Bone Healing and Inflammation: Principles of Fracture and Repair

Hassan ElHawary, MD, MSc[1] Aslan Baradaran, MD, MSc[1] Jad Abi-Rafeh, MSc[1]
Joshua Vorstenbosch, MD, PhD, FRCSC[1] Liqin Xu, MD, MSc, FRCSC[1]
Johnny Ionut Efanov, MD, PhD, FRCSC[2]

[1] Division of Plastic and Reconstructive Surgery, McGill University Health Centre, Montreal, Quebec, Canada
[2] Division of Plastic and Reconstructive Surgery, Centre Hospitalier de l'Université de Montréal, Quebec, Canada

Address for correspondence Johnny I. Efanov, MD, PhD, FRCSC, Division of Plastic and Reconstructive Surgery, Centre hospitalier de l'Universite de Montreal, 1051 Rue Sanguinet, Montreal, Quebec, H2 × 3E4, Canada (e-mail: johnny.ionut.efanov@umontreal.ca).

Semin Plast Surg 2021;35:198–203.

Abstract

Bones comprise a significant percentage of human weight and have important physiologic and structural roles. Bone remodeling occurs when healthy bone is renewed to maintain bone strength and maintain calcium and phosphate homeostasis. It proceeds through four phases: (1) cell activation, (2) resorption, (3) reversal, and (4) bone formation. Bone healing, on the other hand, involves rebuilding bone following a fracture. There are two main types of bone healing, primary and secondary. Inflammation plays an integral role in both bone remodeling and healing. Therefore, a tightly regulated inflammatory response helps achieve these two processes, and levels of inflammation can have detrimental effects on bone healing. Other factors that significantly affect bone healing are inadequate blood supply, biomechanical instability, immunosuppression, and smoking. By understanding the different mechanisms of bone healing and the factors that affect them, we may have a better understanding of the underlying principles of bony fixation and thereby improve patient care.

Keywords
- bone healing
- fracture repair
- bone inflammation
- osteomyelitis

The human body is made up of 206 bones, representing approximately 15% of an adult's total body weight. Fracture incidence varies based on age and gender, but ranges from 2 to 5 per 100 person-years.[1–3] More alarmingly, there has been a significant increase in the fracture incidence over the last several years.[2,3]

Fractures not only affect patients quality of life, but also impute a substantial cost on society.[4] The cost of illness (COI) associated with fractures has been previously reported across different populations.[4,5] Hip fractures have the highest COI with reported numbers over $30,000, mostly due to long-term morbidity costs.[4] More distressingly, almost one in three patients over 50 years of age who sustain a hip fracture die within 1 year of the incident.[6]

One way of improving fracture outcomes is by understanding principles of bone growth and healing. To that end, the primary goal of this paper is to provide a comprehensive review of bone healing and inflammation. Moreover, we hope to provide an evidence-based practical approach to bone pathologies such as fractures and osteomyelitis.

Anatomy and Structure of Bone

Types of Bone

There are two main types of bone, cortical and cancellous. Cortical bone is dense and solid; it contains osteons termed Haversian canals.[7] These are cylindrical structures that form a branching network. The walls of these structures are composed of concentric lamellae that fit inside each other. On the other hand, cancellous bone (spongy bone) is composed of a network of trabecular plates and rods in a honeycomb configuration. It also contains osteons called packets which are semilunar in shape and also composed of concentric lamellae.

Issue Theme Healing, Inflammation, and Fibrosis; Guest Editor: Joshua Vorstenbosch, MD, PhD, FRCSC

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0041-1732334.
ISSN 1535-2188.

The term lamellar bone refers to the orientation of bone where collagen fibrils are deposited in an alternating fashion, thereby providing increased bone strength. On the other hand, woven bone is formed when collagen fibrils are deposited in a disorganized manner (usually present in the formation of primary bone).

Categories of Bone

There are four broad categories of bones. Long bones consist of a long-hollow shaft (diaphysis), a cone-shaped metaphysis proximal to the growth plate, and a rounded epiphysis distal to the growth plate. The shaft is mainly composed of compact bone while the metaphyses and epiphyses are mainly composed of a trabecular bone. Long bones contain both yellow and red bone marrow and are the principal type of bone that produces blood cells. Examples of long bones include the femur, humerus, and radius. The second type is of short bones. These are usually cube shaped with approximately equal horizontal and vertical dimensions. They are mainly composed of trabecular bone and covered by a thin layer of cortical bone. Examples of short bones include the carpal and tarsal bones. The third type are flat bones which are thin bones made up of a layer of trabecular bone within two layers of cortical bone; examples include the mandible and calvaria. The last type of bones are irregular bones. They do not fit in any of the three categories mentioned above. They are made up primarily of trabecular bone and covered by a thin layer of cortical bone. Examples of irregular bones include the vertebrae and the hyoid bone.[8]

Bone Composition

Bone is heterogeneously composed of inorganic minerals and an organic matrix. Hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) is the main inorganic mineral in bone and makes up the majority of bone material. It aids in giving bone its rigidity and strength. Calcium is tightly regulated via different hormones. Parathyroid hormone (PTH) stimulates bone resorption through calcium release from bone into blood. On the other hand, calcitonin prevents bone breakdown by inactivating osteoclasts. Finally, calcitriol has many functions including increasing intestinal absorption of calcium and phosphorous, the main components of the osseus inorganic matrix.[9]

On the other hand, the organic matrix is mainly composed of collagen type I (approximately 90% of organic matrix), glycosylated proteins (approximately 5% of organic matrix), and growth factors such as transforming growth factor-beta (TGF-beta), growth hormone (GH), and insulin-like growth factors (IGF).[10] Collagen has an integral role in maintaining the structure of bone.[10] It also plays an important role in bone function and is involved in processes such as bone apoptosis, cell proliferation, and differentiation.[11–13] Glycosylated proteins, specifically small leucine-rich proteins, are present in bone and play an important role in cell proliferation, bone remodeling and mineral deposition.[14] Finally, growth factors, such as TGF-beta, GH, and IGF, are all important regulators and signaling markers for bone homeostasis, remodeling, and matrix protein synthesis.[15,16]

Bone Modeling and Remodeling

Bone modeling is the process by which bones respond to physiologic stress or mechanical forces, by changing their shape or configuration. It was first described by the German Surgeon Julius Wolff in 1892 where he postulated that long bones change shape to accommodate stresses they endure.[17] Over 100 years later, his hypothesis holds true; it is currently believed that strains within bone tissue are transduced into signals that can control bone deposition and lead to bone formation.[18] Bones may increase in size or change axis by addition and removal of bone through osteoblasts and osteoclasts, respectively. Another distinct concept is bone remodeling. Bone remodeling is the process by which healthy bone is renewed to maintain bone strength, preserve its mineral composition, and maintain calcium and phosphate homeostasis. This tightly organized process involves the continuous resorption of old bone and deposition of newly synthesized proteinaceous matrix which eventually becomes calcified once again. This process is composed of four main phases.

The first phase of bone remodeling is cell activation which involves recruitment and activation of monocyte macrophages and osteoclast precursors from circulation.[19] The second phase is resorption which is mediated by osteoclasts and regulated by a large spectrum of inflammatory markers such as interleukin (IL)-1 and IL-6.[20] Osteoclasts resorb bone through lowering the pH within the bone compartment and secreting tartrate-resistant acid phosphatase and other enzymes that digest the bone organic matrix. The third step is reversal, where preosteoblasts are recruited alongside coupling signals that signal the end of bone resorption and the beginning of bone formation.[21] The final step, bone formation, is mediated by osteoblasts which synthesize new collagenous organic matrix.[22] While osteoblasts deposit bone, they become entrapped within the matrix they secrete, becoming osteocytes which remain in contact and communication through a network that serves as a functional syncytium. The final result of bone remodeling is production of a new osteon.

Bone Healing

Primary Healing

Bone healing is the process of rebuilding bone following a fracture. There are two main types of bone healing, primary and secondary. Primary (direct) healing occurs when the bony fragments are perfectly reduced, aligned, and fixed under compression with no motion at the fracture site. If these requirements are achieved, bone can heal via direct remodeling of lamellar bone and Haversian canals.[23] Bone on one side of the cortex must connect with bone on the other side to reestablish mechanical and physical continuity. Cutting cones are formed at the ends of the osteons closest to the fracture site. These cones cross the fracture line and generate longitudinal cavities (via osteoclasts) which are then filled by bone matrix (via osteoblasts). This results in generation of bony union and restoration of Haversian systems that allow

for blood supply to be reestablished.[24] Finally, osteons mature and undergo remodeling into lamellar bone, thereby healing the fracture site without the formation of callus or inflammation.[25]

Secondary Healing

While primary bone healing can be achieved by open reduction and internal fixation under compression, the more common type of bone healing is secondary (indirect) healing. Secondary healing consists of both intramembranous and endochondral ossification and occurs via four main stages. The first stage is the acute inflammatory response which begins with a hematoma formation. The hematoma coagulates and forms a temporary scaffold that acts as a template for callus formation.[26] Acute inflammatory markers, such as tumor necrosis factor alpha (TNF-α), IL-1, IL-6, are then recruited. These markers attract macrophages, monocytes, and lymphocytes that then serve to remove necrotic tissue and secrete cytokines, such as vascular endothelial growth factor (VEGF), which stimulate healing and promote angiogenesis. This stage lasts approximately 5 days. The second stage is the formation of the fibrocartilaginous network; mesenchymal stem cells are recruited and differentiated into fibroblasts, osteoblasts, and chondroblasts.[27] This initiates chondrogenesis via deposition of a collagen-rich fibrocartilaginous network that spans the fracture site (soft callus). Simultaneously, a layer of woven bone is deposited. The stage usually starts on day 5 postfracture and lasts approximately 5 days. The third stage is the bony callus formation where the cartilaginous callus (soft callus) undergoes endochondral ossification to form the hard callus (via chondro- and osteoblasts and clasts). This occurs via resorption of the cartilaginous callus and deposition of woven bone subperiosteally.[28] This stage usually lasts up until 4 weeks postinjury. It is important to note that there is significant overlap between the second and third stages (mesenchymal cell recruitment and hard callus formation). The fourth and final step is bone remodeling where the bony callus is remodeled via osteoclasts and osteoblasts to form compact bone centrally, and lamellar bone peripherally.[29] This allows the newly formed bone to achieve the rigidity and biomechanical stability of normal bone. This stage can last months to years. Understanding the different stages on bone healing and their timeline allows us to better appreciate treatment protocols and length of immobilization required.

Inflammation

Inflammation is a key response in bone healing. As previously discussed, proinflammatory cytokines are initially recruited to initiate the process of secondary healing. However, increased inflammation could have undesirable effects on bone healing. An experimental rat model that demonstrated increased proinflammatory activity (via administration of lipopolysaccharide) impairs bone healing.[30] Another study found that increasing anti-inflammatory IL-10 was found to improve osseus healing postfractures in rats.[31] In humans, systemic inflammatory conditions, such arthritis, diabetes mellitus, sepsis, or multiple trauma, increase fracture healing time and impair osseus healing.[32]

While excessive inflammation worsens healing, impaired inflammation can also impede healing and increase rates of delayed osseus healing. One topic that has been intensely discussed over the last several years is use of nonsteroidal anti-inflammatory drugs (NSAIDS) following fractures. These drugs have anti-inflammatory and analgesic properties and are frequently prescribed postsurgery. However, multiple studies have shown worsening rates of bony healing, increased nonunions, and weaker bones associated with NSAIDs use.[33–35] While the underlying pathophysiology of impaired healing due to increased or decreased states of inflammation remains a debated topic, a tightly regulated inflammatory response is believed to be critical for adequate osseus healing.

Infection

Osteomyelitis, defined as bone infection, is a dreaded complication that significantly impairs bone healing and leads to loss of function and even amputation.[36] The incidence of infection after bone fixation varies from 1 to 2% in closed fractures, to up to 30% in open fractures.[37] Studies have shown that infection impairs callus formation, wherein fibrous tissue is formed instead, affecting woven bone deposition and thereby decreasing mechanical stability and overall osseus healing.[38] Neutrophils, one of the main immune cell types present in infected tissues, are also associated with increased rates of delayed osseous healing.[38]

Osteomyelitis usually presents with nonspecific signs and symptoms such as pain, fever, chills, and lethargy. Physical examination findings include but are not limited to cardinal signs of inflammation, decreased range of motion, and point tenderness. Clinicians should have a low threshold of susception of osteomyelitis in the context of inserted hardware postreduction.

Blood tests, such a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are useful adjuncts in diagnosing this condition. Blood cultures should always be obtained in cases of query osteomyelitis; however, a negative blood culture does not exclude the diagnosis.[39] Radiological imaging can be of great value in the diagnosis of osteomyelitis. Whereas standard X-ray radiography might show signs of bony resorption, bone scans were previously perceived as the gold-standard radiological study for osteomyelitis; a radioactive substance, usually technecium-99, accumulates in areas of increased blood flow which indicates infection. However, recently, magnetic resonance imaging (MRI) has been hailed as a more accurate radiologic modality (higher sensitivity and specificity), as it shows greater anatomical details and signs of cortical destruction.[40] However, the gold standard for osteomyelitis diagnosis is bone biopsy and histopathologic examination.[39]

Treatment of osteomyelitis should not be delayed as it can significantly affect morbidity and limb salvation. As per infection control principles, the most important treatment

is infection control. This means that any infected hardware should be promptly removed, and surrounding soft tissue infection drained/debrided and washed out. *Staphylococcus aureus* is the most common pathogen causing osteomyelitis in adults. However, board spectrum intravenous (IV) antibiotics should be initiated promptly and stepped down to another antibiotic with more specific coverage once bacterial cultures and sensitivities are obtained. Treatment in adults usually consists of 6 weeks of IV antibiotics. Infected bone has relatively poor blood supply, and therefore require longer duration of treatment in order for the antibiotic levels to reach sufficient concentration to be able to penetrate bone.[39,41,42]

Clinical Significance and Practical Approach

Principles of Reduction and Fixation

In order to strive for optimal fracture healing, it is critical to understand factors that affect bone healing. For successful bone healing to occur, adequate blood supply and fracture stability are crucial. There are four principles of fracture fixation (AO principles)[43] that are integral to optimal fracture fixation and healing. The first of which is fracture reduction to restore anatomical relationships. The second principle is fracture fixation to provide absolute or relative stability. The third principle is preservation of blood supply to soft tissue and bone. The final principle is early and safe mobilization.[44] These principles allow optimal bone healing and the prevention of delayed healing and nonunion. Nonunion is defined as an arrest in fracture healing or presence of the fracture 9 months of postinjury, with at least 3 months without radiologic signs of healing.[45] Delayed union is defined as failure to reach bony union 6 months of postfracture.

There are many different types of bony fixation. An important dichotomy to appreciate is rigid versus nonrigid fixation. The former achieves absolute fracture stability and prevents interfragmentary motion across the fracture site, while the latter achieves relative stability and restores axials, angular, and rotational alignment.[46] Consequently, rigid fixation leads to primary healing (Haversian remodeling) while nonrigid fixation leads to secondary healing with callous formation. Another important concept is fracture compression. Fixation modalities that compress the bony fragments across the fracture site allows for rigid fixation and hence absolute stability. Compression can be achieved by compression plates, overbending of the plate, lag screws, and external tension devices. On the other hand, casting, percutaneous Kirschner's wire placement and external fixation devices are all examples of nonrigid non compression fixation modalities that lead to secondary healing with callous formation.

There exist other local and systematic factors that affect bone healing which clinicians should be aware of and attempt to optimize. Factors, such as obesity, steroid administration, malnutrition, and smoking, are also significantly impair bone healing and need to be addressed in order to provide holistic patient care.[47–53]

Bone Stimulators

One emerging technique to treat delayed unions and nonunions is bone stimulation. This technique consists of delivering an electrical or electromagnetic (EM) field to a fracture site. While the mechanism of action remains incompletely understood, it is believed that the EM field acts like a mechanical load which causes a strain gradient across the bone fracture to stimulate healing.[54] Another novel method of bone stimulation is low-intensity pulsed ultrasound (LIPUS) which delivers ultrasonic stimuli to the fracture site. LIPUS is believed to improve osseus healing through increasing chondrocytes, soft callus formation, and therefore earlier endochondral ossification.[55] While many recent studies have investigated both electrical stimulation, as well as LIPUS, mixed evidence exists regarding their efficacy and more studies are warranted before considering a standardized approach in clinical practice.[55–59]

Conclusion

Understanding bone healing is vital to provide the best care for patients. Inflammation is a key response that initiates osseus healing; however, an excess level of an inflammatory response can impair fracture healing and lead to nonunions. Other factors that significantly affect bone healing are inadequate blood supply, biomechanical instability, immunosuppression, and smoking. By understanding the different mechanisms of bone healing, a better application of principles relating to bony fixation can be implemented which ultimately will lead to improved patient care.

Funding
None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Conflict of Interest
None declared.

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