> **ROBERT A. HOROWITZ[1], ZIV MAZOR[2], CHRISTIAN FOITZIK, HARI PRASAD[3], MICHAEL ROHRER[4], ADY PALTI**

[1] Clinical Assistant Professor, Ashman Departments of Periodontology and Implant Dentistry, Oral Surgery, Biomimetics and Biomaterials, New York University College of Dentistry, New York, New York; Private Practice in Periodontics and Implant Dentistry, Scarsdale, New York, USA

[2] Private Practice in Periodontics and Implant Dentistry, Ra'ananah, Israel

[3] Senior Researcher, Department of Hard Tissue Research, Hard Tissue Research Laboratory, University of Minnesota, School of Dentistry, Minneapolis, Minnesota, USA

[4] Professor and Director, Division of Oral and Maxillofacial Pathology, Director, Hard Tissue Research Laboratory, University of Minnesota, School of Dentistry, Minneapolis, Minnesota

β-tricalcium phosphate as bone substitute material: properties and clinical applications

ABSTRACT

Aim As the scope of implant dentistry widens, hard tissue augmentation is becoming more common. The previous "gold standard" for bone augmentation, autogenous bone, is limited in availability and restricted in harvesting due to increased peri- and postoperative complications. This paper gives guidance to the surgeon about various classes of bone replacement graft substitutes relative to their origin, ability to resorb and their replacement with vital, osseointegratable bone.
A synthetic graft, pure phase β-tricalcium phosphate, has been documented in human and animal studies to be resorbed and replaced by vital bone in a 6 to 12-month time period.
Conclusion The cases and literature shown in this paper demonstrate the predictability and effectiveness of this type of graft material in dental implant-related surgical applications.

KEYWORDS Bone regeneration; Bone resorption; Bone substitute material; Dental implants; Extraction; *Restitutio ad integrum*; Synthetic bone graft; tricalcium phosphate.

INTRODUCTION

There is considerable demand for bone substitutes and bone augmentation materials in the dental and medical fields. Although freshly harvested, autogenous cancellous marrow has always been the most biologically viable material; however, its clinical use is limited. This is due to the need for a second operation or surgical site and the potential complications arising from this and greater time of surgery and anaesthesia (1). There are a large number of biological and synthetic substitute bone materials, which do not differ significantly in their clinical

application and can be easily, cost-effectively and efficiently used with minimum extra expense. This review is intended to provide surgeons who use bone regenerative materials with information so that they can compare materials and select the most suitable one using technical data, current scientific documentation and clinical examples.

BIOMATERIALS

A material is bioinert if it does not cause any reaction that interferes with the functions of the body following implantation. Examples of bioinert materials include carbon, commercially pure titanium and titanium–vanadium-aluminum alloy.
Bioactive materials cause a positive reaction after implantation in terms of bony tissue formation, strengthening or interlocking, which in turn promotes regeneration of the bone and its functions. Bonding osteogenesis occurs as a result. Examples of bioactive materials include synthetic calcium phosphates (tricalcium phosphate [TCP], some formulations of calcium sulfate [CS] and hydroxylapatite [HA]). Materials like TCP are osteoconductive because osteoblasts adhere to them and deposit bony tissue on their surface. The biomaterial forms a scaffold for closing the bony defect (2).
Osteoinductive materials are substances that independently stimulate bone regeneration even in a non-bone forming area. This can occur when stem cells adjacent to osteoinductive substances differentiate to bone forming cells (osteoblasts) and initiate bone regeneration. Various proteins, such as the growth factors Insulin-like growth factor (IGF), fibroblast derived growth factor (FGF), platelet derived growth factor (PDGF) etc., have this characteristic. Bone morphogenetic proteins (BMPs) also have osteoinductive characteristics. Inorganic materials such as ceramics or metals, i.e. all solid

bone substitute materials, do not have osteoinductive characteristics because proteins are required for inducing stem cell differentiation.

Bone formation after implantation in muscle or fatty tissue outside from bone was seen with Poly methyl metacrylic acid (PMMA) (3), with porous titanium (4) and various calcium phosphate ceramics. It was shown that the ectopic osteogenesis is dependant on the implantation site, the grafted material and the porosity of the biomaterial. Even with β-TCP, ectopic bone formation, called osteoinduction after implantation in muscles was seen (5).

Calcium phosphates have a high affinity for proteins (such as BMPs) (6). The pores of the bioceramics have a filter effect and accumulate the growth factors from the surrounding body fluid inside of the micropores (7). Stem cell differentiation and ectopic bone formation can be stimulated by these bone replacement graft materials. Osteopromotion, osteostimulation or osteoproductivity are terms being increasingly used. These terms do not describe any new or additional function of a material and do not have any scientific relevance.

Materials are resorbable if they break down by one of a number of mechanisms and can then be ingested by cells due to their chemical solubility. Only osteoclasts resorb bone or other resorbable materials by releasing acids to dissolve the mineral portion. This action forms resorption lacunae (8) which dissolve the inorganic, calcium-phosphate components of the vital bone or graft. Materials degrade due to their physical characteristics, mechanical forces or they can be dissolved hydrolytically by fluids in the body milieu (9).

Bone substitute/augmentation materials

Features of bone in the human skeleton include high compressive and tensile strength, low flexibility and the ability to resorb and remodel to adapt to changing conditions. The main functions of bone are haematopoiesis, muscle attachment, protection of inner organs and providing the body's support framework. Bone substitute materials are intended to be implanted in a surgical procedure and, over time, become a part of vital bone. HA materials made of bovine bone, processed or partially synthetic are not ideal bone grafting materials as they are non-resorbable (10). Therefore new bone can not completely fill the grafted region. These materials can act as volumetric fillers and scaffolds upon which new bone is deposited. Although this type of HA will neither be resorbed nor replaced by bone, the resultant structure will be firmer than a graft encased in non-mineralized connective tissue alone. Bone physiology demands that grafts go through a number of stages including remodelling to provide a mechanically efficient structure (11). A defect site grafted with non-resorbable HA will not regain its

full biological and biomechanical function. Use of the term "bone substitute material" is therefore highly questionable for these materials.

Bone augmentation materials can assist in the processes of bone regeneration. These resorb/degrade after a certain period of time *in situ* and are then replaced by newly formed bone, which ensures ideal healing of the defect. At the completion of treatment, bone has developed that exhibits all the characteristics and functions of the original bone. Temporary bone augmentation materials degrade hydrolytically and are resorbed by osteoclasts without any cellular problems. Inflammatory reactions have occasionally been observed but only during the early stages of bone healing (9). Materials, which are made up of ultra-fine particles, are removed by phagocytosis which can cause a permanent foreign body response (12). The exact or ultimate destination of the transported particles is not clear.

The groups of materials listed below are available as alternatives to autogenous bone, which is still regarded as the "gold standard" by many clinicians.

> Allogenic bone is harvested from cadaveric donors, where occasional concerns arise about the documentation and procurement of the donated materials. There can be residual immunological risks as well as the risk of the host obtaining a graft-transmitted infection, e.g. HIV, hepatitis or Creutzfeld Jacobs desease (CJD) (13, 14). The patient must be informed of these potential risks. These products can not be surgically implanted in patients in a number of countries around the world due to regulations by the health departments in those countries.

> Xenogenic material, mainly of bovine origin, may also trigger non-specific immune responses during the early healing stages as well as carry immunological and infection risks. As resorption is unpredictable, it can lead to encapsulation with the material remaining in the defect for years, possibly provoking macrophage activity (15). If the graft material is not resorbed, the resulting mixture of vital bone and graft material may not remodel nor handle the physical stress. There are parts of the world where these materials can also not be utilized in surgical procedures.

> Partially synthetic material is harvested from biological raw material, generally from bovine bone and then, chemically or thermally converted to the end product. It is not a practical replacement material as there is no significant resorption during the time period between grafting and implant placement (16).

> Synthetic substitute materials, e.g. ß-TCP, which can be manufactured with precisely definable physical and crystalline chemical properties, have a consistent batch quality (17). These grafts allow the biological reaction to be more easily predicted (1).

They are nontoxic, immunologically inert, noncarcinogenic and nonteratogenic.

SELECTION CRITERIA

A material suitable for patient treatment should ideally have the properties of bioactivity, osteoconduction and resorption/degradation described above. Allogenic and xenogenic bone carry biological risks that are not present in synthetic materials. Although these materials are harvested after careful donor selection and are processed and sterilized, graft materials from biologic sources may be of concern to some patients. Nonresorbable materials made from highly crystallized HA are osteoconductive, osseointegrated but not resorbed (16). Bovine-derived graft materials are not resorbed in the time frame of 3–24 months in dogs (10). In the 3 month time frame in this animal study, healing was delayed in the bovine HA grafted site compared to both control and pure phase β-tricalcium phosphate (β–TCP) grafted defects. Biodegradation of calcium phosphate ceramics can be divided into two processes. Physicochemical degradation of the biomaterial depends on the solubility of the material itself, while particle decomposition of the material depends on the solubility product of the "sinter necks", which hold the individual grains together. β-TCP biomaterials with the properties described above are converted and metabolized without any potentially toxic byproducts by hydrolysis and cellular resorption (18).

According to tests with isotope labelled ceramics, the calcium component of resorbable calcium phosphate materials plays a role in local mineralization processes and also in the surrounding calcium pool (19).

A highly reproducible and consistent quality in both the composition of the graft and size of the particles are essential characteristics for predictable, successful bone regeneration. A bone augmentation material should, therefore, have the characteristics listed below. The first case demonstrates some of these characteristics. After extraction of a lower premolar, a large alveolar defect remained (Fig. 1). The site was grafted with a pure-phase, β–TCP (Cerasorb M, 150-500 μ particle size, Curasan Pharma, Kleinostheim, Germany) (Fig. 2), covered with a resorbable barrier and primary closure was obtained and maintained through healing. The site was reentered six months postoperatively where complete alveolar healing was noted, enabling the placement of a dental implant in an ideal location, completely surrounded by alveolar bone (Fig. 3). The graft material had resorbed and been replaced by vital alveolar bone. After healing was completed, the implant was restored with a solid abutment and cementable crown, in ideal position with keratinized tissue on the facial and lingual surfaces (Fig. 4).

Chemical purity

The mineral phase of bone comprises small, platelet-shaped crystals of calcium deficient β-type carbonate apatite, with the mineral name of dahllite which was first described in the 1920s (20). The

Fig. 1 *After extraction, a large facial alveolar defect was noted around tooth #21 (all surgery in this case performed by Dr. Z. Mazor, Ra'anana, Israel).*

Fig. 2 *The site was grafted to full contour with the material mixed with the patient's own blood then covered with a pericardium membrane.*

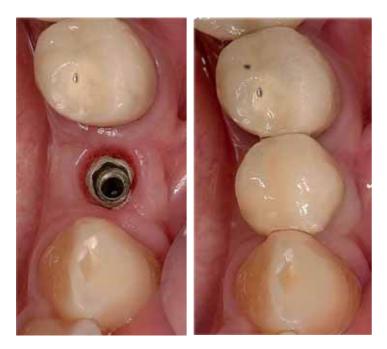Fig. 3 *Six months later, an implant was inserted into the healed ridge.*

Fig. 4 *A) The Occlusal view of the implant after uncovering shows sufficient facial and lingual keratinized tissue and the implant centered in the wide alveolar ridge.*
B) After restoration, the ideal contour of the alveolar ridge including a root prominece can be seen.

calcium to phosphorus ratio (Ca/P ratio) in human bone is 1.3 to 1.66 depending on the person's age and state of health (21). β-TCP with a Ca/P ratio of 1.5 is in the physiological range.

When implanting any soluble and/or resorbable foreign materials into the body, it is essential to ensure that the concentrations of breakdown products are not excessive for the physiological environment. These materials should only be used if they are bioinert or if their resulting substances released into the metabolism are in physiologically harmless (very low) concentrations. Caution should be exercised with biomaterials that contain silicon dioxide (NovaBone, Jacksonville, FL, USA), as high concentrations of these types of materials have been shown to be toxic (22).

Phase purity

Graft materials from animal donors should be deproteinated fully to decrease the chance of disease transmission, and from human hosts should be completely sterilized without changing the composition of the material. In physical chemistry and materials science, phase is defined as a uniform state, in which the chemical and physical properties, including density, crystal structure and chemical composition, do not vary. Calcium phosphate materials are phase pure if they do not contain another phase of the calcium phosphate system or any crystalline

components outside the primary phase. Phase purity should not be confused with chemical purity. A phase pure material is not necessarily chemically pure and vice versa. A calcium phosphate that contains only calcium, phosphorus and oxygen, i.e. a chemically pure calcium phosphate, can contain different phases of the material: alpha tricalcium phosphate (α-TCP), beta tricalcium phosphate (β-TCP), both with the chemical formula $Ca_3(PO_4)_2$ and calcium pyrophosphate ($Ca_2P_2O_7$) in various modifications (arrangement of atoms in relation to one another) etc. The different phases are created by different chemical and thermal treatments during the production process. The phase purity of a β-TCP material is an accurate indication of the quality of the production of the product. β-TCP products with lower phase purity and a variable type or proportion of other calcium phosphate phases indicate that the production process is neither consistent nor reproducible. Some phase impurities have components that are more difficult to degrade than β-TCP, e.g. HA, which can remain in the bone defect long after the β-TCP has resorbed or degraded, altering the physiologic properties of the resulting area.

If slowly degrading components are uniformly distributed in the biomaterial, they can cause difficulties even if their amounts are small. Ultra-small particles of HA stay in the defect and can lead to foreign body immune responses. Some phase impurities like calcium pyrophosphate degrade more readily than β-TCP in the body milieu. The space maintenance function essential for bone regeneration is disrupted and connective tissue can enter the grafted defect site. In addition, if the subparticles are too small, it can lead to inflammation of the surrounding tissue triggered by phagocytic responses of macrophages.

One of the materials shown in this paper, Cerasorb® bone augmentation material (Curasan AG, Kleinostheim, Germany) has very high phase purity with over 99% β-TCP; which was verified by measurements using maximum resolution measuring units (23). This material demonstrated the highest purity of all the β-TCP materials measured and the International Center of Diffraction Data (ICDD) made this new measurement and refinement its standard for its files. This material has been declared as the "standard of material purity" for all measurements of b-TCP's [ICDD 55-898] (24).

Primary particle size

In the 1980s de Groot observed that some materials manufactured from micro and macro porous ß-TCP rapidly degraded into ultra-fine particles, which could then be detected in adjacent lymph nodes. Particle degradation, rather than the ideal decomposition through resorption, of these materials was due to low mechanical stability and the small particle components of the material (25). Tests comparing the relationship

between particle size and foreign body response indicated that any smaller particles than a few micrometers (µm) were phagocytized by macrophages and then removed through the lymph system. Excessive foreign body responses to a large amount of implanted ultra-fine particles can cause inflammatory reactions of the surrounding soft tissue. Biomaterials for implantation should therefore be manufactured to produce particles of 7-10 µm in size and at the same time possess adequate mechanical stability to provide structural integrity in the grafted site and prevent the kind of reactions described by de Groot (12, 25).

Mechanical stability

The volumetric mass of resorbable/degradable bone augmentation material should ideally reduce at the same rate as new bone forms. Fast resorption/degradation can result in the material no longer fulfilling a function as a space maintainer and soft tissue can then grow into the defect. Slower resorption/degradation on the other hand can inhibit integration and conversion of the material, decrease bone regeneration or even prevent it. Porosity and stability are therefore essential properties of a functioning bone augmentation material, and have different effects.

A resorbable/degradable material can not permanently provide a uniformly high mechanical stability: a material that is slowly degraded in the body and is converted to vital bone, changes its mechanical parameters. Highly porous materials often have low primary stability, so inserting them can result in degradation into subparticles due to the mechanical stress applied to the intimate biomaterial/bone contact. As noted above, ultra-fine particles carry the risk of inflammatory reaction in the surrounding soft tissue, not an osteogenic reaction, and should be avoided.

Materials with low abrasion resistance can release ultra-fine particles in the repository and on the surface in the mixing and/or transport of granular biomaterials, causing an inflammatory response.

A thick sintered framework can increase mechanical stability. Sintering particles means heating the material until the surface is molten. The individual particles are bonded together by the fusion of their contact surfaces. The result after cooling is a porous structure of primary particles firmly sintered together (Fig. 5 A). If a material is overheated and/or subjected to an extended ceramic sintering process, the primary particles are melted so much that the framework is no longer porous (Fig. 5 B), delaying or inhibiting resorption and replacement with vital bone.

Porosity

A resorbable biomaterial should have adequate porosity to allow infiltration of blood, bodily fluids and cells. Micropores (<10 µm) assist degradation of the material, while mesopores (>10 µm) and macropores (>100 µm) play a significant part in stabilization of the initial blood clot and subsequent vascularization and integration of the material in the bony tissue (Fig. 6). Eggli et al. demonstrated that interconnections of 20 µm with a pore size of 50-100 µm enabled bone infiltration (27). Vascularization is important for successful bone regeneration, especially when using a biomaterial because of its role in the nutrition of the migrating cells. A pore size up to 60 µm is ideal for vascularization (28).

Solubility

Bone augmentation materials have to be soluble to be degradable or resorbable. The solubility rate is a material constant and an important parameter for successful bone regeneration. Manufacturers of bone
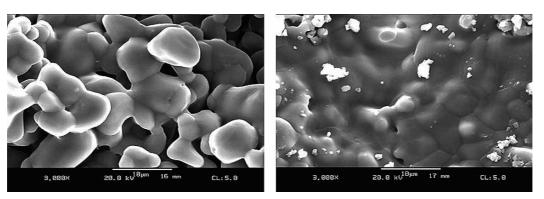

Fig. 5 *Scanning electron microscope images of the structure of two* β*-tricalcium phosphates with varying degrees of sintering. Magnification x 3000. A: Sinter framework of the material. The sintered primary particles, which form an interconnecting microporous framework, are clearly visible. Mechanical stability and microporosity are optimally coordinated. B: Sinter framework of a highly sintered material heated for too long and at too high a temperature. The primary particles are still evident and so tightly fused together that there is no longer any microporosity. There is high mechanical stability, but the resorbability rate in the bone is greatly reduced due to the small surface area.*

augmentation material tailor their products to the requirements of different types of defects, as recommended in published material (29). Figure 7 provides information about the solubility rate in water of the standard version of two types of a pure-phase β-TCP, one a rounded shape (overall porosity approx. 35%) and the other with more surface area per volume of graft (overall porosity approx. 65%). This degradation correlates to *in vivo* resorption and bone replacement as has been confirmed by clinical results in human and animal studies at time intervals from 4 to 6 months (10, 30-33).

In 2000 Merten et al. reported that pure phase ß-TCP ceramic in an artificial medullary cavity defect in Göttingen minipigs was completely substituted by bone within 15–18 months (33). In another animal experiment with adult minipigs the same working group demonstrated that after 68 weeks, 96% of the ß-TCP was resorbed without stimulus and substituted by
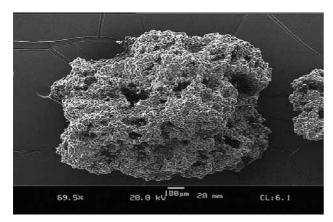
bone. The loading of the reticuloendothelial system with ß-TCP ceramic particles was ruled out histologically (34). In a histomorphological comparison based on animal experiments to evaluate oral surgical augmentation materials, Merten et al. (35) came to the conclusion that this particular ß-TCP is the gold standard for bone augmentation materials (35).

Figures 8 – 12 illustrate a patient who is a heavy smoker whose only remaining maxillary teeth are the right second premolar and first molar and left second molar which are used for mastication and retention of a poorly fitting removable prosthesis. After extraction and debridement of the socket of tooth #31, the site was grafted with β-TCP (Cerasorb, 150–500 μ size) mixed with the patient's blood and covered with a long-term resorbable collagen barrier (Cytoplast RTM, Osteogenics, Lubbock, Tx) (Fig. 8). Ten months after the procedure, the site was opened, an osteotomy prepared
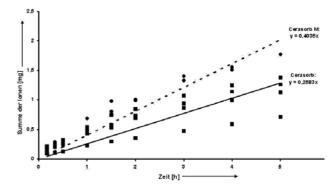

Fig. 6 *Scanning electron microscope image of a granulate of the material magnified 69.5 times.*

Fig. 7 *Solubility measurement of the material (solid line) and Cerasorb® M (broken line). The material was eluted in 0.5 M Tris/HCl buffer solution with a pH of 7.4 and at 37°C (0.6 g in 200 ml). To record the ion release at predetermined periods, 2 ml of the solution was removed and replaced by the same amount of buffer solution. The amount of Ca2+ and PO43- was determined using ICP-OES. If the regression line is continued, it can be seen that 1 g of the material is completely resorbed after 6 months and 1 g of the M type is completely resorbed after 4 months. This concurs very well with the clinical results.*

Fig. 8 *The extraction site has been grafted with the material mixed with the patient's heme and is going to be covered with a collagen barrier (all surgeries performed in this case by Dr R Horowitz, Scarsdale, USA).*

Fig. 9 *Ten months after socket grafting, the site was opened for implant placement and graft evaluation .*
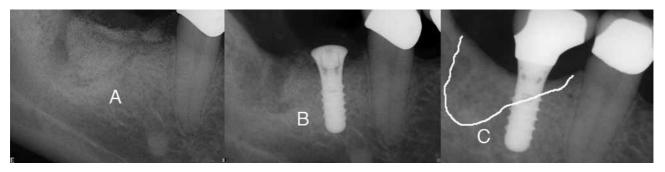
Fig. 10 *A series of radiographs taken during the process from extraction socket grafting(A) through implant placement (B) to one year post loading (C) showing full graft resorption with maintenance of alveolar volume.*

Fig. 11 *The final restoration was placed 4 months after implant insertion.*

Fig. 12 *Histologic analysis of the regenerated material demonstrated vital bone formation and bone replacement graft resorption. There is no residual ß-TCP and the beginning of lamellar bone formation is evident.*

in an ideal location (Fig. 9) and a secondary, small portion of the regenerated material was removed with the patient's consent for evaluation of healing. This series of radiographs (Fig. 10) shows the grafted site (A) and the amount of resorption and graft remodelling and location of the secondary sample site (B). Section C shows where the outline of the original grafted defect was and the full turnover of graft into what appears, radiographically, to be trabeculated, vital alveolar bone, one year after extraction and grafting. The final restoration is shown (Fig. 11) with maintenance of the mucogingival junction, vestibular depth and alveolar width. Histologic evaluation of the harvested material (Fig. 12) demonstrated that the section was taken from the grafted site, not the residual alveolar bone. There is 75% bone in the core, all of it vital and less than 1% residual β-TCP. Careful analysis of the structure of the regenerated bone shows the beginning of osteon and Haversian system formation. This is woven, young bone maturing into lamellar bone. The different staining qualities reflect the varying degrees of maturity of the regenerated bone. The darker staining red bone is less mature than the pinker staining areas (histologic processing and analysis Dr. M. Rohrer, H. Prasad, Univ. of Minnesota Hard Tissue Research Lab, Minneapolis, MN). It was important to make a direct comparison of the osteoregenerative potential of autologous bone and a

bone substitute material on the same patient in a controlled comparative study. The results of the first clinical, prospective, randomized comparative study with a simultaneous, bilateral sinus lift using autologous bone on one side and a synthetic bone augmentation material (Cerasorb®) on the other side was published 2005 by Szabo (36). In this multi-center study, the patients at four clinical centers had their bone augmentation sites monitored carefully by x-rays and by histology read by a blinded expert. The authors concluded that, even without adding autogenous bone, ß-TCP is a satisfactory bone substitute material and that there was also no statistical significant difference in the clinical comparison for this indication.

CONCLUSION

The excellent clinical results attained using ß-TCP are because of its outstanding material properties.
When using any synthetic bone replacement graft material, patients do not have to be informed of the residual immunological and infection risks, as is the

case with materials of biological origin. The basic concept of phase purity, porosity with a surface specifically adapted to the area of application and the mechanical stability of the sinter structure in combination with large primary particles is the result of over 30 years of interdisciplinary academic research. Pure phase β-TCP is fully resorbed and replaced by vital bone over 6 months time as shown histologically in animal studies, where bovine derived grafts (10), are not. Graft replacement ensures the regenerated bone will be able to remodel according to the stresses placed upon it in the future. This non-immunogenic and resorbable material provides the basis for complete, predictable and reproducible bone regeneration. There is always an adequate supply of the material, it is easy to handle and its change in radio-opacity allows healing in the area to be monitored over time. For these reasons, pure phase ß-TCP is an ideal bone augmentation material as has been shown in multiple publications (5, 6, 7, 9, 10, 18, 32-36).

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