Current Use of Calcium Sulfate Bone Grafts

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Abstract
Bone graft placement is the most widely used therapeutic strategy for the surgical correction of osseous defects. In recent years, increasing attention has been given to the development of synthetic bone grafts. Of those currently available, calcium sulfate materials exhibit several unique properties that warrant discussion. These include their intrinsic osteogenic potential, their stimulatory effect on angiogenesis, the fact that they are fully biodegradable, the lack of proinflammatory responses following their placement in situ, and their lost cost of production. However, despite the attractiveness of these features, the use of calcium phosphate materials for bone grafting continues to be more widespread. This review examines the current use of calcium sulfate bone grafts in regenerative medicine. It also considers their clinical drawbacks before providing insight into the development of new calcium sulfate grafting constructs that might address these concerns.
Introduction

Bone is representative of a highly dynamic living tissue with an intrinsic capacity for self-repair after injury. However, the regenerative capacity of host bone tissue is subject to limitation in cases of extensive skeletal breakdown. Such cases often necessitate the placement of bone grafts to achieve complete osseous regeneration. Bone grafts serve multiple purposes. They serve to uphold the structural integrity of damaged osseous tissues by maintaining their skeletal architecture during host bone remodeling. They also prevent against further skeletal breakdown by buttressing the surrounding walls of osseous defects that might otherwise collapse under mechanical load. In addition, bone grafts can improve the osseointegration of implanted devices by reducing void formation at the tissue/prosthesis interface, thereby improving the functional stability of prostheses in situ. For these reasons, bone graft placement represents the most widely used therapeutic strategy for the surgical correction of osseous defects.

At present, host-derived autografts represent approximately 58% of all bone grafts in current use. Their harvesting, however, requires patients to undergo an additional surgical procedure, thereby placing them at risk for morbidity at a second surgical site. In addition, the amount of autogenous bone available for grafting is limited and may be insufficient for filling large scale osseous defects. When autograft harvesting is contraindicated or declined by patients, allografts are the most common alternative. Allografts though tend to be expensive and pose risks for viral transmission. The transplantation of allogeneous bone also carries a risk for the development of graft versus host disease. Furthermore, it is not uncommon for patients to express reservations against receiving bone grafts from unknown donors. The same can be said if not more so for xenografts. Most xenografts are harvested from bovine bone. Despite their reported safety, the presence of bovine prion proteins and the possibility for violent rejection reactions cannot be disregarded. To these ends, alternative sources for bone grafts deserve exploration.

With the potential to circumvent some of the drawbacks associated with bone grafts harvested from living tissues, a preponderance of US Food and Drug Administration (FDA) approved alloplastic bone grafts have emerged on the market in recent years. Many of these synthetic constructs are purported to have widespread application in bone tissue engineering. As a result, clinicians are faced with a diverse array of alloplastic materials from which to choose. In short, alloplastic materials used as bone grafts should be capable of promoting three processes. First, they should promote bone formation over their surfaces via direct bone bonding (osteoconduction). Second, they should be capable of inducing the differentiation of osteoprogenitor cells toward the osteoblast phenotype (osteogenesis). Lastly, they should have a stimulatory effect on the activity of bone-forming osteoblasts (osteogenesis).
Alloplastic bone grafts are designed to function as scaffolding units capable of housing the cellular regulators of bone remodeling and supporting the deposition of osseous matrix by resident osteoblasts.\textsuperscript{11} Several biochemical and physical parameters must be considered in the course of their development. Foremost, any biomaterial contemplated for human implantation must be entirely non-toxic. Their biomechanical strength, moreover, needs be carefully assessed to determine whether their use is suitable for the correction of load bearing osseous defects. They should also be fully biodegradable. This last feature is particularly important because the presence of residual graft material in the bone fill can adversely affect the architecture of regenerated osseous tissues.\textsuperscript{12-15} For this reason, the biodegradation rate of alloplastic bone grafts should closely match the rate at which new bone is formed. If it is too slow, it becomes embedded in the bone fill and can interfere with the otherwise normal secretion and cross-linking of osseous matrix proteins. On the other hand, if it is too fast, the graft may not afford adequate structural support time for complete bone regeneration to occur. This is undesirable as it increases the likelihood of voids being present within the bone fill.

Currently, calcium phosphate (CP) bone grafts are the most used alloplastic materials. The most common variants of which are $\beta$-tricalcium phosphate ($\beta$-TCP) and synthetic hydroxyapatite (HA).\textsuperscript{6, 16} Over the past 40 years, significant research efforts have been made to develop effective CP based bone grafting systems. As recently reviewed, however, their clinical efficacy continues to be hindered, owing to their limited osteogenic potential and low tensile strength.\textsuperscript{17} In addition, a recurrently cited limitation of CP bone grafts is the unpredictability surrounding their biodegradation profile. Most exhibit slow resorption rates that are not commensurate with the rate of host bone regeneration \textit{in vivo}.\textsuperscript{16-17} Their slowness to resorb is likely due to their limited porosity and low water solubility. The former feature is undesirable in that it can impede the diffusion of nutrients needed by the cellular inhabitants of the grafting system. As for the latter, several authors have commented on the adverse consequences of having non-resorbed CP particles present in the bone fill.\textsuperscript{16-18} Some of these include the incitement of proinflammatory responses and the disruption of osteoclastic processes that mediate bone remodeling.\textsuperscript{18} Impaired resorptive processes warrant concern since these processes are coupled to the ossification of inorganic osseous matrix by bone-forming osteoblasts.\textsuperscript{19} In their absence physiological bone regeneration would not occur. On a final note, impaired resorptive processes are also problematic since the degradation of alloplastic materials \textit{in situ} is ultimately dependent on their uptake and metabolism by bone-resorbing osteoclasts.\textsuperscript{20-21}

Considering the prognostic complications associated with CP bone grafts, there has been considerable effort devoted to the exploration of alternative synthetic constructs. Recently, there has been a resurgence of interest in the use of calcium
sulfate (CS) for bone grafting. CS bone grafts hold a unique position with respect to other regenerative biomaterials. The raw material from which they are synthesized tends to be inexpensive and relatively abundant. They are also fully biodegradable and can function as a barrier membrane supportive of guided tissue regeneration. The latter feature is noteworthy as it has motivated recent increases in the use of CS by dentists for bone augmentation procedures prior to implant placement. Aside from this, evidence suggests that CS bone grafts are promotive of angiogenesis. Strocchi and colleagues found greater microvascular vessel density in the bone fills of osseous defects in rabbits treated with CS bone grafts versus those treated with autografts. On a different note, some of the most cited disadvantages of CS bone grafts is their rapid resorptive rate and their poor biomechanical strength. This has limited their use primarily to the correction of small non-load bearing osseous defects. This paper reviews the current use of CS in the surgical correction of osseous defects. It also considers recent research into new CS based bone grafting systems that might address some of the limitations associated with conventional CS bone grafts.

**Clinical Applications**

From a historical perspective, reports on the clinic use of CS (Plaster of Paris) for bone grafting date as far back as 1892 where it was used by Dressman of the Trendelenburg clinic to fill osseous defects in patients with tuberculosis osteomyelitis. Further reports exist on its successful use by surgeons during the Vietnam War for filling craniofacial bone defects. In 1980, Coetzee described 110 patients that were treated with CS bone grafts for filling craniofacial bone defects. He found that CS bone grafts ensured complete bone regeneration with results comparable to autografts, if not better. With the progress of time, CS has been used in a wide range of clinical procedures that include osseous augmentation for dental implant placement, orthopedic surgeries, and for the purposes of bone regeneration following oncologic resections. CS can be manipulated into different forms such as hard pellets or an injectable paste that hardens in situ. Compared to autografts, injectable CS bone graft cements have the advantage of not requiring bone resection to accommodate their implantation. Other reasons underlying the attractiveness of CS for bone grafting include its low risk for inducing a proinflammatory response to its established potential to promote osteogenesis. Evidence also shows that CS can be treated with various pharmacologic agents and osteogenic growth factors prior to its placement into wound sites and can effectively release these agents from its inner constructs. For instance, studies indicate that the incorporation of antibiotics into CS can reduce the risk of post implantation infections in patients with chronic osteomyelitis. In addition, CS has been shown to be a suitable carrier of morphogens and growth factors that promote the differentiation of mesenchymal stem cells toward the osteoblast phenotype and enhance the metabolic activity of human osteoblastic cells *in vitro* and *in vivo*. It is beyond the scope of this review to provide a full description of the many studies detailing the
successful surgical application of CS for bone tissue engineering. This discussion is therefore limited to the clinical arenas wherein CS has shown the most success as a grafting material for bone repair. These include dentistry and skeletal tumor surgery.

**Extraction Socket Preservation**

In dentistry, partial or complete resorption of the residual alveolar ridge is an undesirable sequelae of tooth extractions. To this end, multiple studies support the use of CS bone grafts for alveolar ridge preservation. A study conducted by Aimetti et al evaluated the healing of human extraction sockets filled only with CS in patients awaiting maxillary dental implant placement. These authors report that filling the sockets with injectable CS cement effectively reduced alveolar ridge resorption and accelerated bone maturation. The bone regenerative potential of CS bone grafts can be further enhanced by the addition of osteogenic growth factors; a common source of which is platelet-rich plasma (PRP). When lysed, platelets release growth factors capable of stimulating the activity of bone-forming osteoblasts. In this regard, an attractive feature of injectable CS cements is that they undergo an exothermic crystallization reaction upon their implantation in situ. When mixed with PRP, the heat released from this setting reaction is sufficient to induce platelet lysis. A clinical study performed by Kutkut et al examined the amount of bone regeneration in sixteen patients who underwent dental extractions. Eight of the patients received CS mixed with PRP in their extraction sockets, while the other eight received collagen resorbable plugs. At the conclusion of the 3-month study, the sockets of the patients who received CS mixed with PRP demonstrated greater vital bone volume and improved wound healing. More recently, a study by Cheah et al examined alveolar ridge preservation in twelve patients who underwent non-molar extractions followed by placement of either CS alone or CS mixed with PRP in the sockets. After a 4-month healing period, the six patients who had received CS bone grafts mixed with PRP demonstrated greater mineralized bone volume than the six who that received CS bone grafts alone.

**Maxillary Sinus Augmentation**

Another common use of CS bone grafts in dentistry is for maxillary sinus floor augmentation. This surgical procedure is known as a sinus-lift or sinus floor elevation. It is used to increase the vertical dimension of maxillary alveolar bone. The main indication for performing a sinus-lift is when the amount of bone in the posterior maxilla is inadequate to support dental implant placement. Another indication is when the quality of maxillary alveolar bone is prone to compromise the stability of dental implants after their placement. In a longitudinal prospective study conducted by De Leonardis and Pecora, the histologic characteristics of bone formed in situ after sinus augmentation procedures done with CS bone grafts were investigated. Histologic biopsies from the participants were harvested at 6 and 9 months post-operatively. Examination of the specimens revealed that the placement of CS into surgical sites facilitated the formation of vital trabecular bone that was suitable for
accommodating the integration of dental implants. On a side note, residual CS particles were found to be present in radiographs taken at 6-months but not at 9-months. Furthermore, the quality of the bone formed was found to correlate with time elapsed. A study carried out by Dasmah et al evaluated the effectiveness of using CS for augmenting posterior maxillary bone in ten patients with edentulous maxillae. During the first phase of this study, the patients underwent sinus lifts followed by CS bone graft placement. After a 4-month healing period, the authors observed new bone formation with a mean value of 22.1%. In the second phase of the study, 40 dental implants were placed. Of the 40 implants placed, only 1 was lost at the one-year follow-up. The authors concluded that CS bone grafts can be used successfully for osseous augmentation in the endentulous posterior maxilla, promoting the generation of vital bone supportive of dental implant placement.

**Bone Tumor Surgery**

The surgical resection of bone tumors often leaves behind a large contained osseous defect. Emerging evidence suggests that CS bone grafts can be successfully used to repair these defects. In support of this, a study by Gitelis et al reports that CS is an effective alternative to autogenous bone grafts for the surgical correction of osseous defects generated from the curettage of benign bone lesions. Furthermore, Clayer reported that CS bone grafts can be used successfully for the regeneration of bone in osseous defects produced after the excision of aneurismal bone cysts. This author found that defects filled with CS cements showed favorable healing rates and radiological responses with a low incidence of complications. In a later study performed by Kim et al, 56 patients with either benign or low-grade malignant bone tumors underwent surgical curettage. The bony defects produced following the tumor resections were then filled with either injectable CS or allogenic demineralized bone matrix (DBM). The radiographic results of the study showed that bone regeneration in defects filled injectable CS was comparable to those filled with DBM. However, the mean healing time of patients who received injectable CS tended to be more delayed versus those who received DBM.

**Clinical Drawbacks**

As mentioned, the most cited limitations to the clinical application of CS bone grafts are their rapid resorptive rate and lack of biomechanical strength. The rapidity of their biodegradation profile relative to CP-based bone grafts can be attributed to the greater solubility of CS in physiological body fluids. This warrants attention in clinical cases where bone healing might be compromised or delayed, such as in elderly patients or those who are immunocompromised. To this end, Jepeganam and von Schroeder reported on early implant failure in the cases of 2 elderly patients who received CS bone grafts for the management of malunited distal radius fractures. CS bone grafts have been further criticized for having a resorptive rate that is higher than new bone growth. In this regard, Glazer et al found that CS bone grafts resorbed too quickly to support spinal fusion in a rabbit model.
The lower biomechanical strength of CS versus CP-based bone grafts can be attributed to the greater porosity of their crystalline architectures in situ. Moreover, the hardening of CS cements in situ is often accompanied by volumetric expansion, thereby contributing to the generation of a scaffold substructure with a lesser material density than would be the case otherwise. These features have limited the use of CS primarily to the filling of small non-load bearing osseous defects. On a final note, some studies could not find evidence supportive of the purported intrinsic osteogenic potential of CS bone grafts. Shaffer and App used CS to fill periodontal defects in a small number of patients. In postoperative radiographs taken at 6-months, these authors observed complete resorption of the graft without any indication of new bone formation.

Future Directions

Although the results of selective studies do not advocate the use of CS bone grafts in skeletal reconstructive surgery, reports published within the past year provide evidence to the contrary. For instance, Tamboowalla et al retrospectively assessed the clinical outcomes in patients that received antibiotic impregnated CS bone grafts for the treatment of either osteomyelitis or non-union long bone fractures. At a 1-year postoperative follow-up, this group found that 9 of the 10 patients with osteomyelitis demonstrated good radiographic healing of the osseous defects and complete resolution of infection. With respect to the patients being treated for nonunion long bone fractures, most demonstrated evidence of union at an average of 3.75 months after surgery.

CS bone graft composites

Some studies have provided insight into ways in which CS bone grafting systems can be modified to enhance their bone regenerative potential. Tan et al retrospectively reviewed the clinical outcomes of 25 patients who underwent treatment with CS/CP bone graft composites following bone tumor resection. These authors found that CS/CP bone grafts exhibit a characteristic resorption rate and demonstrate a familiar radiographic pattern of graft dissolution in combination with new bone ingrowth. In this regard, knowledge of the radiographic appearance of CS bone grafts and their changing appearance over time owing to their resorption can allow clinicians to discriminate between the dissolution of the graft in situ versus tumor recurrence.

When comparing CS to synthetic HA bone grafts, the consensus seems to be that CS grafts have greater osteogenic potential and HA grafts provide longer-term space-maintenance in lieu of their slower resorption rates in situ. Crespi et al assessed the amount of bone formed in tooth extraction sockets filled with either CS or magnesium-enriched HA grafts (MHA) at 3-months. Their research group used a split mouth design that involved 15 patients who required the extraction of three teeth on each side of the jaw. Extraction sockets on one side were filled with CS and those on the other were filled with MHA grafts. The results of this study revealed that sockets filled with CS demonstrated a greater reduction in the
vertical bone height of the alveolar ridge versus those filled with MHA grafts. On the other hand, histologic examination indicated more bone formation and faster graft resorption in the CS group and more residual graft material in the MHA group. To these ends, some studies have focused on developing bone grafting systems that combine the osteogenic potentiating effects of CS bone grafts with the slower resorption times of synthetic HA grafts.²³-²⁴

At present, there is increasing attention being given to slowing the biodegradation rate of CS in situ by the addition of synthetic HA to the bone graft material. Hence, the bone graft is comprised of a combination of both CS and synthetic HA. Recent findings suggest that composite CS/HA bone grafts have slower resorption rates versus CS bone grafts, thereby imparting them with a longer-term space-maintaining ability.²³-²⁴ With respect to the issue of having residual HA present in the bone fill, one research group evaluated the percentage of HA particles present in the bone fill of dental defects treated with CA/HA composite grafts. Analysis at 8 months revealed that HA residual graft particles constituted only 3% of the bone fill. A recent review by Barnes and Kurtzman discusses the successful use of a CS/HA composite graft product called Bond Apatite for the dental treatment of osseous defects in 454 clinical cases.²³ These included defects associated with extraction sockets, periodontal lesions, and infected apices of tooth roots. Of those, a failure rate of less than 2% was noted.

**Nanocrystalline CS**

Because large-scale osseous defects often require lengthy recovery times, grafting materials with slower resorption rates and higher compressive strengths are most suitable for their treatment. In a study by Hu et al, the authors studied the effect of particle size on the biophysical properties of CS bone grafts.⁶⁴ This group found that grafts comprised of smaller sized CS particles demonstrated increased compressive strength and a slower in vitro degradation rate. In this regard, various nano-sized bone grafting materials have received FDA approval in the past decade for osseous corrective surgeries.⁶⁵ Several groups have commented on the advantages of nanomaterials compared to conventional-sized bulky constructs.⁶⁶-⁶⁷ Examples include superior mechanical strength, exponentially higher surface area, increased porosity, and a biodegradation rate that is commensurate with new bone growth. Slower resorption rates are desirable as more time is allotted for cell proliferation and bone remodeling to occur. This feature among others are suggested to permit osteoconduction to occur at deeper levels within the three-dimensional architecture of the scaffolding system, thus leading to improved bone formation.⁶⁵

An ideal nanomaterial for bone grafting should be capable of releasing growth factors or drug content in a controlled fashion, thereby keeping it localized to the wound site.⁶⁹-⁷⁰ In this regard, the following properties of nanomaterials deserve additional comment: exponentially increased surface area and nanoporous architectures. An increased surface area provides more space for growth factor adsorption and
therefore increases the amount of biologic agent available for delivery. A nanoporous architecture, on the other hand, can effectively slow the outward diffusion of pre-loaded growth factor content from its inner constructs.\textsuperscript{71} Timeframe of release is a critical parameter because different growth factors have characteristic half-lives that effectively dictate the duration of time in which they remain biologically active.

Recent translational studies provide evidence supportive of the clinical use of nanocrystalline CS (nCS) for the reconstruction of osseous defects.\textsuperscript{72-77} Compared to CS, nCS offers many advantages. These include superior mechanical strength, increased resistance to fracture, higher surface area, and a slower resorptive rate. Moreover, unlike conventional sized CS, nCS can release growth factors and various pharmacologic in a sustained fashion overtime, thereby keeping these therapeutic agents confined to wound sites and preventing their diffusion outward. Accumulating evidence indicates that nCS is virtually non-toxic and may represent a functional vehicle for the delivery of osteogenic factors, such as platelet-derived growth factor (PDGF-BB) and melatonin.\textsuperscript{74, 77} In an \textit{in vitro} study conducted by Barone et al, the cellular viability of mesenchymal stem cells and human osteoblastic cells cultured on solid discs fabricated from nCS mixed with human platelet lysate (hPL) were measured.\textsuperscript{74} The authors found that both cell types demonstrated increased metabolic activity when cultured on nCS/hPL discs versus nCS discs alone. In a study using a rat model, nCS scaffolds containing PRP and BMP-2 modified mesenchymal stem cells were shown to successfully promote bone regeneration in critical-sized cranial vault defects.\textsuperscript{75} Additional evidence of the bone regenerative ability of nCS was observed in a preclinical critical size canine mandibular bone defect model in which nCS filled sites displayed significantly greater bone yield in comparison to unfilled control sites.\textsuperscript{78} Based on these findings, there is a strong basis for further development of nCS as a clinical regenerative therapeutic.

**Conclusion**

Based on a long history of published research and clinical reports, there appears to be distinct advantages of the use of CS in bone augmentation procedures, particularly in dentistry as well as bone tumor surgical procedures. Safety and efficacy has been consistently demonstrated and clinically experienced. These studies, reviewed here, also provide some insight into the need for further investigations to improve on the physical properties of CS to optimize bone fill with the use of nanosizing the material and to fabricate composites with other materials to enhance the bone augmentation properties of CS.
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