Review article

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THE EFFECT OF TEMPERATURE TREATMENT OF XENOGENEIC BONE SUBSTITUTE ON THE TISSUE RESPONSE – A MINI REVIEW

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In general, it has been revealed that interaction of bone substitute material with the host immune system is dependent upon their physico-chemical properties. In the case of xenografts, different purification methods are applied to process the precursor tissue. One purification method that differs the most is the applied temperature. Materials treated with low and high temperatures are available. In this context, the question remains as to the influence of the different temperature treatments on the physical and chemical material properties and, thus, on the tissue reactions during the healing processes. It has been hypothesized that materials that induce mononuclear cells induce physiological healing processes, while a pathological reaction is accompanied with the induction of multinucleated giant cells (MNGCs). In this mini-review, the focus is on the comparison of preclinical research into tissue reactions to sintered and non-sintered bovine-derived xenograft. Interpretation of this data showed that an induction of higher numbers of MNGCs by sintered xenograft also induced a higher implant bed vascularization. Finally, the higher number of MNGCs and increased vascularization presumably resulted in a higher expression of anti-inflammatory molecules that may support the process of bone remodeling.

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Key words: *bone substitute, xenograft, multinucleated giant cells, implant bed vascularization, inflammation*

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Introduction

Bone tissue is a hard tissue and a type of dense connective tissue which has the ability to grow and heal itself in the case of minor defects. However, more pronounced bone defects and bone augmentation sites require a scaffold as a platform for bone regeneration. Bone substitution means the implantation of substitute materials into bone defects with the aim of allowing defect regeneration, ideally up to the condition of *restitution ad integrum*, i.e., the complete bone defect healing. A large variety of bone substitute materials are nowadays available on the market. Bone grafts can generally be classified based on their origin. Bone substitute materials can originate from autografts, allografts, xenografts and synthetic grafting materials. An autogenic graft is harvested from the patient itself, i.e., most often from the iliac crest bone. However, its harvesting is often accompanied with the effects of a surgical intervention, such as pain or infections at the donor side (1, 2). Furthermore, an allograft is derived from the individuals of same species, i.e., most often living human donors. Xenografts are derived from non-human species, i.e., mostly animal sources such as bovines. In contrast, synthetic grafting materials are manufactured mostly based on calcium phos-phates such as hydroxyapatite (HA) or beta-trical-cium pho-

sphate (β-TCP) as these compounds are parts of the natural mineral component of bone tissue (3).

In general, an optimal bone graft should be easy to handle and should become incorporated, revascularized and integrated (4). Additionally, it should be biocompatible, non-immunogenic, physiologically stable and in simple words, it should be acceptable by patient and without the risk of disease transmission (4).

Interestingly, it has already been revealed that both "natural" bone substitute materials such as bovine-based xenografts and synthetic grafting materials induce an immune response within the implantation bed of the recipient, called a "foreign body reaction to biomaterials" (5, 6). In this cascade, macrophages and their fused relative cell type, the so-called multinucleated giant cell (MNGC), have manifoldly shown to be involved (5). It has been revealed that both these cell types are regulatory elements of the tissue reaction cascade as they express pro- and anti-inflammatory molecules that guide the cascade and, thus, the bone healing process (Figure 1.) (5, 7). In this context, it has been shown in more detail that the severity and the inflammatory alignment of the material-associated tissue reaction cascade is mainly influenced by different physical and chemical properties of bone substitute materials, such as their chemical composition, the granule size or the granule porosity, amongst others (8-10). Interestingly, these physicochemical properties of a bone substitute have also shown to have importance for the clinic as these factors have influence on the bony regeneration process (5, 11).

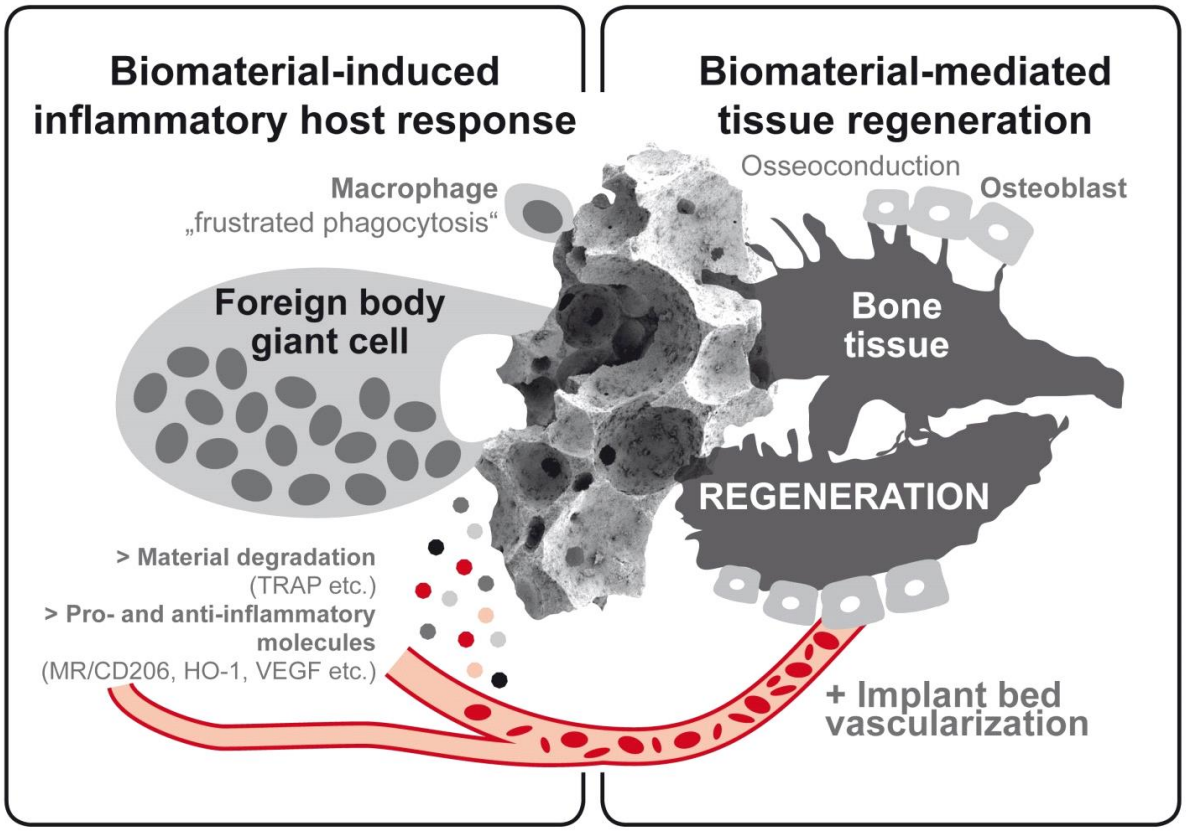

Figure 1. Schematic illustration of the correlation between cellular and inflammatory processes caused by bone materials, the process of implant bed vascularisation and the process of bone tissue regeneration

In case of both allo- and xenografts, the donor tissue has to be purified from immunologically effectual components such as cells or different proteins prior to their application as a bone graft material. Xenografts based on bovine donor tissue or bovine hydroxyapatite (BHA) are widely used and researched bone substitute materials due to their similar physiochemical properties compared to human bone, their osteoconductivity potential and availability (12). Two of the most popular and commonly used bovine-derived xenografts are Bio-Oss™ (Geistlich Biomaterials, Wolhusen, Switzer-land) and cerabone® (botiss biomaterials, Berlin, Germany). Although it has been shown that both these bovine-derived bone substitutes provide acceptable regenerative potential, there are still essential differences in their purification processes (13, 14). The most prominent variation in these processes is the treatment of the precursor bone tissue at different temperatures. While Bio-Oss™ undergoes a low heat treatment with temperatures around 300 °C, cerabone® becomes treated at temperatures of up to 1250 °C (so-called

"sintering") (15, 16). Based on the different temperature treatments, it is presumable that there are differences in the material structure, subsequent tissue reactions and maybe in the healing capacity of both materials. The present mini-review aims to compare the tissue reactions to these two xenogeneic bone substitute materials and gives an overview of preclinical results.

The preparation processes of the xenogeneic bone substitute materials

In order to have a successful bone substitute produced from natural sources, it is extremely crucial to carry out physical and/or chemical treatments in order to remove all organic material and immunologically active contents, such as pathogens and cells. Most often, only the mineral content of the former bone tissue remains and should function as a bone substitute. Interestingly, different purification methods are applied for manufacturing of the available xenogeneic bone substitute materials.

In case of Bio-Oss™, an initial purification step that includes a heat treatment with temperatures up to 300 °C and a further cleansing step by means of a strongly alkaline agent, sodium hydroxide (NaOH) are applied (17). In this context, it has been stated that the treatment of the bovine bone matrix at lower temperatures, as in case of Bio-Oss™, leads to the preservation of the mineral crystals of the bone matrix (18). However, it has been revealed that the crystallinity changes during the heat treatment, although the bone substitute material consists of phase-pure hydroxyapatite (HA) (19). In contrast to human bone, the heat-treated HA causes an in-crease of the crystal size by 200 – 300%, quantified via transmission electron microscopy (TEM) and X-ray diffraction (XRD) measurement (19).

For the synthesis of cerabone®,a two-stage heat-based process, including an initial oxidative combustion at temperatures around 800 °C and a second heat treatment at higher temperatures of up to 1,250 °C (sintering), is applied (20). Although cerabone® also consists of 100% HA, further differences in the crystallinity have been revealed (19). A larger increase of the crystal size by 500-1000% and a higher crystal density in comparison to human bone have been measured, which leads to the conclusion that cerabone® is comparable to a ceramic-based material (21).

Results of preclinical in vivo studies

The inflammatory tissue reactions to both xenogeneic materials have comparatively been analyzed using the subcutaneous implantation model and established histomorphometrical methods (7-10, 13, 14, 16, 21-26). Different numbers of multinu-cleated giant cells (MNGCs), which showed partial expression of the lytic enzyme tartrate-resistant acid phosphatase (TRAP), have been found besides a large number of mononucleated cells such as macrophages (26). The comparative measurements showed initially that larger numbers of (TRAP-positive) MNGCs were found in the case of Bio-Oss™, which was related to the smaller material particles triggering the tissue reaction even at early study time points, while their numbers significantly decreased at later time points. In contrast, comparatively high numbers of MNGCs were found within the implantation beds of cerabone® starting after 10 days post *implantationem*. However, the MNGC numbers did not decrease with time and remained at a comparable level up to 60 days post *implantationem*. Interestingly, implant bed vascula-rization also differed: while a fast and continuously high implantation bed vascularization was measured for Bio-Oss™, vascularization was initially low and increased over time to a high level in case of cerabone®.

Moreover, it has been shown that the MNGCs in the implant bed of Bio-Oss™ seem to be foreign body giant cells (FBGCs), as also found in case of a synthetic hydroxyapatite-based bone substitute, which indicates that the different treatments based on different physical and chemical methods lead to a conversion of the former bone matrix in the direction of a foreign material (7). In this context, it is possible that the MNGCs found in the implant beds of cerabone® are also FBGCs. However, it has been shown that this cell type is not restricted to express only pro-inflammatory molecules but also anti-inflammatory mediators such as the vascular endo-thelial growth factor (VEGF) or the mannose receptor (MR, CD206), which leads to a related increased implant bed vascularization (22). Thus, it is pres-umable that a higher induction of MNGCs also might also cause a better bone regeneration, as implant bed vascularization is a key component for (bone) tissue regeneration (27, 28). Interestingly, the first results of a new study also confirm this theory, as it could be shown that a higher severity of a material-related inflammatory process, including MNGCs, supports directly and indirectly the bony regene-ration process (unpublished data by Barbeck et al.).

Different preclinical implantation studies have been conducted to evaluate the material-related bone growth by means of Bio-Oss™ and cerabone® (Table 1) (29-39). In the case of cerabone®, only a few preclinical *in vivo* studies quantitatively analyzing bone regeneration have been conducted (Table 1) (29, 30). Interestingly, these studies report very diverse results. The studies give the range of newly built bone using cerabone® at different time points to be; 0 and 40% for between 21-28 days, 14-78% between 42-84 days and finally 21–30% for up to 168 days (Table 2) (29, 31, 39). In contrast, a variety of *in vivo* studies have been carried out to analyze the bone regeneration capacities of Bio-Oss™ (Table 1) (32-38, 39). A comparable variety of histomorphometrical results have been presented as in case of Bio-Oss™ (Table 1). Altogether, percent values of newly built bone tissue are between 8 and 34% for a time frame between 14-30 days, 4-57% for a time frame between 42-84 days and finally 39-47% for the time frame between 112-168 days have been found (Table 2) (32-38, 39). Altogether, the comparison of these preclinical data shows comparable bone healing capacities for both bone substi-tute materials (Table 2). However, even in case of cerabone®, more studies are necessary to evaluate the healing properties of this xenograft treated at high temperatures.

Table 1. Overview of preclinical *in vivo* studies analyzing the bone healing capacities of both xenogeneic bone substitutes

Implantation model	Time point(s)	Bone growth	Authors
Cerabone			
Calvarian critical size defect model, rat	28 and 56 days	28 days (42.10%) 56 days (77.60 %)	Shakir *et al.* (31)
Calvarian critical size defect model, rabbit	60 days	55%	Huber *et al.* (29)
Periapical implantation model, cat	84 and 168 days	30.2% 5.7% at the grafted membrane-protected sites	Artzi *et al.* (30)
Bio-Oss, Cerabone			
Calvarian critical size defect model, rabbit	21 and 42 days	cerabone® 60.6% new bone growth for BioOss® 52.1% new bone growth for	Institute of Bone Scienc, Seoul, Korea
Bio-Oss			
Calvarian critical size defect model, rabbit	14 and 28 days	14 days (8.6 3.1%) 28 days (15.7 5.4%)	Park *et al.* (c) (34)
Calvarian critical size defect model, rabbit	28 days	11.7 2.4 %	Rokn, Khodadoostan (35)
Calvarian critical size defect model, rabbit	28 and 56 days	28 days (12.9 5.8%) 56 days (14 7.2%)	Park *et al.* (b) (33)
Calvarian critical size defect, rat	30 and 60 days	30 days (54.05% 5.78) 60 days (63.58% 5.78)	Oliviera *et al.* (36)
Calvarian critical size defect, rat	42 and 84 days	42 days (6.4 4.3%) 84 days (8.2 3.9%)	Park *et al.* (a) (32)
Calvarian critical size defect model, sheep	84 and 168 days	84 days (21 ± 1.2 %) 168 days (39 ± 3.3 %)	Scarano *et al.* (38)
Calvarian critical size defect, rat	112 days	47.4 7.1 %	Mah *et al.* (39)
Calvarian critical size defect model, rabbit	8 weeks	57.76 ± 7.75 %	Takauti *et al.* (37)

Table 2. Comparison of the preclinical in vivo data

	Bio-Oss	**cerabone**
14 – 30 days	**8 – 34% (18.69%)**	**0 – 40% (20%)**
42 – 84 days	**4 – 57% (23.76%)**	**14 – 78 % (46,56%)**
112 – 168 days	**39 – 47% (43.2%)**	**21 – 30% (25,9)**

Conclusion

The sintering temperature of bone substitutes including bovine hydroxyapatite based materials has shown to be an important parameter that can affect the properties of HA. In this context, the sintering temperature has influence on phase stability, densification behavior, crystallinity and porosity of HA. The data outlined in the present mini-review show that the heat treatment at different temperatures influence the tissue response to the bone matrix based bone substitute materials. Although it has been shown that both Bio-Oss™, which is purified at temperatures of 300 °C, and cerabone® with a treat-ment at 1250 °C, allow for comparable outcomes of bone healing, the number of the MNGCs and the related implant bed vascularization seem to be influenced by the material differences, induced by the different temperature treatments. Thus, it is also conceivable that variations in the expression of pro- and anti-inflammatory molecules by both macrophages and MNGCs are induced by these material differences. Thus, the question arises as to how the temperature treatment affects material properties to be more favorable for optimal bone tissue regeneration.

Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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EFEKAT TERMIČKOG TRETMANA KSENOGENIH KOŠTANIH ZAMENIKA NA TKIVNI ODGOVOR – MINI PREGLED

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Uopšteno govoreći, otkriveno je da materijali za zamenu kosti izazivaju interakcije sa imunskim sistemom domaćina zavisno od njihovih fizičko-hemijskih osobina. U slučaju ksenografta, primenjuju se različite metode prečišćavanja za obradu izvornog tkiva. Jedna od najzastupljenijih metoda koja se primenjuje za njihovo prečišćavanje je termička, pošto se dostupni materijali tretiraju zagrevanjem na različitim temperaturama. U ovom kontekstu ostaje pitanje kako različite temperature tretmana mogu da utiču na fizička i hemijska svojstva materijala, a time i na reakcije tkiva na njih i procese lečenja. Pretpostavljeno je da materijali čiju tkivnu reakciju karakterišu mononuklearne ćelije izazivaju fiziološke procese zarastanja, dok uz patološku reakciju ide indukcija multinuklearnih gigantskih ćelija (MNGC). U ovom mini pregledu fokus je na komparaciji tkivnih reakcija na sinterovane i nesinterovane govеđe ksenografte u pretkliničkim ispitivanjima. U tumačenju ovih podataka pokazalo se da indukcija većeg broja MNGC pomoću sinterovanog ksenografta indukuje i veću vaskularizaciju ležišta implanta. Konačno, veći broj MNGC i veća vaskularizacija, zajedno sa verovatno većom ekspresijom antiinflamatornih molekula mogu podržati proces remodelovanja kostiju.

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Ključne reči: *koštani zamenik, ksenograf, multinuklearne gigantske ćelije, vaskularizacija ležišta implantata, inflamacija*