

Orthoss[®] – the ideal scaffold for osseous regeneration

Restoring skeletal integrity in the presence of osseous defects remains a significant challenge. The decision as to which treatment option will be the most successful is influenced by the etiology and pathogenesis of the osseous defect, as well as by the location of the defect, vitality of the surrounding bone and previous, possibly unsuccessful, surgeries.

The biological prerequisites for successful osseous regeneration are osteogenic cell populations, osteoinductive stimuli and an osteoconductive scaffold [1, 2]. A micro-environment with vascular sufficiency is essential in bone formation since angiogenesis is a pre-requisite for vascularisation and therefore bone formation (Figure 1).

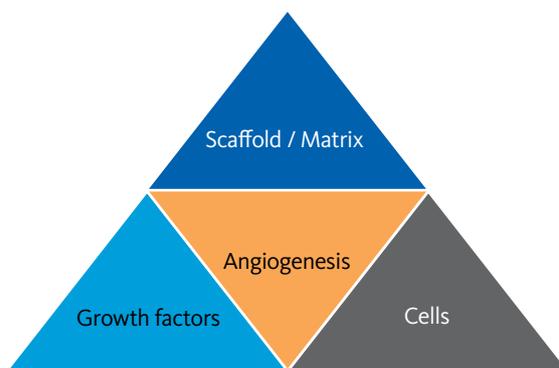


Figure 1: The full potential of osseous regeneration is reached in a mechanically stable environment with the presence of the full complement of cells, growth factors and an ideal osteoconductive scaffold which facilitates osteogenesis and angiogenesis.

Osteogenesis

Bone formation is dependent on the recruitment of endothelial progenitor cells, hematopoietic stem cells, mesenchymal stem cells and their supporting accessory cells to the defect site. Their main functions are defined below:

- > Endothelial progenitor cells:
Stimulate angiogenesis, release BMP-2 and BMP-6 and upregulate the production of BMP-2
- > Hematopoietic stem cells:
Orchestrate bone formation and directly convert to stromal cells (CD34⁺)
- > Mesenchymal stem cells:
Convert to osteoblasts in support of new bone formation

- > Platelets:
mediate cell-to-cell adhesion through the release of various adhesion and growth factors such as SDF-1 α
- > Lymphocytes:
support the migration and proliferation of endothelial progenitor cells
- > Granulocytes:
release vascular endothelial growth factor in support of angiogenesis

Osteoinduction

Several growth factors, as well as hormones and other biologically active agents are relevant to osseous regeneration [2]. These include:

- > PDGF (Platelet-derived growth factor): inducing the proliferation of undifferentiated cells (Potent mitogen and chemotactic factor for cells of mesenchymal origin. Anabolic action on bone formation in vivo)
- > IGF (Insulin-like growth factor): Enhances osteoblast activity, blocks apoptosis and induces bone formation
- > VEGF (Vascular endothelial growth factor): an important component of the regeneration of the vascular system at the fracture site. VEGF mediates the capillary invasion that constitutes a prerequisite for the complex process of endochondral ossification [3].
- > BMPs (Bone Morphogenic Protein): stimulates differentiation of osteoblasts
- > TGF- β (Transforming growth factor): inducer of committed bone cell replication and osteoblast matrix production

Osteoconduction

A bone graft substitute (BGS) which acts as an osteoconductive scaffold should particularly promote the binding and osteogenic differentiation of progenitor cells. This is achieved through highly hydrophilic and porous materials. Ideally, the surface integrity and the porosity should be similar to human bone.

The rapidity and extent of new bone formation is strongly influenced by the structural interconnectivity between the pores. Survival of cells within a large defect is important for osteogenesis. The cells are initially preserved by diffusion from the surrounding host tissues until revascularisation takes place [4].

Ideally the BGS enables a close integration of the scaffold material into the bony tissue with a gradual replacement of the scaffold through endogenous bone.

Osseous regeneration options with Orthoss®

Autologous cancellous bone graft is an effective grafting material because it provides all elements required to induce osteogenic regeneration. It is however associated with the limitations of donor site morbidity (including bleeding, infection, and chronic pain at the donor site) and insufficient amount or quality of available autologous material.

BGS represent a valid alternative to supplement or even replace autologous bone and are available from natural or synthetic origin. Natural materials are manufactured from human, animal or coralline sources whereas synthetic bone grafting materials are nonhuman and artificially produced. Examples include Demineralised Bone Matrix (DBM), hydroxyapatite (HA), calcium sulphate, calcium phosphate, beta-tricalcium phosphate (β-TCP), collagen composites and bioactive glass (bioglass). The large variety of substitute materials available have varying compositions and geometry as well as diverse biological properties.

In contrast to synthetic materials, which are often very compact with limited interconnecting pore system, Orthoss® as a natural hydroxyapatite offers the advantage

of being very similar to human bone with regard to pore morphology, porosity and crystalline structure.

As a result of the excellent biofunctionality, which is described later in detail, Orthoss® is an ideal bone graft substitute which can be used alone or during composite bone grafting using autologous bone, bone marrow aspirate (BMA), bone marrow aspirate concentrate (BMAC) or growth factors when treating large defects.

The more complex a defect becomes and the lower the healing potential is, the more the interaction between cells, growth factors and an osteoconductive scaffold, together with an optimal mechanical environment and sufficient vascularisation, becomes relevant. This is demonstrated in Figure 2 in combination with a treatment concept using Orthoss®. Examples of such complex defects are substance defects which do not heal spontaneously (critical sized defect), osseous defects which exhibit poor bone healing or are characterised by a high recurrence rate or osseous defects with contributing comorbidities.

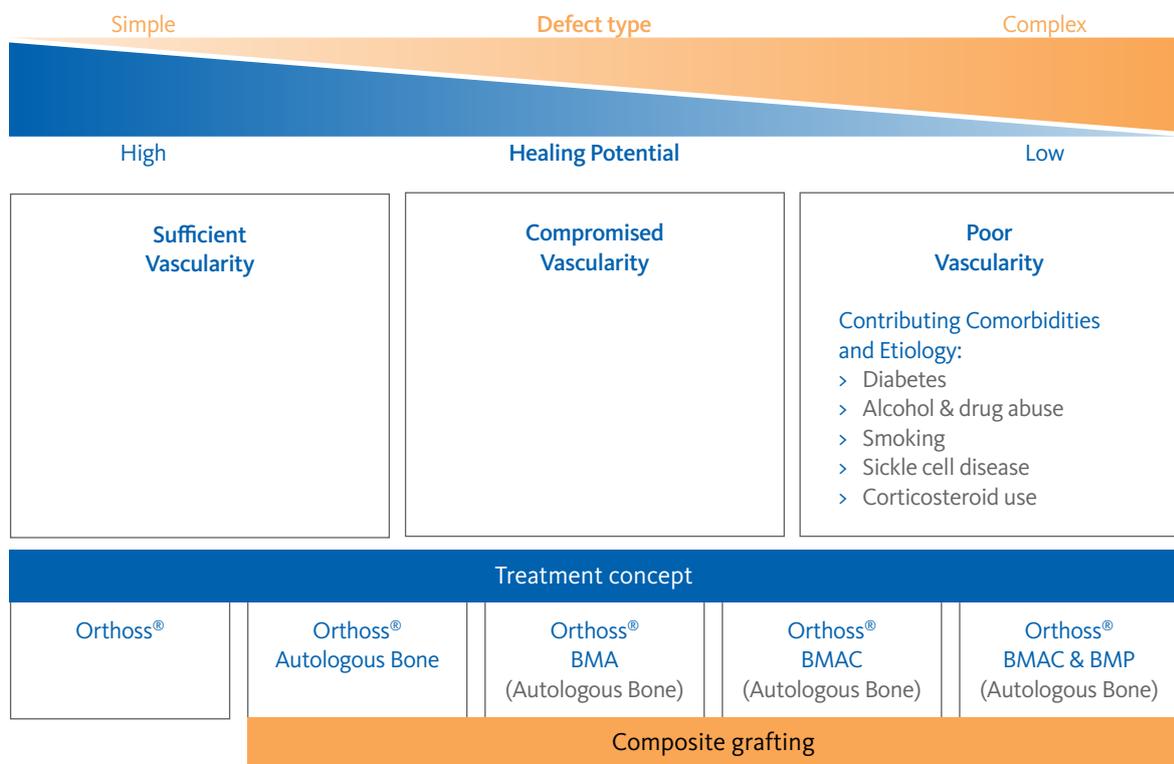


Figure 2: Healing potential of osseous defects in dependence of the defect complexity and available vascularity. A treatment concept utilising osteoprogenitor cells and growth factors with an ideal scaffold (Orthoss®) as composite graft is suggested for defects with impaired bone healing ability.

Orthoss® and Orthoss® with autologous bone

The biofunctionality of Orthoss® comprises several properties which make it a superior osteoconductive scaffold and carrier matrix when compared to other bone graft substitutes. These are:

- > a morphology similar to that of human bone
- > an interconnecting pore system
- > a distinct high porosity and large inner surface area comparable to human bone
- > a unique bimodal pore structure
- > exceptional osteoconductivity and osseointegration

The trabecular structure, porosity and crystallinity of Orthoss® are comparable to human bone. Due to the interconnecting pore system, a large surface area of $80.3 \pm 1.2 \text{ m}^2/\text{g}$ with a porosity $77 \pm 2 \text{ Vol.-%}$ is created. The capillary effect of the nanopores (10-20nm) facilitates complete and spontaneous wetting whilst the macroporous surface (100-200µm) promotes osteoblast passage and adherence.

These characteristics allow for rapid absorption of proteins and enable adequate conditions throughout the scaffold whilst facilitating the migration and distribution of cells involved in bone formation and vascularisation throughout the matrix.

Therefore, Orthoss® is ideal as BGS in filling smaller bone voids with sufficient vascularity and is well suited as a volume extender for composite bone grafting using autologous bone for larger defects. Orthoss® combined with 25% autologous bone has been shown to be sufficient to accelerate new bone formation in the treatment of critical sized defects, thereby limiting the amount of harvested bone and reducing potential complications [5].

Orthoss® and BMA

For osseous regeneration in larger defects with compromised vascularity the addition of osteoprogenitor cells and growth factors is recommended [1, 2, 6, 7]. Orthoss®, together with bone marrow aspirate (BMA) from the iliac crest offers a suitable, cost efficient source for achieving this goal whilst decreasing the limitations of autologous bone harvesting.

Orthoss® and BMAC

Critical sized defects or defects with an impaired bone healing ability as a result of poor vascularity or contributing comorbidities, require a complex strategy to encourage osseointegration. Utilisation of a high concentration of biological factors (growth factors and cells) in combination with a suitable carrier matrix with osteoconductive properties has been shown to encourage osseous regeneration [8].

The iliac crest contains bone marrow which is a rich source of the regenerative cells needed for angiogenesis, optimal bone formation and healing. Concentrated nucleated cells from marrow aspirate (BMAC) offer an alternative to iliac crest autograft.

Systems available on the market for the concentration of bone marrow aspirate (Harvest BMAC system, Harvest Technologies GmbH, Germany) offer a safe and easy to use, autologous system that can rapidly produce a concentration of mononuclear cells and growth factors to help optimise the conditions for healing. Jäger et al. [7] have reported an average concentration of BMAC compared to the initial BMA of 5.2 ± 1.3 (n=17) using this system.

The macroporosity of Orthoss® allows bony ingrowth and a solid integration within the transplantation site. It is incorporated into the physiological remodelling process and therefore has a volume maintaining effect which, in comparison to rapidly resorbing synthetic BGS, reduces the risk of persisting local bone defects or fractures occurring.

Using Orthoss® in combination with BMAC system offers an osseous regeneration solution with a highly osteoconductive carrier matrix in combination with concentrated regenerative cells and growth factors. This combination has shown excellent results in bone regeneration with an accelerated healing in comparison to other scaffolds [8]. The use of Orthoss® and BMAC could result in a reduction or substitution of autologous bone transplants.

Orthoss® with BMAC and BMP

Transforming growth factor beta one (TGF-β1) is known to affect osteogenesis and chondrogenesis by stimulating mesenchymal cells [9, 10].

The bone morphogenetic proteins (BMP-2 and BMP-7) represent members of the TGF-β superfamily which stimulate the formation of new bone and offer an established method in clinical practice for biological healing enhancement in areas of delayed fracture healing or nonunions which are complicated by local environment adverse circumstances [1, 11,12].

An in vitro study from Gille et al. [13] showed that Orthoss® functions as a carrier for growth hormones and continuously release TGF-β1 during the investigated time period of 28 days. This time frame matches the early window between 2 and 6 weeks in which TGF-β1 stimulates bone ingrowth according to Goodman et al. [14].

Osseous Regeneration Concept

	Osteoconduction: Scaffold	Osteoinduction: Cytokines & growth factors	Osteogenesis: Regenerative cells	Angiogenesis / Vascularity	Most comprehensive solution
DBM					
Allograft or β-TCP					
Orthoss					
Autograft					
BMAC					
Orthoss® with BMAC					

Absent
 Present in low concentration
 Present in high concentration

Figure 3: Suitability of available options for osseous regeneration. The inverted triangle symbolises the „V“ for vascularity.

Due to the excellent carrier and release properties of Orthoss, a clinical application of cells and growth factors at the same time are possible.

Osseous regeneration solutions

The overview in Figure 3 shows a number of solutions which are currently available and which have varying efficacy for osseous regeneration. The combination of Orthoss® and BMAC offers the most comprehensive solution for a high concentration of potent osteogenic cell populations and osteoinductive growth factors in combination with an ideal osteoconductive matrix.

Bone regeneration using a composite graft which includes osteogenic precursor cells, osteoinductive growth factors and a highly osteoconductive scaffold has the greatest potential for success. Composite bone grafting using Orthoss and BMAC has shown excellent results in bone regeneration with an accelerated healing and offers an eligible alternative to autologous bone grafting.

References

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