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Fracture Healing Overview

Authors

Jonathon R. Sheen[1]; Ahmed Mabrouk[2]; Vishnu V. Garla[3].

Affiliations

[1] Torbay Hospital
[2] National Health Service (NHS), United Kingdom
[3] University of Mississippi Medical Center

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Definition/Introduction

Bone fracture healing: is an intricate and fluent regenerative process that aims at restoring the damaged bone to its pre-injury state and cellular composition.[1] A fracture is a breach in the structural continuity of the bone cortex, with a degree of injury to the surrounding soft tissues. Following the fracture, secondary healing begins, which consists of four steps:

1. Hematoma formation
2. Granulation tissue formation
3. Bony callus formation
4. Bone remodeling

The type of fracture healing is governed by the achieved mechanical stability at the fracture site and, consequently, the strain. An appropriate mechanical stimulation, such as strain, facilitates tissue formation at the bony ends. The amount of the involved strain dictates the biological behavior of the cells involved in the healing process and, consequently, the type of bone healing.[2][3][4] Primary bone healing ensues with mechanical strain below 2%, whereas secondary bone healing ensues when the mechanical strain is between 2 and 10%.[5][6][7][8] In contrast, a strain >10% results in non-union or delayed union.[9][10][6][5]

There are two main modes of bone healing; **primary bone healing** is dictated by absolute stability constructs that achieve a mechanical strain below 2%. It is an **intramembranous** bone healing that occurs through **Haversian remodeling**. The other type is **secondary bone healing** which occurs in non-rigid fixation modalities such as braces, external fixation, plates in bridging mode, intramedullary nailing, ..etc. These fixation modalities achieve a mechanical strain between 2-10%. And it occurs via **endochondral** bone healing. Bone healing can involve a combination of primary and secondary processes based on the stability throughout the construct.

Failed or delayed healing can affect up to 10% of all fractures and can result from factors such as comminution, infection, tumor, and disrupted vascular supply. During this article, we will work through each of these steps in order and detail before touching on primary healing, factors affecting fracture healing, and methods of stimulation of fracture healing.[11][1]

Issues of Concern

Fracture healing starts with **an anabolic phase** where there is recruitment and differentiation of stem cells with

subsequent increases in the skeletal and vascular tissue volume. A cartilaginous callus forms at the fracture site, whereas at the periphery of this callus, the periosteum swells, and the primary bone formation starts.[12] Simultaneously with cartilaginous callus formation, the cells involved in angiogenesis are recruited and differentiated in the nearby muscle mass. With further progression of chondrocyte differentiation, the extracellular matrix is mineralized, and the chondrocytes undergo apoptosis. This is followed by **a catabolic phase** where cartilage resorption ensues, resulting in tissue and callus volume reduction.[1]

Fracture healing is complex, and it involves the following stages: **hematoma formation, granulation tissue formation, callus formation, and bone remodeling**. However, there is considerable overlap between these stages. Principle cells and their secretions are involved in the healing process, in which the mesenchymal stem cells play a pivotal role. They are delivered mainly by two major sources; periosteum and endosteum. Others involved include inflammatory cells, endothelial cells, fibroblasts, osteoblasts, and osteoclasts.[1][13]

Hematoma Formation: (Immediately after the fracture)

This forms the key step in fracture healing. The blood vessels supplying the bone and periosteum are disrupted during the fracture, causing a hematoma to form at the fracture site, which is rich in hematopoietic cells. The hematoma clots and forms the temporary frame for subsequent healing. An adequate number of MSCs is recruited at the fracture site from the nearby tissues and the circulation.[14][15] MSCs express matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), both influence MSCs' migration capacity.[16][17][18]

Macrophages, neutrophils, and platelets release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), bone morphogenetic proteins (BMPs), platelet-derived growth factors (PDGF), transforming growth factor beta (TGF-Beta), vascular endothelial growth factor (VEGF) and interleukins (IL-1, IL-6, IL-10, IL-11, IL 12, IL-23). These cytokines further stimulate essential cellular biology at the fracture site.

Granulation Tissue Formation (Primary or fibrocartilaginous callus): (Within two weeks) This provides provisional stability.

Platelets are recruited to the fracture site. Among the products secreted by platelets are fibronectin (FN), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β), which collectively trigger an inflammatory response. Subsequently, other mesenchymal cells and inflammatory cells are recruited to the fracture site, such as fibroblasts and endothelial cells, with resultant **fibrin-rich granulation tissue** formation and angiogenesis. [19] The granulation tissue withstands the greatest strain prior to failure during the healing process.

Mesenchymal stem cells begin to differentiate (driven by BMPs). As a result, chondrogenesis begins to occur, laying down a **collagen-rich fibrocartilaginous** network spanning the fracture ends, with a surrounding hyaline cartilage sleeve. At the same time, adjacent to the periosteal layers, the osteoprogenitor cells lay down a layer of woven bone.

The release of cytokines such as VEGF and TGF B induces angiogenesis at the fracture site.[20] Angiogenesis is critical for the morphological structure of the bone-bridging tissue and the whole fracture healing process. Delayed union or non-union could be a consequence of deficient angiogenesis.[21][22]

Bony Callus Formation (If bone ends are not in contact, then a soft bridging callus forms):

The endosteum and periosteum serve as primary sources for the Fibroblasts involved in fracture healing.[23] The fibroblasts play a pivotal role by secreting the matrix constituents such as collagen, elastic and mesh fibers, and glycoproteins.

Fibroblasts differentiate into osteoblasts guided by various bone morphogenic proteins (BMPs) and fibroblast growth factors (FGFs) released by the body at the fracture site.[24][25] With resultant increased levels of alkaline phosphatase (ALP), total calcium content, and osteogenic marker genes encoding for integrin-binding sialoprotein (IBSP), runt-

related transcription factor 2 (Runx2), and osteoblast-associated transcription factors.[26][27]

The cartilaginous (soft) callus begins to undergo endochondral ossification, and a medullary callus further supports the bridging soft callus. RANK-L is expressed, stimulating further differentiation of chondroblasts, chondroclasts, osteoblasts, and osteoclasts. As a result, the cartilaginous callus is resorbed and begins to calcify. Subperiosteally, woven bone continues to be laid down. The newly formed blood vessels continue to proliferate, allowing further migration of mesenchymal stem cells. At the end of this phase, a hard, calcified callus of immature bone forms. Bone callus formation is dependent upon appropriate relative motion between fracture fragments.[28][29]

Bone Remodelling (Continues for months to years after clinical union)

This involves a complex interaction of signaling pathways, including BMP, fibroblast growth factor (FGF), parathyroid hormone-related peptide (PTHrP), and Indian hedgehog (Ihh). All of which are involved somehow in the differentiation of the appendicular skeleton.

The hypertrophic chondrocytes express type X collagen while the extraarticular matrix is being calcified, then degraded by proteases. Cartilaginous calcification occurs at the junction of the maturing chondrocytes and newly forming bone. Then, the chondrocytes undergo apoptosis, and new vessels form with further VEGF release.

Osteoclasts have the capacity for bone matrix resorption, while osteoclasts' differentiation and activity are coordinated by osteoblasts.[30][31] Osteoblasts express the receptor activator of nuclear factor-B ligand (RANKL), which interacts with the receptor activator of nuclear factor-B (RANK) expressed by osteoclasts. This interaction results in osteoclasts differentiation and activation.[32][33] Additionally, osteoblasts produce osteoprotegerin (OPG), which is a decoy receptor for RANKL. OPG can occupy the binding site of RANK, thereby inhibiting the activation of osteoclast precursor cells.[33]

With the continued migration of osteoblasts and osteoclasts, the hard callus undergoes repeated remodeling - termed 'coupled remodeling.' This 'coupled remodeling' is a balance of resorption by osteoclasts and new bone formation by osteoblasts. The center of the callus is ultimately replaced by compact bone, while the callus edges become replaced by lamellar bone. Substantial remodeling of the vasculature occurs alongside these changes. The process of bone remodeling lasts for many months, ultimately resulting in the regeneration of the normal bone structure.[34][35][15][36]

The newly formed bone (woven bone) is remodeled via organized osteoblastic-osteoclastic activity and further shaped in response to mechanical stress (Wolff's law) and electric charges (piezoelectric charges); compression side is electronegative and stimulates bone formation, and the tension side is electropositive and stimulates osteoclasts.

An important point to expand on is endochondral ossification, which is the name given for the process of conversion of cartilage to bone. As described above, this occurs during forming a bony callus, in which the newly formed collagen-rich cartilaginous callus gets replaced by immature bone.

This process is also the key to forming long bones in the fetus, in which the bony skeleton replaces the hyaline cartilage model. The second type of ossification also occurs in the fetus; this is intramembranous ossification; this is the process by which mesenchymal tissue (primitive connective tissue) is converted directly to the bone, which no cartilage intermediate. This process takes place in the flat bones of the skull.[37]

Clinical Significance

Aspiration for ideal fracture healing necessitates a comprehensive knowledge and understanding of all the factors that directly or indirectly influence the healing process. The main pillars of fracture healing are a good biological environment with adequate blood supply and a good mechanical environment with adequate stability.

The AO has set four principles for ideal fracture healing. This includes fracture reduction to restore the anatomy, fracture fixation to achieve absolute or relative stability, preservation of the blood supply to the bone and surrounding soft tissues, and early and safe mobilization.

The list of factors that affect fracture healing is exhaustive; however, it can broadly be categorized into local and systemic categories.[38]

Local Factors

- **The blood supply and the biological environment are** the most important local factors affecting the fracture healing process. Immediately after the fracture, the blood vessels in the surrounding area get disrupted with resultant low blood. This improves over the next few hours to days after the fracture and reaches its highest at two weeks, then declines back to normal between 3 to 5 months. Reduced blood supply to the fracture site can lead to delayed union or non-union. Bone blood supply should also be considered in the operative treatment of fractures and the used prosthesis. For example, reaming for intramedullary nailing would compromise 50% to 80% of the endosteal circulation. Also, canal tight-fitting nails compromise the endosteal blood supply compared to looser-fitting nails, which allow better endosteal reperfusion.
- **Fracture Characteristics and the mechanical environment:** Excessive movement and malalignment. Extensive soft tissue damage and soft tissues caught within the fracture site can lead to delayed union or non-union, as well as the amount of bone comminution and loss. Additionally, specific fracture patterns have more probabilities of developing non-union or delayed union, such as segmental fractures or fractures with butterfly fragments.
- **Infection: c**an significantly compromise the healing process with a consequent non-union or delayed unions.

Systemic Factors

- **Advanced age:** elderly have a lower capacity for fracture healing when compared to their younger population. Aging influences the inflammatory response during fracture healing. With aging, there is a weakness in the immune response and increased systemic pro-inflammatory status.[39]
- **Obesity:** In animal studies, lower levels of FGF and TGF-β, and higher levels of TNF-α, were reported more in obese mice and contributed to delayed fracture healing.[40]
- **Anemia**
- **Endocrine conditions:** diabetes mellitus affects the fracture healing process in multiple aspects; fracture callus would have low cellular content with resultant weak callus. Endochondral ossification is delayed, and fracture healing is generally prolonged compared to the general population. Menopause and parathyroid problems also compromise the fracture-healing process.
- **Steroid administration**.[41]
- **Malnutrition:** a high proportion of the patients developing delayed union or non-union were reported to have metabolic compromise, especially of vitamin D. Calcium deficiency is another compromising factor of the bone union. Calcium deficiency can be secondary to gastrointestinal malabsorption or endocrinal problems such as secondary hyperparathyroidism.[42]
- **Smoking:** nicotine inhibits angiogenesis and forms weak calluses with an overall delay in the fracture healing process.

- Medications: Certain medications can directly or indirectly affect the fracture healing process. NSAIDs can result in delayed union due to COX enzyme inhibition. For example, systemic corticosteroids have been reported to increase the non-union rate of intertrochanteric femur fracture. Conversely, long-term use of bisphosphonates has been associated with osteoporotic fractures such as subtrochanteric femoral insufficiency fractures. Quinolones have been reported to be toxic to chondrocytes with the consequent compromise of the fracture healing process.[43][44]

Fractures have significant mortality and morbidity; an interprofessional approach is essential for good outcomes.[45][46][47] There are multiple methods that the interprofessional team can utilize to promote/stimulate fracture healing, including:

- **Dietary supplements** - calcium, protein, vitamins C and D.
- **Bone stimulators** - which can be electrical, electromagnetic, and ultrasound. The current effectiveness of these methods is still equivocal, and this area requires further research. There are **four principal modes** of electrical stimulation; the **direct current** reduces osteoclast activity and increases osteoblast activity by creating an alkaline tissue environment and reducing oxygen concentration. In contrast, the **alternating current** (AC) affects collagen synthesis and cartilage calcification. The other two types are magnetic, either **pulsed electromagnetic fields** that result in the calcification of fibrocartilage or **combined magnetic fields** that increase the concentrations of transforming growth factor beta and bone morphogenic proteins.[48] Ultrasound such as (LIPUS) low-intensity pulsed ultrasound has been reported to augment fracture healing and increase the strength of the formed callus, with healing rates in non-union and delayed unions approaching 80%. **LIPUS** improves fracture healing by increasing chondrocytes, soft callus formation, and, consequently, earlier endochondral ossification.[49][50]
- **A bone graft involves using** bone to help provide a scaffold to the newly forming bone. This graft can be from the patient's body (autograft) or a deceased donor (allograft).[48][51]

Nursing, Allied Health, and Interprofessional Team Interventions

Fracture healing is regulated by the type and extent of the fracture, the stability of the fracture's fixation, and biological processes, which include various processes associated with skeletal ontology.[1] The interprofessional team needs to follow up with the patient regularly throughout the healing process to ensure that proper healing is taking place and that the stability of the fixation is intact. In some instances, physical therapy will be necessary, and the PT must communicate back the patient's progress, along with any possible concerns, to the team. As mentioned above, counsel to eat a nutritious diet and refrain from smoking and drinking alcohol are crucial factors in enhancing fracture healing. The interprofessional approach with open communication between all team members will help drive optimal fracture healing.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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