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Fracture healing: The diamond concept

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Summary Fracture healing is a complex physiological process. With the latest advances made in molecular biology and genetics it is now known that it involves the spatial and temporal coordinated action of several different cell types, proteins and the expression of hundreds of genes working towards restoring its structural integrity without scar formation. The standard tissue engineering approach to provide solutions for impaired fracture healing, bone restoration and regeneration includes the utilisation of growth factors, scaffolds and mesenchymal stem cells (triangular concept). However, although the mechanical environment is discussed and is considered as an important element in bone regeneration, its importance is often underestimated and it is not always given the necessary attention. The available scientific evidence supports the view that all the 4 known factors contributing to bone restoration should be given an equal acknowledgment and recognition. The traditional discussed triangular concept therefore should be reconsidered and be accepted as the 'diamond concept'.

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Bone is one of the few organs that retains the potential for regeneration in adult life, as it possesses considerable capacities of repair. Unlike other tissues that heal by the formation of a connective tissue scar of poor quality, bone is regenerated and the pre-fracture properties are mostly restored. The expression of this unique characteristic applies either to the periodical remodelling of the human skeleton or to the healing cascade of bone fractures.²⁷

The contemporary consensus and understanding of fracture healing implicates a large numbers of factors at the molecular level in conjunction with physiological and biomechanical principles.^{1, 6, 31} The coordinated interaction of these different

elements creates the complex pathways of bone healing. Any deficit expressed at any point of the healing cycle alters the physiological sequence of fracture healing and predisposes to complications. Well-timed and well-aimed interventions are needed to reverse these conditions in order to allow the physiological process of fracture healing to progress to union and thus increase the efficacy of orthopaedic trauma therapies. To achieve this goal the scientific effort has been focused in eliciting the molecular, patho-physiological and biomechanical aspects of bone fracture repair.^{7, 10, 34, 41}

The stages of fracture healing reiterate the sequential stages of embryonic endochondral bone formation. Two basic histological types of bone healing are described. Primary healing is rare and refers to a direct attempt of the cells in cortical bone to re-establish the disrupted continuity. It requires absolute contact of the fragments and almost complete stability and minimisation of the inter-fragmentary strains.²⁹ Secondary bone healing occurs in the vast majority of bony injuries,

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involves both intramembranous and endochondral ossification and leads to callus formation. Committed osteoprogenitor cells of the periosteum and undifferentiated multipotent mesenchymal stem cells (MSCs) are activated. Callus is a physiological reaction to inter-fragmentary movement and requires the existence of residual cell vitality and adequate blood flow.^{12, 29}

In this cascade of events certain biologic prerequisites have been identified. Many local and systemic regulatory factors, cytokines and hormones, as well as extracellular osteoconductive matrix are seen to interact with several cell types. A vibrant cell population is a mandatory first element for an unimpeded bone repair process. Multipotent mesenchymal cells are recruited at the fracture injury site or transferred to it with the blood circulation. Bone marrow response to a fracture includes an early reorganization 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.^{5, 9, 18} Following the identification and quantification of the osteogenic role of bone marrow cells, genetically engineered MSCs and differentiated osteoblasts have been utilized to enhance fracture healing in a number of *in vitro* and *in vivo* studies.^{8, 26, 35}

The fracture hematoma has been proven to be a source of signalling molecules (interleukins / IL-1, IL-6, tumor necrosis factor- α / TNF- α , fibroblast growth factor / FGF, insulin-like growth factor / IGF, platelet-derived growth factor / PDGF, vascular endothelial growth factor / VEGF, and the transforming growth factor β / TGF β superfamily members) that may induce a cascade of cellular events that initiate healing.^{4, 14} These factors are secreted by endothelial cells, platelets, macrophages, monocytes, but also by the mesenchymal stem cells, the chondrocytes, the osteocytes and the osteoblasts themselves.^{39, 40} The investigation of the clinical use of these factors has increased dramatically in the last decade. The bone morphogenetic proteins (BMP-2 and BMP-7) represent members of the TGF β superfamily that have been studied extensively. They have already passed from the experimental level of testing to the clinical practice and are established methods of biological healing enhancement at areas of delayed fracture healing or nonunions.^{13, 15, 16, 19, 21, 43}

A third element of fracture healing is the extracellular matrix that provides the natural scaffold for all the cellular events and interactions. Various osteoconductive materials alone or usually enriched with osteogenic and osteoinductive

factors have been used in the clinical practice. Porous biomaterials such as allograft or xenograft trabecular bone, demineralised bone matrix (DBM)¹¹, collagen, hydroxyapatite, polylactic or polyglycolic acid, bioactive glasses and calcium-based ceramics have been used alone as bone void fillers. They have also been combined with bone-active growth factors in an attempt to achieve a maximal osteogenic effect.^{3, 28, 36, 38}

These three biological prerequisites for fracture healing enhancement have gained most of the scientific attention. A triangular-shaped complex of interactions between the potent osteogenic cell populations, the osteoinductive stimulus and the osteoconductive matrix scaffolds are often analysed and extensively studied in the quest for the optimal grafting material.

However, a fourth element, which is also mandatory for optimisation of bone fracture repair, should also be taken under consideration and be given the same recognition in terms of significance. Mechanical stability is a crucial factor for bone healing, and is essential for the formation of a callus that bridges the fracture site allowing loads to be transmitted across the fracture line. The progressive maturation of the fracture callus from woven to lamellar bone depends on this stability. Surgical interventions such as the application of systems of internal or external stabilisation are designed to improve stability of fixation and thereby enhance healing. Fracture fixation methods have evolved from the era of ORIF (open reduction and internal fixation) as originally popularised by the AO³⁰, to the contemporary concept of biologic fixation.^{25, 32, 37} Wolff's law⁴⁴ describes the interaction of bone to the applied stresses and its unique characteristic of altering its mechanical properties according to them. The application of this law to the clinical setting of fracture healing together with the interplay between parameters as implant rigidity, relative or absolute fracture stability, fracture gap size, and interfragmentary strain are all efforts to express and compute the complex phenomena of bone fracture repair.³³ Relative stability and maximal respect of the soft tissue envelope and the vascularity around the fracture site are considered essential. Scientific research has quantified the essence of relative stability. Splints, casts, intramedullary nails, external fixators and locking plates, after open or mostly closed reduction stabilise the fracture site by minimizing the interfragmentary gap size, and keeping the interfragmentary strain below 10%.^{2, 23}

In the clinical setting of fracture fixation in conjunction with bone grafting the mechanical

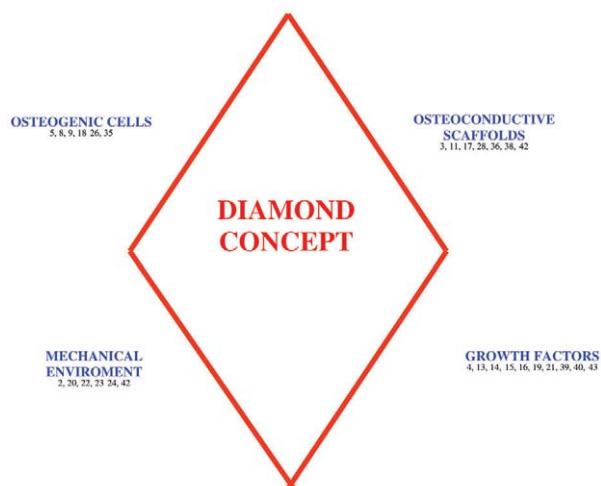


Figure 1: The Diamond Model of Bone Fracture Healing Interactions

stability necessary for optimal healing has not been adequately studied. The general consensus is that a certain load-shielding period has to be achieved to protect the graft in its initial phase of incorporation.^{20, 24}

The role of mechanical stability in the microenvironment of implanted grafts, scaffolds or graft carriers is also essential and sometimes overlooked. These properties vary greatly among the various biomaterials and depend on their macro and micro architecture, as well as porosity.^{22, 42} Significant parameters that differentiate the indications of the different scaffolds and biomaterials are the quality and density of the host bone bed and the local biomechanical demands of the fracture site (weight bearing limb or not). Moreover, bone graft biomechanics evolve parallel to the progress of its incorporation and to callus remodelling. All these issues have formed the bases for intense research efforts to improve initial the mechanical properties of the available biomaterials as well as to guarantee the presence of a mechanically reliable construct throughout all the remodelling phase of fracture healing. Recently, 3D porous polymer scaffolds with pore sizes ranging from 150-500 μ m have shown optimal results related to their biomechanical properties.^{17, 42}

The operative or non-operative techniques of fracture stabilisation, the utilised implants and fixation devices, as well as the mechanical properties of any grafting material all interact and affect the fracture repair process. The mechanical environment where any graft material is expected to act has equal significance to the biologic properties of the graft itself whether it is the gold standard of autograft or synthetic grafting

material. An additional apex to the triangular-shaped model of bone healing elements has to be added to include the mechanical environment of the fracture site. The result is a diamond shaped concept of interaction (Figure 1).

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Conflict of Interest

The authors state that they received nothing of value with regard to this manuscript. There is no conflict of interest.

References:

- [1] Aaron RK, Ciombor DM, Wang S, Simon B. Clinical biophysics: the promotion of skeletal repair by physical forces. *Ann N Y Acad Sci* 2006; 1068 513-31
- [2] Augat P, Margevicius K, Simon J, et al. Local tissue properties in bone healing: influence of size and stability of the osteotomy gap. *J Orthop Res* 1998; 16 475-81
- [3] Babis GC, Soucacos PN. Bone scaffolds: the role of mechanical stability and instrumentation. *Injury* 2005; 36 Suppl 4 S38-44
- [4] Bolander ME. Regulation of fracture repair by growth factors. *Proc Soc Exp Biol Med* 1992; 200 165-70
- [5] Brighton CT, Hunt RM. Early histological and ultrastructural changes in medullary fracture callus. *J Bone Joint Surg Am* 1991; 73 832-47
- [6] Carter DR, Beaupre GS, Giori NJ, Helms JA. Mechanobiology of skeletal regeneration. *Clin Orthop Relat Res* 1998; S41-55
- [7] Chao EY, Inoue N. Biophysical stimulation of bone fracture repair, regeneration and remodelling. *Eur Cell Mater* 2003; 6 72-84; discussion -5
- [8] Connolly JF. Clinical use of marrow osteoprogenitor cells to stimulate osteogenesis. *Clin Orthop Relat Res* 1998; S257-66
- [9] Connolly JF. Injectable bone marrow preparations to stimulate osteogenic repair. *Clin Orthop Relat Res* 1995; 8-18
- [10] Dimitriou R, Tsiridis E, Carr I, et al. The role of inhibitory molecules in fracture healing. *Injury* 2006; 37 Suppl 1 S20-9
- [11] Dinopoulos HT, Giannoudis PV. Safety and efficacy of use of demineralised bone matrix in orthopaedic and trauma surgery. *Expert Opin Drug Saf* 2006; 5 847-66
- [12] Einhorn TA. The cell and molecular biology of fracture healing. *Clin Orthop Relat Res* 1998; S7-21
- [13] Einhorn TA. Clinical applications of recombinant human BMPs: early experience and future

- development. *J Bone Joint Surg Am* 2003; 85-A Suppl 3 82-8
- [14] Einhorn TA, Majeska RJ, Rush EB, et al. The expression of cytokine activity by fracture callus. *J Bone Miner Res* 1995; 10 1272-81
- [15] Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. *J Bone Joint Surg Am* 2001; 83-A Suppl 1 S151-8
- [16] Giannoudis PV, Tzioupis C. Clinical applications of BMP-7: the UK perspective. *Injury* 2005; 36 Suppl 3 S47-50
- [17] Gil-Albarova J, Salinas AJ, Bueno-Lozano AL, et al. The in vivo behaviour of a sol-gel glass and a glass-ceramic during critical diaphyseal bone defects healing. *Biomaterials* 2005; 26 4374-82
- [18] Gould SE, Rhee JM, Tay B-B, et al. Cellular contribution of bone graft to fusion. *J Orthop Res* 2000; 18 920-7
- [19] Harwood PJ, Giannoudis PV. Application of bone morphogenetic proteins in orthopaedic practice: their efficacy and side effects. *Expert Opin Drug Saf* 2005; 4 75-89
- [20] Higgins TF, Dodds SD, Wolfe SW. A biomechanical analysis of fixation of intra-articular distal radial fractures with calcium-phosphate bone cement. *J Bone Joint Surg Am* 2002; 84-A 1579-86
- [21] Kain MS, Einhorn TA. Recombinant human bone morphogenetic proteins in the treatment of fractures. *Foot Ankle Clin* 2005; 10 639-50, viii
- [22] Khan SN, Tomin E, Lane JM. Clinical applications of bone graft substitutes. *Orthop Clin North Am* 2000; 31 389-98
- [23] Lacroix D, Prendergast PJ. A mechano-regulation model for tissue differentiation during fracture healing: analysis of gap size and loading. *J Biomech* 2002; 35 1163-71
- [24] Lanyon LE. Control of bone architecture by functional load bearing. *J Bone Miner Res* 1992; 7 Suppl 2 S369-75
- [25] Leunig M, Hertel R, Siebenrock KA, et al. The evolution of indirect reduction techniques for the treatment of fractures. *Clin Orthop Relat Res* 2000; 375 7-14
- [26] Lieberman JR, Daluiski A, Stevenson S, et al. The effect of regional gene therapy with bone morphogenetic protein-2-producing bone-marrow cells on the repair of segmental femoral defects in rats. *J Bone Joint Surg Am* 1999; 81 905-17
- [27] Lyritis GP. The history of the walls of the Acropolis of Athens and the natural history of secondary fracture healing process. *J Musculoskelet Neuronal Interact* 2000; 1 1-3
- [28] Matziolis G, Tuischer J, Kasper G, et al. Simulation of cell differentiation in fracture healing: mechanically loaded composite scaffolds in a novel bioreactor system. *Tissue Eng* 2006; 12 201-8
- [29] McKibbin B. The biology of fracture healing in long bones. *J Bone Joint Surg Br* 1978; 60-B 150-62
- [30] Muller ME, Allgower M, Schneider R, Willenegger H. *Manual of internal fixation*. 1991
- [31] Olsen BR, Reginato AM, Wang W. Bone development. *Annu Rev Cell Dev Biol* 2000; 16 191-220
- [32] Perren SM. The concept of biological plating using the limited contact-dynamic compression plate (LC-DCP). Scientific background, design and application. *Injury* 1991; 22 Suppl 1 1-41
- [33] Perren SM. Physical and biological aspects of fracture healing with special reference to internal fixation. *Clin Orthop Relat Res* 1979; 138 175-96
- [34] Perren SM, Rahn BA. Biomechanics of fracture healing. *Can J Surg* 1980; 23 228-32
- [35] Pountos I, Giannoudis PV. Biology of mesenchymal stem cells. *Injury* 2005; 36 Suppl 3 S8-S12
- [36] Sammarco VJ, Chang L. Modern issues in bone graft substitutes and advances in bone tissue technology. *Foot Ankle Clin* 2002; 7 19-41
- [37] Sporer SM, Paprosky WG. Biologic fixation and bone ingrowth. *Orthop Clin North Am* 2005; 36 105-11
- [38] Stylios G, Wan T, Giannoudis P. Present status and future potential of enhancing bone healing using nanotechnology. *Injury* 2007; 38 Suppl 1 S63-74
- [39] Tsiridis E, Giannoudis PV. Transcriptomics and proteomics: advancing the understanding of genetic basis of fracture healing. *Injury* 2006; 37 Suppl 1 S13-9
- [40] Tsiridis E, Upadhyay N, Giannoudis P. Molecular aspects of fracture healing: which are the important molecules? *Injury* 2007; 38 Suppl 1 S11-25
- [41] Tsiridis E, Upadhyay N, Giannoudis P. Molecular aspects of fracture healing: Which are the important molecules? *Injury* 2007; 38 Suppl 1 S11-25
- [42] Vaccaro AR. The role of the osteoconductive scaffold in synthetic bone graft. *Orthopedics* 2002; 25 s571-8
- [43] Westerhuis RJ, van Bezooijen RL, Kloen P. Use of bone morphogenetic proteins in traumatology. *Injury* 2005; 36 1405-12
- [44] Wolff J. *Das gesetz der transformation der knochen*. Berlin: Verlag von Augsut Hirschwald 1892