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REVIEW ARTICLE

Optimized bone grafting

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1 | INTRODUCTION

Originally, bone-grafting materials were developed to serve as a passive, structural supporting network with their main criterion being biocompatibility.[1,2] However, advancements in tissue engineering and regenerative medicine have further improved various classes of bone grafts, each possessing various advantages and disadvantages (Figure 1). Today, many bone-grafting materials have been designed with specific surface topographies at both the micro- and nanoscales to further guide new bone formation once implanted in situ. The growing number of bone grafts currently available now has an estimated global market surpassing $2.5 billion annually, with over 2 million procedures performed on a yearly basis.[3] As such, the need for better "smart" biomaterials becomes vital owing to the aging population and the increased number of bone-grafting procedures performed yearly for diseases such as osteoporosis, arthritis, tumors, and trauma.[4]

Bone-grafting materials have been extensively studied in the field of dentistry (similar to orthopedic medicine) to fill bone defects caused in large part by periodontal disease. The clinical indications for using bone-grafting materials range from single sites to extensive full arch cases. Some grafts need to be highly osteoinductive to facilitate the regrowth of vertical or horizontal bone (such as autografts), whereas others must be nonresorbable to prevent future resorption (bovine-derived xenografts). Considering the wide range of uses for bone-grafting materials, no single material can fulfill each of these tasks. Furthermore, it is often necessary to combine two or more classes of bone grafts to obtain a successful and predictable result. While each of the grafting materials needs to fulfill several properties related to their use, including optimal biocompatibility, safety, ideal surface characteristics, proper geometry and handling, and good mechanical properties, bone grafts are routinely characterized based on their osteogenic, osteoinductive, and osteoconductive properties (Table 1). The ideal grafting material should therefore (1) contain osteogenic progenitor cells within the bone grafting scaffold capable of laying new bone matrix, (2) demonstrate osteoinductive potential by recruiting and inducing mesenchymal cells to differentiate into mature bone-forming osteoblasts, and (3) provide a scaffold that facilitates three-dimensional tissue ingrowth.

Consequently, the gold standard for bone grafting is autogenous bone, harvested either as a bone block or bone particles. Autografts display an excellent combination of three important biological properties of bone grafts, including osteoconduction, osteoinduction, and osteogenesis.[5] Despite their potent ability to improve new bone formation, limitations including extra surgical time and cost, as well as limited supply and additional patient morbidity/risk of bacterial contamination[6–8] have necessitated alternatives. These include bone allografts (from freeze-dried bone allografts [FDBAs], free frozen bone, and demineralized free-dried bone allograft [DFDBAs]), xenografts (derived from animals, corals, calcifying algae or wood) and an array of synthetic alloplasts (HA, hydroxyapatite; β-TCP, β-tricalcium phosphates, biphasic calcium phosphates, polymers, glass ceramics, and bioactive glasses).[9–13] Although these materials are osteoconductive by definition, only a limited number of osteoinductive materials are available.[2]

1.1 | Bone regeneration

Predictable bone regeneration in the oral cavity is one of the most difficult surgical procedures faced by the treating dentist. An understanding of the number of key factors is nevertheless necessary to better optimize regenerative outcomes. The field of tissue engineering proposes that three main factors are necessary for bone and tissue regeneration. First, a scaffold (bone-grafting material or fibrin clot) is required to facilitate cell repopulation and tissue regrowth in the defect area. Second, signaling molecules are required to stimulate new tissue regeneration and to recruit future progenitor cells to the

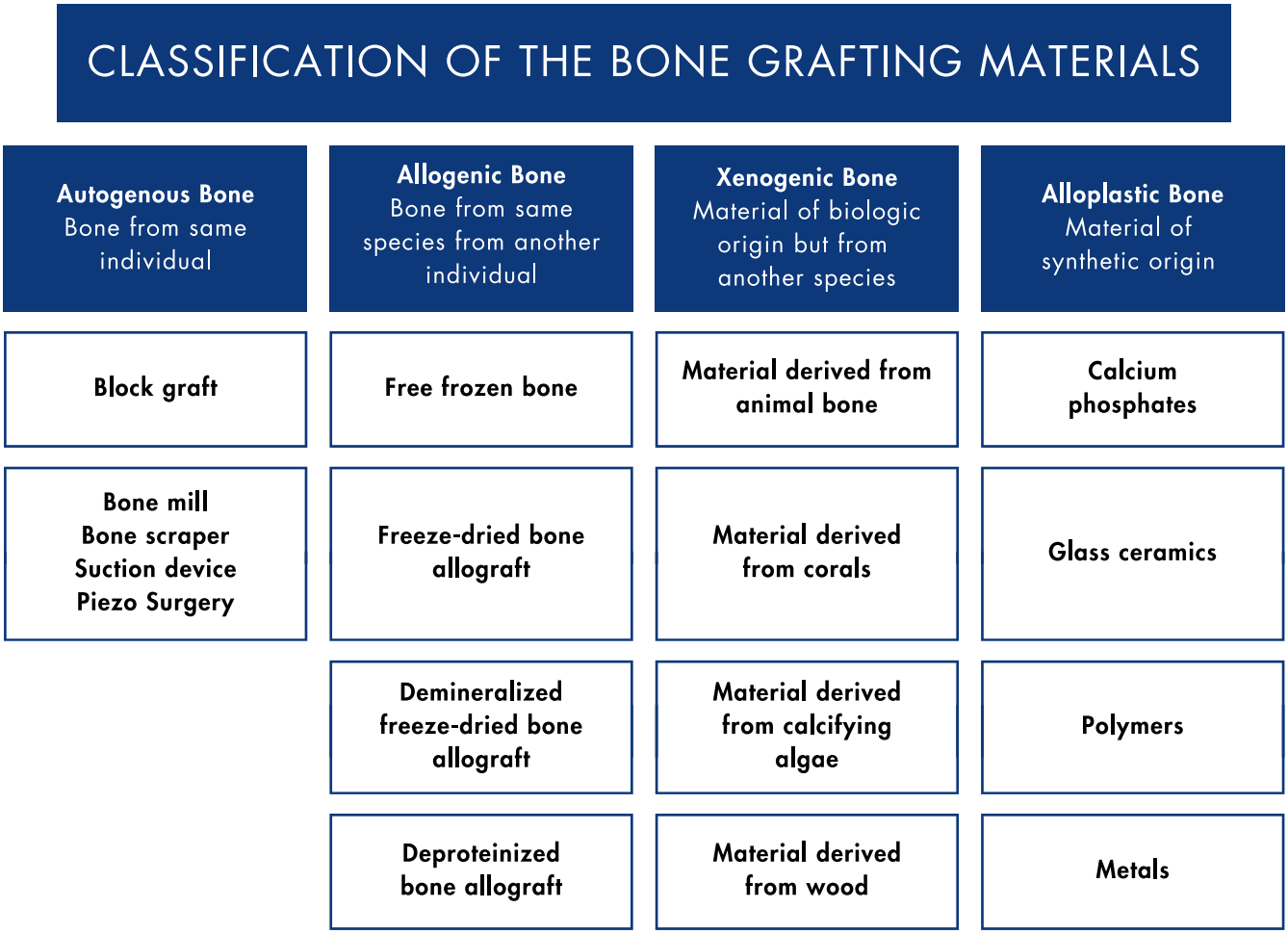


FIGURE 1 Classification of bone-grafting materials, including autografts, allografts, xenografts, and alloplasts.

TABLE 1 Classification of bone-grafting materials used for the regeneration of bone and periodontal defects. Reprinted from Jensen et al. Osteology.

Material characteristic	Ideal	Autograft	Allograft	Xenograft	Alloplast
Biocompatibility	+	+	+	+	+
Safety	+	+	+/−	+	+
Surface characteristics	+	+	+	+	+
Geometry	+	+	+	+	+
Handling	+	+	+/−	+	+
Mechanical characteristics	+	+	+/−	+	−
Osteogenic	+	+	−	−	−
Osteoinductivity	+	+	+/−	−	−
Osteoconductivity	+	+	+	+	+

defect site. Third, osteogenic cells are required to lay new bone matrix. While these three properties optimize tissue engineering, it remains equally essential to understand that both time and an optimal environment (stability, loading stimulation, perfusion of oxygen, pH of bone tissues, viability of surrounding bone walls, etc.) are necessary to further optimize new bone formation. A variety of bone-grafting materials, barrier membranes, and signaling molecules (BMP2, PDGF, EMD, FGF2) have been brought to market to fulfill this task.

While all grafting materials are osteoconductive based on their ability to promote new bone formation and support three-dimensional tissue ingrowth, little additional benefit is provided. In contrast, autogenous bone is osteogenic due to its incorporation of living progenitor cells that may further induce new bone formation and is osteoinductive based on its ability to secrete growth factors into the local microenvironment. All other bone grafts, including allografts, xenografts, and alloplasts, are completely devoid of

living cells and are therefore not considered osteogenic (Table 1). The majority of research to date on bone-grafting materials has focused on optimizing their osteoinductive potential. Simply put, an osteoinductive biomaterial (which was defined by Dr. Marschall Urist, an orthopedic surgeon in the 1960s) was defined as a biomaterial that was capable of inducing extraskeletal ectopic bone formation (in other words, in areas where bone should be formed, such as in muscle, epithelial tissue, or soft tissue). Originally, osteoinductive materials were characterized by investigating methods in which demineralized bone allografts could induce ectopic bone formation in the gastrocnemius and pectoralis muscle of rats and mice.[14] Today, allografts are the only class of replacement bone grafts that are considered osteoinductive and have advantages over xenografts and synthetic bone grafts owing to their superior biocompatibility. Below, a characterization of the four classes of bone-grafting materials is briefly presented, including their advantages and limitations.

1.2 | Autogenous bone

Autogenous bone grafting involves the harvesting of bone obtained from the same patient. Typical sites in the oral cavity include the mandibular symphysis (chin area) or anterior mandibular ramus (the coronoid process). Interestingly, it has been demonstrated in various studies that the harvesting technique has a significant influence on the viability of cells within the scaffold as well as future integration within bone.[5,15–17] Of critical importance to the success rates of autografts is the ability for clinicians to successfully harvest autografts containing vital osteoprogenitor cells and osteocytes. It has previously been demonstrated that autograft preparations may be compromised by mechanical harvesting techniques as well as the duration of time between harvesting and implantation.[18] Grafts, which are primarily composed of bone matrix and osteocytes, are known to release a wide variety of growth factors, including BMPs, PDGF, TGF-beta, and VEGF, as well as to regulate bone formation/resorption via the RANKL/OPG pathway.[17] A number of studies using autogenous bone alone have been documented with respect to defect healing.[19–22] Autografts remain the gold standard, and complicated bone defects often require at least partial incorporation of autografts to improve graft consolidation.

Autogenous bone is clinically harvested in two forms, either in a bone block or via particles. Bone blocks were initially utilized as a means to augment major bone deficiencies.[23–26] Their advantages include the fact that they may be locally harvested within the oral cavity and have excellent biocompatibility within host tissues. Disadvantages include additional patient morbidity and the chance of nerve paralysis. While autogenous bone blocks have been previously utilized with great frequency, autogenous bone particles are more commonly harvested due to their ease of use and excellent predictability.

Previous research by our team investigated the optimization of harvesting techniques for autogenous bone particles.[5] In that study, four modalities were compared (Figure 2):

a. Cortico-cancellous block grafts harvested with a 6 mm trephine and ground to particulated bone chips using a bone mill (R. Quétin).
b. Bone particles harvested with a piezo-surgery device (Mectron®).
c. Bone particles collected from the aspirator with a bone trap filter during the preparation of the osteotomy (Schlumbohm GmbH & Co. KG).
d. Bone chips harvested with a sharp bone scraper (Hu-Friedy).

The impact of autogenous bone harvesting techniques on the final graft consolidation and the ability of cells to attach and differentiate was greatly impacted. Autogenous bone chips prepared by a bone scraper- and bone mill-demonstrated particles with the largest particle size, and the bone mill demonstrated a combination of both cortical and trabecular bone, with a greater presence of collagen fibrils when compared to other modalities (Figure 3A). Bone slurry harvested with a bone trap had the smallest mean projection area and particle size, with many fine powder-like residues remaining in the sample (Figure 3D).[5] Osteoblasts seeded onto bone-mill and bone-scraper samples both attached and differentiated faster than those on piezo-surgery and bone-slurry samples and led to higher cell viability (Figure 4).[5] Based on these findings, it was clinically recommended to avoid harvesting techniques with extensive rinsing, as the main autogenous proteins were potentially washed away from the surface during collection.

Autografts harvested in particulate form have been shown to be superior in their bone-forming ability when compared to other commonly utilized replacement grafts, including allografts, xenografts, and alloplasts.[27–29] Since autogenous bone is available in a limited supply, autografts are routinely mixed with additional commercially available bone grafts; most commonly, the use of a xenograft termed deproteinized bovine bone mineral (DBBM; BioOss, Geistlich) owing to its low substation rate. In this way, autogenous bone can maximize the graft's ability to induce new bone formation, while the xenograft provides space maintenance following bone regeneration without risk of resorption.[30–32] This will be covered in greater detail later in this article.

1.3 | Allografts

Bone allografts involve the harvesting of bone obtained from another human cadaver that has been safely processed and decontaminated.[33–40] One of the main advantages of allografts in contrast to other replacement grafting materials is that although grafts are always osteoconductive by supporting three-dimensional tissue ingrowth, allografts are potentially osteoinductive since they contain growth factors incorporated within their bone scaffold.[2] Allografts therefore possess osteoinductive potential, unlike xenografts and synthetically fabricated alloplasts.[36–40]

The properties of the allograft material are directly related to its processing and to its donor source.[41] Allografts are available as fresh, frozen, demineralized, or freeze-dried particles. Currently, the vast

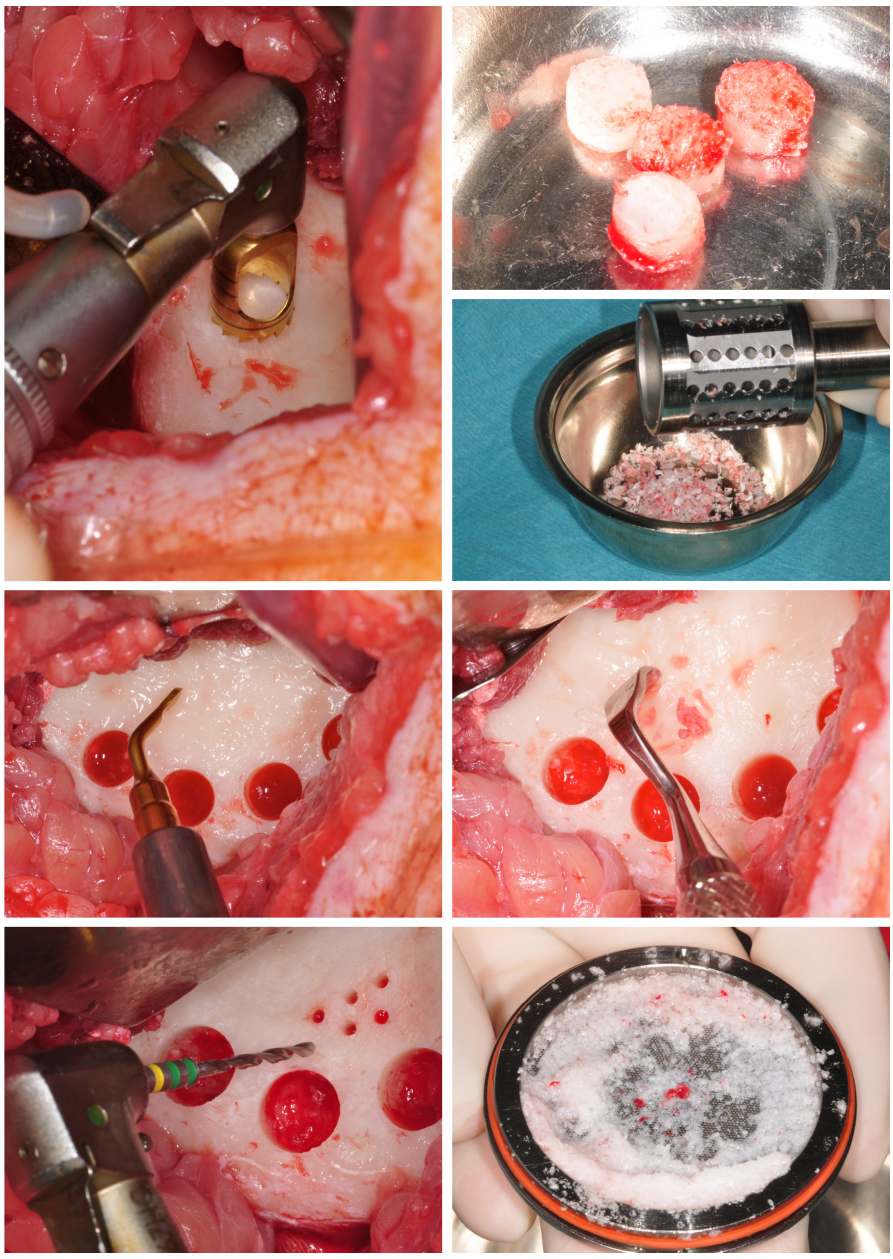


FIGURE 2 Instrumentation utilized to harvest autogenous bone via four different surgical methods: (1) bone mill, (2) piezo-surgery device, (3) bone dust/slurry, and (4) bone scraper.

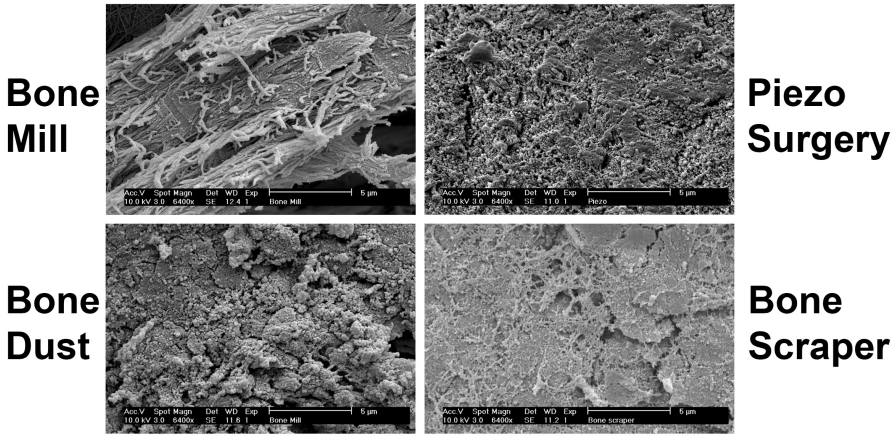


FIGURE 3 High-resolution SEM analysis of four techniques commonly employed for harvesting autogenous bone, including the (1) bone mill, (2) piezo-surgery device, (3) bone dust/slurry, and (4) bone scraper. Note the number of proteins found on the surface of the bone mill and bone scraper. In contrast, piezo-surgery and bone dust surfaces were devoid of proteins. Figured adapted with permission from Miron et al.[5]

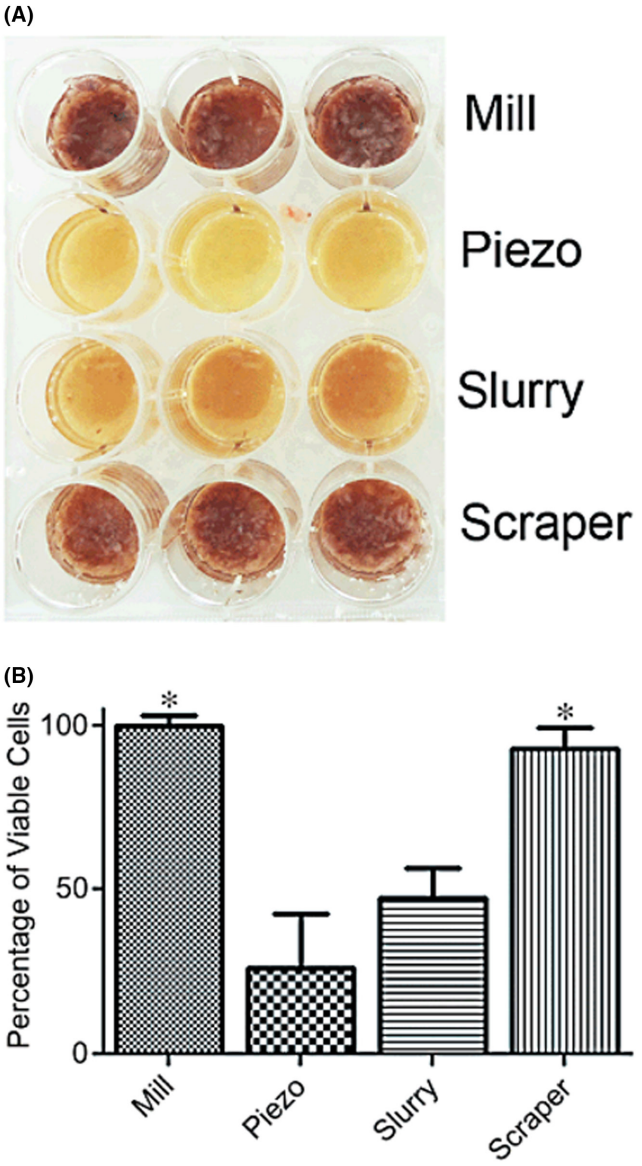


FIGURE 4 Cell viability of autogenous bone from four commonly employed harvesting techniques. (A) Photographic image of autogenous bone particles incubated with MTS for 4 h. (B) Relative absorbances at 490 nm measured after transfer of incubation media into a fresh 96-well plate. Samples were normalized to the bone mill, averages ± SE (*significant difference between the bone mill and bone scraper when compared to piezosurgery and bone slurry). SE, standard error. Figured adapted with permission from Miron et al.[17]

majority of grafts are harvested, processed, and distributed through the American Association of Tissue Banks. Hence, the risk of disease transmission is minimized, as a thorough analysis of the cadavers prior to selection of the grafting bone is routinely performed.[42,43] In addition, processing of the graft aims to remove antigenic components to reduce the host immune response.[42]

As mentioned above, fresh/frozen allografts not only hold osteoconductive capacity but may also be osteoinductive. Freeze-dried allografts have less inherent osteoinductive potential, and their immune response is reduced.[44] When the grafts are demineralized,

TABLE 2 Comparison between FDBAs and DFDBAs.

FDBAs	DFDBAs
Mineralized	Demineralized
Better space maintenance	More release of bone morphogenetic proteins (BMPs)
Slower resorption rate	Rapid resorption
Osteoconductive	Possibly osteoinductive
More radiopaque	Radiolucent
Primary indications: Bone augmentation, extraction sockets, sinus augmentation	*Primary indications*: Periodontal regeneration

Abbreviations: DFDBA, demineralized free-dried bone allograft; FDBA, freeze-dried bone allograft.

however, greater and faster access to growth factors improve their osteoinductive potential. Generally, a DFDBA is demineralized with hydrochloric acid for different periods of time and/or concentrations, which facilitates the access and release of a multitude of growth factors, including BMP-2.[37] In general, this makes DFDBAs more osteoinductive than FDBAs. Several differences have therefore been reported between FDBAs and DFDBAs (Table 2). The advantages of FDBA are that the graft material resorbs much slower, which gives it better space maintenance properties. FDBAs are also more radio-opaque and can be visualized better on X-rays than radiolucent DFDBAs (due to their loss of mineralized components).

From a biological point of view, it is important to note that since allograft bone is obtained from cadavers, variability does exist. Reports have shown that some commercially available DFDBAs are less osteoinductive than others.[36,45,46] Schwartz et al. tested commercial lots of DFDBAs from six different bone banks and found that not all were osteoinductive based on the variability that existed when implanted in extraskeletal locations in nude mice. They concluded that the variability in osteoinductivity between commercial DFDBA batches may be ascribed to donor age, method of preparation and/or sterilization.[36,46]

Many studies from around the world have demonstrated the effectiveness of allografts in promoting new bone formation across a wide array of defect types.[32,47–50] Allografts remain the ideal replacement material for a number of common procedures utilized in dentistry, including extraction socket healing, sinus lifting procedures, and guided bone regeneration (GBR) procedures, and in conjunction with implant dentistry. Specifically, allografts are much more suitable for extraction site management than xenografts because of their better bone-forming ability, as well as their ability to turnover into native host bone over time.[31,32]

1.4 | Xenografts

While allografts are the most commonly utilized biomaterial in countries that permit them owing to their superior biocompatibility, xenografts derived from animal donors offer other significant advantages. While it was first relatively unknown to what extent

bone resorption would occur following bone augmentation procedures with xenografts, the most prominent advantage of these biomaterials remains that augmented bone can be maintained even several years following their surgical implantation. Unlike allografts, which are prone to resorption over time, xenografts maintain their volume owing to their nonresorbable properties. For these reasons, a variety of procedures in dentistry have since been adapted to take advantage of these low-substitution rate materials.

The most widely used xenograft in the world is DBBM (Bio-Oss). When work was first pioneered in this field, it remained relatively unknown how quickly these particles would resorb in humans. Today, DBBM is perhaps the most widely studied bone-grafting material in the dental field, with its use being internationally widespread (whereas allografts are not permitted in various countries). It is also understood that the main advantage of DBBM is that it holds volume, and the graft is deemed non/low resorbing. The results of histological analyses of human samples have clearly demonstrated the ability for xenografts to be found within native bone even several years following their grafting (Figure 5). As such, DBBM particles have been utilized in a number of clinical indications, including contour/veneer grafting in implant dentistry (especially in the esthetic zone), filling narrow gaps in immediate implant placement, sinus augmentation procedures, vertical augmentation procedures, and major bone reconstructive surgery to maintain volume.

Thus, in summary, the advantages of utilizing DBBM as a bone graft include its documented safety, mineral content, which is comparable to human bone, and nonresorbable characteristics. Xenografts do not possess any form of osteogenic or osteoinductive potential due to their complete deproteinization process (allografts are better bone inducers); however, their nonresorbable features make them attractive bone grafts under a variety of clinical settings.[51–55]

1.5 | Alloplasts

Alloplasts are synthetically developed bone grafts that are fabricated in a laboratory and derived from different combinations of HA, β-TCP, polymers and/or bioactive glasses.[56–59] Although they possess an osteoconductive surface that allows cell attachment and proliferation and three-dimensional bone growth, in comparison with the other classes of bone grafts, they have generally demonstrated inferior bone-forming ability in a number of comparative studies.[28,29,32,60] Therefore, in summary, alloplasts do not possess the same bone-inducing properties as autogenous bone and allografts. For these reasons, their use has primarily been limited to patients with personal or cultural reasons for preference.

1.6 | Proportional use of bone grafting materials in North America

Figure 6 demonstrates the proportional use of each grafting material utilized in the USA. The largest proportion of bone augmentation procedures performed in the USA are conducted with mineralized allografts (37%), with another 16% of the market using demineralized bone allografts. Therefore, a total of 53% of grafting procedures performed in the dental field are routinely augmented with allografts.

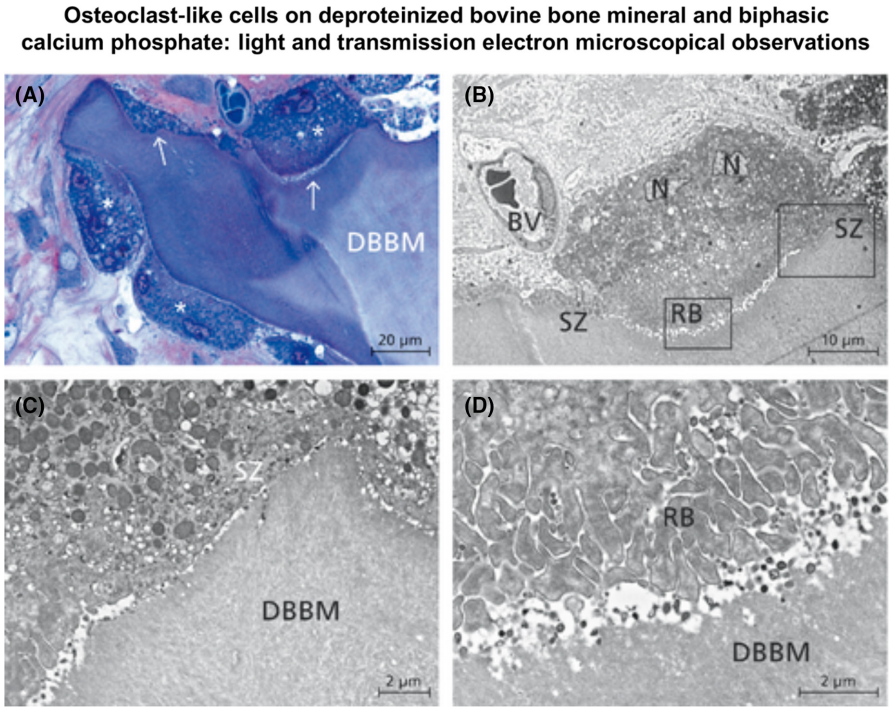


FIGURE 5 (A) Multinucleated giant cells (MNGCs) (*) situated on a deproteinized bovine bone mineral (DBBM) surface of a particle placed in the soft tissue outside the bone defect. Pronounced resorption lacunae are seen (arrows). (B) TEM magnification of the rectangle in (A). A multinucleated giant cell with two nuclei (N) in a resorption lacuna on deproteinized bovine bone mineral (DBBM). A blood vessel (BV) is seen directly next to the MNGC, as often observed during bone remodeling. The MNGC demonstrates a sealing zone (SZ) and ruffled border (RB). (C) Higher magnification of the sealing zone (SZ). (D) Higher magnification of the ruffled border (RB). Reprinted with permission from Jensen et al.[83]

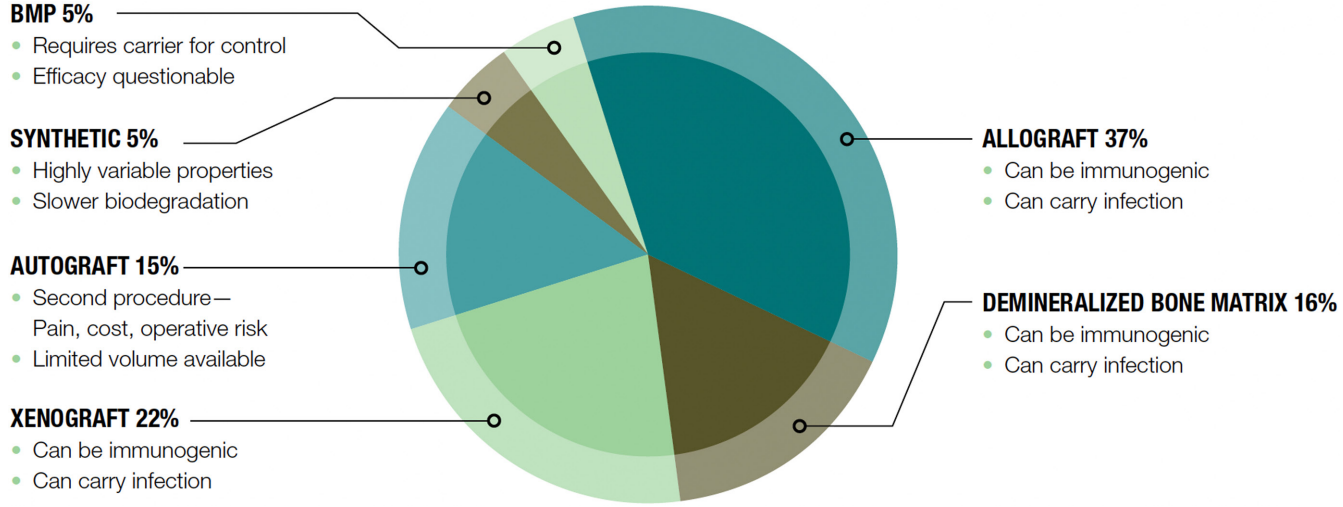


FIGURE 6 Proportional use of bone-grafting materials in North America. The largest percentage (slightly over 50%) is dedicated to allografts, with approximately 15% of cases being autografts, 22% being xenografts, 5% synthetic materials, and 5% recombinant human BMP2.

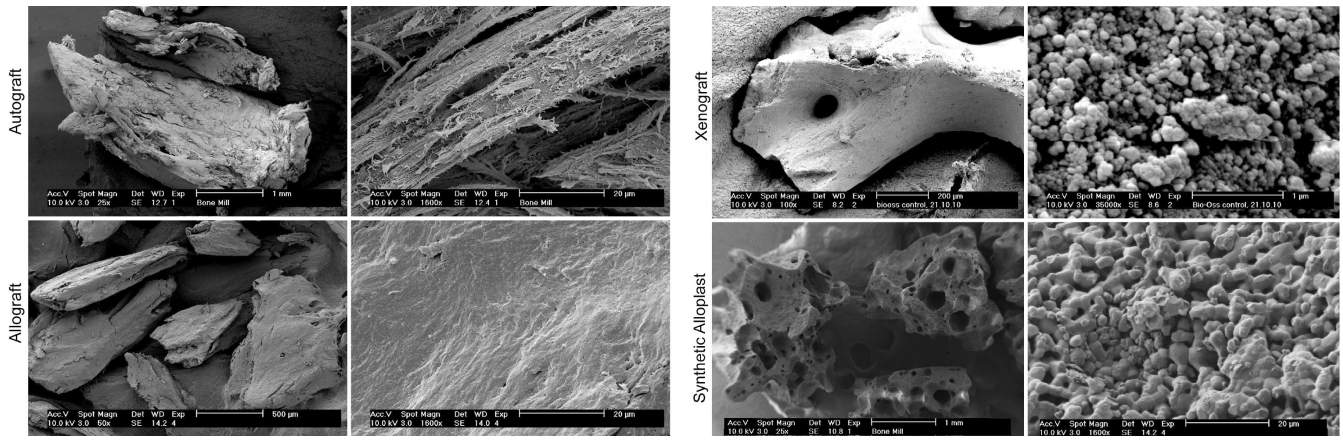


FIGURE 7 Scanning electron microscopy of four commonly utilized bone-grafting materials in dentistry, including autogenous bone harvested with a bone mill, a demineralized freeze-dried bone allograft (DFDBA), a commonly employed xenograft of bovine origin (deproteinized bovine bone mineral [DBBM], and a synthetically fabricated biphasic calcium phosphate [BCP]). Reprinted with permission from Miron et al.[27]

Interestingly, 22% of all bone-grafting procedures are performed with xenografts. Approximately 15% of dental bone augmentation procedures are performed with autografts despite being the gold standard. Interestingly, 5% of bone augmentation procedures are performed with recombinant human BMP2 from Medtronic, whereas only 5% are conducted with synthetic alloplasts, primarily limited to "holistic" clinics or patients requesting the use of nonhuman/nonanimal-derived products.

1.7 | Regenerative properties of autografts, allografts, xenografts, and synthetic alloplasts

As part of a series of experiments performed from 2009 to 2016, our research group was interested in the regenerative potential of various bone-grafting materials and, more specifically, how each class of bone graft compared with one another. Figure 7 illustrates the typical morphology of each of these bone-grafting materials, including autografts, allografts, xenografts, and alloplasts. One common trait between all grafts is their roughened surface topography. Cells of the bone-forming lineage (osteoblasts) act much more favorably on roughened surfaces than on smooth surfaces. A Transwell assay was utilized to investigate the ability of each class of bone graft to recruit cells utilizing this cell migration assay (Figure 8). Briefly, mesenchymal stem cells are placed into the upper compartment with small pores. The bone-grafting material is then introduced into the lower chamber, and cells that are attracted to the material then pass through the pores and may thereafter be counted to investigate the potential for each of the biomaterials to recruit cells. Figure 8 clearly demonstrates that only autografts and allografts are capable of recruiting cells, likely as a result of their incorporation

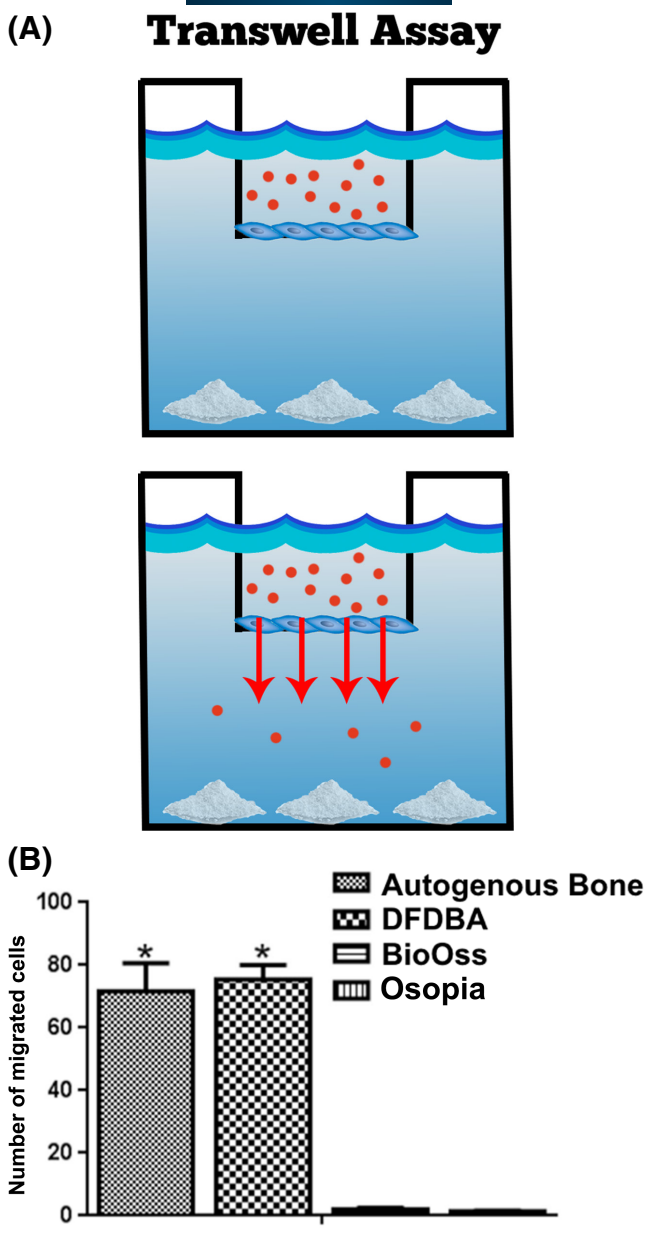


FIGURE 8 (A) Transwell assay investigating the ability of mesenchymal stem cells (MSCs) to migrate toward a bone-grafting material. MSCs are placed in the upper compartment with small pores, and shortly thereafter, a bone-grafting material/growth factor is placed in the lower compartment. After 24 h, cells that have passed through the pores are counted and quantified to determine the ability of each material to be recruited toward the introduced biomaterial. (B) Migration assay using a Boyden chamber of bone marrow stromal cells (BMSCs) seeded in the presence of (1) autogenous bone harvested with a bone mill, (2) a demineralized freeze-dried bone allograft (DFDBA), (3) a commonly employed xenograft of bovine origin, and (4) synthetically fabricated biphasic calcium phosphate (BCP). The results from this study demonstrated that only autogenous bone and the allograft were able to recruit cells due to their incorporation of growth factors, including BMPs and PDGF. Reprinted with permission from Miron et al.[27] *Significance $p < 0.05$.

of chemotactic growth factors, including BMP2 and PDGF, while xenografts and synthetic alloplasts have limited ability. These grafts are also able to better induce osteoblast proliferation and differentiation as well as induce ectopic bone formation, whereas xenografts in particular have extremely limited bone-inducing potential.[27,61]

In summary, each graft class has a different potential for bone regeneration (Table 3). Not surprisingly, autogenous bone performs significantly better than all other classes of bone grafts and remains the gold standard replacement material. The ability of allografts to participate in osteoinduction corresponds well with data within North America that demonstrate that allografts are the most heavily utilized replacement biomaterial for bone grafting (Figure 6). Interestingly, the xenografts have no ideal properties for bone regeneration, yet they are still routinely utilized in >20% of all grafting procedures. Xenografts are unable to promote cell recruitment or cell proliferation, and furthermore, they are the only group that does not induce spontaneous osteoblast differentiation of MSCs or have any ability to induce ectopic bone formation.[27,61] Xenografts are an extremely important class of bone grafts and are mainly utilized for their nonresorbable properties. Their relevance and importance for various clinical indications will be discussed in detail below. Last, it must be noted that, typically, synthetic bone-grafting materials have shown no capability of enhancing bone formation and are primarily utilized for cultural and religious reasons.

2 | CLINICAL INDICATIONS

2.1 | Extraction sockets

The effects of tooth loss on alveolar ridge dimensional changes have been well documented in the literature.[62–64] Extraction sockets are routinely filled with bone biomaterials to minimize ridge loss and provide adequate bone for implant placement.[62–64] While no biomaterial can entirely prevent resorption, a variety of studies have favored certain biomaterials over others.

As a standard replacement material, allografts (and more specifically FDBAs) are utilized most effectively to minimize dimensional changes.[62,65] Allografts provide a mineralized matrix that contains growth factors specific to bone. Typically, the FDBA is covered with various barriers to prevent soft tissue infiltration. These may include d-PTFE membranes, collagen membranes or plugs, and platelet-rich fibrin (PRF) membranes (specifically extended PRF, which has a 4-month resorption profile covered in this issue of *Periodontology* 2000).

Important for the biomaterial utilized for extraction site management is its ability to be resorbed and replaced by native bone over time. As such, nonresorbable xenografts should not be utilized for extraction sockets and should be considered a contraindication in the majority of cases (Figure 9). Critical to long-term implant stability is the resulting bone-to-implant contact. Since xenografts will not be resorbed and replaced over time, bone-to-implant contact may be reduced since some DBBM particles will be cut during the osteotomy preparation and later remain in contact with the implant surface over time (Figure 9). This is the

TABLE 3 Clinical indications and contraindications of various bone-grafting materials utilized frequently in regenerative dentistry.

Biomaterial	Indications	Limitations/contraindications
Autogenous bone	• Vertical bone augmentation • Directly adjacent to exposed threads on an implant surface to optimize new bone formation • Block grafts utilized for large horizontal and vertical augmentations such as congenitally missing maxillary laterals	• Fast resorption rate—in many cases may be optimized by combining with a nonresorbable xenograft • Little use during ridge preservation following tooth extraction • Little additional benefit during sinus augmentation procedures
FDBAs	• Biomaterial of choice for ridge preservation • Utilized frequently for sinus augmentation procedures • Standard replacement grafting option for horizontal/vertical augmentation and peri-implant defect regeneration	Although the most utilized grafting material on the market, less osteoinductive when compared to DFDBA
DFDBAs	• Periodontal regeneration of intrabony and furcation defects • Liberates more growth factors and considered more osteoinductive when compared to FDBA	Fast resorption rates limit its use for ridge preservation and GBR procedures
Xenografts	• Contour augmentation as a second outer nonresorbable layer • Vertical ridge augmentation (combined with autografts) • Sinus augmentation procedures to maintain bone gain over time (combined with allografts) • Packing narrow gaps in immediate implant dentistry (especially in the esthetic zone) • Frequently utilized as a grafting material when a fear of fast resorption may be possible (for example, osteoporotic patients) and to limit dimensional bone loss	• Use of nonresorbable xenografts contraindicated for extraction sockets • Poor ability to induce new bone formation when compared to autografts and allografts. For these reasons, often combined with other bone grafts during regenerative therapy
Synthetically fabricated bone grafts	• Primary indications are for "holistic" patients • Utilized when personal/religious beliefs necessitate alternative solutions	Are typically not as osteopromotive as other available replacement grafts

Abbreviations: DFDBA, demineralized free-dried bone allograft; FDBA, freeze-dried bone allograft.

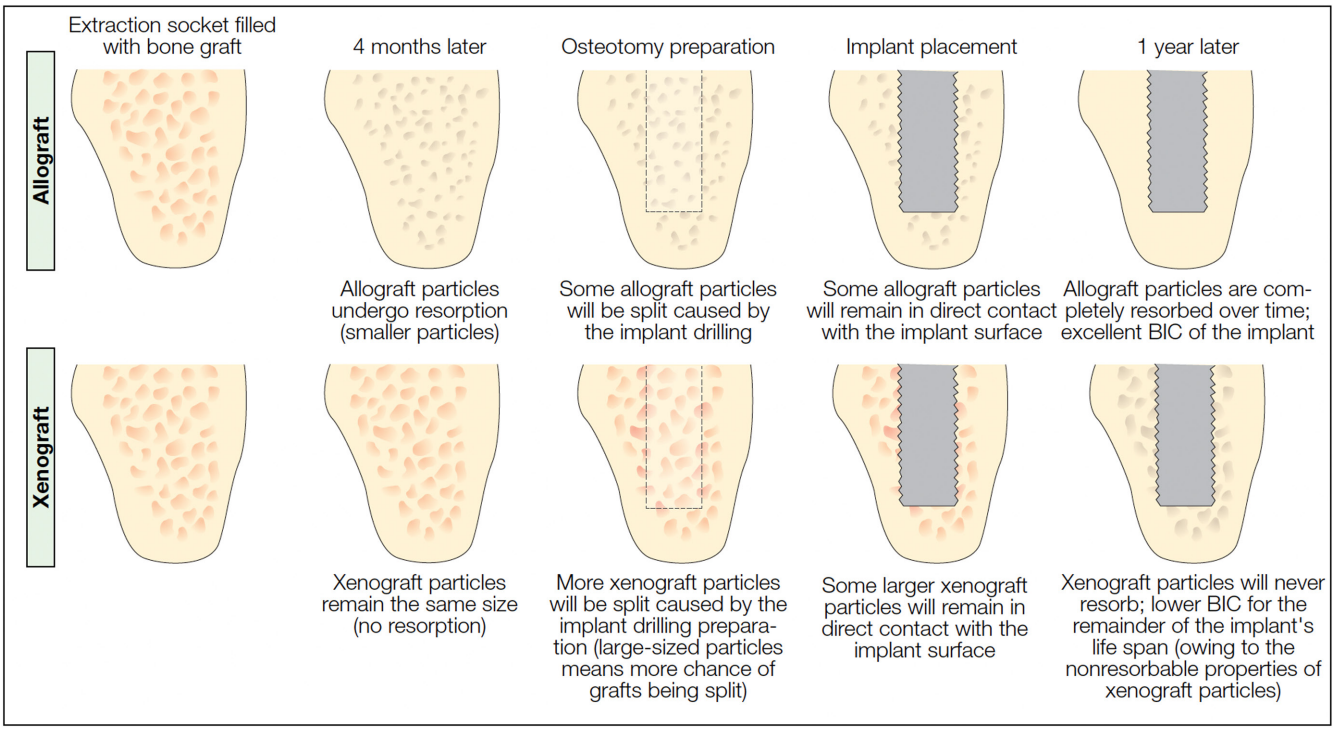


FIGURE 9 Differences between filling an extraction socket with an allograft versus a xenograft. While both are adequately able to regenerate new bone formation, the allograft will be replaced over time, while the xenograft will remain even years after implantation. The main limitation of utilizing a nonresorbable xenograft in an extraction socket is the significantly lower bone-to-implant contact (BIC) that results from the xenograft remaining within the socket and in contact with the implant surface. Reprinted with permission from Miron and Zhang.[32]

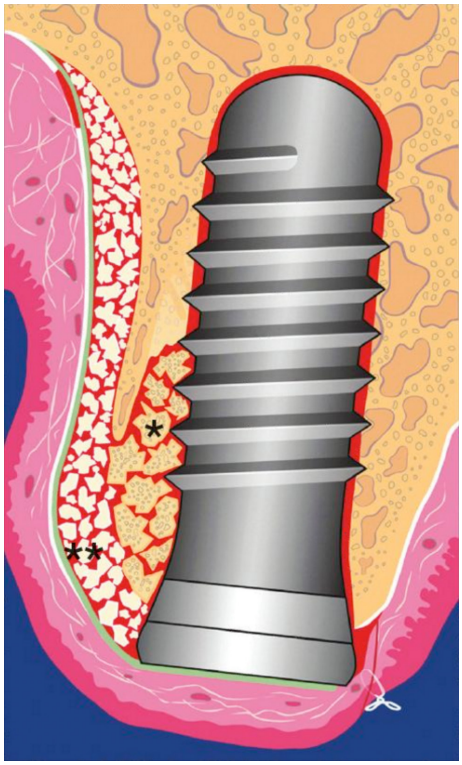


FIGURE 10 Illustration demonstrating early implant placement in the esthetic zone. Implants are placed slightly palatally following 8 weeks of healing. In this dual-layer bone-grafting procedure, autogenous bone chips (*) cover the exposed implant surface and are augmented with a second layer of low-substitution filler DBBM (**). The biomaterials are protected by tension-free primary wound closure using a collagen barrier membrane. Reprinted with permission from Buser "20 years of Guided bone regeneration in implant dentistry".

primary reason why nonresorbable xenografts should be avoided and rarely utilized in countries that permit allografts. Additionally, since allografts are considered far more osteoinductive than xenografts,[27,61] implants are generally placed 3–4 months after grafting procedures, whereas a typical 4- to 6-month healing period is required for xenografts. This highlights an appropriate use of allografts and demonstrates the negative impact xenografts may possess in a similar grafting case.

2.2 | Implant placement using contour augmentation

The xenograft, on the other hand, displays quite drastic differences in their clinical use, and contour augmentation (particularly in the esthetic zone) is an ideal use of a low substitution/nonresorbable xenograft. Since immediate implants have been shown to lead to greater mucogingival recessions and esthetic failures, the International Team for Implantology has advocated that early implant placement with contour augmentation is one of the more predictable ways to place implants in the esthetic zone (Figure 10). As presented in Chapter 5, after an 8-week healing period following tooth extraction to allow for bone remodeling of the buccal plate, implants are placed in their proper lingual position. Thereafter, autogenous bone chips harvested with a bone scraper are utilized directly on the implant surface with a second layer of nonresorbable DBBM utilized to shape the final contour of the augmentation procedures. The advantage of this second layer is that the augmentation will remain stable owing to the nonresorbable properties of DBBM.

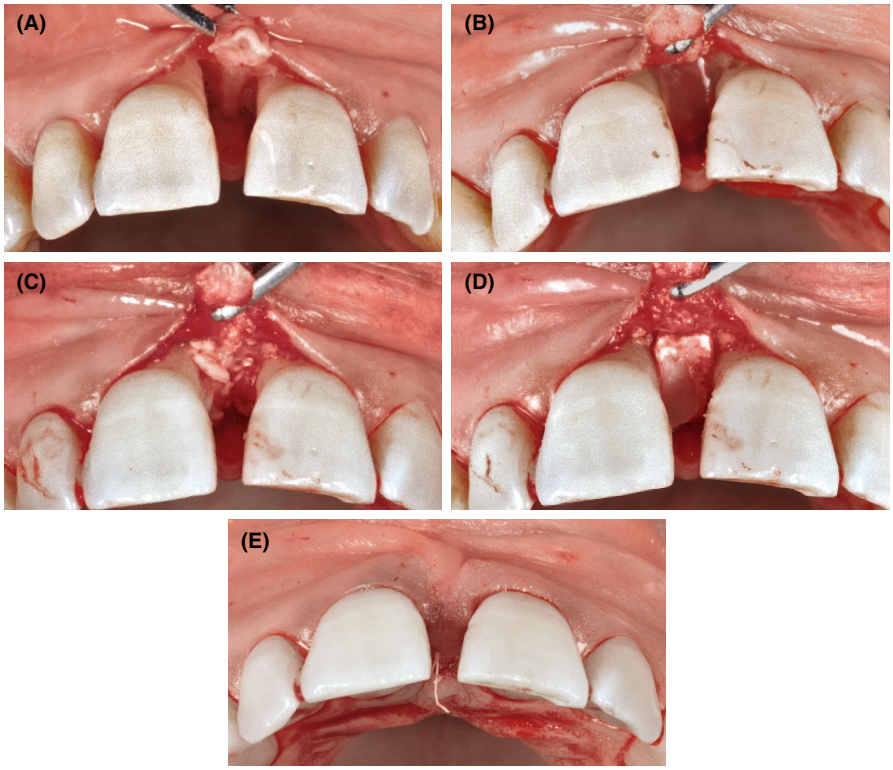


FIGURE 11 Intrabony defect regeneration with an allograft (70% DFDBA and 30% FDBA). (A) Deep intrabony defects observed on the mesial surfaces of teeth 11 and 21. (B) Application of Emdogain (Straumann). (C) Application of an allograft in a 70:30 ratio of DFDBA:FDBA. (D) Use of a collagen membrane (Creoss, Nobel Biocare). (E) Final closure. Case performed by Dr. Alberto Monje.

2.3 | Periodontal regeneration of intrabony and furcation defects

Periodontal disease is one of the most common diseases known to humans, with millions of people affected worldwide.[66,67] Many attempts have been made to regenerate periodontal defects, including intrabony and furcation defects. One of the complexities regarding periodontal regeneration has been the necessity to regenerate three tissue types (periodontal ligament, cementum, and bone) in comparison with bone augmentation, which requires one tissue type. Furthermore, many of the defects are narrow vertical defects, requiring less graft stability but greater potential for tissue regrowth.

As such, many clinicians, especially in North America, have advocated the use of a DFDBA for periodontal regeneration owing to its faster release of growth factors promoting better periodontal regeneration. Additionally, many colleagues have favored the incorporation of DFDBAs with additional regenerative growth factors, such as enamel matrix derivative (EMD; Emdogain, Straumann) or PRF (Bio-PRF; Figure 11). Notably, owing to the faster than ideal resorption of pure 100% DFDBAs,[32,68] many clinicians have further shifted toward a 70/30 ratio of DFDBA/FDBA to provide some additional graft stability while maintaining the core protein release potential from the DFDBA.

2.4 | Sinus augmentation

The sinus represents one of the more challenging areas in which to regenerate bone in the oral cavity as a result of its devoid cavity with minimal blood supply to the area prior to surgery. For these reasons, many clinicians have advocated utilizing PRF in combination with the graft procedure.

Interestingly, the majority of clinicians have the ability to use both allografts and xenografts during these procedures owing to the

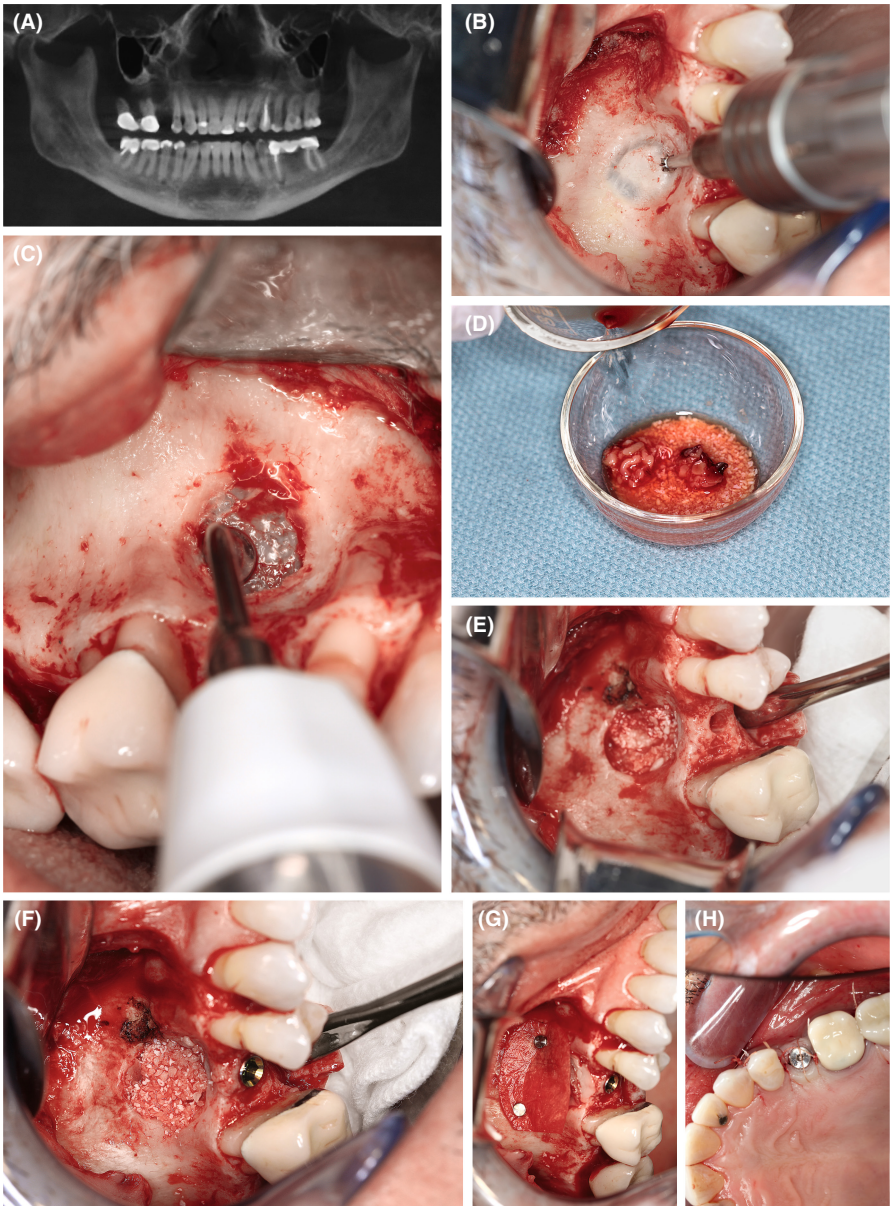


FIGURE 12 Sinus lift procedure with an allograft/xenograft combined graft in a 1:1 ratio. (A) CBCT demonstrating inadequate residual bone height. (B) Surgical flap elevated to expose the lateral window. Use of a round burr to create the outline of a lateral window. (C) Elevation of the Schneiderian membrane. (D) Two platelet-rich fibrin (PRF) membranes were cut into small fragments and mixed with FDBA and DBBM in a 1:1 ratio. (E) The composite graft of allograft/xenograft/PRF was placed into the sinus. (F) Implant placement. (G) The lateral window was then covered with a collagen membrane with fixation. (H) Occlusal view of the completed soft tissue closure. Case performed by Dr. Michael A Pikos.

biological/mechanical advantages of each. It is known that bone regeneration with an allograft will result in faster new bone formation but also lead faster to resorption over time.[32] In contrast, if grafting is performed with a xenograft, slower bone regeneration will take place, and a greater percentage of the implant surface will be in direct contact with the nonresorbable xenograft. Therefore, it has been clinically recommended by many experienced clinicians to use a combination of FDBA and a nonresorbable xenograft for sinus augmentation procedures, typically done in a 1:1 ratio (Figure 12). In this way, the allograft is utilized to regenerate bone faster and provides growth factors that facilitate bone formation, whereas the xenograft assures that the regenerated bone is maintained over time without fear of resorption over time. An additional advantage of xenograft incorporation is that should an additional implant be required in future years, the augmented bone will remain owing to the mechanical stability of DBBM.[69,70]

This example highlights how combination approaches with two types of bone grafts may yield better and more predictable outcomes.

2.5 | Guided bone regeneration

Guided bone regeneration is a large avenue of clinical practice, with many clinicians reporting their experiences utilizing various biomaterials and surgical protocols.[71–73] Entire textbooks have been dedicated to the topic.[71] While this article does not intend to cover this extensive topic, guidelines depicted from a previously written textbook on biomaterials[32] are provided with emphasis placed on the biological background for choosing the ideal biomaterials and, more specifically, bone grafts.

A variety of biomaterials have been utilized to achieve desired end goals. In general, the greater the bone volume required to regenerate, the better the bone-inducing bone graft/growth factor must be. GBR procedures in North America have routinely been augmented with either autografts and/or FDBAs. Allografts provide an excellent means to augment bone.

Nevertheless, major augmentation procedures with either autografts alone or allografts alone have also been experienced and are prone to significant resorption over time. While this article does not

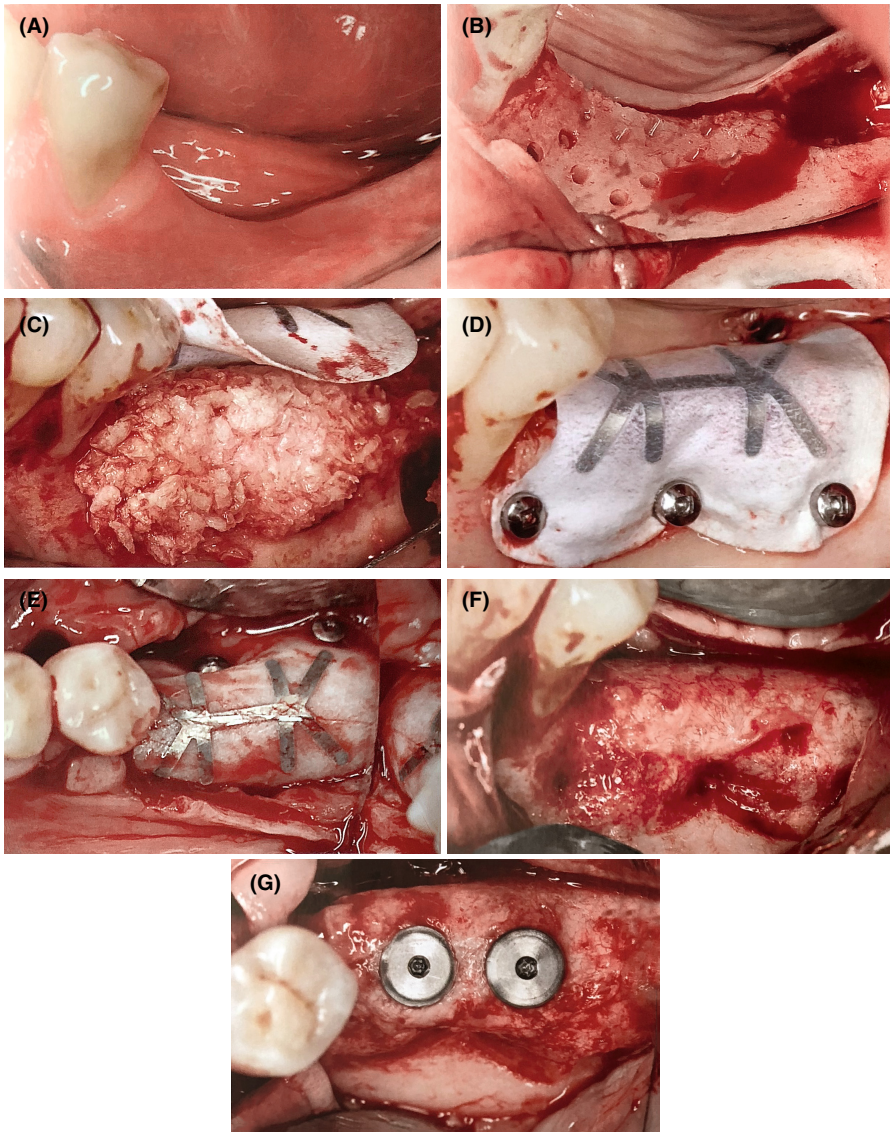


FIGURE 13 Representative case of vertical ridge augmentation using autogenous bone and xenografts. (A) Buccal view of an atrophic posterior mandibular area. (B) Following flap elevation, cortical bone was perforated. (C) Particulated autogenous bone from the ramus bone mixed with a xenograft (1:1 ratio) was placed on the ridge and an e-PTFE-TR membrane was secured on the lingual side before applying the bone graft. (D–E) Buccal and occlusal view of the e-PTFE-TR membrane secured over the graft with titanium pins. (F) View of the well-integrated bone graft after flap elevation following 9 months of uneventful healing. (G) Occlusal view of two implants placed into the regenerated bone. Reprinted with permission from Urban 2017.

intend to cover precisely each clinical scenario where resorption may be possible, several cases are presented to discuss the biological rationale for biomaterial choices. Therefore, in attempts to maintain bone volume, nonresorbable xenografts are routinely utilized to maintain space in bone augmentation. The advantage is that once regeneration has taken place, the bone volume can be maintained years later owing to the nonresorbable features of DBBM. For such cases, autogenous bone has typically been combined with xenografts in a 1:1 ratio (Figure 13). In North America, similar attempts are made with allografts, often utilizing the expensive but osteoinductive recombinant human growth factor rhBMP2.[74] The advantages of using rhBMP2 are its ease of availability and ability to replace the requirement for harvesting autogenous bone. Typically, owing to the greater bone-inducing potential of allografts versus autografts, a greater percentage of the final bone graft complex typically encompasses approximately 70% allograft and 30% xenograft, as presented in Figure 14.

2.6 | Nonresorbable features of xenografts

For many years, xenografts have been debated with much controversy owing to their nonresorbable properties, their uses, and whether they are in fact nonresorbed versus slowly resorbed. Since then, evidence has existed demonstrating their complete resorption in certain tissues (mainly soft tissue), whereas much evidence from long-term human histology has showcased the fact that they remain even after nearly a decade of being grafted within the oral cavity. For years, many clinicians attributed this phenomenon to the fact that xenografts were mainly derived from animal sources and unable to be "broken down" as efficiently by the human body.

Around the year 2018, other xenografts emerged in the market, yet many remained fully resorbable. Accumulated research by our team investigated the links between sintered time and temperature on the inability for the body to no longer be able to resorb bone. Simply put, human and animal hydroxyapatite has a dissolution rate that is modified with temperature. Thus, following high-temperature sintering of human or animal bone, the standard acidic pH released by osteoclasts once capable of resorbing bone is no longer able to do so following the change in dissolution of the heat-treated bone.

2.7 | Prepackaging allografts and xenografts for specific dental indications?

One of the main questions posed by clinicians to various bone-graft companies and manufacturing companies has been the

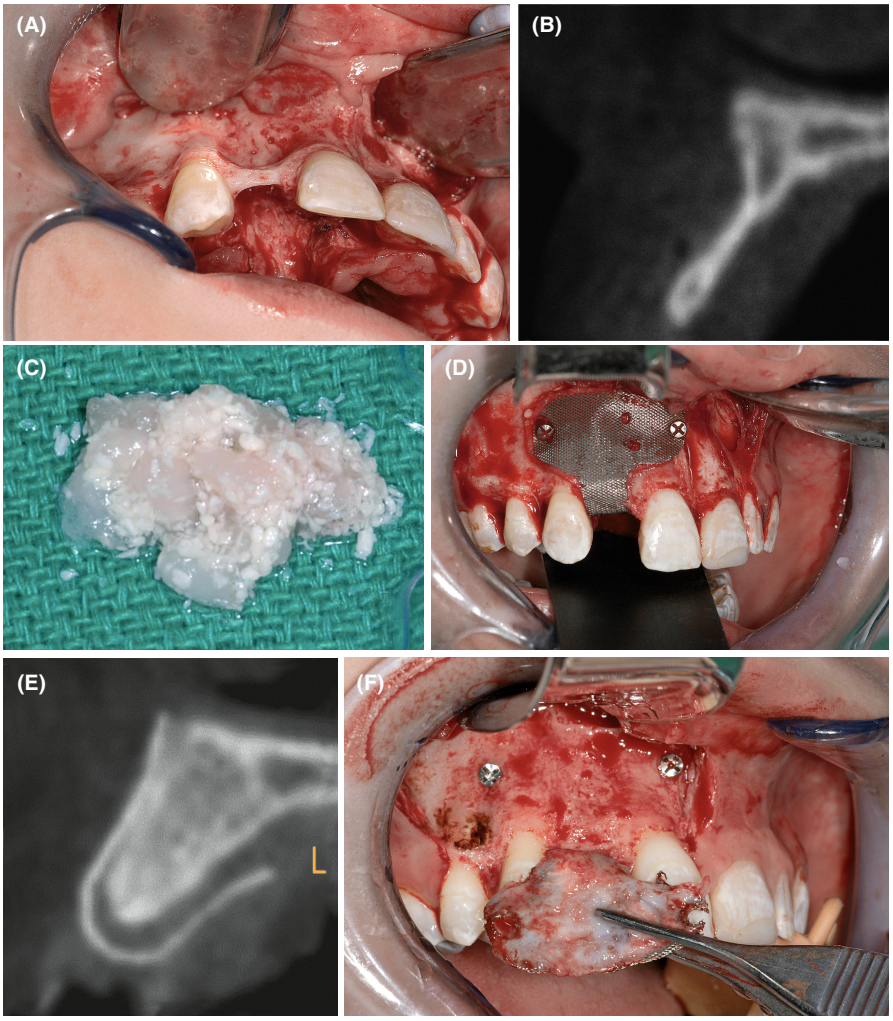


FIGURE 14 Use of rhBMP2 for bone augmentation of a congenitally missing maxillary lateral incisor. (A) Clinical view of congenitally missing maxillary lateral incisor following flap elevation. (B) Note the extensive bone loss as observed by CBCT. (C) Composite graft using rhBMP2 mixed with FDBA. (D) Final titanium mesh fixated over the composite graft. (E) CBCT demonstrating substantial bone gain after 7 months. (F) Clinical photo 7 months postoperatively following flap elevation prior to implant placement. Case performed by Dr. Michael A Pikos.

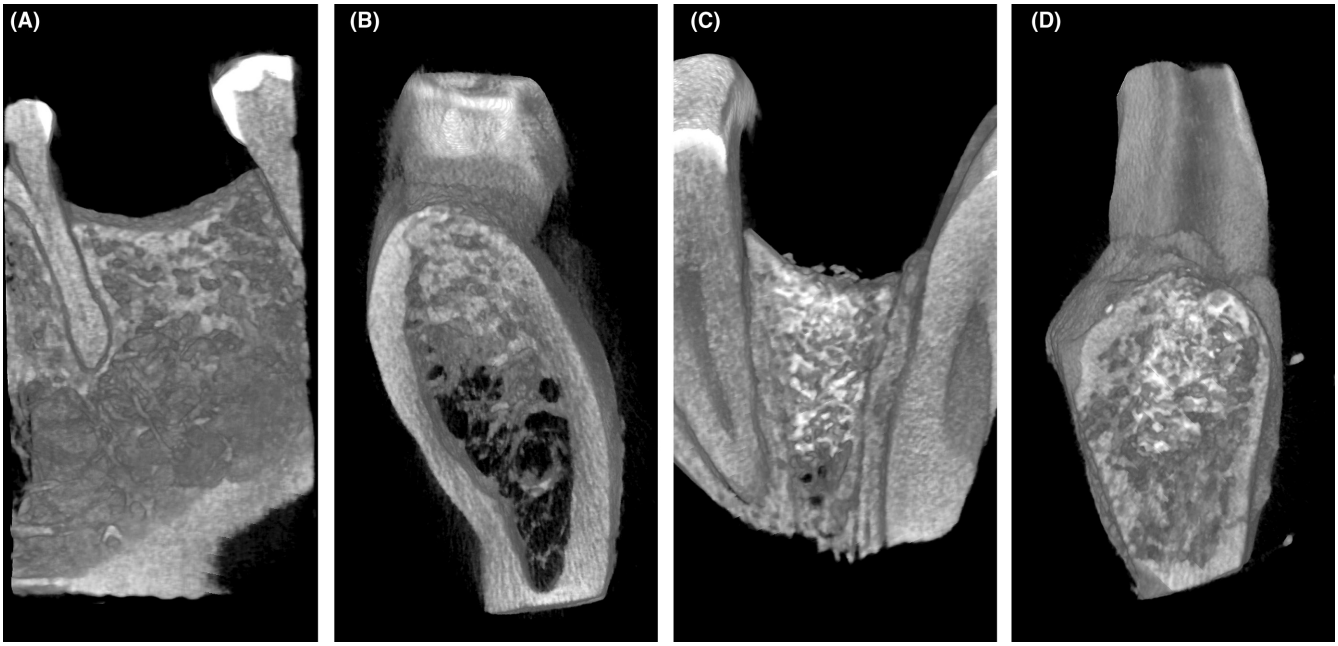


FIGURE 15 CT images revealing the differences in ridge dimensions after 52 weeks post-op for extraction site management in beagle dogs using either standard FDBA or nonresorbable bone allografts (NRBA). (A, B) It was found that after 52 weeks, the presence of standard bone allografts (FDBA) was completely resorbed at 52 weeks with some signs of dimensional ridge loss. (C, D) Note, however, the NRBA that were sintered at high temperatures (1300°C for 1 h) demonstrated maintenance of the graft even after 1 year with maintained dimensional ridge stability.

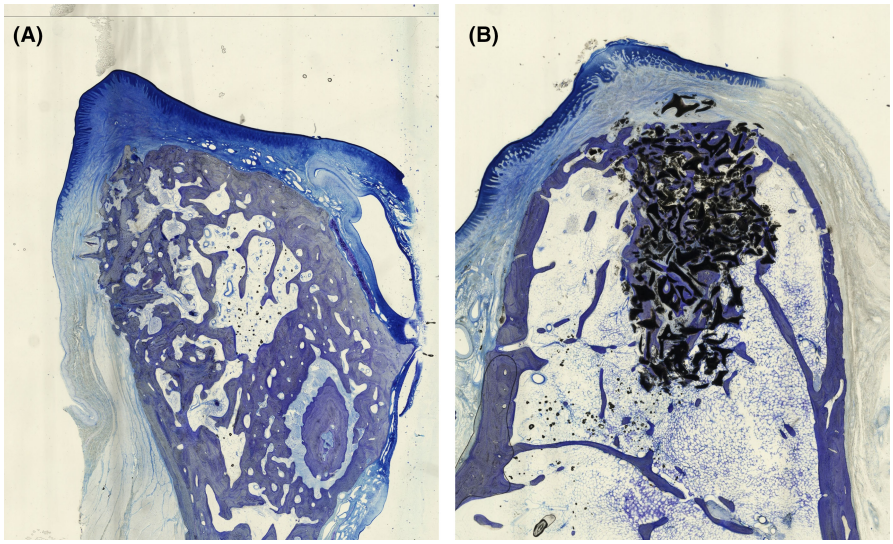


FIGURE 16 Histological differences at 52 weeks post extraction site grafted with FDBA versus NBDA. (A) New bone formation was observed around the residual FDBA particles which were resorbed over time and nearly absent by 52 weeks. (B) The black stained particles in the nonresorbable bone graft group heated at 1300°C remained within the extraction site even after 52 weeks keeping their shapes without resorption by osteoclasts. Dense new bone formation occurred between and along the NRBA particles.

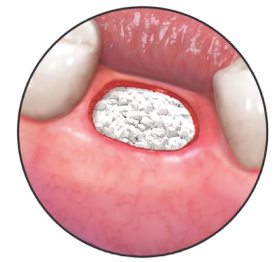
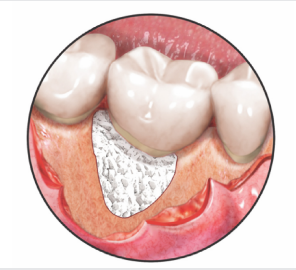
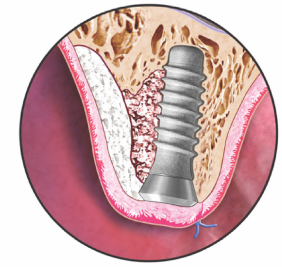
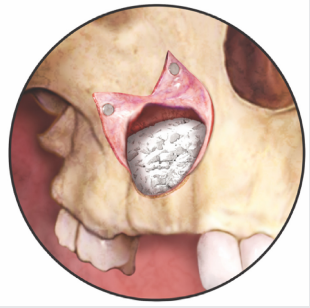
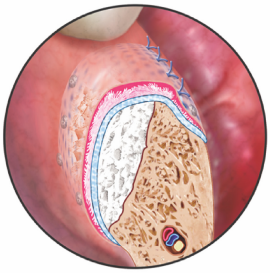
following: "Why not prepackage our standard ratios used in clinical practice (such as a 1:1 ratio of allografts and xenografts), into a single unit package specific to certain clinical indications like sinus grafting?" This would prevent clinicians from having to buy two types of bone-grafting materials (saved costs) but, more importantly, would greatly simplify the procedure and choice of biomaterials, especially among general practitioners who may not possess the same depth of knowledge as practicing periodontists and oral surgeons.

Unfortunately, owing to regulatory and government bodies, it is not possible to premix biomaterials from two different donors (such as an allograft from a human and a xenograft from a cow). Should this graft be deemed contaminated, too many questions would arise regarding whether the former or the latter was the cause. As such, for decades, clinicians have incorporated dual bone grafts into many procedures.

2.8 | Optimized bone grafting: introducing nonresorbable bone allografts

Because of the regulatory guidelines, it was conceived by our research group to process standard bone allografts in the same sintering environment as xenografts. As such, our research group has

TABLE 4 Various clinical grafting procedures including the potential ability to pre-mix FDBA, DFDBA and non-resorbable bone allografts (NRBAs) in various ratios. This would allow for the formulation of combined grafting materials specific to each clinical procedure included in a single packaged biomaterial specific to the indication.

Grafting procedures	Historic use of bone grafts	Optimized use of bone graft	Advantages
Extraction Site Management 	Freeze-dried bone allografts (FDBA)	EXTRACT OSS® 3:1 ratio of FDBA/DFDBA	• Maintains ridge owing to its large incorporation of FDBA but possesses an ability to release quickly growth factors responsible for bone formation in DFDBA. • 25% DFDBA with an ability to 'kick start' the bone regeneration process
Intrabony/Furcation Defects 	Demineralized freeze-dried bone allograft (DFDBA)	PERIO OSS® 3:1 ratio of DFDBA/FDBA	• Faster ability to release growth factors necessary for periodontal regeneration owing to demineralization process of DFDBA • 25% of the graft remains FDBA to hold volume slightly better than pure DFDBA
Contour Augmentation 	Non-resorbable xenograft: Deproteinized Bovine Bone Mineral (DBBM)	CONTOUR OSS® 3:1 ratio of non-resorbable bone allograft (NRBA) with DFDBA	• Non-resorbable bone allograft (NRBA) acts like a xenograft yet more biocompatible owing to its human base source • 25% of the graft is DFDBA to dramatically 'kick start' the bone regeneration process when compared to pure xenografts
Sinus Grafting 	1:1 mixture of: Freeze-dried bone allografts (FDBA) mixed with Non-resorbable xenograft: Deproteinized Bovine Bone Mineral (DBBM)	SINUS OSS® 1:1 ratio of NRBA and FDBA	• Non-resorbable bone allograft can now be premixed with standard FDBA together in a single pre-mixed package • Cheaper costs having to buy only 1 bone graft and faster clinical procedures with less room for error
Guided Bone Regeneration 	70:30 mixture of: Freeze-dried bone allografts (FDBA) mixed with Non-resorbable xenograft: Deproteinized Bovine Bone Mineral (DBBM)	GBR OSS® 3:1 ratio of FDBA and NRBA	• Non-resorbable bone allograft can now be premixed with standard FDBA together in a single pre-mixed package • Cheaper costs having to buy only 1 bone graft and faster clinical procedures with less room for error

developed nonresorbable bone allografts (NRBAs) produced at various temperatures ranging from 300 to 1400°C for 1–8 h.[75] Following this development, a 52-week monkey study demonstrated the ability for the grafts to remain integrated into bone without fear of resorption, displaying maintained ridges after 52 weeks, as confirmed by CBCT (Figure 15) and histological analysis (Figure 16; data not yet published). Thus, it is possible to recreate the biological/mechanical properties of xenografts utilizing allograft bone.

2.9 | Optimized bone grafting and the future of simplified grafting

With the development of NRBAs, it has recently been possible to manufacture a combination of xenograft/allograft premixes by utilizing NRBAs/allograft mixes coming from the same donor. As such, a variety of premixed bone grafts according to their clinical indication can be made available to clinicians, as presented in Table 4, with advantages highlighted regarding their combinations. These premixed bone grafts purposefully designed in various ratios can more greatly enable the treating clinician not only to perform the highlighted grafting procedures following the evidence-based use of various biomaterials but also simplify and optimize the described techniques by requiring the purchase of one bone graft as opposed to multiple.

2.10 | Use of growth factors in combination with bone grafts

The present narrative review did not focus on the use of growth factors in combination with bone grafting materials for the above-mentioned clinical scenarios and instead focused on the appropriate selection of bone grafting materials. Naturally, the use of rhBMP2 for instance has shown promising results specific to additional bone formation[2,76–78] and other growth factors such as EMD/rhPDGF/PRF/FGF2[79–82] have further supported periodontal regeneration. Future work supporting more research on specific growth factors for bone and periodontal regeneration is certainly warranted.

3 | CONCLUSION

This review article has summarized the four classes of bone grafts, including autografts, allografts, xenografts and alloplasts. While the gold standard remains autogenous bone grafts because of their combination of osteogenesis, osteoinduction, and osteoconduction, more commonly, allografts and xenografts have been utilized either alone or in various combinatorial approaches owing to their greater availability and biological/mechanical properties. This article has also summarized the biomaterial selections utilized in routine practice to manage extraction sites, periodontal defects, contour augmentation procedures, sinus grafting and GBR procedures. Finally, this article has presented ongoing research on the development of NRBAs and their future potential to simplify and optimize bone grafting for the treating clinician.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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