

THE BIOLOGY OF BONE REPAIR AND REGENERATION

Tovasharov Mukhammadali Yuldashevich

Master of 2nd year of study, direction Maxillofacial Surgery,
Tashkent State Medical University,
Uzbekistan, Tashkent

Yakubov Shohruh Norkulovich

Scientific supervisor, PhD, Department of Maxillofacial Surgery,
Tashkent State Medical University,
Uzbekistan, Tashkent

Abstract: *Bone healing is a biologically and mechanically regulated process that requires sufficient blood supply, osteogenic cells, and appropriate stability. The degree of interfragmentary motion determines the healing pathway, which may occur as primary bone healing under absolute stability, secondary bone healing with callus formation under relative stability, or may fail, resulting in nonunion. Primary healing involves direct intracortical remodeling without callus, whereas secondary healing progresses through a cascade of tissue differentiation from hematoma to mature bone. Disruption of mechanical stability or biological conditions can lead to delayed union or nonunion, highlighting the importance of optimizing both biological and biomechanical factors in fracture management.*

Keywords: *Vascularization; Mechanical stability; Interfragmentary motion; Callus formation; Intracortical remodeling; Haversian remodeling; Hematoma; Granulation tissue; Connective tissue; Fibrocartilage; Woven*

bone; Compact bone; Differentiation cascade; Nonunion; Pseudarthrosis; Osteosynthesis; Fracture fixation; Biomechanical environment;

Introduction

Adequate vascularization, the availability of specialized cells, and appropriate mechanical stability are essential conditions for normal fracture repair. Bone healing can take place under varying levels of interfragmentary movement, from complete stabilization of the fracture site—where no separation or compression occurs at the fracture line during functional loading—to a certain degree of fragment displacement when fixation is absent or insufficiently stable.

The amount of motion between fracture fragments, which depends on whether the fracture is treated and the method of treatment used, determines the mode of healing. Based on the biological and biomechanical conditions present, fracture healing can proceed in one of three fundamental ways:

1. Primary bone healing, which includes contact healing or gap healing
2. Secondary bone healing, characterized by callus formation
3. Failure of bone healing (nonunion)

1. Primary bone healing

When interfragmentary movement is entirely eliminated, a specific healing mechanism develops that is marked by pronounced intracortical remodeling within and between the fracture fragments. For stability to be maintained, direct bony contact between the fragment ends is required. Such conditions are typically achieved with compression osteosynthesis, buttress fixation, or load-bearing fixation techniques.

Morphologically, the interface between the fracture fragments consists of areas of direct contact interspersed with gaps of varying width. In the contact regions, Haversian remodeling progresses directly across the fracture line, resulting in immediate osseous bridging by mature bone that is aligned along the bone's original axial orientation.

In the adjacent, non-load-bearing gap areas, a small degree of movement may occur; however, this motion is restricted by the elastic properties of the neighboring contact zones. Provided that the contact areas remain intact, the interfragmentary strain within the gaps stays below approximately 2%, which is low enough to permit direct bone formation. Initially, granulation tissue develops within these gaps, establishing a new blood supply. Loose connective tissue appears only briefly in the central portion of the gap, while lamellar bone is deposited early on along the surfaces of the fracture ends. This lamellar bone gradually fills the entire gap.

Once the gaps are completely filled with lamellar bone oriented parallel to the fracture plane, osteons originating from one fragment extend across the healed gap into the opposite fragment. As a result, the bone fragments become united by lamellar bone structures aligned parallel to the long axis of the bone. This mechanism is known as primary, or direct, bone healing because it bypasses the full sequence of tissue differentiation seen in secondary healing with callus formation.

Radiographically, primary bone healing is characterized by the gradual fading of the fracture line. Because there is no visible callus formation, assessing healing progress on X-rays can be challenging. Intracortical remodeling proceeds slowly, requiring prolonged protection of the fracture by a fixation plate. The duration for which the plate must remain in place depends

on factors such as mechanical loading, bone quality, fracture configuration (simple versus comminuted), and patient compliance. On average, a fixation period of about six months is sufficient.

Direct bone healing itself is not necessarily the desired objective. Rather, the absence of this pattern—evidenced by periosteal callus formation under plate fixation—indicates that complete immobilization was not achieved. Excessive interfragmentary motion, particularly when combined with impaired blood supply or infection, can lead to delayed union or even nonunion.

2. Secondary bone healing via callus formation

When a fracture is left untreated or stabilized only with loose or nonrigid fixation, significant movement occurs between the fracture fragments.

Under such circumstances, direct bone healing cannot take place because the interfragmentary strain exceeds the tolerance of bone tissue. Any newly forming bone at the fracture site would be disrupted by motion before it could mature.

In addition to the mechanical disruption, a fracture also damages the vascular supply of the bone. The injury leads to interruption of larger blood vessels and, more importantly, to impairment of the microcirculation within the bone. Within the first few hours after trauma, the blood vessels in the Haversian and Volkmann canals become occluded for several millimeters from the fracture ends. This vascular compromise results in resorption of bone at the fragment margins.

Secondary fracture healing is characterized by the formation of both periosteal and endosteal callus. Between the fracture fragments, a sequential process of tissue differentiation occurs, during which the mechanical stiffness and strength of the healing tissue progressively increase, while its tolerance to

strain gradually decreases. This biological cascade begins with the formation of a hematoma, followed by granulation tissue. The tissue then differentiates into fibrous connective tissue, fibrocartilage, mineralized cartilage, woven bone, and finally mature compact bone. As this process advances, the fracture site becomes increasingly stable, culminating in complete reossification of the interfragmentary space.

3. Stages of the differentiation cascade – Hematoma.

In the early phase after a fracture, a hematoma forms between the fractured bone ends. The exact role of this hematoma in fracture repair remains a subject of debate. Some studies suggest that leukocytes present in the blood clot may differentiate into fibroblasts and other cells involved in the formation of supporting connective tissues. Additionally, the hematoma may serve as a provisional framework or spacer, helping to define the eventual size and shape of the developing callus. As healing progresses, fibroblasts begin to appear and proliferate within the hematoma.

Granulation tissue and connective tissue.

Following the initial hematoma stage, the fracture site evolves into granulation tissue, which subsequently matures into connective tissue. As this granulation tissue develops, its mechanical stiffness gradually increases. The elongation at failure of this tissue typically ranges from about 5% to 17%. Fibrous connective tissue predominantly forms in regions exposed to tensile stresses, whereas, as described by Pauwels, cartilage tends to develop in areas subjected to hydrostatic pressure.

Fibrocartilage and bone formation.

The next phase involves the formation of fibrocartilage, which with continued maturation becomes mineralized cartilage. This mineralized

cartilage is then replaced sequentially by woven bone and ultimately by mature compact bone. The process of fibrocartilage mineralization advances from the fracture fragment ends toward the center of the fracture gap. This mode of healing is associated with a rapid increase in mechanical stability, mainly due to the progressive accumulation of bone tissue. However, if excessive interfragmentary motion persists, this reparative cascade may be disrupted, potentially resulting in nonunion or the development of a pseudarthrosis.

4. Nonunion.

Nonunion is present when spontaneous repair fails and surgical intervention is necessary to achieve bone union. It may occur when the gap between fracture fragments is excessively wide, when unfavorable or excessive movement persists at the fracture site, when biological conditions such as blood supply are compromised, or when infection is present. These factors can prevent complete healing and lead to abnormal, pathological mobility at the fracture site. In German terminology, nonunion and pseudarthrosis are considered synonymous, whereas in English-language literature, pseudarthrosis refers specifically to a nonunion that has progressed to the formation of a true false joint and represents the final stage of nonunion.

In the craniofacial region, nonunions are uncommon, and in most cases, adequate stabilization with a fixation plate is sufficient to achieve healing.

5. Delayed union.

Delayed union is mainly a clinical designation describing an unusually prolonged healing period. Histologically, however, the sequence of tissue differentiation remains similar to that seen in normal fracture healing. This condition often arises in biologically compromised environments, such as those with reduced vascular supply or following irradiation.

Conclusion.

Bone repair and regeneration are governed by a complex interaction between biological factors, such as vascularization and cellular activity, and biomechanical conditions, particularly the degree of stability at the fracture site. The amount of interfragmentary motion largely determines the pathway of healing, resulting in either primary bone healing under conditions of absolute stability, secondary bone healing with callus formation under relative stability, or failure of healing in the form of delayed union or nonunion. Primary healing involves direct intracortical remodeling without callus formation and requires prolonged rigid fixation, whereas secondary healing proceeds through a well-defined cascade of tissue differentiation that progressively restores mechanical strength. Disruption of mechanical stability or impairment of the biological environment can delay or prevent union. Therefore, successful fracture management depends on achieving an optimal balance between mechanical fixation and preservation of the biological conditions necessary for bone regeneration.

REFERENCES:

1. Einhorn & Gerstenfeld (2014) – General overview of fracture healing biology, including direct and indirect mechanisms.
2. Sheen et al. (StatPearls, 2023) – Summary of fracture healing stages and mechanisms, including hematoma and callus formation.
3. Bahney et al. (2018) – Detailed cellular biology of fracture healing, including the role of osteogenic cells.
4. Sagalovsky & Schönert (2014) – Review of molecular and cellular processes in bone fracture repair.

5. MDPI Review on Nonunion (2024) – Modern concepts of delayed union and nonunion, and how healing pathways are affected by mechanical and biological factors.
6. MDPI Bone Healing Gone Wrong (2023) – Overview of primary versus secondary healing and nonunion pathology.
7. Principles of Bone Healing (2023) — From Surgery (Oxford), a current review of direct and indirect bone healing mechanisms.