

# Xenogeneic bone grafting materials

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Nowadays, a variety of bone substitutes are available for the clinical user. Interestingly, these materials significantly differ regarding their raw materials or manufacturing processes. As an alternative to autologous bone tissue (autograft), which is still applied as "gold standard" due to its extensive regenerative properties, bone substitutes from other natural sources become more and more relevant in regenerative dentistry. These bone substitute materials are either derived from human (allograft) or animal origin (xenograft).

In case of these materials, the obtained bony extracellular matrix based on calcium phosphates should finally serve as bone substitute (Figs. 1–3). Based on the physicochemical similarity of this class of bone substitutes to the autologous bone tissue, it can be assumed that these materials are the ideal choice for osseous regeneration. Preferentially, bovine bone is used as source tissue in the daily dental practice, as in case of the two primarily applied bone substitute materials Bio-Oss™ and cerabone®.

## Safety aspects and purification processes

For the clinical application of bone substitutes from natural sources it is inalienable to purify the donor tissue from immunogens to guarantee a re-

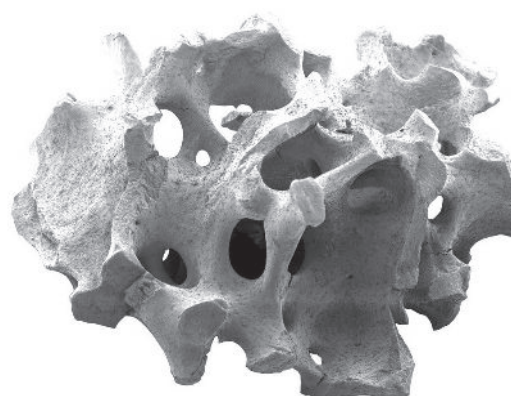


Fig. 1

generation process without complications such as rejections or disease transmissions. To ensure the safe application of such bone substitute materials, different purification steps of the donor tissue are applied.

The first step is the suitable selection of donor animals before the initiation of the purification process. Hence, for the production of Bio-Oss™ and cerabone® bovine femoral heads from registered suppliers located in Australia and New Zealand are processed as both countries are recognised to have a negligible BSE risk according to the World Organi-

**Fig. 1:** (Ultra-)Structure of a cerabone® particle revealing the preservation of its trabecular natural architecture.

**Fig. 2:** Surface pattern of a cerabone® particle showing the retention of the natural microstructure and the purification status based on cell-free osteocyte lacunae.

**Fig. 3:** Cross-section of a cerabone® particle (μ-CT) revealing the retention of the lamellar natural structure after completed purification of the xenogeneic bone graft.

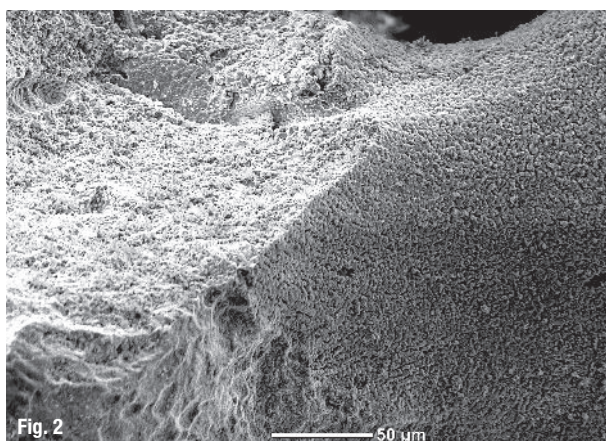


Fig. 2

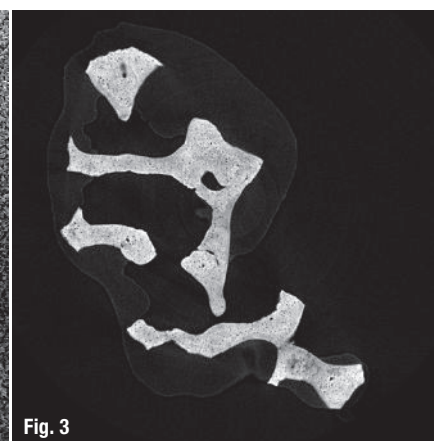
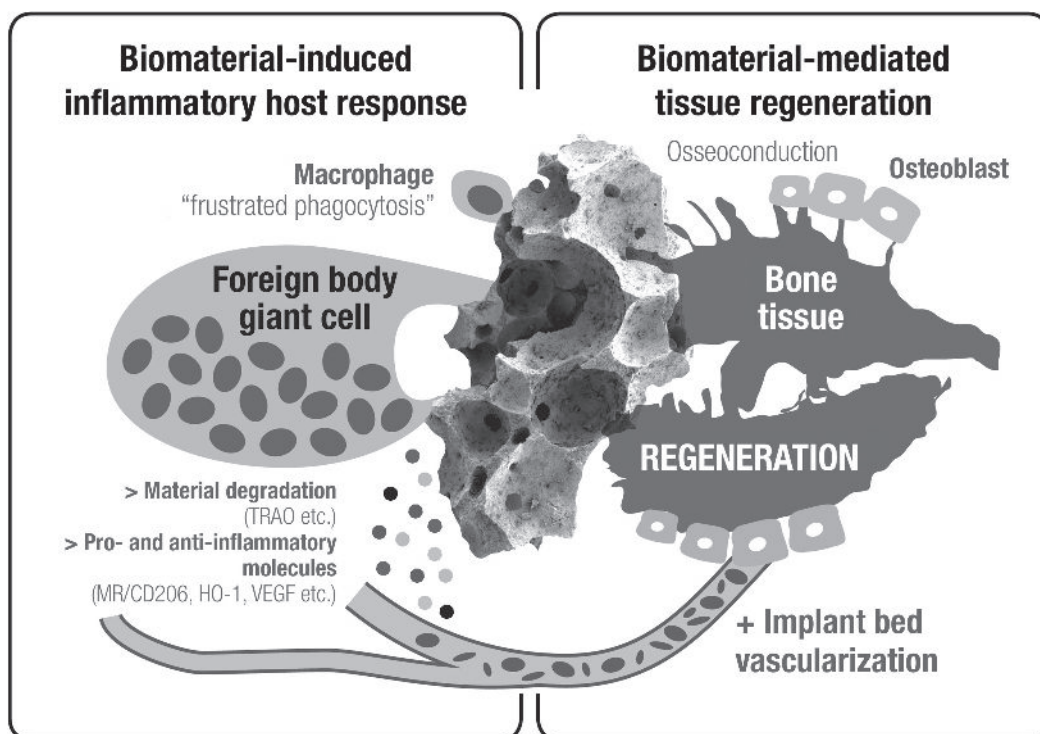


Fig. 3



**Fig. 4:** Schematic illustration of the correlation between cellular and inflammatory processes caused by most of the applied bone grafting materials, the process of implant bed vascularisation and the process of bone tissue regeneration (based on a previous publication by Barbeck et al.<sup>9</sup>).

sation for Animal Health (OIE). Afterwards, complex purification steps including both chemical and physical methods are applied for a complete purification. However, those methods are occasionally discussed because of possible rejection reactions or a transfer of pathogens while applying bone grafting materials. In this context, the temperature treatment for the purification plays a major role. Bio-Oss™ is processed at temperatures of approximately 300 °C, while the bone substitute material cerabone® is purified by notably higher temperatures of up to 1,250 °C.<sup>1,2</sup> This difference in temperature seems to be of significant importance for the safe application of xenogeneic bone substitutes.

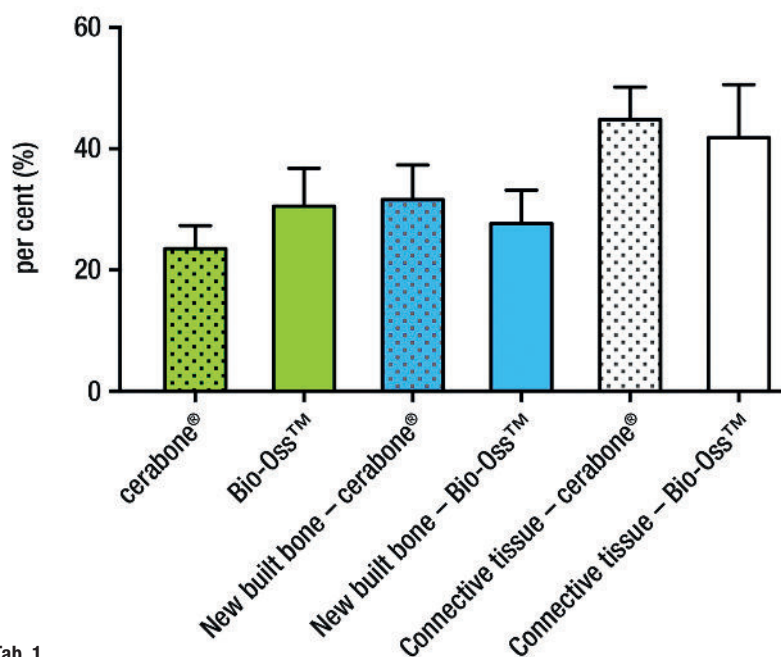
The purification process of bovine bone tissue was evaluated in a recent review by Kim et al.<sup>3</sup> Interestingly, the authors concluded that the inactivation of prions in Bio-Oss™ is rather based on the applied

temperature than a result of the treatment with highly concentrated sodium hydroxide (NaOH). While this chemical process was described as efficient by Wenz et al.,<sup>4</sup> the reliability and sensitivity of the used tests were questioned by Kim et al.<sup>3</sup> In this review, the authors describe that prions will only be effectively destroyed by heating up to 1,000 °C for five minutes. Furthermore, the according EU-guidelines for medical devices utilising animal tissues and their derivatives (Part 1: Application of risk management, EN ISO 22442-1), point out that a treatment at temperatures above 800 °C is reducing the risk of the transmission of Transmissible Spongiform Encephalopathies (TSEs) to an acceptable minimum.

To assure a maximum level of safety, cerabone® is heated to temperatures above 1,200 °C during processing. Thus, organic parts like cells and proteins are removed and even potentially contained prions and



**Fig. 5:** The cerabone® product family—naturally, safe and pure.



Tab. 1

**Tab. 1:** Histomorphometrical results showing comparable values of newly formed bone, remaining bone grafting materials and connective tissue for Bio-Oss™ and cerabone® (based on previous publications<sup>2,5</sup>).

other pathogens are destroyed. Despite the treatment at high temperatures, the natural bone structure is preserved (Figs. 1–3) making cerabone® a safe and reliable product for bone regeneration applications.

### Inflammation and bone regeneration

Data from preclinical and clinical studies show comparable values for new bone formation, remaining bone grafting material and connective tissue for both xenogenic bone substitutes mentioned above (Tab. 1).<sup>1,2,5</sup> These results refer to similar biological activities of Bio-Oss™ and cerabone®. However, in case of cerabone® higher numbers of multinucleated giant cells (MNGCs) were found within the first days after its implantation.<sup>2</sup> Furthermore, the comparison to different other studies shows that the initial number of MNGCs in case of cerabone® is significantly lower as found in the implant bed of fast degradable synthetic materials based on tricalcium phosphates. These results confirm several other studies claiming the long-term stability of xenogenic bone substitutes as it was shown that MNGCs are involved in the biodegradation of bone-grafting materials by phagocytosis.<sup>6,7</sup>

Interestingly, the MNGCs were identified as foreign body giant cells (FBGCs) based on their molecule expression.<sup>8</sup> However, more information is still needed to get further conclusion regarding their differentiation.<sup>8,9</sup> Interestingly, the degradation process of bone substitutes and the process of bone tissue regeneration are closely connected via the relevant cell types such as macrophages and MNGCs (Fig. 4). In this context, it was shown that both

macrophages and MNGCs on the one side express pro-inflammatory molecules that are relevant for the degradation process, but also secrete anti-inflammatory substances needed for tissue regeneration.<sup>9</sup> One of the most important signaling molecules is the vascular endothelial growth factor (VEGF), which has direct and indirect impact onto different processes important for successful tissue regeneration.<sup>8,9</sup> Thus, VEGF induces angiogenesis at the implant site, which has indirectly a positive influence on bone tissue growth, and also direct influence on the development and activity of osteoblasts.<sup>8,10</sup>

In case of the xenogenic bone substitute material cerabone®, it can be assumed that the observed higher numbers of MNGCs might have a positive effect on bone regeneration. Interestingly, an initially improved bioactivity for cerabone® combined with a higher vascularisation at the implant site was demonstrated, which might be based on the increased number of MNGCs compared to Bio-Oss™.<sup>2</sup> Thus, an improving effect on bone regeneration could be concluded after the application of cerabone®. In combination with the hydrophilic nature of this material,<sup>1</sup> which has been shown to significantly support the regeneration process by promoting the growth of osteoblasts, cerabone® can be considered as a reliable bone grafting material with an assured safety for both clinical user and patient.

### Summary

Altogether, it can be concluded that the xenogenic bone substitute material cerabone® is able to ensure the highest possible safety from disease transmission due to the high temperature treatment. Furthermore, it is assumable that the relatively high numbers of multinucleated giant cells express high amounts of anti-inflammatory molecules and support a fast and high implant bed vascularisation and therefore, might favour the bone regeneration process.

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