

Editorial

Enhancement of fracture healing with the diamond concept: The role of the biological chamber

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ABSTRACT

Bone regeneration presents a unique challenge to both clinicians and scientists. Recently, a vast amount of knowledge has been attained with regard to the molecular mediators, cell populations and the overall cascade of events participating in the bone repair processes. For the treatment of bone non-unions or bone defects, the 'diamond concept' for biological enhancement supports the implantation of mesenchymal stem cells, a scaffold and a growth factor. Prior to the implantation of any or all of these materials however, the surgeon must develop the ideal biological environment (non-union bed) where molecular and physiological processes will evolve facilitating an early and successful osteogenesis leading to bone continuity and functional restoration of the affected limb. At the end of the surgical procedure the non-union bed should have been transformed to a 'biological chamber' active enough to support efficiently all the necessary physiological processes for a successful outcome. The notion of creating the optimum 'biological chamber' represents the centre of the highest biological activity and in a sense the heart of the diamond concept.

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One of the few organs that retain the potential for regeneration in adult life is bone. Bone possesses great properties for restoration of the injured or lost tissue namely fracture or bone defect. The absence of connective tissue scar and the deposition of identical tissue ensure restoration of the pre-fracture properties. This unique characteristic is well seen in the healing cascade of fractures.¹⁰

During the bone repair process, the pathway of normal embryonic development is repeated with coordinated participation from several cell types.¹⁷ The four components present at the injury site (the cortex, the periosteum, the bone marrow, and the external soft tissues), all contribute to the healing process. The extent to which each component is involved depends on the conditions present at the injured tissue (the level of growth factors, hormones, nutrients, pH, oxygen tension, the electrical environment, and the mechanical stability of the fracture).⁵

A large number of factors at the molecular level in association with physiological and biomechanical principles are known to be implicated in the fracture healing process.

In general terms, three vital constituents have been assumed to be of paramount importance: (a) the signalling molecules or growth factors, (b) the osteoprogenitor cells and (c) the extracellular matrix/natural scaffold.

The promoting signalling molecules can be categorised into three groups: (1) the pro-inflammatory cytokines, (2) the TGF- β superfamily and other growth factors, and (3) metalloproteinases and angiogenic factors.¹⁷ A source where all of these molecules (interleukins – IL-1, IL-6, tumour necrosis factor- α – TNF- α ,

fibroblast growth factor – FGF, insulin-like growth factor – IGF, platelet-derived growth factor – PDGF, vascular endothelial growth factor – VEGF, etc.) are found in abundant quantities is the fracture haematoma. Different cell types such as endothelial cells, platelets, macrophages, monocytes, but also mesenchymal stem cells secrete these biologically active molecules. Bone morphogenetic proteins (BMPs) (members of the TGF- β superfamily) are well known signalling molecules possessing osteoinductive properties thus exerting their effects on osteoprogenitor cells promoting their proliferation and differentiation to the appropriate cell lineage.

A vibrant cell population constitutes the mandatory second element for an unimpeded bone repair process. Multipotent mesenchymal cells are recruited at the site of injury with the blood circulation. Bone marrow response to a fracture includes an early reorganisation of the cellular population of the bone marrow to areas of high and low cellular density. The areas of high cellular density are where the MSCs transformation to cells with an osteoblastic phenotype occurs.^{14,16}

The third important constituent of fracture healing is the extracellular matrix that provides the natural scaffold for all the cellular events and interactions. In the clinical setting, various osteoconductive materials (scaffolds) alone or enriched with osteogenic and osteoinductive factors have been used to promote fracture healing. Such materials include allograft or xenograft trabecular bone, demineralised bone matrix (DBM), collagen, hydroxyapatite, polylactic or polyglycolic acid, bioactive glasses and calcium based ceramics.³

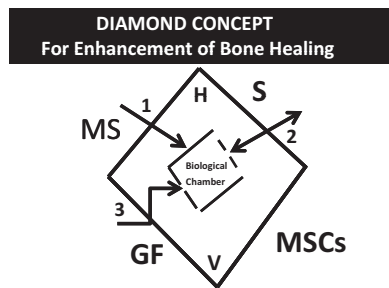


Fig. 1. Diamond concept and the biological chamber. V = vascularity, H = host, MS = mechanical stability, MSC = osteoprogenitor cells, S = scaffold, GF = growth factor. 1. Closed chamber; 2. Open chamber; 3. Partially closed chamber.

We have previously reported that in addition to this triangular shaped complex of interactions (osteogenic cell populations, the osteoinductive stimulus and the osteoconductive matrix/scaffolds), a fourth element, being the mechanical stability at the fracture site, represents a vital factor for bone healing.⁶ The extent of the mechanical stability that can be achieved at the fracture site is relevant to the type of fixation method that has been selected. Methods of fixation have been evolving from the era of ORIF (open reduction and internal fixation) as originally popularised by the AO30, to external fixation systems to the contemporary concept of biologic fixation and more recently to locking plating systems.

It has been suggested that the triangular shape of interactions should be replaced by a diamond shape of interactions at the molecular environment supporting the theory of the 'diamond concept'.^{6,7} The presence of vascularity is considered as an important pre-requisite of the diamond configuration. More over the physiological profile of the host (patient) as well as the presence of comorbidities must not be ignored. The diamond concept represents a conceptual framework of what parameters and what co-factors a clinician should contemplate for optimisation of the bone repair process.

But what actually is at the centre of the diamond configuration of interactions? What represents the heart of the diamond? The non-union site, or else the bone defect area symbolise the heart of the diamond conceptual framework. This zone of the impaired bone healing in our opinion constitutes the area where all the cascade of events of bone repair processes must progress in a time dependent fashion so that bone continuity can be restored. One can argue that this zone signifies the centre of the highest biological activity and as such it can be considered as a unique sector namely the 'biological chamber'.

What therefore should be the properties of the 'biological chamber'? There is no doubt that vascularity is a 'must' prerequisite.¹¹ A good vascular bed guarantees transportation and delivery of oxygen, nutrients, signalling molecules and osteoprogenitor cell migration. Besides the vascular bed however, one has to consider whether the biological chamber should operate as a closed, a partially open or even a completely open compartment in relation to the surrounding tissues (Fig. 1). Converting the biological chamber to a closed compartment obviously enhances the containment of the implanted cellular elements, growth factors or any other form of graft material that the surgeon may wish to implant at this area. On the other hand, if the chamber has a 'closed door' the only natural source of vital osteoprogenitor cells and release of molecular mediators would be the intramedullary canal. But if we decide to convert the chamber to a closed compartment thus creating a local 'bioreactor' what should be the material to use? A collagen membrane implanted at the time of surgery? A bioresorbable membrane?¹³ Mobilisation of

the surrounding soft tissues, muscle and underlying fascia? A tricortical graft harvested from the iliac crest creating a medial or lateral wall with or without another material? The induced membrane technique represents the ideal material to close the biological chamber as it is naturally produced and has the capacity to secrete growth factors.^{12,15} Should the surface of the material used for coverage of the BC have a porosity for diffusion of molecules and selective communication with the outer environment? If so, what should be the porosity or the thickness of the material? Should it have any biomechanical properties? Should it be a composite material? Monolayer? Bilayer or even trilayer? Moreover, should the material be impregnated with any signalling molecules?^{2,1}

Other important issues to consider is the quantities and the state of the graft materials to be implanted in order to achieve the maximum potential of biological activity within the chamber.⁵ Should we implant differentiated or undifferentiated MSCs?⁸ Is it better to implant autologous graft material or allograft?⁴ What should be the ideal dose of the growth factor at the time of implantation?⁹ If the chamber represents a bone defect what should be the ideal method of fixation? An intramedullary nail? Perhaps a plate? If we use a plate is it better to close the chamber and apply the plate in an epi-periosteally manner or should we close the wall of the chamber over the plate?

The concept of the biological chamber sitting at the heart of the diamond concept allows the clinician to consider in a more structured way the molecular environment. It provides the stimulus to visualise and analyse in a more sophisticated way what should be the properties of this in situ bioreactor. Focusing our research activities on this important zone will allow us to understand better the reactions and interactions that must evolve in order to achieve the desirable outcome of bone regeneration in a very efficient accelerated fashion.

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