba T, Kaji Y, Iwata K, Komatsubara S. Human parathyroid hormone (1–34) accelerates natural fracture healing process in the femoral osteotomy model of cynomolgus monkeys. *Bone*. 2007;40(6):1475–82.
136. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, et al. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res*. 2010;25(2):404–14.
137. Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1–84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *J Bone Joint Surg Am*. 2011;93(17):1583–7.

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