Bone Regeneration
Properties and Clinical Applications of Biphasic Calcium Sulfate

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KEYWORDS

- Calcium sulfate • Biphasic calcium sulfate • Graft • Bone cements
- Sinus augmentation • Socket preservation • Ridge augmentation
- Osseous defect repair

KEY POINTS

- Biphasic calcium sulfate has a complete conversion to host bone over a period of 4 to 6 months.
- The material sets hard, acting like a "bone cement" and has been used for decades in orthopedics.
- Minimal flap reflection; flap closure is done under tension by stretching without releasing incisions to induce a tension-free flap.
- No membrane is required, with primary closure not mandatory; when gaps in the soft tissue of 3 mm or less are present, the soft tissue migrates across to close the gap over a short period without inflammation.
- Various grafting applications are achievable with biphasic calcium sulfate at a more cost-effective material cost and similar clinical results can be achieved as with other grafting products used in dental surgery.

INTRODUCTION

Clinically, there are situations in dental treatment that require osseous grafting. Pathologic voids (defects) or those surgically created during treatment may require grafting to restore the osseous anatomy. Conversely, resorption of the osseous contours may requiring grafting to place implants or augment around those implants to contain the entire implant within bone.

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Various osseous grafting materials have been used clinically and reported in dental surgical applications. These include autografts, allografts, xenografts, and nonbiological-derived products (both synthetic and mineral based). Osseous grafts essentially act as a scaffold, maintaining the volume while allowing native bone formation over time. Some materials will resorb fully, whereas others never fully resorb. Autografts and allografts will resorb and, depending on mineralization and compaction if cortical, cancellous or a mixture resorbs quickly (cancellous) or takes longer (cortical). Xenografts, specifically bovine materials do not fully resorb and residual particles remain long term.[1] Synthetic graft materials, depending on their chemistry, may be replaced by conversion to host bone or remain partially or fully. The goal of grafting is conversion to native host bone that has vascularity that will remain in the long term, restoring the area to function; thus, selection of the material to be used is important to achieve that goal.

With those goals in mind, calcium sulfate, a natural mineral and one of the oldest biomaterials, has been used as a bone void filler, binder, grafting material, and as a delivery vehicle for pharmacologic agents and growth factors for more than 120 years, having a longer history of clinical use than most currently available biomaterials.[2] The material has been used in a wide range of clinical applications in orthopedic, plastic surgery, oncologic, and maxillofacial applications in the treatment of osseous voids and traumatic or inflammatory bone deficiencies. Calcium sulfate exists in 3 different forms; calcium sulfate anhydrate, calcium sulfate dehydrate, and calcium sulfate hemihydrate. The difference between these chemical species is represented by the amount of water molecules residing within a single molecule unit. The crystalline structure defines its physical, mechanical, and dissolution properties. The hemihydrate state of hydration exists as either an α or a β form, both of which are found in medical-grade calcium sulfate products. When this hemihydrate is mixed with water, a dehydrate is formed in a mild exothermic reaction with crystallization taking place, and the material sets and hardens.[3] Calcium sulfate as an augmentation material was first reported by Dressman in 1892 to obliterate bone cavities caused by tuberculosis.[4] Later, in the 1920s and 1930s, Nystrom,[5] and Edberg[6] reported results on the use of calcium sulfate plaster of Paris as bone filler without any reported postoperative complications. An extensive review in 1966 regarding the use of calcium sulfate reported the material as a simple, inexpensive substance that offers many advantages as a graft material for bone filling.[7] Studies have demonstrated that calcium sulfate is resorbable and is well tolerated by the tissues, acting primarily as a space filler, restoring morphologic contour, and preventing soft tissue ingrowth into the defects during the healing phase.[8,9] Peltier and colleagues[10–12] confirmed the osteoconductive properties of calcium sulfate allowing ingrowth of blood vessels (angiogensis) and osteogenic cells. When calcium sulfate is implanted in the body, over time (short term) it completely dissolves leaving behind calcium phosphate deposits that stimulate bone growth.[13,14] Evidence has been reported that biphasic calcium sulfate not only serves as a 3-dimensional scaffold but also is able to promote osteoinduction.[15] Therefore, it is considered a bioactive material.

A study reported 26 patients who had been treated with calcium sulfate for unicameral bone cysts, with a follow-up of 1 to 20 years. Of the study participants, 24 had successful healing of the defect with bone formation in the cyst, without complications or the need for additional surgery.[16] Another study reporting on 110 patients treated with calcium sulfate, primarily for osseous defects in the skull and facial bones, concluded that calcium sulfate was an outstanding bone graft substitute that ensured bone formation and produced results comparable with, if not better than, autogenous bone graft.[17] Extensive research has accumulated during the past few decades

confirming the effective and safe use of calcium sulfate in both orthopedic and dental applications, consistently reporting high biocompatibility. In dental (maxillofacial and periodontal) applications, calcium sulfate has been used in a variety of clinical applications, including periodontal defect repair, the treatment of osteomyelitis, radicular cyst defect repair, sinus augmentation, socket preservation, ridge augmentation, and as an adjunct to dental implant placement.[18,19] Following graft placement, it can be monitored radiologically; during its placement, it appears radiopaque, after 2 to 3 weeks it appears radiolucent, and it regains radiopacity after 12 weeks, reflecting the transformation of the material into newly formed uncalcified osteoid turning gradually to calcified young native bone.

Following placement, during the healing phase, calcium sulfate dissolves into its component elements naturally found in the body. When placed in direct contact with viable host bone, new bone growth occurs in apposition to the calcium of the graft material. Calcium sulfate bioresorption studies and clinical experience have shown consistent osteoconduction and complete resorption, replaced by newly formed bone that is ultimately remodeled.[20] Calcium ions activate platelets to release bone morphogenetic proteins and platelet-derived growth factors that stimulate proliferation and osteogenic differentiation of mesenchymal stem cells.[21,22] This makes this osseous graft material well tolerated and nonimmunogenic, with no adverse reactions or failure to heal being reported in the literature.[23,24]

Biphasic calcium sulfate acts as a cement, and its hard structure after fast setting prevents infiltration of epithelio-conjunctive cells into the material, acting as a barrier membrane. Yet, connective cells are able to proliferate over the surface of the material, promoting rapid healing of the overlaying soft tissue. Therefore, its related surgical protocols are less invasive compared with other grafting materials in which a tension-free flap and primary closure are mandatory. The opposite is found with biphasic calcium sulfate surgical protocols, indicating minimal flap reflection, and flap closure is done under tension with no releasing incisions to induce a tension-free flap,[25] taking advantage of the flexibility of the mobile mucosa to stretch the flap into place for closure. Thus, the flap and graft are not influenced by muscle movements during the healing phase. In addition, maximal closure with graft exposure of 3 mm is acceptable. The hardness and stability of the biphasic calcium sulfate placed into the defect being grafted means that no membrane or other intermediary barrier is needed. Biphasic calcium sulfate graft material has been shown not to compromise the desired results. Soft tissue cells at the flap margin proliferate over the exposed hardened graft, closing the flap margin fairly quickly over a few days to a week or so.

Calcium sulfate is considered to be one of the bone graft materials of choice in orthopedics due to its excellent osteoconductive bioactivity capacity.[26,27] It can be concluded that calcium sulfate is a biocompatible osteoconductive bioactive material that is well tolerated by the tissues when used for the treatment of osseous defects and guided tissue regeneration in animals and humans.
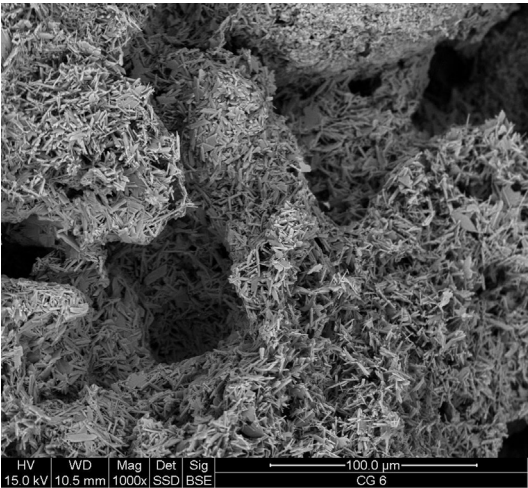
BIPHASIC CALCIUM SULFATE

In maxillofacial applications, however, difficulties with hardening calcium sulfate in the presence of saliva and bleeding have hampered its routine use. This obstacle to its use dentally was overcome in 2010 by Dr Amos Yahav by modifying the material behavior without changing its chemical structure or adding any additives making it biphasic. The biphasic calcium sulfate form allows the calcium sulfate to harden in the presence of saliva and blood, expanding its use in the maxillofacial arena. As
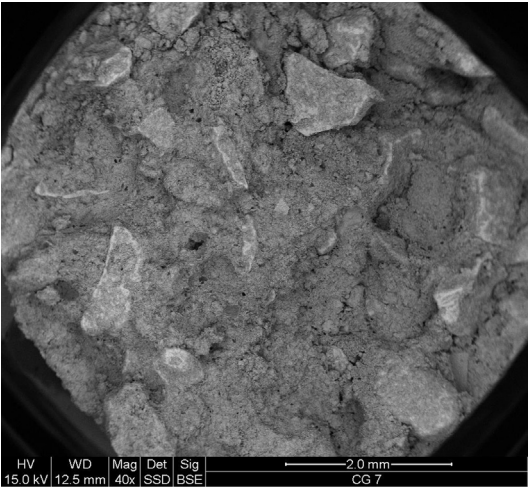
Fig. 1. HA consists of particles of different sizes and shapes incorporated within the biphasic calcium sulfate matrix (scanning electron microscopy).

calcium sulfate is a completely resorbable synthetic material with short-term space-maintaining abilities, in the case of large osseous defects, the use of biphasic calcium sulfate as a composite graft in a mixture slows the resorption time allowing space maintenance, and the host replaces it with early bone. This is available as an already-made composite graft product called Bond Apatite (Augma Biomaterials), a biphasic calcium sulfate composite bone graft cement containing an average of one-third hydroxyapatite in a controlled particle distribution. The hydroxyapatite particles are of various sizes and shapes of 90 μm to 1 mm (**Fig. 1**). On setting, the

Fig. 2. Postsetting structure of biphasic calcium sulfate at higher magnification, which is composed of needle-like crystals presenting microporosity (1–50 μm) and macroporosity (300–800 μm) promoting growth factor infiltration angiogenesis formation and cell proliferation (scanning electron microscopy).
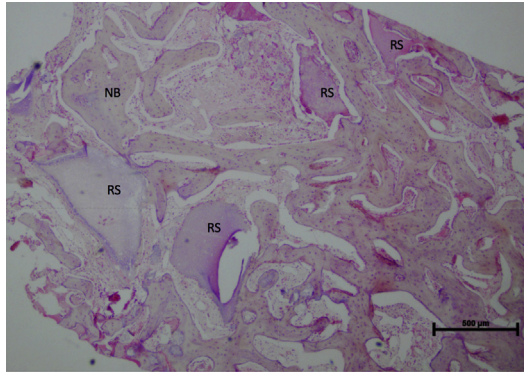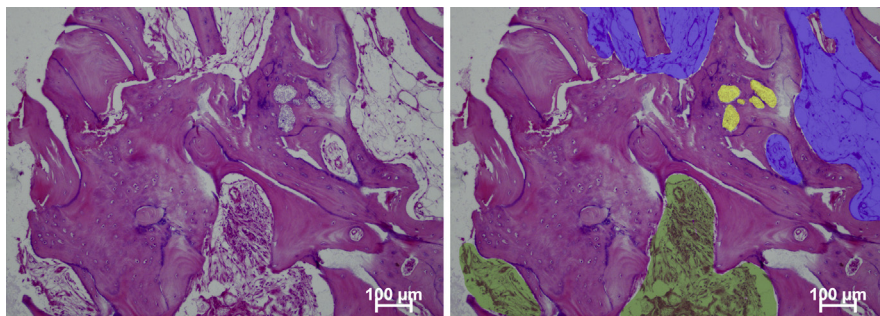
Fig. 3. Histology of Bond Apatite graft specimen at 3 months after graft placement showing residual graft scaffold (RS) and new bone (NB) within the sample studied.

material has a needle-like crystal structure (**Fig. 2**). This allows maintenance of the material in the defect for a much longer period, as the calcium sulfate component resorbs first, with later (slower) resorption of the hydroxyapatite component. This allows space maintenance of the defect while the host vascularizes the grafted area and develops bone, preventing soft tissue ingrowth. The cement has 2 resorption pattern mechanisms related to its components. The biphasic calcium sulfate portion has a resorption pattern of 4 to 10 weeks, which enables fast bone modeling and angiogenesis formation between the hydroxyapatite (HA) particles that act as a longer space maintainer to slow down the overall resorption of the graft. The small to middle-sized HA particles resorb completely after 3 to 5 months, then the larger particles, which are less than 10% by volume, remain for a longer period until complete resorption takes place. The resorption mechanism of the HA particles within the Bond Apatite cement is unique; the HA particles do not integrate with the newly formed bone. Instead, they become encapsulated by connective tissue where degradation occurs as the connective tissue undergoes ossification into a vital host bone.

Histologically, in samples taken at 3 months after graft placement, new bone can be observed in close approximation to remaining residual scaffold particles of Bond Apatite (**Fig. 3**). Analysis at this stage of healing demonstrates ∼10% of residual graft particles surrounded by connective tissue. At 8 months after graft placement, histologically, little remains of the Bond Apatite and bone marrow is noted in the organizing new bone (**Fig. 4**). Some areas of connective tissue are also noted, indicating that the graft is maturing and the host is converting the graft material into native bone without any observed inflammatory process. Analysis at 8 months demonstrates the components of the sample to be 79% bone, 11% bone marrow, 7% connective tissue, and only 3% residual graft particles.

Bond Apatite is provided in a double-compartment syringe with one side containing the composite mixture of biphasic calcium sulfate powder with hydroxyapatite and the other compartment containing sterile saline solution. Advancing the syringe shaft until the first plunger on the syringe reaches the blue line marked on the syringe activates the material. The syringe cap is then removed, and the graft is ready for placement directly into the osseous defect. After placement into the defect, sterile gauze is pressed firmly over the graft for 3 seconds to remove residual moisture and harden the material, while compressing it to the

Fig. 4. Histology of Bond Apatite graft specimen at 8 months after graft placement showing (*right*) bone (*purple*), bone marrow (*blue*), connective tissue (*green*), and residual graft particles (*yellow*).

osseous bed. Soft tissue is then reapproximated by stretching, and sutures are placed to fixate the flap margins. The flap should be positioned in direct contact with the graft with tension and secured with sutures. A membrane is not required between the graft material and soft tissue. Exposure of the graft material of up to 3 mm does not require membrane coverage or mobilization of the soft tissue to achieve primary closure. Because of the biocompatible nature of the biphasic calcium sulfate and its set hardness, any minimal exposure will result in peripheral soft tissue migration to cover the material without loss of graft material in the interim period.

As a salt, the graft material has bacteriostatic qualities, which are induced by the presence of sodium chloride in the physiologic saline used to mix the powder with the liquid.[28] The cement obtained after mixing the biphasic calcium sulfate powder with the physiologic saline has bonding qualities. After mixing, it is deposited into the osseous defect in a dehydrated (wet) form. The material is then compressed with sterile gauze for 3 seconds to remove any residual liquid, resulting in a dehydrated crystallized form, which hardens and sticks to the osseous defect walls, thus forming a stable block unlike graft materials in granule or paste form. Bond Apatite may be used in small and large defects, such as socket grafting, periodontal defects, lateral ridge widening, and horizontal sinus augmentation (crestal and lateral approaches).

## CLINICAL APPLICATIONS
Extraction Socket Preservation (Grafting)

Extraction socket grafting is often indicated to preserve the osseous crestal margins and prevent resorption during healing (**Fig. 5**). This may also be performed in anticipation of implant placement at a later date or simultaneous with the extraction. After extraction, the sockets are thoroughly curetted to remove any residual tissue or pathologic matter. Bond Apatite is mixed and placed into the extraction socket by injection from the syringe. It is not necessary to place a membrane over the graft material. However, exposure of several millimeters (>3 mm) of set material at the superior aspect of the crest requires a simple collagen sponge with average resorption of 7 to 10 days, which should be secured in place to cover and protect the exposed material during the first healing stage until soft tissue proliferation takes place above its surface; this does not affect the clinical results. Sutures are placed to help maintain the soft tissue margins with the collagen sponge in contact with the graft material during initial healing (**Fig. 6**). After 4 months

Fig. 5. Radiograph demonstrating failure of bridge abutments related to endodontic failure and periodontal bone loss.
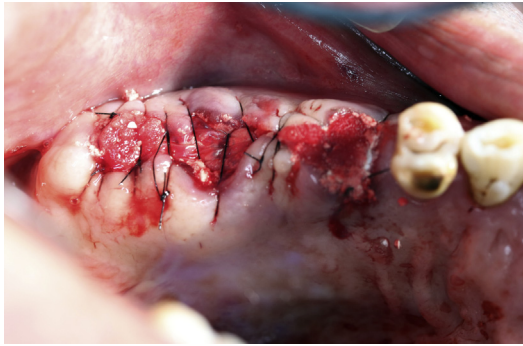

Fig. 6. After extraction of the bridge abutment teeth, the extraction sockets were curetted and filled with Bond Apatite, and exposed material over 3 mm was covered by a collagen sponge secured in place by sutures to help contain the graft material without primary closure of the soft tissue.
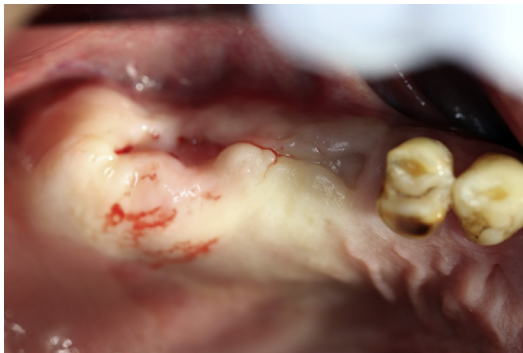
Fig. 7. Presentation at 4 months after surgery demonstrating complete coverage of the area with keratinized soft tissue and closure of the areas of Bond Apatite that had been left exposed at completion of the surgical appointment.

Fig. 8. Radiograph at 4 months after surgical placement of Bond Apatite demonstrating early bone fill and conversion of the graft material.
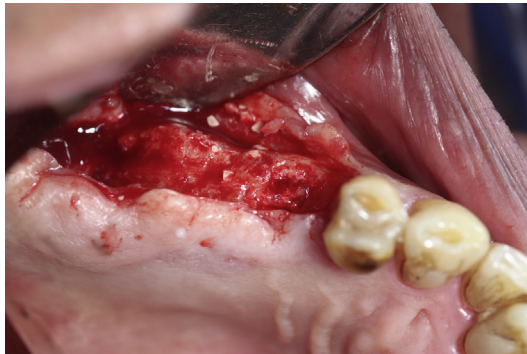
Fig. 9. Site was flapped at 4 months after surgical grafting demonstrating bone filling the extraction sockets previously grafted.
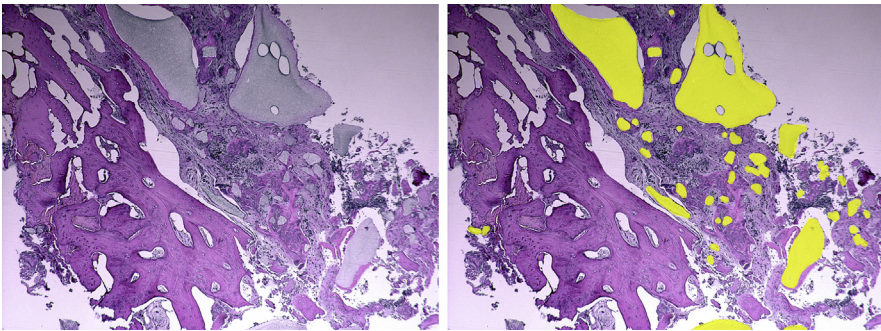

Fig. 10. Core sample retrieved with a trephine from a surgical site that had been grafted with Bond Apatite 4 months previously.
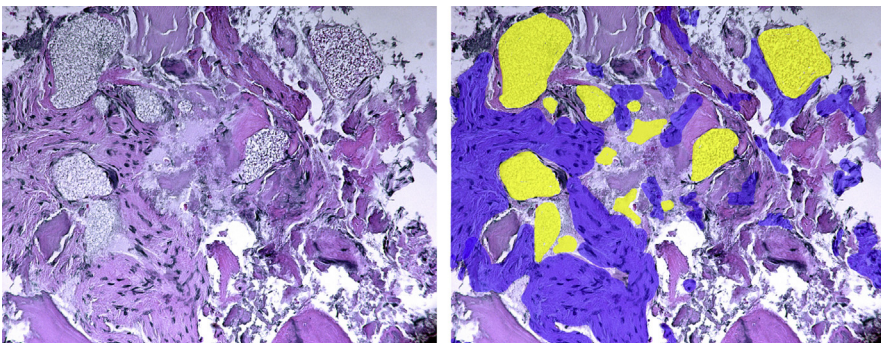
Fig. 11. Radiograph after implant placement at 4 months and socket grafting with Bond Apatite.

Fig. 12. Histologic evaluation of the core specimen at 40× demonstrating residual particles of Bond Apatite (*yellow*, *right side*) and young bone in proximity with the particles.


Fig. 13. Microscopic evaluation of the core specimen at 200× demonstrating residual particles of Bond Apatite (*yellow*, *right side*) and young bone (*blue*, *right side*) in proximity with the particles.

Fig. 14. Periapical radiograph with a lesion associated with previous endodontic treatment on the left mandibular lateral and central incisors.
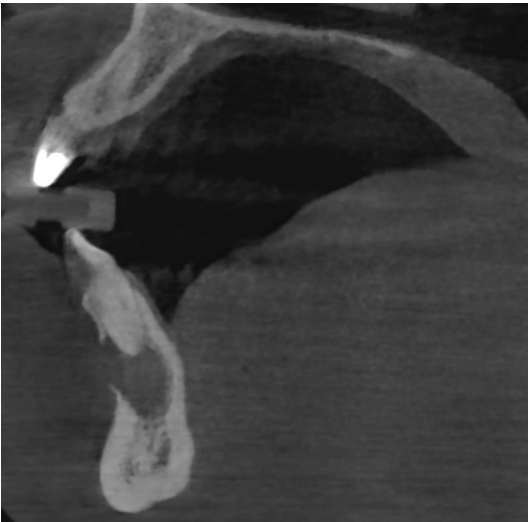
Fig. 15. Cone beam computed tomography cross-section demonstrating the size of the odontogenic cyst associated with failing endodontic teeth in the mandibular anterior, with lack of facial plate noted.
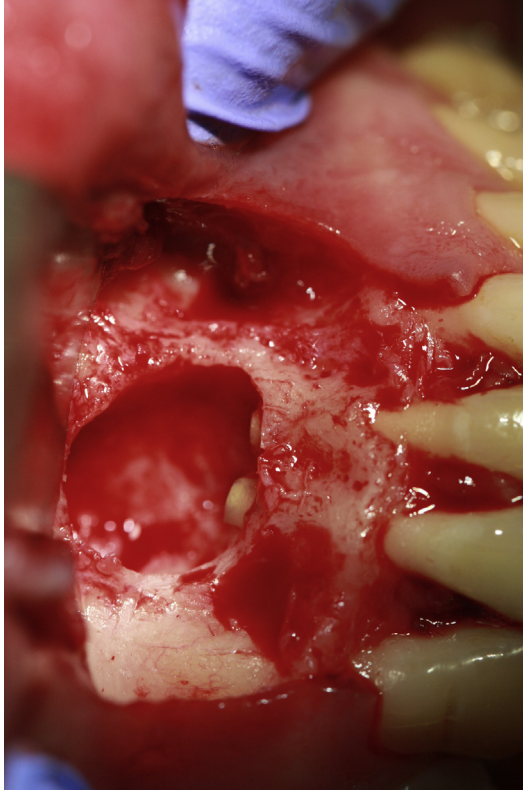
Fig. 16. Size of the defect after enucleation of the odontogenic cyst, root resection, and retrograde filling.

of site healing, the previously exposed areas at the superior aspect of the crest are covered with keratinized gingiva (**Fig. 7**). A radiograph confirms osseous fill of the extraction sockets (**Fig. 8**). The area is flapped for implant placement, demonstrating osseous fill of the sockets (**Fig. 9**), and a core sample is removed by trephine (**Fig. 10**). Implants are placed as planned and a radiograph is taken (**Fig. 11**). Histologic evaluation of the core specimen demonstrates residual particles of Bond Apatite with young bone in proximity with the few remaining particles (**Figs. 12** and **13**). The remaining graft particles will convert while the implants are integrating.

Radicular Cyst or Defect Grafting

An osseous defect resulting from pathologic lesions may necessitate surgical intervention to remove the source of the lesions (**Figs. 14** and **15**). The area is flapped and pathologic tissue is excised, leaving an osseous defect that will require grafting (**Fig. 16**). Bond Apatite is mixed and placed into the osseous defect until the graft material is flush with the exterior aspect of the ridge (**Fig. 17**). After a healing period, radiographs are taken to verify conversion of the graft material placed into host bone (**Figs. 18** and **19**). Histologic analysis via a trephined core sample of the site demonstrates some residual particles of Bond Apatite with new young bone formulation with the absence of an inflammatory reaction (**Fig. 20**). Immuno-histochemical study (CD68, a surface antigen used for detection of bone cells)
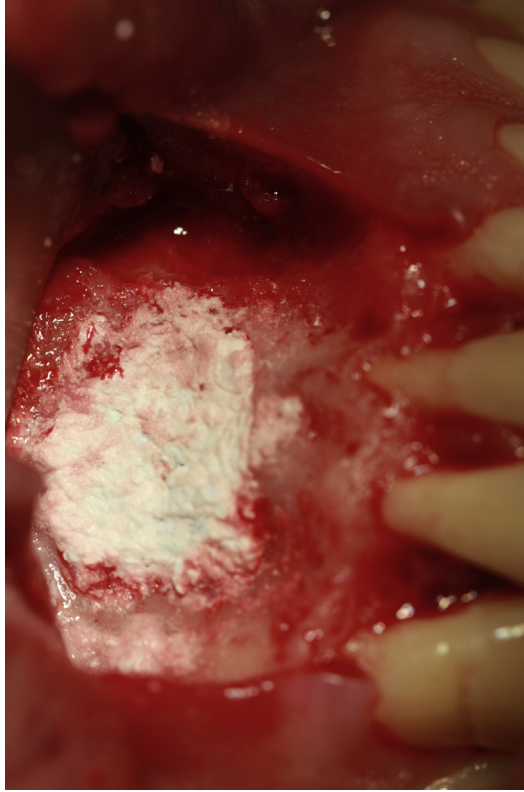
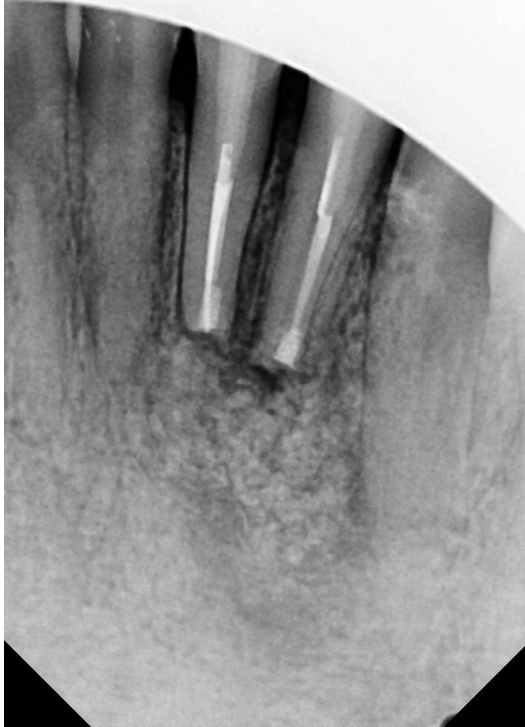**Fig. 17.** Bond Apatite placement to fill a large osseous defect.

demonstrates active osteoblasts in the tissue and little remaining Bond Apatite (Fig. 21).

Sinus Elevation via a Crestal Approach

The osteotomy is prepared in anticipation for crestal sinus elevation. The sinus is elevated using Summers' technique. Bond Apatite is activated in its syringe and then injected into a sterile dish and left to harden for 3 minutes. Thereafter, the semi-hard material is reloaded back into the Bond Apatite syringe barrel or any other bone graft carrier and introduced into the osteotomy (Fig. 22). An osteotome is used to gently place the graft material into the elevated sinus area (Fig. 23). When the implant can be placed at that appointment, it is introduced into the site, a cover screw placed, and the site closed with a suture across. Should an implant not be able to be placed at that appointment, the entire osteotomy is filled with additional Bond Apatite, compressed with gauze, and the site closed with a suture over the socket. After a period of 4 months to allow the sinus augmentation graft to heal, implants were placed in the new available crestal height and further healing was allowed for implant integration (Fig. 24).

Sinus Elevation via a Lateral Approach

Conventional preparation of the lateral window for sinus elevation is performed after flap elevation and the sinus membrane is elevated (Fig. 25). Bond Apatite
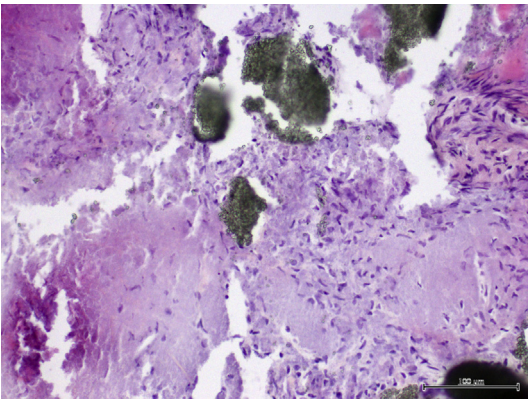
**Fig. 18.** Bond Apatite placement to fill a large osseous defect.
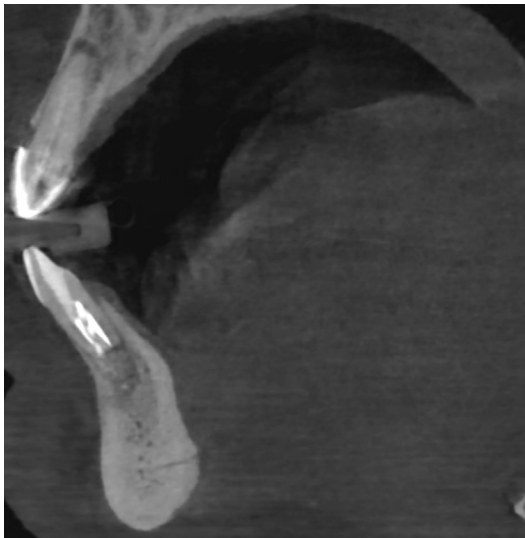
Fig. 19. Cone beam computed tomography cross-section at 6 months demonstrating replacement of the Bond Apatite with new host bone maintaining the facial contour of the mandible cortical plate that was affected by the lesion that was removed.

Fig. 20. Histology after 3 months, shown at 100× with visible new young bone formulation (*dark purple spots*) and residual Bond Apatite (*dark areas*) that is converting to bone with the absence of an inflammatory reaction.
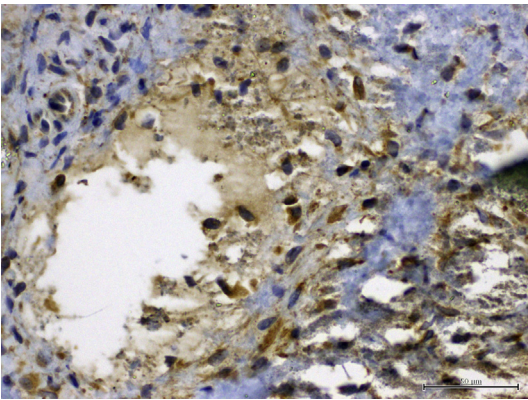

Fig. 21. Immunohistochemical study of CD68, a surface antigen used for detection of bone cells, demonstrates active osteoblasts in the tissue and little remaining Bond Apatite (*green*).
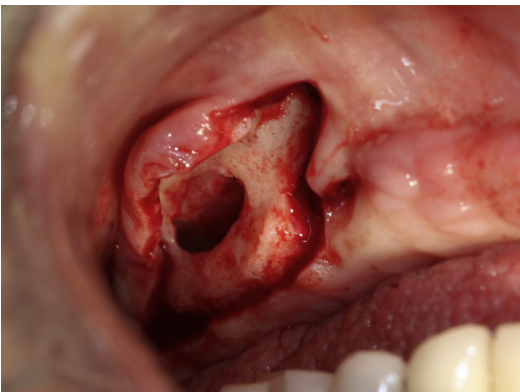

Fig. 22. Bond Apatite is introduced into the crestal sinus elevation with the syringe.
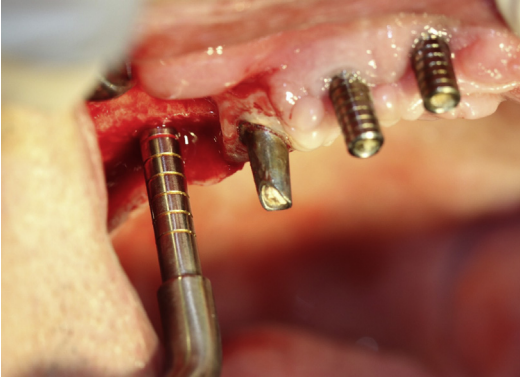
Fig. 23. An osteotome is used to compact the Bond Apatite graft material into the crestally elevated maxillary sinus before implant placement.
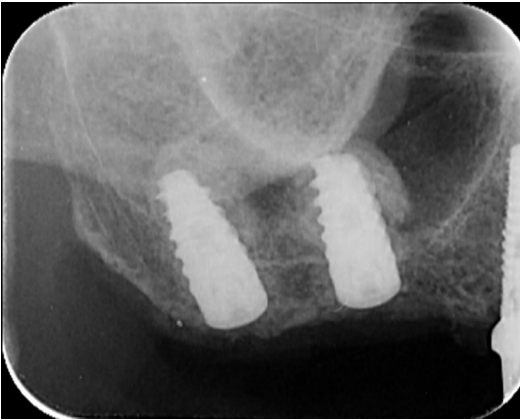

Fig. 24. After a healing period of 4 months to allow the sinus augmentation graft to heal, implants were placed in the new available crestal height and with further healing, allowed implant integration.
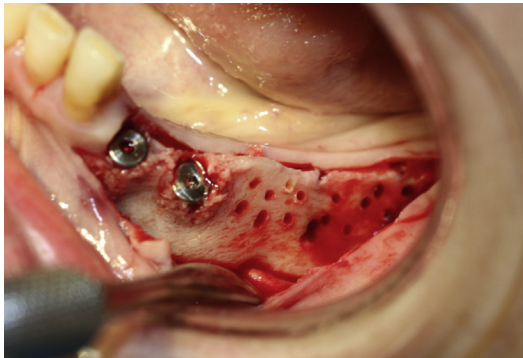

Fig. 25. A lateral osseous window has been created in the posterior maxilla as a prelude to sinus augmentation.
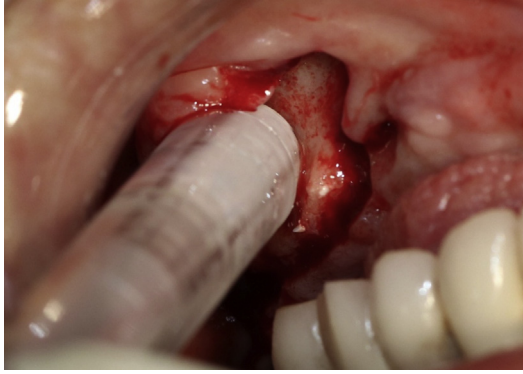
Fig. 26. Bond Apatite is mixed and a syringe is used to introduce the graft material into the elevated maxillary sinus.
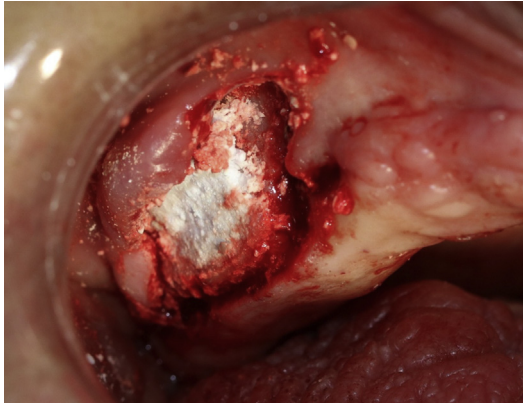
Fig. 27. The elevated maxillary sinus is filled with Bond Apatite graft material to the exterior contour of the lateral wall of the sinus.

Fig. 28. Posterior mandible with insufficient width to accommodate implants has had the buccal aspect of the ridge perforated to create bleeding points in preparation for graft placement.
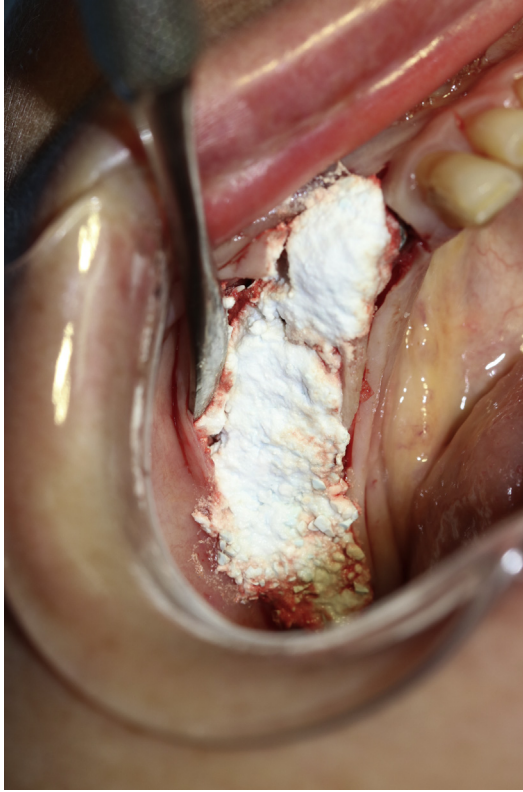
Fig. 29. The lateral aspect of the ridge has been grafted with Bond Apatite before flap closure.

is mixed and after a 1-minute waiting time, is injected into the sinus that was created by elevation of the sinus membrane (**Fig. 26**). The graft is dispersed in the sinus cavity first mesial, then distally, and finally in the center until two-thirds of the sinus is filled. During graft dispersion, the graft material should be compressed against the crest and the sinus walls and, if needed, dry sterile gauze is used to tap gently over the graft surface to absorb excess fluids and blood. When filling the last one-third and closing the sinus window, the last syringe of Bond Apatite is activated and immediately injected into the sinus, followed by pressing firmly for 3 seconds with dry sterile gauze. The augmentation is finished with graft material level with the buccal aspect of the bony window that was created (**Fig. 27**).

Lateral Ridge Grafting (Osseous Width Deficiency)

A full thickness flap extended 2 to 3 mm past the mucogingival line is reflected to visualize the site. If the crestal incision is long enough in the mesial distal direction, a vertical releasing incision may not be necessary and an envelope technique may be used. Decortication with a surgical carbide in a handpiece is performed on the buccal aspect of the ridge. This aids in providing stem cells for the graft to be placed (**Fig. 28**). Bond Apatite is activated in the syringe and placed over the buccal lateral aspect of the ridge, then compressed with gauze
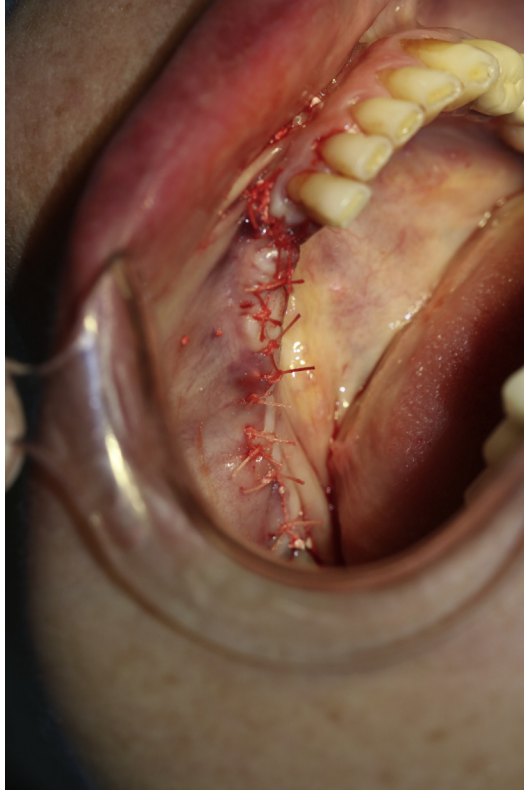
Fig. 30. The flap has been reapproximated over the graft and secured with sutures.

for 3 seconds (**Fig. 29**). The flap is repositioned directly on the graft under tension by stretching it for maximal closure over the graft. If primary closure cannot be achieved, 3 mm of graft exposure is acceptable and a membrane is not required to cover any of the exposed graft material. Sutures are placed to fixate the soft tissue (**Fig. 30**). After a 3- to 4-month healing period, the site is reflapped for implant placement, demonstrating ridge width that can accommodate
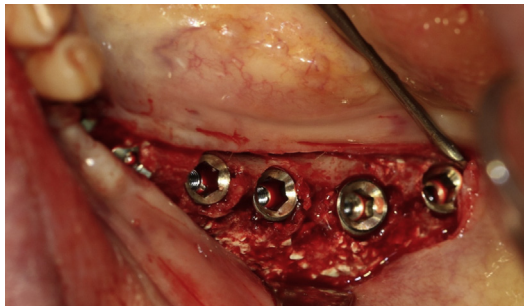
Fig. 31. At 3 months after grafting surgery, implants have been placed in the wider resulting ridge, with some particles of the Bond Apatite remaining that will finish conversion while the implants integrate.

the planned implants (**Fig. 31**). Residual graft particles may be noted at this phase and will fully convert as the implants integrate.

SUMMARY

The goal of osseous grafting is to maintain a space to provide a scaffold for the host to peripherally accomplish angiogenesis and replace the graft by host bone. To accomplish this, the graft material needs to be biocompatible and resorbable over time, but remain long enough to allow host conversion. Biphasic calcium sulfate provides a graft material with a long history in both orthopedic and maxillofacial applications. The addition of HA increases the resorption time and remains within the practical time frame for dental clinical applications with most of the graft material converting to young bone in a 3- to 6-month period and the remainder resorbing shortly thereafter. As outlined, these applications include elimination of osseous defects created either pathologically or as a result of surgical treatment and those clinical situations where osseous development is a prelude to implant treatment.

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