Level V Evidence

Biological Methods to Enhance Bone Healing and Fracture Repair

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Abstract: This article looks into normal physiological fracture healing with special emphasis on the diamond concept. A precise definition of nonunion of long bones is described. Most often inadequate fixation (too rigid or too loose) is the reason for nonunion in long bone fractures. Because a critical bone defect cannot be bridged, it may lead directly or indirectly (lack of fixation) to nonunion. Individual inadequate local biological characteristics are also often found to be the cause; poor soft tissue coverage as well as a lack of periosteum and muscle or fascia or skin defects can lead to compromised vascularity in situ. Systemic factors are now much more recognized, e.g., smoking, diabetes, and cachexia, as well as the limited impact of some medications, e.g., nonsteroidal anti-inflammatory drugs and steroids. Today's mode of treatment for nonunion is approached in this article, and suggestions for appropriate treatment of long bone nonunion is presented.

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The diamond concept[1-4] illustrates 4 conditions for successful healing in fractures, necessitating an appropriate mechanical environment, requiring osteoconductivity (scaffolds), and encouraging osteoinductivity with growth factors and cells (osteoblasts) to induce effective osteogenesis.

Normal Fracture Healing

Bone has a forceful tendency to heal. More specifically, long bones have the intrinsic capacity to heal and regenerate, and this healing is usually uneventful and without complications. In natural physiological circumstances, bone healing occurs as a secondary bone healing mechanism. Callus is formed because of micromovement and there is no need for rigid fixation. This process is rapid and leads to solid consolidation, although it is slightly elastic in the first phase. There is an absolute need to restore axial alignment, rotation, and length to obtain anatomic healing. Moreover, this process is easy to evaluate using standard radiographic techniques (Fig 1).

Because of absolute stable fragment fixation in primary bone healing, no callus will appear. This approach is obviously preferred in the case of periarticular fracture healing in which perfect reduction is necessary to guarantee normal function. This is a slower process of healing and more difficult to evaluate during follow-up using radiographic imaging.

The Diamond Concept

The diamond concept[1-3] illustrates 4 conditions for successful healing in fractures, requiring an appropriate mechanical environment and osteoconductivity (scaffolds) and encouraging osteoinductivity with growth factors and cells (osteoblasts) to induce effective osteogenesis (Fig 2).

The *mechanical environment* requires a relatively stable fixation for diaphyseal fractures in which micromotion is mandatory but limited, noting that large bone gaps cannot be bridged because this is causing a nonstable situation. The appropriate mechanical environment needs absolute stable fixation for periarticular fractures, allowing for anatomic reconstruction by perfect reduction. Today, this rigid

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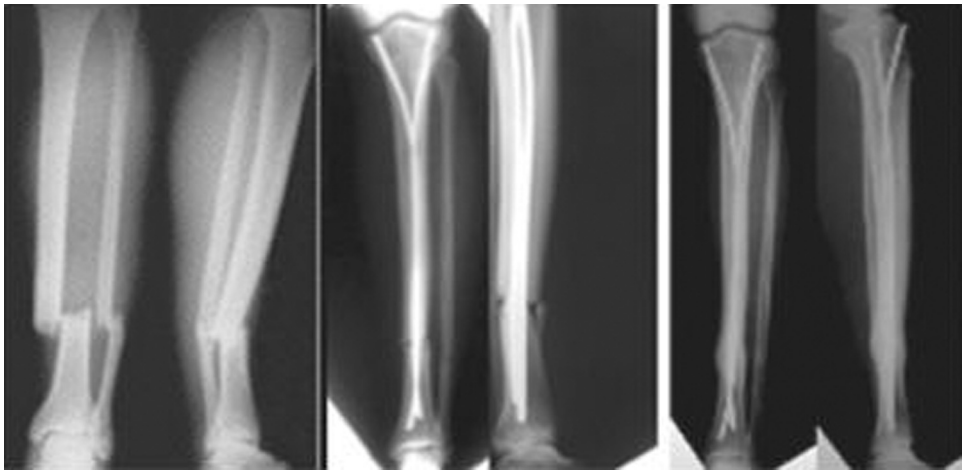

Fig 1. This lower limb fracture with axial displacement is appropriately immobilized with elastic fixation using a 3-point stabilization intramedullary rod, leading to obvious healing with good callus formation.

fixation is obtained by angular stable screws and plates that inhibit motion. If the mechanical environment is not obtained, fixation will fail and there is a higher risk of nonunion developing.

The *osteoconductive scaffolds* are the "rails" along which regenerative cells perform their functions,[4] making and distributing hydroxyapatite and tricalcium phosphate. *Osteoinductivity* requires growth factors that stimulate the osteoprogenitor cells to differentiate and also stimulate osteoblasts to form new bone when bone morphogenetic protein (BMP), transforming growth factor β, and insulin-like growth factor are required.[5-7] *Osteogenesis* is present because of osteoblasts that are stimulated by growth factors[8-10] that produce the extracellular matrix, such as collagen and minerals.

Nonunion

Definition

There are 2 main types of nonunion: hypertrophic and the atrophic (Fig 3).

This definition is based on radiographic imaging in which there is no evidence of progression in fracture healing seen 6 months after injury.

Etiology

Most often, inadequate fixation (too rigid or too loose) is the reason for nonunion to occur in long bone fractures. A critical bone defect cannot be bridged, leading directly or indirectly (lack of fixation) to nonunion. Individual inadequate local biological characteristics are also often found to be the cause; poor soft tissue coverage as well as a lack of periosteum and muscle, fascia, or skin defects, can lead to compromised vascularity in situ. Systemic factors are now also recognized more, e.g., smoking, diabetes, and cachexia as well as the limited impact of some medications, e.g., nonsteroidal anti-inflammatory drugs and steroids.

Treatment

Routinely one has to identify the correct causal mechanism as a general principle to approach a nonunion. As such, a chance of enhancing previous fixation system is most effective. Improving local biological features may require a multidisciplinary approach, sometimes including surgery for extensive soft tissue coverage. Autologous bone grafting will cover gapping, and bone substitutes and growth factors may be required. External therapies such as electrical stimulation can be considered.

To *change and enhance the fixation*, one needs to provide adequate stability of the bone fragments, keeping in mind the principles of absolute and relative stability as described earlier. Reaming and exchange intramedullary nailing may lead to better harvesting of graft material toward the injury site. This will enhance fracture biological characteristics in situ.

To *improve local biological features*, a multidisciplinary approach is most probably a prerequisite because it may include vascular surgery in situ as well as extensive free-flap surgery or sliding-flap surgery (Fig 4). Bone grafting is a prerequisite. Osteoconductive, osteoinductive, and osteogenetic effects are optimal in autografts. It is the gold standard approach to improve

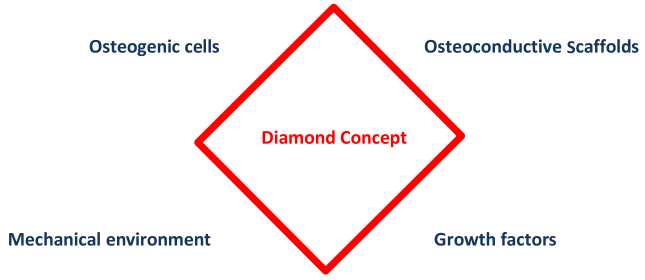

Fig 2. The diamond concept.