Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 5, 2536-2541
2024
Publisher: Learning Gate
DOI: 10.55214/25768484.v8i6.3738

Inflammatory immune response and its key roles in the process of bone fractures healing

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Abstract: Bone fractures, which represent 2% - 5% of adults annually, are considered a significant health concern, particularly as their incidence has recently increased. Bones are composed of minerals such as calcium and phosphate, and organic components like type I collagen, provide structural integrity and strength. The periosteum plays a vital role in bone healing, with children's thicker periosteum contributing to faster recovery compared to adults. This review emphasizes the critical role of the immune system in bone fracture healing, highlighting the inflammatory response as a key factor in bone healing. Immediately after the occurrence of a fracture, immune cells are recruited to the site of the fracture, initiating a cascade of healing processes that include angiogenesis and tissue repair scenarios. The healing process is classified into primary and secondary healing, each with distinct mechanisms. Factors influencing healing include fracture location, patient age, physical activity levels, medical conditions, medication use, smoking, and the biomechanical environment. The healing phases—inflammatory, repair, and remodeling—are regulated by the immune cells, particularly macrophages and T-cells, which can either facilitate or hinder recovery. Understanding the immune response is essential to developing effective therapeutic strategies for the healing of the bone structures.

Keywords: *Bone fractures, Bone healing, Immune response, Inflammation.*

1. Introduction

Bones represent 15% of the total body weight of an adult. The percentage of the fracture ranges from 2% to 5% per year. Recently, significant increase in the fracture percentage was obviously noticed [2, 3].

Bones are a mixture of minerals and organic substances; The minerals include calcium, phosphate, and hydroxyl ions, which are incorporated into a compound called hydroxyapatite ($Ca_5(PO4)_3(OH)$). This skeletal structure provides the strength, hardness, and rigidity of bone. The organic or protein component consists of type I collagen, which provides elasticity and tensile strength. The periosteum, which is the outer layer of bone, provides blood supply and plays a crucial role in bone healing. Children's periosteum is thicker and stronger than that of adults, which explains reason why bone healing in children is faster than adults[4, 5]. As hard and rigid tissue lacking elasticity, bones may be subjected to fracture, which must be repaired to perform the normal functions of the bones.

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The immune system has a crucial role in the process of bone fracture healing. The body initiates a complex healing process just after the bone is fractured, such process includes several stages. The immune system is actively incorporated in each of these stages.

The current review aimed to highlight the role of the inflammatory immune response mediated by the presence of inflammation and cellular responses as critical factors in the process of fractured bone healing.

When the bone is injured and fractured, the cellular inflammatory response is triggered by recruiting and accumulation of the immune cells at the fracture site. Those cells are activated and secrete a variety of factors including inflammatory molecules. Inflammatory response is essential to obtain normal healing of the fractured bone through the process of angiogenesis of the surrounding blood vasculature and repair of the surrounding injured tissues until new bone is formed. This strong inflammatory action is required to achieve normal healing through angiogenesis of new blood vessels, repair of the surrounding injured tissue until remodeling is completely achieved [6-9]. Although the immune response is short-lived, the effects of the recruited immune cells extend beyond the early stages of fracture healing. The effects of inflammation are a key factor in the recruitment of the mesenchymal stem cells. Hence, cellular immunity is integral to the healing of the fractured bone.

The healing process can be classified into primary and secondary healing, each has its own distinct mechanisms and requirements for healing.

1.1. Primary Bone Healing

Primary healing is known as direct bone healing, it occurs when the fractured bone fragments are precisely reduced, aligned, and fixed under compression, ensuring no movement at the fracture site. Under these conditions, the bone heals through direct remodeling of lamellar bone and Haversian canals., the bone can heal through direct remodeling of lamellar bone and Haversian canals [3, 10]. Bone on one side of the cortex must connect physically with bone on the other side to re-establish the mechanical and physical continuity. Cutting cones are formed at the ends of the osteons nearest to the fracture site [10]. These cones cross the fracture line, forming longitudinal cavities via the activity of osteoclasts, then these cavities are filled with bone matrix, leading to formation of bony union and restoration of Haversian systems and re-establishing blood supply [11]. Eventually, the osteons mature and remodel into lamellar bone, healing the fracture site without the formation of callus or inflammation [12].

1.2. Secondary Bone Healing

The secondary bone healing is called indirect bone healing, it is the most common method of bone healing to exist, including both endochondral and intramembranous processes [13]. Anatomical reduction or rigid stability are not required in such types of healing but enhanced by micro-motion and weight-bearing activities. However, excessive movement or load can result in delayed healing or non-union [14]. Secondary bone healing typically occurs in non-operative treatments and certain surgical procedures that allow some movement at the fracture site, such as intramedullary nailing, external fixation, or internal fixation of complex comminuted fractures [15-17].

1.3. Stages of Bone Healing

The bone fracture healing can be classified into 3 or 4 phases as seen in figure 1, those phases are:

1.3.1. Inflammatory Phase (hematoma formation)

Immediately after a fracture, blood vessels at the injury site are damaged, leading to the formation of hematoma (blood clot). This hematoma acts as a scaffold for the healing process. The immune system responds by sending immune cells, such as macrophages and neutrophils as well as blood platelets, to the fracture site. These cells help to clear debris and release interleukins cytokines such as (IL-1, IL-6, IL-10, IL-11, IL 12, IL-23), transforming growth factor beta (TGF-Beta), tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMPs) and platelet-derived growth factors (PDGF) [18]. Furthermore, these cytokines stimulate the essential

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 5: 2536-2541, 2024
DOI: 10.55214/25768484.v8i6.3738

cellular biological sense at the fracture site to promote inflammation and attract other cells necessary for healing [19].

1.3.2. Repair Phase (Formation of Cartilaginous and Bony Callus)

During this phase, the immune cells continue to play a role by secreting factors that promote the formation of a soft callus made of fibrocartilage anastomosis. This callus gradually transforms into a hard bony callus through endochondral ossification [20] as new bone tissue begins to form. Immune cells like macrophages help in the transformation of progenitor cells (mesenchymal stem cells) into chondroblasts, fibroblasts and osteoblasts, which are cells responsible for bone formation [21, 22].

1.3.3. Remodeling Phase

In the final phase, the newly formed bone is remodeled to restore its original shape and strength through transformation of the bony callus by osteoclasts and osteoblasts into compact bone in the center, and lamellar bone at the peripheral side of the callus [23]. Immune cells continue to regulate this process by balancing bone formation and resorption. Dysregulation of the immune response can lead to complications such as delay in the expected healing time or non-union of the fracture [21].

1.4. Factors Influencing Healing

1.4.1. The Location of the Fracture

The location of bone fracture is a key factor in predicting healing time owing to varying blood flow bone fractures close to the center – like the shaft – heal quicker than those at the edges or articular regions. The latter present with less blood supply causing delayed healing [24].

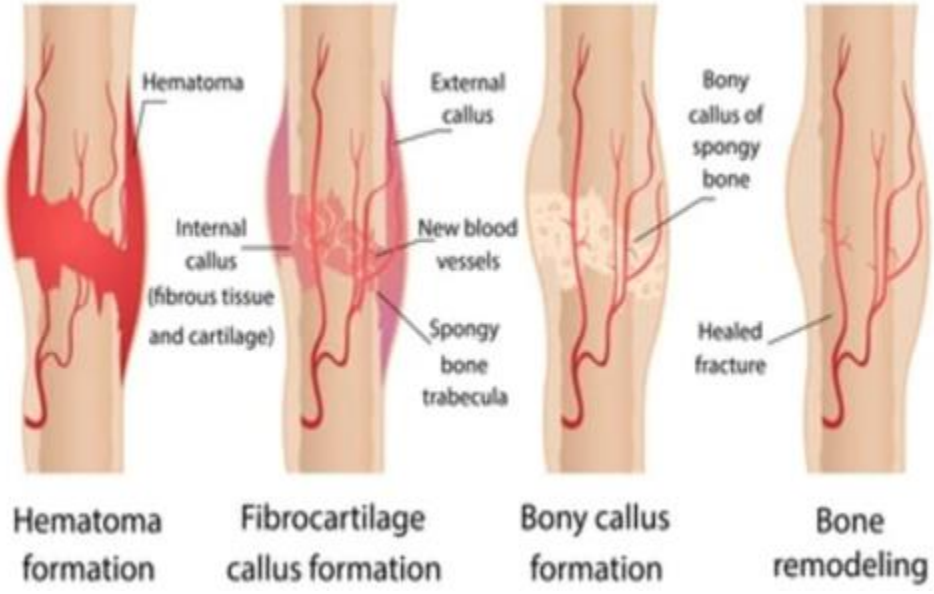

Figure 1.
Shows the phases of the bone fracture healing [1].

1.4.2. Patients' Age

The process of fracture healing is influenced by aging, which alters the inflammatory response. This alteration is attributed to the aging immune system itself and an increased systemic pro-inflammatory state. Immune key cells involved in inflammatory response, including macrophages, T cells, and mesenchymal stem cells, undergo age-related changes that can affect healing negatively. Furthermore, older adult patients encounter difficulties with vascularization and angiogenesis during fracture repair.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
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Finally, there is a reduction in the activity and number of osteochondral cells and their progenitors within the callus [25].

1.4.3. Level of Physical Activity

The impact of physical activity on the healing process is well studied. Patients who have become bedridden have a significantly increased risk of both muscular atrophy and impaired bone density. Conversely, high levels of physical activity might cause the fracture site to become more stressful, leading to delay in healing time. Optimum healing occurs as best when the condition of patients is stable and balanced [26].

1.4.4. Medical Conditions

Chronic high blood sugar levels can lead to oxidative stress, inflammatory reactions, and an imbalance between adipocytes and osteocytes formation. This condition can also lead to altering in the signaling pathways and bone microvasculature [27]. The early accumulation of aging cells may accelerate bone aging, resulting in reduced bone strength and impaired bone formation [28]. Furthermore, high blood sugar is linked to the formation of advanced glycation end-products (AGEs), which play important roles in the impaired healing of bones in diabetic patients and may increase the risk of fractures in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [27-31]. Therefore, managing these conditions is essential alongside treating fractures.

1.4.5. Use of Medication

The use of some commonly prescribed medications can influence healing. Non-steroid medications for example can delay bone repair by inhibiting cell activity and impairing the granulated tissue and callus formation through inhibiting the inflammatory response which may delay the bone delay [32]. Hence the consideration of A patient's medication history is important in the formulation of treatment plans.

1.4.6. Smoking

Smoking is known to prolong the healing process. Nicotine and other chemicals in tobacco smoke reduce blood flow to the bones [33]. This significantly decreases the nutrients and oxygen required for proper healing and consequently delay in the healing capacity [34]. Therefore, quitting Smoking is essential for optimal fracture healing.

1.4.7. Biomechanical Environment

The significance of the stability of the fracture greatly affects the healing. Healing with rigidity stabilization occurs in primary healing [35, 36]. Whereas healing in the secondary fracture type needs some motion to enhance callus formation [37, 38].

1.4.8. Cellular Mechanisms

Various skeletal cells and biochemical factors play essential roles in the healing process, influencing outcomes and potential complications. [39].

Bone fracture healing is a complex physiological process that involves multiple stages and factors. Understanding these stages is crucial for effective treatment and management of fractures.

1.4.9. Role of Specific Immune Cells in Bone Healing

Certain immune cells, specifically macrophages and T-cells, are particularly important. Macrophages help clear debris and secrete factors that promote tissue repair [40]. T-cells, especially CD8+ T-cells, can influence the healing process, whereas those cells negatively impact bone healing if they misinterpret the fracture as an infection and release inflammatory cytokines [41].

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1.4.10. Balanced Immune Response

The balanced immune response is very important for effective bone healing, it should in the optimum manner, attenuated or too much active immune responses affect the healing negatively, for example HIV patients with bone fractures show low rate of healing [6, 42]. On the other hand, patients with autoimmune diseases with high level of inflammatory response such as rheumatoid arthritis are suffering from inhibition of the bone fracture healing [43, 44]. In diabetic patients who have a chronic high level of inflammation and increased TNFα with increasing the apoptotic activity of the cartilage forming cells, thus leading to the disappearing of the formed cartilaginous callus at the site of the fractures and hence, failing of the fracture healing [45-47].

2. Conclusion

The immunity of the body is a key factor in the process of bone fracture healing, healthy patients with normal and balanced immune response showed normal rates of fracture healing. On the other hand, those with over expressed inflammatory immune response or immunocompromised patients may show delay or inhibition in the fracture healing. Thus, understanding the roles of the inflammatory immune response in bone healing can help in developing successful therapy to improve fracture healing outcomes.

Acknowledgement:

The authors extend their appreciation to the Deanship of Scientific Research at Northern Border University, Arar, Saudi Arabia.

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ISSN: 2576-8484
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