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Fracture repair: general aspects and influence of osteoporosis and anti-osteoporosis treatment

Jean-Marc Féron[a,*], Raphaël Mauprivez[b]

[a] Professor of Orthopaedic Surgery, Chair of the Orthopaedic and Trauma Department, Saint Antoine Hospital. UPMC- Sorbonne Universities, Paris, France
[b] Senior lecturer, Orthopaedic and Trauma Department, Saint Antoine Hospital. UPMC-Sorbonne Universities, Paris, France

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ABSTRACT

Bone differs from other tissues in its capacity to self-repair after a fracture. The low bone mass and structural deterioration of bone associated with osteoporosis increases the risk of fragility fracture compared with healthy individuals. The intention of this article is to review the complex process of fracture repair and essential requirements for a successful fracture healing response summarized as the "diamond concept" in terms of aging and osteoporosis. The current preclinical and clinical evidence for a beneficial or harmful influence of anti-osteoporosis medications such as bisphosphonates, parathyroid hormone (PTH), strontium ranelate and antibodies of Wnt-inhibiting signaling proteins on bone healing is presented and discussed. Literature suggests that there are no detrimental consequences of such therapeutics on fracture repair processes. Following a fragility fracture, it seems that early start of preventive anti-osteoporotic treatment right after surgery does not delay the union of the fracture, except perhaps in the case of very rigidly fixed fracture requiring direct bone healing. There is some promising experimental and clinical evidence for possible enhancement of the bone repair process via administration of systemic agents. Further well designed studies in humans are necessary to accumulate more evidence on the positive effects and to translate this knowledge into valid therapeutic applications.

Introduction

Bone differs from other tissues in its capacity to self-repair after a fracture. The role of the orthopedic surgeon is to reduce the bone fragments anatomically, stabilize the fracture to allow healing without malunion, and thus restore function. The healing process is a cascade of events, mainly influenced by the mechanical fracture fixation stability and the biological environment, summarized as the "diamond concept" [1]. Depending on various factors, bony union occurs either by primary or secondary healing. Basic knowledge of fracture healing is a prerequisite to understanding how the repair of fragility fractures can be improved. The osteoporotic elderly population could present an increased risk of impaired fracture healing due to the combination of the poor bone quality and the aging process. Experimental studies have demonstrated a delayed healing in osteoporotic fractures, but the clinical studies remains controversial. Van Wunnik has shown that osteoporosis was not *per se* an independent risk factor of disturbed healing of the fracture [2]. The occurrence of delayed or non-union in elderly osteoporotic patients seems to be more related to the low bone regenerating capacity than to the bone density or the bone matrix properties.

Anti-osteoporotic drugs target either reduced bone remodeling or stimulate bone construction in order to increase bone strength and prevent fractures. It is important to know their potential interactions on the fracture healing process and to assess their ability to promote bone healing. Most preclinical studies, largely involving osteoporotic rodent models, have demonstrated a stimulation of fracture healing by bone-forming agents; there is no evidence of any deleterious effect on the early stage of fracture healing by anti-resorptive drugs [3]. In humans, several case reports and well-designed clinical trials seem to confirm the potential beneficial effects of bone-forming agents on fracture repair. More studies are needed to evaluate this systemic approach of enhancing fracture repair, especially in people diagnosed with osteoporosis.

Mechanisms of normal fracture repair

Bone differs from other tissues in its capacity to self-repair after a fracture without leaving a scar. Once the continuity of the bone and its mechanical properties are restored, the bone structure recovers its pre-injury state. Fracture healing is a complex process involving biological factors and mechanical principles [4]. The stability of the fracture, depending of the

* Corresponding author at: Professor of Orthopaedic Surgery, Chair of the Orthopaedic and Trauma Department, Saint Antoine Hospital. UPMC- Sorbonne Universities, 184 rue du faubourg St Antoine 75571 Paris Cedex, France.
E-mail address: jean-marc.feron@aphp.fr (J.-M. Féron).

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method of fixation chosen by the surgeon determines the type of bony union [5]. Bone healing occurs either by primary or secondary healing [6].

Primary fracture healing or direct bony union

Primary fracture healing or direct bony union occurs when there is no motion at the fracture site usually achieved after a surgical procedure: open anatomical reduction with a very rigid internal fixation [7]. A direct contact of compact bone is required and the fracture gap should be less than 200 μm so that cutting cones are formed at the end of the osteons closest the fracture site. This "contact healing" involves osteoclasts, which cross the fracture line and create small cavities. These cavities are filled by new bone generated by osteoblasts from the surrounding mesenchymal cells. Bony union and haversian remodeling occur simultaneously. This is a slow process, quite similar to intramembranous ossification during fetal skeletogenesis and to normal bone remodeling. The fracture heals directly without formation of a periosteal callus (Fig. 1). In the same mechanical and anatomical conditions, the process differs when the gap is wider but still less than 1 mm in any case. In this "gap healing" process, the gap is primary filled with lamellar bone remaining mechanically weak after 4 to 8 weeks and is followed by remodelling which starts as the "contact healing" cascade takes place.

Secondary fracture healing or indirect bony union

Secondary fracture healing or indirect bony union is the most common process through which bone union occurs after a fracture. If the anatomical reduction and the mechanical stability of the fracture are fundamental prerequisite to get union, the rigidity of the fixation can be less rigid as described above. In such cases, with some elasticity remaining at the fracture site, the biological response under loading is the formation of an external callus bridging the fracture gap. The fracture is considered healed when bone continuity is visible on x-rays. Indirect bone healing is characteristic in non-operative fracture treatment and in elastic fixation preserving some micro-motion at the fracture level such as intramedullary nailing, external fixation or plate fixation in complex and comminuted fractures. The process recapitulates the steps of the endochondral ossification during the fetal period [8].

The histological morphology of bone after fracture was first described in 1930 by Ham. Later, McKibbin has emphasized the cellular mechanism [9]. The better understanding of bone biology over the last decades has increased the knowledge of the molecular control of the cellular events [10].

The healing process involves a combination of intramembranous ossification and endochondral ossification similar to bone formation during osteogenesis.

The fracture repair follows a characteristic course which can be divided into three partially overlapping phases: inflammatory, repair and remodelling [11]. The first two phases last 10 to 18 weeks and correspond to the restoration of the bone continuity and the mechanical properties to allow a full weight bearing. The last phase takes months to years and can be considered a gradual adaptation of the restored bone to the usual strains of the life.

Hematoma and inflammatory phase

Hematoma and inflammatory phase are the immediate reactions to the fracture: bleeding occurs from the bone and the surrounding soft tissues; the microvascular disruption leads to hypoxia and bone necrosis. The hematoma coagulates around bone extremities and within the medulla forming a template for callus formation. The fracture hematoma houses blood derived inflammatory cells which release cytokines and initiate the inflammatory response: increased blood flow, increased vessel permeability, increased cell migration [12]. Osteoclasts are activated to resorb bone debris and vascular proliferation provides stem cells which differentiate into cells with osteogenic potential based upon mechanical environment and signalling molecules. This inflammatory response peaks within 24 hours and is complete after 7 days. A tissue called callus forms at the fracture site and stiffens as it calcifies.

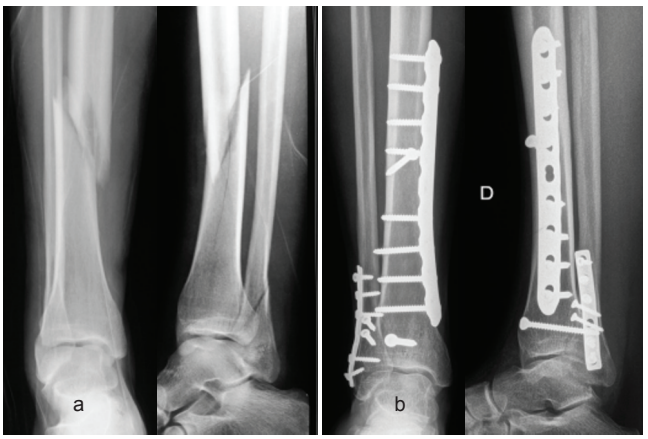

Fig. 1. Example of primary healing of a tibia fracture. (a) Pre-op X-rays of tibia and fibula fracture. (b) Control X-rays at 1 year: rigid plate fixation and primary healing.

Repair phase

Its nature is dependent on mechanical and anatomical conditions in the fracture healing zone (primary or secondary healing). In the secondary healing process, the fracture repair has been classically divided into the formation of soft callus which subsequently calcifies to form the hard callus. During the soft callus formation (3–4 weeks) the clot is invaded by a fibrin-rich granulation tissue. Within this tissue an endochondral formation develops between the bone extremities and external to the periosteum. This chondroid cartilaginous matrix rich in proteoglycans and type 2 collagen is replaced by an osteoid matrix rich in type 1 collagen. The ossified cartilage is replaced progressively by a woven bone. The soft callus enveloping the bone extremities becomes more solid and mechanically rigid. The hard callus formation (3–4 months) is characterized by an intramembranous ossification occurring in the subperiosteal area adjacent to the distal and proximal ends of the fracture forming the peripheral hard callus (Fig. 2). The inner layer of the periosteum contents osteoblasts which synthesize a matrix rich in type 1 collagen and directly generates calcified tissue [13]. This final central bridging by woven bone provides the fracture with a semi-rigid structure allowing weight bearing and restoring function of the limb. At this stage the woven bone is identical to the secondary spongiosa of the growth plate and the fracture is considered healed.

Remodeling phase

Once the fracture has been bridged by the callus, the process of fracture repair slowly replacing the new woven bone with lamellar bone continues. The remodelling results in a balanced resorption of the hard callus by osteoclasts and lamellar bone deposition by the osteoblasts. This last phase is initiated as early as the first month and it takes years to achieve the reconstruction of the original bone structure.