The Processing of Xenografts Will Result in Different Clinical Responses

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Purpose: Clinicians might decide to use a xenograft to reconstruct an osseous defect. Xenografts are processed differently depending on the manufacturer. The purpose of this article is to review the processing methods and clinical ramifications of these processing methods on the behavior of xenografts.

Materials and Methods: Differences in surface morphology of xenografts based on processing, xenografts used for sinus augmentation, onlay grafting using particulate xenografts, and available clinical trials are reviewed.

Results: When used for grafting the extraction socket or preserving or reconstructing the ridge contour, xenografts can result in different resorption rates over time.

Conclusion: Based on the available information gleaned from the literature, clinical recommendations are included for specific clinical applications.

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Patients might require bone volume restoration. The choice of material and method of restoration should be dictated by the clinical needs and goals of the procedure. The proposed suggestions reflect the author's hypothesis based on the referenced material available that could be used for further development for randomized trials to confirm the author's conclusions.

The purpose of this review is to provide reference material that can be used to choose a xenograft that matches clinical need. Unfortunately, randomized clinical trials are not available; thus, available evidence based on small cases series is used to generate "food for thought."

Clinical situations requiring bone augmentation include, but are not limited to:

1. Restoration of bone volume after tooth removal
2. Vertical height restoration for placement of implants in the posterior maxilla by grafting the inferior aspect of the sinus floor
3. Restoration of bone width for a narrow alveolar ridge

This article focuses on xenografts because the method of processing does change the material's behavior. Allograft bone material is used for grafting; however, this material is not discussed to focus on xenografts. A future discussion concerning the effects of processing allografts on their clinical behavior is needed as a separate article.

Xenograft bone material is provided to the clinician as a sterile product in different lot sizes and different particle sizes. The size of the particle in general ranges from smaller to larger than 1 mm. For this article, the particle size discussed is smaller than 1 mm but larger than 250 μm. References for this article include patent applications, laboratory testing, and clinical evaluations. Many manufacturers resist providing specific processing steps to avoid exposing information concerning proprietary processing to other manufacturers.

Processing Methods

The method for processing xenograft bone can affect its resorption characteristics and its osteoconduction. The processing method should result in a graft that promotes uneventful healing and

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osteoconduction for bone formation. An overall general characteristic is that the resultant graft must be anorganic. All remnants of the donor animal must be removed to minimize antigenic responses.

Variables affecting healing and bone formation include the pore size within the xenograft particles, the grain size of the mineral phase, surface morphology, and the crystallinity of the material.[1]

Donor bovine, equine, or porcine animals are euthanized and their long bones are collected. The bone is cut into small pieces and dried. The cortical and marrow bones are often separated to provide cortical and cancellous graft materials, respectively. The bone is "degreased" by copious washes in solvents that remove the lipids, proteins, and collagen on the bone. The bone is washed copiously and the final anorganic process involves heat treatment.[2]

EFFECTS OF TEMPERATURE DURING PROCESSING

Resorption or biodegradability is believed to be related to the calcium phosphate structure. This is a cell-mediated or dissolution process. As the crystallinity and density of the processed xenograft increases owing to the processing method, the resorption of the material decelerates.[3]

Different manufacturers have their specific protocols for bone preparation (Table 1).[1,2,4-26] The heat-drying process can involve room temperature, temperatures from 250°C to 600°C,[1,2] or temperatures from 900°C to 1,200°C. At these temperatures, the resultant bone is a calcium phosphate material with a lower crystallinity compared with synthetic calcium phosphates sintered at high temperatures under pressure.[3] When the final heat treatment is at a higher temperature, the calcium phosphate crystals in the xenograft have a high crystallinity and, hence, slow resorption.[4-7]

Xenografts prepared at a low temperature have a lower calcium-to-phosphate ratio compared with xenografts processed at high temperatures. Using energy-dispersive x-ray spectroscopy analysis, Ramírez Fernández et al[8] showed that a xenograft treated at a lower temperature had faster resorption compared with a xenograft treated at a higher temperature because of greater crystallinity and density. Degidi et al[9] compared residual xenograft presence in a patient who had a sinus graft biopsy specimen taken 6 months after placement and then 8 years after placement. Percentages of anorganic bovine bone that was prepared at a low temperature were 25.1% at 6 months and 6.2% after 8 years. This confirms that over time a xenograft processed at a low temperature can resorb. There are no known randomized clinical trials comparing xenograft behaviors based on temperature-drying methods.

Xenografts heated at a lower temperature have a faster resorption rate in situ compared with xenografts heated at higher temperatures.[27] This might be important to consider when choosing a xenograft for a specific clinical indication.

SURFACE CHARACTERISTICS

The ability of bone to form on a material and intermingle with the graft can be termed *osteoconduction*. It might be important for the surface morphology of a graft material to be similar to that of native bone. A comparison of osteoconduction and grain size was performed on a xenograft from the same source yet processed differently. The graft, heat processed at 600°C, had greater osteoconduction compared with a graft specimen that was heat processed at 1,000°C. The grain size of the surface at 600°C was similar to that of native bone. The grain size of the material heat processed at 1,000°C had a larger grain. The investigators proposed that when the grain size of the processed xenograft is similar to that of native bone, then bone formation osteoconduction is increased compared with when processed at a higher temperature with grain size enlargement.[1] The efficacy of this has not been confirmed in clinical applications. The author is unaware of a clinical trial

Table 1. XENOGRAFTS AND KNOWN PROCESSING METHODS

Commercial Name (Source)	Source of Xenograft	Drying/Processing Temperature (°C)	Source of Information	Resorption Rate	References
Collagen Matrix (Oakland, NJ)	Porcine	Air	Brochure	Fast	
Bio-Oss (Geistlicht Pharma NA, Princeton, NJ)	Bovine	300-500	Patent	Slow	2,4-26
OCS-B (NIBEC, Jincheon-gun, Korea)	Bovine	600	Reference	Minimal	1
Endobon (Zimmer Biomet, West Palm Beach, FL)	Bovine	900/1,200	Brochure	Minimal	10, 11, 16, 21

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comparing grain size differences in regard to actual bone formation.

PORE SIZE

Pore size has an effect on bone tissue formation. Pores larger than 50 μm favor osteogenesis because of vascularization with cell recruitment. Interconnecting pores might be beneficial for bone formation within graft material.[2,27] However, this has not been confirmed in a clinical trial with retrieved histology. Small case series and animal studies seem to confirm this observation.[2,27]

Materials processed at high temperatures must have confirmation of maintenance of pore structure and grain size on the graft particle's surfaces. This information should be provided to the clinicians by the manufacturers, in addition to clinical evaluation of the effect of treatment on clinical results.

Removal of organic materials can be achieved in a 2-stage process with heating at 900°C followed by sintering at higher than 1,200°C. In a xenograft produced from marrow and processed at a higher temperature, the morphology of the source material maintained an interconnecting system with pore sizes of 100 to 1,500 μm. The porosity of the xenograft also was within the range of 45 to 85 volume percentage and a density of 0.4 to 1.6 g/cm^3, which is similar to native bone.[10] However, the specifics of the processing method are not published. The incorporation of bone within the particles treated by 2 heat treatments was confirmed in a sinus graft study by Nevins et al.[11] The specific methods of processing affect the surface morphology of a material. The material referenced maintained surface characteristics of native bone, although treated at high temperatures.[10,11] This might need to be confirmed by an independent evaluation.

The clinician should choose a xenograft whose characteristics match clinical need. If resorption is desired, such as within a socket, then a xenograft dried at a relatively low temperature should be used. If the xenograft is to be used in the sinus, where space maintenance is critical and a slow resorption rate is useful, then a xenograft that resorbs slowly because of moderate heat treatment should be used. If ridge contour is needed, then a xenograft that has been heat treated at higher temperatures with maintenance of grain size and surface topography, resulting in very slow resorption, should be used.

Physical characteristics can play an important role in the osteoconduction and osteogenesis features of a processed xenograft. This process seems to be a balance of the graft's resorption properties, porosity, crystallinity, and mechanical strength.[28] Nano-sized calcium phosphate particles were shown to have a positive influence favoring bone formation with osteogenic cells derived from osteoporotic rats.[29] When a titanium surface was prepared with blasting using nano-sized particles, bone formation on the titanium surface was enhanced. Surface texture does have an effect on bone formation.[30]

Hydroxylapatite ceramics that were sintered at high temperatures were found to not affect macro-porosity. The investigators found that the presence of micro-pores within macro-pores was necessary to create an osteoconductive material. They postulated that the combination of micro-pores and macro-pores had a positive effect of bone formation on the calcium phosphate ceramic.[31]

With this basic information, the clinician can start evaluating which xenograft to use for a specific clinical need. As an example, a graft with microporosity within interconnecting macro-pores and high crystallinity might be ideal for ridge augmentation.

Restoration of Bone Volume After Tooth Removal

An extraction socket undergoes a process of healing that includes bone formation within the socket. In the anterior maxilla, the remaining thin labial or facial bone will most likely resorb, resulting in loss of ridge contour. This is a normal consequence of removing the tooth.[12,13] In the posterior mandible, where the buccal bone is thicker, there is less resorption of the buccal bone over time.[32] The clinical question that is difficult to answer is how important is it to graft a socket when the buccal, lingual, or palatal bone is thick.

After the tooth has been removed, there might be insufficient bone volume to achieve primary implant stability at time of placement. If the socket is not grafted in the presence of a large defect, then clinicians are concerned about incomplete bone formation. The literature supports placement of a graft material within the extraction socket to promote bone formation, resulting in appropriate bone volume and ridge contour, in preparation for implant placement.[14,33,34]

A systemic review by Jambhekar et al[35] evaluated grafting the extraction socket with different materials. The mean loss of ridge width was lowest with xenografts, followed by allografts, alloplasts, and non-grafted sockets. Based on histologic retrievals, the highest bone content within the 12-week healed sockets was found with alloplasts and sockets with no grafting. Xenografts and allografts used for socket grafting resulted in less bone than empty control sockets. The amount of residual graft material present was greatest with xenografts. The effect of specific different-sourced xenografts was not evaluated, although it appears that most studies used a

low-temperature anorganic bone material such as Bio-Oss (Geistlicht Pharma NA, Princeton, NJ).

As the socket heals with bone formation, any material used to graft a socket should have the characteristic to resorb and be replaced by bone, without interference from normal bone formation. If a graft material resorbs at a similar rate as the patient's bone, then a grafted socket might support an implant as soon as the bone density within the socket approaches that of normal bone. If the graft material has a slow resorption rate, then the clinician might need to wait a longer time before placing an implant, allowing time for the material with slow resorption to be replaced in part with new bone.[15] Viable bone is required for integration of the implant. With a sintered hydroxylapatite material, which clinically has no resorption because of its ceramic characteristic, scar formation occurs with delayed healing[36,37] with minimal bone formation within the socket.

In the maxilla in the presence of thin or lost facial bone, it might be necessary to use a graft material with fast turnover, such as an allograft within the socket, with a covering of a slower resorbing material to maintain ridge contour.[16] This provides newly formed bone within the socket yet has a covering of a very slow resorbing xenograft to maintain ridge contour.[12,13] Block et al[16] evaluated ridge contour grafting using a xenograft dried at a high temperature (Endobon, Biomet, Paris, France) and found an approximately 1-mm decrease in ridge augmentation after 2 years.

Other ridge contour studies involve onlay grafting to restore ridge width, including mixtures of autogenous bone with anorganic bovine bone (Bio-Oss) covered with membranes for guided bone regeneration. These studies indicate that a xenograft dried at a low temperature can be successfully used to maintain a substantial percentage of the ridge contour when involved with an extraction site that has lost bone on its facial aspect.[17-19,38]

In an extraction site with loss of labial bone, for restoration of ridge contour,[12,13] the use of a xenograft, with clinically slow resorption, as the outer most layer of the socket can result in ridge contour preservation. When placing an implant immediately into an anterior maxillary tooth site, the gap between the implant and the intact yet thin labial bone can be grafted with a xenograft anticipating thin bone resorption.[20,39] The underlying xenograft will be sufficient to maintain ridge contour by its presence. Because a dense crystalline calcium phosphate material heals with a dense scar, scarring of the soft tissue around the xenograft particles results in thicker gingiva.[37]

Studies evaluating different xenografts in extraction sites showed bone formation in the sockets, but there was 1 to 2 mm of ridge shrinkage over time.[40-42] Empty sockets allowed to heal by natural means had more bone than bovine or allograft.[41] Based on these findings, the clinician might elect to avoid a graft in sockets that have minimal chance of shrinkage.

These studies indicate that, in the extraction socket, most graft materials work well with minimal difference between allografts and xenografts processed at a low or high temperature. The major difference is the time it takes to form bone within the socket with replacement of the graft material.

Clinical evaluations of ridge contour after tooth removal include documenting ridge width changes after implants are placed, with or without graft material placed in the gap between the implant and labial bone. These studies measured the ridge width and confirmed that grafting the gap between the implant and the intact labial bone resulted in greater ridge contour preservation compared with non-grafted sites. These studies imply that placement of a material will help preserve ridge contour, but the identification of which material provides the best ridge width and contour preservation is still not clear.[20]

CONTOUR MAINTENANCE

In this situation, the bone defect within the alveolar ridge needs to be grafted to form sufficient bone for implant placement. One solution is to use a material that will resorb with bone formation within the "socket" and a second material that has a very slow resorption rate over the socket graft to maintain ridge contour.

Wang et al[43] described a layering technique of using different graft materials to augment dehisced or deficient alveolar bone around dental implants. In their case series of 5 patients, implant defects averaging 10.5 mm were treated with a layering technique. Autogenous bone, collected during osteotomy preparation for the implant, was used as an inner layer in close contact with the implant. When autogenous bone harvest volume was not adequate, demineralized bone allograft was used. An outer layer of xenograft was placed on the allograft to maintain the width of the augmented ridge. A third layer of absorbable collagen was placed to prevent soft tissue and nonosteogenic cells invading into the grafted site. Six months later, on re-entry, grafted sites were found to be covered with bone.

Poulias et al[44] reported on a modified layered approach in 24 patients. Socket grafting was performed with allograft alone in 12 patients, and the other 12 received an intra-socket allograft and an overlay of xenograft on intact thin buccal bone. The 2 groups had a resorbable membrane placed over the graft. Measurements were recorded before bone

grafting and then 4 months later. A mean horizontal width loss of 1.6 ± 0.8 mm ($P > .05$) was seen in the group with only socket allografting compared with 0.3 ± 0.9 mm ($P > .05$) in the group with allograft and xenograft onlay. Overall, they found a relevant difference between the 2 groups.

In general, a graft must have characteristics that fit the needs of the site. For anterior maxillary sockets, the graft material of choice should:

1. Not interfere with normal bone formation, or
2. Maintain space for optimal bone dimensions for later implant placement and maintain ridge contour when the facial bone is lost owing to the process that led to tooth removal[3]

VERTICAL HEIGHT RESTORATION FOR PLACEMENT OF IMPLANTS IN THE POSTERIOR MAXILLA—SINUS AUGMENTATION

Different xenografts with different processing methods have been used for increasing bone height in the posterior maxilla. Does the resorption rate of the xenograft affect the outcome with sinus grafts?

Using biopsy specimens 9 months after grafting for analysis of xenografts used in sinus grafting, the results indicated a varying pattern of resorption of particles, with some particles more resorbed than others. Bone was closely attached to the xenograft.[45]

When comparing a xenograft processed at a low temperature with a xenograft processed at a high temperature for sinus grafting, the remaining biomaterial was similar in each group and the mean volume of new bone formation did not differ when comparing materials.[21]

Bone biopsy specimens obtained 14 years after sinus floor augmentation using a 20:80 mixture of autogenous bone and anorganic bovine bone (Bio-Oss) material showed percentages of xenograft and newly formed bone of 11.47 and 14.96%, respectively. The xenograft processed at a low temperature resulted in long-term bone formation with the xenograft still present in the graft sites after 14 years.[22] This was confirmed in other publications.[23,24] For sinus augmentation, the literature supports the use of a material that holds the space and is osteoconductive. There does not seem to be a relevant difference for different xenografts in sinus grafting.

Restoration of Bone Width for a Narrow Alveolar Ridge

A patient presents with an edentulous area that requires a horizontal width augmentation. The goal of the augmentation is to provide bone width that is capable of integrating to the implant and is maintained over time without substantial resorption. The graft should be able to conduct bone through 2 to 3 mm of the onlay graft adjacent to the underlying bone to provide bone for implant integration. In most situations, the implant is placed with most of its bulk within the residual bone and a small amount of the labial or facial surface in contact with the graft, explaining the need for only a few millimeters of bone ingrowth into the onlay particulate graft.

Another scenario often encountered is when a tooth is failing or an implant is failing, resulting in loss of substantial bone volume. This clinical situation requires removal of the source of the infection, whether tooth or implant, with grafting necessary to reconstruct the alveolar ridge.

Is there a difference in implant success in autogenous grafts compared with xenografts? Xenografts were equivalent to autogenous bone grafts when evaluating implant survival and the reaction of the peri-implant hard and soft tissues.[46]

Is there a volume difference over time in autografts versus xenografts? Araújo et al[47] reported that cortical bone used as an onlay graft on the lateral aspect of the alveolar ridge, during a 6-month period of healing, integrated with the host bone but underwent marked peripheral resorption. Approximately 30% of the graft was replaced with connective tissue. They concluded that grafts of autologous cortical bone might undergo marked resorption during healing, whereas a similar graft of bovine xenograft might retain its dimension. Limited amounts of new bone formed within the biomaterial.

Meijndert et al[25] compared grafts of chin bone, chin bone covered by a resorbable collagen membrane, and bovine granules covered with a collagen membrane as an onlay. At the time of implant placement, the grafting material, chin bone or bovine, was not fully replaced by new vital bone. In contrast, most of the bovine grafting material was still present at the time of biopsy sampling. Despite these differences, the 1-year clinical results were comparable among the grafting techniques applied.

In a study evaluating buccal autogenous grafts and single-implant restorations, all sites showed resorption during the first year after grafting ($P < .01$). Three patients (38%) lost all increased volume at their second surgery to place implants.[48] These investigators concluded that after 6 months autogenous bone grafting can create sufficient bone volume for implant placement, but individual variations in resorption pattern make the grafting procedure unpredictable for long-term prognosis.

Sbordone et al[49] used 32 iliac crest or chin grafts for onlay augmentation in the mandible and maxilla in 14 patients. Computed tomograms taken before implant positioning and after 1 year showed a mean volume

resorption of 35 to 51%. For iliac crest grafts, the average resorption was 42% in the anterior maxilla and 59% in the posterior mandible. Although this resulted in sufficient bone width augmentation in the long-term, the clinician must anticipate this resorption to prevent thread exposure after a portion of the graft has resorbed.

Johansson et al[50] evaluated changes in the volume of onlay and inlay autogenous iliac crest grafts in the maxilla. Measurements were recorded at the 6-month postoperative visit, just before dental implant insertion. Average volume decreases of 50% for onlay grafts and 47% for inlay grafts were found.

Hellem et al[26] used a 50:50 combination of bovine (Bio-Oss) and autogenous bone chips stabilized with fibrin glue for lateral augmentation of the alveolar crest, achieving implant stability and high implant survival results. Follow-up of 74 implants over 3 years showed the mean marginal crestal bone loss during the 3-year observation period was 0.3 ± 0.2 mm.

Von Arx and Buser[12] evaluated the clinical outcome of horizontal ridge augmentation using autogenous block grafts covered with a bovine particulate graft and a collagen membrane. The presented technique of ridge augmentation using autogenous block grafts with bovine particulate filler and collagen membrane coverage showed successful horizontal ridge augmentation with high predictability. The mean initial crest width measured 3.06 mm. At re-entry, the mean width of the ridge was 7.66 mm, with a calculated mean gain of horizontal bone thickness of 4.6 mm (range, 2 to 7 mm). A previous study showed that a nonresorbable membrane with autografts in 38 patients exhibited excellent ridge augmentation, whereas 2 had compromised results.[13] Measurements before and after augmentation showed enlargement of the mean crest width from 3.5 to 7.1 mm. Onlay grafting using autogenous bone combined with anorganic bovine bone (Bio-Oss) can result in substantial ridge augmentation over time. The clinician must overcorrect the ridge width and anticipate some facial resorption. These longer-term studies staged the augmentation and implant placement procedures by anticipating the need for additional grafting at the time of implant placement.[12,13,18,19,38]

Bone remodels in its normal fashion. In a dog extraction site study in which teeth were removed and the sockets were left empty as a control or grafted with a particulate nonresorbable calcium phosphate material, similar bone remodeling was present in the 2 sites.[37] The presence of a particulate nonresorbable calcium phosphate material maintained the shape of the ridge but did not necessarily form bone outside the confines of the normal bone process. If bovine graft particles are very slow to resorb, then one can expect bone formation within the confines of the bone defect, but not outside the confines of the adjacent cortical bone borders.

Xenografts processed at a high temperature were used to augment a thin edentulous ridge, with a long-lasting collagen membrane of a resorbable foil used to retain the graft. In a retrospective follow-up evaluation, there was 1-mm loss of augmentation width after 2 years.[16] This showed that xenografts processed at a high temperature can be used to augment ridge width, with maintenance of the ridge form within the follow-up period reported. This is different than the use of allografts alone and is consistent with the finding that the choice of graft material does influence ridge form.[33,51,52]

Discussion

To choose a method for their patient, clinicians need to know the long-term outcome of all procedures. Serial measurements using a cone-beam scanner, with standardization of the technique, can be used to objectively review a grafting material and method.

Clinicians choose a material for grafting based on information they glean from the literature, attending meetings, talking to colleagues, and information provided to them by manufacturers. The manufacturers do provide a general explanation and description of the material they sell. Unfortunately, there is a lack of randomized studies that compare these different materials within the same patient model. This article attempted to sort out the information currently available to guide the surgeon in choosing the material that has high potential of achieving the desired result in the long-term.

Currently available xenografts have different processing protocols that can affect the material's behavior in situ. The surface morphology of these materials is not well documented in the literature. The grain size and true pore size of these materials, with documentation of their effects on bone conductivity, are not readily available to the clinician. Randomized clinical or even large case series comparing these variables are not available. Clinicians should ask manufacturers to provide this information so they can choose a material for grafting based on its biologic profile rather than marketing information.

Summary

RESTORATION OF BONE VOLUME AFTER TOOTH REMOVAL

Within the socket, an allograft or xenograft processed at a low temperature should be used. For ridge contour, an onlay with a xenograft processed at a higher temperature should be considered. For a gap,

a xenograft processed at a low or high temperature should be considered.

VERTICAL HEIGHT RESTORATION FOR PLACEMENT OF IMPLANTS IN THE POSTERIOR MAXILLA BY GRAFTING THE INFERIOR ASPECT OF THE SINUS FLOOR

All xenografts work in the sinus. There is evidence that xenografts processed at a higher temperature might have less resorption over time, but the clinical data do not show a clinical difference.

RESTORATION OF BONE WIDTH FOR A NARROW ALVEOLAR RIDGE

Xenografts processed at a low temperature have a tendency for resorption from time of placement to implant placement. Xenografts processed at a high temperature might be preferred for this application because of their low rate of resorption characteristics.

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