

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

Mike Barbeck<sup>1</sup>, Željka Perić-Kačarević<sup>2</sup>, Faraz Kavehei<sup>3</sup>, Patrick Rider<sup>4</sup>, Stevo Najman<sup>5</sup>, Sanja Stojanović<sup>5</sup>, Denis Rimashevskiy<sup>6</sup>, Sabine Wenisch<sup>7</sup>, Reinhard Schnettler<sup>8</sup>

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

<sup>1</sup>Department of Oral and Maxillofacial Surgery, University Hospital Hamburg-Eppendorf, Hamburg, Germany

<sup>2</sup>Department of anatomy histology and embryology, Faculty of dental medicine and health, University of Osijek, Osijek, Croatia

<sup>3</sup>Department of Chemical Engineering, Imperial College London, UK

<sup>4</sup>Research and Development, botiss biomaterials GmbH, Berlin, Germany

<sup>5</sup>University of Niš, Faculty of Medicine, Department for Cell and Tissue Engineering; Institute of Biology and Human Genetics, Niš, Serbia

<sup>6</sup>Department of Traumatology and Orthopedics, Peoples' Friendship University of Russia, Moscow, Russia

<sup>7</sup>Clinic of Small Animals, c/o Institute of Veterinary Anatomy, Histology and Embryology, Justus Liebig University of Giessen, Giessen, Germany

<sup>8</sup>Justus Liebig University, Giessen, Germany

**Contact:** Mike Barbeck  
Department of Oral and Maxillofacial Surgery,  
University Hospital Hamburg-Eppendorf, Hamburg, Germany  
E-mail: mike.barbeck@icloud.com

### Introduction

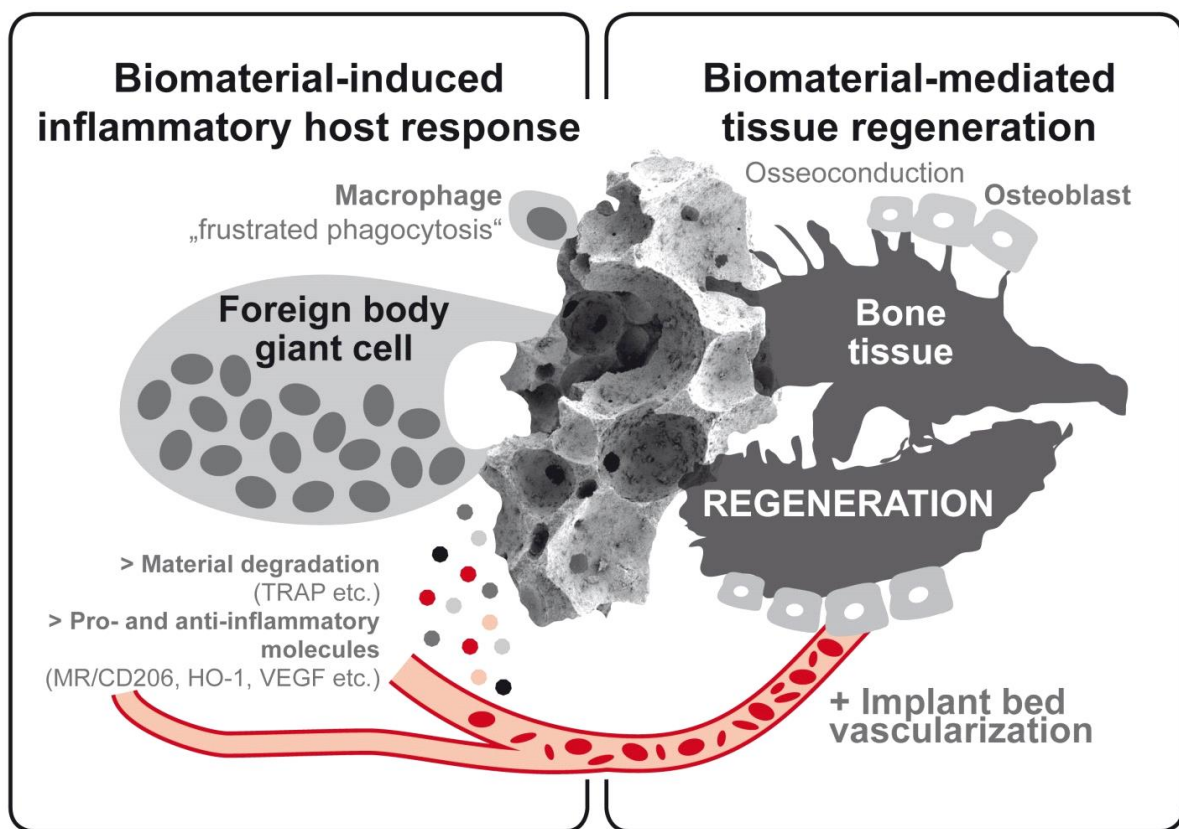
Bone tissue is a hard tissue and a type of dense connective tissue which has the ability to grow and heal itself in the case of minor defects. However, more pronounced bone defects and bone augmentation sites require a scaffold as a platform for bone regeneration. Bone substitution means the implantation 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 phosphates such as hydroxyapatite (HA) or beta-tricalcium phos-

sphate ( $\beta$ -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 mani-

foldly 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 physicochemical 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 Bio-

materials, Wolhusen, Switzerland) 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 increase 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 multinucleated 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 trig-

gering 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 vascularization 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 endothelial growth factor (VEGF) or the mannose receptor (MR, CD206), which leads to a related increased implant bed vascularization (22). Thus, it is presumable 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 regeneration 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 substitute 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 <i>et al.</i> (31)
Calvarian critical size defect model, rabbit	60 days	55%	Huber <i>et al.</i> (29)
Periapical implantation model, cat	84 and 168 days	30.2% 5.7% at the grafted membrane-protected sites	Artzi <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (b) (33)
Calvarian critical size defect, rat	30 and 60 days	30 days (54.05% 5.78) 60 days (63.58% 5.78)	Oliviera <i>et al.</i> (36)
Calvarian critical size defect, rat	42 and 84 days	42 days (6.4 4.3%) 84 days (8.2 3.9%)	Park <i>et al.</i> (a) (32)
Calvarian critical size defect model, sheep	84 and 168 days	84 days (21 ± 1.2 %) 168 days (39 ± 3.3 %)	Scarano <i>et al.</i> (38)
Calvarian critical size defect, rat	112 days	47.4 7.1 %	Mah <i>et al.</i> (39)
Calvarian critical size defect model, rabbit	8 weeks	57.76 ± 7.75 %	Takauti <i>et al.</i> (37)

**Table 2.** Comparison of the preclinical *in vivo* data

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

## 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 treatment 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.

## References

- Hill NM, Geoffrey Horne J, Devane PA. Donor site morbidity in the iliac crest bone graft. *Aust N Z J Surg* 1999; 69(10):726-8. [[CrossRef](#)] [[PubMed](#)]
- Arrington DE, Smith WJ, Chambers HG, Bucknell AL, Davino NA. Complications of iliac crest bone graft harvesting. *Clin Orthop Relat Res* 1996; (329):300-9. [[CrossRef](#)] [[PubMed](#)]
- Vallet-Regí M, González-Calbet JM. Calcium phosphates as substitution of bone tissues. *Prog Solid State Ch* 2004; 32(1-2):1-31. [[CrossRef](#)]
- Damien CJ, Parsons JR. Bone graft and bone graft substitutes: A review of current technology and applications. *J Appl Biomater* 1991; 2(3):187-208. [[CrossRef](#)] [[PubMed](#)]
- Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. *Semin Immunol* 2008; 20(2):86-100. [[CrossRef](#)] [[PubMed](#)]
- Nuss KMR, von Rechenberg B. Biocompatibility issues with modern implants in bone - A review for clinical orthopedics. *Open Orthop J* 2008; 2:66-78. [[CrossRef](#)] [[PubMed](#)]
- Barbeck M, Booms P, Unger R, Hoffmann V, Sader R, Kirkpatrick CJ, et al. Multinucleated giant cells in the implant bed of bone substitutes are foreign body giant cells-New insights into the material-mediated healing process. *J Biomed Mater Res A* 2017; 105(4):1105-11. [[CrossRef](#)] [[PubMed](#)]
- Barbeck M, Najman S, Stojanović S, Mitić Ž, Živković JM, Choukroun J, et al. Addition of blood to a phyco-genic bone substitute leads to increased *in vivo* vascularization. *Biomed Mater* 2015; 10(5):055007. [[CrossRef](#)] [[PubMed](#)]
- Ghanaati S, Barbeck M, Detsch R, Deisinger U, Hilbig U, Rausch V, et al. The chemical composition of synthetic bone substitutes influences tissue reactions *in vivo*: histological and histomorphometrical analysis of the cellular inflammatory response to hydroxyapatite, beta-tricalcium phosphate and biphasic calcium phosphate ceramics. *Biomed Mater* 2012; 7(1): 015005. [[CrossRef](#)] [[PubMed](#)]
- Lorenz J, Barbeck M, Sader RA, Kirkpatrick CJ, Russe P, Choukroun J, et al. Foreign body giant cell-related encapsulation of a synthetic material three years after augmentation. *J Oral Implantol* 2016; 42(3):273-7. [[CrossRef](#)] [[PubMed](#)]
- Cheyn Z, Klein T, Murray RZ, Crawford R, Chang J, Wu C, et al. Osteoimmunomodulation for the development of advanced bone biomaterials. *Mater Today* 2016; 19(6):304-21. [[CrossRef](#)]
- Campana V, Milano G, Pagano E, Barba M, Cicione C, Salonna G, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice. *J Mater Sci Mater Med* 2014; 25(10):2445-61. [[CrossRef](#)] [[PubMed](#)]
- Barbeck M, Udeabor SE, Lorenz J, Kubesch A, Choukroun J, Sader RA, et al. Induction of multinucleated giant cells in response to small sized bovine bone substitute (Bio-Oss) results in an enhanced early implantation bed vascularization. *Ann Maxillofac Surg* 2014; 4(2):150-7. [[CrossRef](#)] [[PubMed](#)]
- Ghanaati S, Barbeck M, Booms P, Lorenz J, Kirkpatrick CJ, Sader RA. Potential lack of "standardized" processing techniques for production of allogeneic and xenogeneic bone blocks for application in humans. *Acta Biomater* 2014;10(8):3557-62. [[CrossRef](#)] [[PubMed](#)]
- Chappard D, Fressonnet C, Genty C, Baslé MF, Rebel A. Fat in bone xenografts: Importance of the purification procedures on cleanliness, wettability and biocompatibility. *Biomaterials* 1993; 14(7):507-12. [[CrossRef](#)] [[PubMed](#)]
- Barbeck M, Udeabor S, Lorenz J, Schlee M, Holthaus MG, Raetscho N, et al. High-temperature sintering of xenogeneic bone substitutes leads to increased multinucleated giant cell formation: *in vivo* and preliminary clinical results. *J Oral Implantol* 2015; 41(5):e212-22. [[CrossRef](#)] [[PubMed](#)]
- Barbeck M, Unger R, Schnettler R, Wenisch S, Witte F. Xenogeneic bone grafting materials. *Implants. International Magazine of Oral implantology* 2017; 17(3): 34-6.

18. Bufler MA. Calciumphosphate Synthese, Reaktionen in Wässrigen Median und Charakterisierung von Oberflächen und Grenzflächen [dissertation]. Siegen: der Universität Siegen; 2004.
19. Weber U. Calciumorthophosphate mit kontrollierter Kristallmorphologie und ein injizierbares, poröses Biomaterial: Materialentwicklung und Charakterisierung [dissertation]. Rostock: der Universität Rostock; 2013.
20. Ramirez Fernandez MP, Gehrke SA, Perez Albacete Martinez C, Calvo Guirado JL, de Aza PN. SEM-EDX study of the degradation process of two xenograft materials used in sinus lift procedures. *Materials (Basel)* 2017; 10(5):542. [[CrossRef](#)] [[PubMed](#)]
21. Barbeck M, Dard M, Kokkinopoulou M, Markl J, Booms P, Sader RA, et al. Small-sized granules of biphasic bone substitutes support fast implant bed vascularization. *Biomatter* 2015; 5(1):e1056943. [[CrossRef](#)] [[PubMed](#)]
22. Barbeck M, Motta A, Migliaresi C, Sader R, Kirkpatrick CJ, Ghanaati S. Heterogeneity of biomaterial-induced multinucleated giant cells: Possible importance for the regeneration process? *J Biomed Mater Res A* 2016; 104(2):413-8. [[CrossRef](#)] [[PubMed](#)]
23. Lorenz J, Eichler K, Barbeck M, Lerner H, Stubinger S, Seipel C, et al. Volumetric analysis of bone substitute material performance within the human sinus cavity of former head and neck cancer patients: A prospective, randomized clinical trial. *Ann Maxillofac Surg* 2016; 6(2):175-81. [[CrossRef](#)] [[PubMed](#)]
24. Barbeck M, Lorenz J, Kubesch A, Böhm N, Booms P, Choukroun J, et al. Porcine dermis-derived collagen membranes induce implantation bed vascularization via multinucleated giant cells: a physiological reaction? *J Oral Implantol* 2015; 41(6):e238-51. [[CrossRef](#)] [[PubMed](#)]
25. Ghanaati S, Barbeck M, Lorenz J, Stuebinger S, Seitz O, Landes C, et al. Synthetic bone substitute material comparable with xenogeneic material for bone tissue regeneration in oral cancer patients: First and preliminary histological, histomorphometrical and clinical results. *Ann Maxillofac Surg* 2013; 3(2):126-38. [[CrossRef](#)] [[PubMed](#)]
26. Lorenz J, Kubesch A, Korzinskas T, Barbeck M, Landes C, Sader RA, et al. Trap-positive multinucleated giant cells are foreign body giant cells rather than osteoclasts: results from a split-mouth study in humans. *J Oral Implantol* 2015; 41(6):e257-66. [[CrossRef](#)] [[PubMed](#)]
27. Yang YQ, Tan YY, Wong R, Wenden A, Zhang LK, Rabie AB. The role of vascular endothelial growth factor in ossification. *Int J Oral Sci* 2012; 4(2):64-8. [[CrossRef](#)] [[PubMed](#)]
28. Michalski MN, Koh AJ, Weidner S, Roca H, McCauley LK. Modulation of osteoblastic cell efferocytosis by bone marrow macrophages. *J Cell Biochem* 2016; 117(12):2697-706. [[CrossRef](#)] [[PubMed](#)]
29. Huber FX, Berger I, McArthur N, Huber C, Kock HP, Hillmeier J, et al. Evaluation of a novel nanocrystalline hydroxyapatite paste and a solid hydroxyapatite ceramic for the treatment of critical size bone defects (CSD) in rabbits. *J Mater Sci Mater Med* 2008; 19(1):33-8. [[CrossRef](#)] [[PubMed](#)]
30. Artzi Z, Wassersprung N, Weinreb M, Steigmann M, Prasad HS, Tsesis I. Effect of guided tissue regeneration on newly formed bone and cementum in periodontal tissue healing after endodontic surgery: an *in vivo* study in the cat. *J Endod* 2012; 38(2):163-9. [[CrossRef](#)] [[PubMed](#)]
31. Shakir M, Jolly R, Khan AA, Ahmed SS, Alam S, Rauf MA, et al. Resol based chitosan/nano-hydroxyapatite nanoensemble for effective bone tissue engineering. *Carbohydr Polym* 2018; 179:317-27. [[CrossRef](#)] [[PubMed](#)]
32. Park JW, Jang JH, Bae SR, An CH, Suh JY. Bone formation with various bone graft substitutes in critical-sized rat calvarial defect. *Clin Oral Implants Res* 2009; 20(4):372-8. [[CrossRef](#)] [[PubMed](#)]
33. Park JW, Kim ES, Jang JH, Suh JY, Park KB, Hanawa T. Healing of rabbit calvarial bone defects using biphasic calcium phosphate ceramics made of submicron-sized grains with a hierarchical pore structure. *Clin Oral Implants Res* 2010; 21(3):268-76. [[CrossRef](#)] [[PubMed](#)]
34. Park JW, Ko HJ, Jang JH, Kang H, Suh JY. Increased new bone formation with a surface magnesium-incorporated deproteinized porcine bone substitute in rabbit calvarial defects. *J Biomed Mater Res A* 2012; 100(4):834-40. [[CrossRef](#)] [[PubMed](#)]
35. Rohn AR, Khodadoostan MA, Reza Rasouli Ghahroudi AA, Motahhary P, Kharrazi Fard MJ, Bruyn HD, et al. Bone formation with two types of grafting materials: a histologic and histomorphometric study. *Open Dent J* 2011; 5:96-104. [[CrossRef](#)] [[PubMed](#)]
36. Oliveira MR, deC Silva A, Ferreira S, Avelino CC, Garcia IR Jr, Mariano RC. Influence of the association between platelet-rich fibrin and bovine bone on bone regeneration. A histomorphometric study in the calvaria of rats. *Int J Oral Maxillofac Surg* 2015; 44(5):649-55. [[CrossRef](#)] [[PubMed](#)]
37. Takauti CA, Futema F, Brito Junior RB, Abrahao AC, Costa C, Queiroz CS. Assessment of bone healing in rabbit calvaria grafted with three different biomaterials. *Braz Dent J* 2014; 25(5):379-84. [[CrossRef](#)] [[PubMed](#)]
38. Scarano A, Piattelli A, Pecora G, Petrizzi L, Valbonetti L, Varasano V, et al. A histomorphometric comparison of anorganic bovine bone (ABB) and calcium sulfate (CaS) used in sinus augmentation procedures: a study in sheep. *J Osseointegr* 2010; 2(2):38-44. [[CrossRef](#)]
39. Mah J, Hung J, Wang J, Salih E. The efficacy of various alloplastic bone grafts on the healing of rat calvarial defects. *Eur J Orthod* 2004; 26(5):475-82. [[CrossRef](#)] [[PubMed](#)]

Revijalni rad

UDC: 615.832:616-089.843  
doi:10.5633/amm.2019.0118**EFEKAT TERMIČKOG TRETMANA KSENOGENIH KOŠTANIH ZAMENIKA  
NA TKIVNI ODGOVOR – MINI PREGLED***Mike Barbeck<sup>1</sup>, Željka Perić-Kačarević<sup>2</sup>, Faraz Kavehei<sup>3</sup>, Patrick Rider<sup>4</sup>, Stevo Najman<sup>5</sup>,  
Sanja Stojanović<sup>5</sup>, Denis Rimashevskiy<sup>6</sup>, Sabine Wenisch<sup>7</sup>, Reinhard Schnettler<sup>8</sup>*<sup>1</sup>Odeljenje za oralnu i maksilofacijalnu hirurgiju, Univerzitetska bolnica Hamburg-Eppendorf, Hamburg, Nemačka<sup>2</sup>Departman za anatomsku histologiju i embriologiju, Fakultet za dentalnu medicinu i zdravstvo, Univerzitet u Osijeku, Osijek, Hrvatska<sup>3</sup>Departman za hemijsko inženjerstvo, Imperial College London, UK<sup>4</sup>Istraživanje i razvoj, Kompanija botis biomaterijali GmbH, Berlin, Nemačka<sup>5</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za ćelijsko i tkivno inženjerstvo; Institut za biologiju i humanu genetiku, Niš, Srbija<sup>6</sup>Departman za traumatologiju i ortopediju, Ruski univerzitet narodnog prijateljstva, Moskva, Rusija<sup>7</sup>Klinika za male životinje, Institut za veterinarsku anatomiju, histologiju i embriologiju, Justus Liebig Univerzitet u Gisen, Gisen, Nemačka<sup>8</sup>Justus Liebig University, Gisen, Nemačka*Kontakt:* Mike Barbeck

Univerzitetska bolnica Hamburg-Eppendorf, Hamburg, Germany

E-mail: mike.barbeck@icloud.com

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 goveđe 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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