



# Ceramic Biologics for Bony Fusion—a Journey from First to Third Generations

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## Abstract

**Purpose of Review** To provide information on characteristics and use of various ceramics in spine fusion and future directions.

**Recent Findings** In most recent years, focus has been shifted to the use of ceramics in minimally invasive surgeries or implementation of nanostructured surface modification features to promote osteoinductive properties. In addition, effort has been placed on the development of bioactive synthetics. Core characteristic of bioactive synthetics is that they undergo change to simulate a beneficial response within the bone. This change is based on chemical reaction and various chemical elements present in the bioactive ceramics. Recently, a synthetic 15-amino acid polypeptide bound to an anorganic bone material which mimics the cell-binding domain of type-I collagen opened a possibility for osteogenic and osteoinductive roles of this hybrid graft material.

**Summary** Ceramics have been present in the spine fusion arena for several decades; however, their use has been limited. The major obstacle in published literature is small sample size resulting in low evidence and a potential for bias. In addition, different physical and chemical properties of various ceramics further contribute to the limited evidence. Although ceramics have several disadvantages, they still hold a great promise as a value-based graft material with being easily available, relatively inexpensive, and non-immunogenic.

**Keywords** Ceramics · Synthetics · Hydroxyapatite · Beta-tricalcium phosphate · Bioactive · Spine fusion

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## Introduction

The incidence of spinal fusion has been steadily increasing over the past couple of decades [1, 2]. Over the last 18 years, the annual mean for spinal fusion procedures performed in the USA was 317,534 [2]. It has been well established in the spine literature that the gold standard for achieving arthrodesis is iliac crest bone graft (ICBG). However, potential complications including donor site morbidity, increased operative time and blood loss, increased length of stay, and limited supply have been reported [3]. As a result, there has been a growing trend in the use of bone graft substitutes and bone graft extenders in an effort to mitigate these risks. Although there are various graft substitutes, none of them has all three characteristics of ICBG: being osteoconductive, osteogenic, and osteoinductive.

Ceramics are a class of bone graft substitutes that provide osteoconductive properties without any osteogenic or osteoinductive potential [4, 5]. Examples of the most

commonly used ceramics include hydroxyapatite (HA), beta-tricalcium phosphate ( $\beta$ -TCP), calcium phosphate (CaP), calcium sulfate, and bioactive synthetics such as silicate-substituted calcium phosphate (Si-CaP) and bioglass (BAG). In newer generation of ceramics, bioactive synthetics go beyond osteoconductive role, and they have osteopductive characteristics which promote cell stimulation towards osteogenesis and growth factor production. Ceramics are an attractive alternative given that they are an inert substance that is non-toxic, non-immunogenic, and without risk of infection. They are fully customizable, easily stored, and available in virtually unlimited supply. Lastly, when compared with other graft materials, they are also a less expensive option [6]. The main disadvantage is the inherent lack of mechanical strength (Fig. 1). Ceramics are brittle with low fracture resistance and tensile strength [7]. Therefore, they are commonly protected until bone ingrowth has occurred.

The purpose of this review was to describe evolution of various ceramics and their use in spine fusion.

### Hydroxyapatite

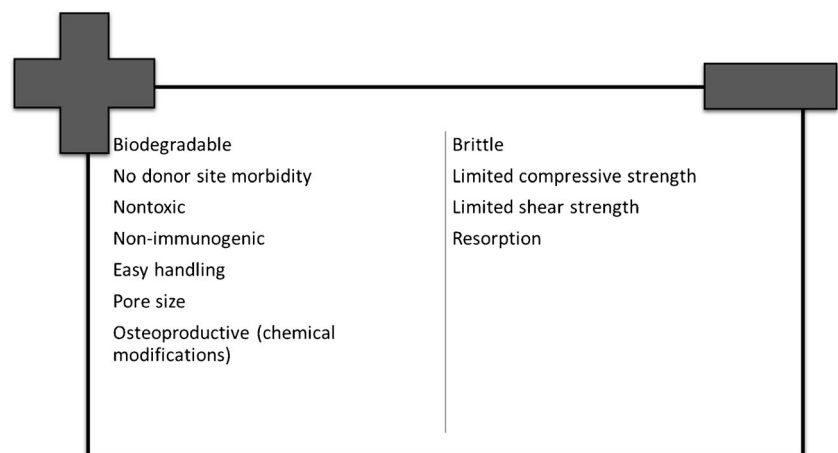
Hydroxyapatite (HA) is one of the most commonly used ceramic in orthopedics. HA is a crystalline structure composed of calcium phosphate and is a major component of the inorganic bone matrix. HA functions as an osteoconductive matrix without any osteogenic cells or osteoinductive potential. HA shares many of the advantages as other types of ceramics, such as being an inert substance that is easy to sterilize and readily available as an off the shelf product. However, one of the main disadvantages is its inherent lack of strength. Therefore, HA is rarely used as a stand-alone bone substitute and must be augmented with instrumented fusion to allow for its incorporation within the surrounding bone. Multiple studies have demonstrated its clinical effectiveness in both the cervical and lumbar spine.

In a prospective randomized controlled trial (RCT) by Korovessis et al., 60 patients with degenerative lumbar stenosis undergoing posterior lumbar fusion (PLF) were divided into three groups: autologous iliac crest bone graft (ICBG) bilaterally, ICBG on one side and HA + local bone (LB) + bone marrow (BM) on the contralateral side, or HA + LB + BM bilaterally [8•]. All three groups, regardless of graft used, progressed to fusion based on radiographs and CT scans performed at 12 months postoperatively. Authors noted incomplete fusion between transverse processes, which they attributed to the progressive resorption of HA that began at the 6-month time point. This, however, had no effect on the overall fusion rate or functional outcomes.

Similarly, HA has also been used to achieve high fusion rates in the cervical spine. Yoshi et al. performed a prospective study evaluating patents who underwent anterior cervical discectomy and fusion (ACDF) with either HA + percutaneously harvested ICBG vs tricortical ICBG alone [9]. They found that at 2-year follow-up, there were no significant differences in recovery rates, fusion rates, or sagittal alignment.

In addition to augmenting fusion rates, HA has also been used as a bone graft extender. Multiple studies have demonstrated that HA can be used a bone graft extender to address some of the drawbacks with ICBG harvest, while at the same time achieving comparable fusion rates to the gold standard [10–12]. Yoo et al. evaluated 88 patients undergoing minimally invasive transformational lumbar interbody fusion (MI-TLIF) [13]. Patients were divided into three groups: group I autograft, group II HA + autograft (> 50%), and group III HA + autograft (< 50%). Fusion rates at 2 years postoperatively increased as the amount of autograft increased (90.9%, 87.8%, and 85.7% for groups I–III respectively); however, there was no statistical significant difference between the groups showing the value of ceramic graft extenders.

**Fig. 1** Pros and cons of ceramics—first to third generations



## Beta-Tricalcium Phosphate

Another commonly used ceramic is  $\beta$ -TCP.  $\beta$ -TCP is a synthetic bone graft substitute similar to normal bone [14]. It is composed of 39% calcium and 20% phosphate [5].  $\beta$ -TCP shares the same osteoconductive properties of other ceramics, enabling it to function as an effective carrier for both cells and growth factors. When compared with other ceramics such as hydroxyapatite (HA),  $\beta$ -TCP has a higher porosity and therefore resorbs at a much faster rate, typically within 6 weeks [15]. Despite this limitation, multiple studies have used it successfully as a bone graft substitute as well as a bone graft extender.

Dai et al. conducted a prospective randomized control trial (RCT) evaluating fusion rates in patients undergoing instrumented PLF for degenerative lumbar spinal stenosis treated with either  $\beta$ -TCP combined with local autograft or ICBG [16]. Out of the 62 patients included in this study, all 32 patients in  $\beta$ -TCP group and 30 patients in ICBG group demonstrated evidence of radiographic fusion within the 3-year follow-up period. Authors found no significant difference in fusion rates or functional outcome scores between groups at the time of final follow-up. Gan et al. used  $\beta$ -TCP combined with autologous enriched mesenchymal stem cells (MSCs) in 41 patients undergoing posterior spinal fusion (PSF) [17]. At 34.5 months, 95.1% of patients had a successful fusion based on radiographic and clinic assessment. Authors attributed the success of this composite graft to the osteogenic and osteoinductive properties of MSCs that when combined with an osteoconductive scaffold, such as  $\beta$ -TCP, allows for the ingrowth of cells and blood vessels. A systematic review by Nickoli et al. found 30 studies that used ceramics as a bone graft extender in patients undergoing PLF [11]. They found that the fusion rate for  $\beta$ -TCP was 92.5% (319 patients out of 349). This was significantly higher than the fusion rate for all ceramic-based bone grafts, which was 86.4%.

More recently, there have been number of studies that have evaluated the use of  $\beta$ -TCP with newer minimally invasive surgery (MIS) techniques. A retrospective review by Abassi et al. used  $\beta$ -TCP with autologous bone marrow aspirate (BMA) in 24 patients undergoing oblique lateral lumbar interbody fusion (OLLIF) [18]. After discectomy was performed, authors packed all available disc space with  $\beta$ -TCP and BMA. Fusion was confirmed radiographically by two independent observers in all 24 patients at the 1-year follow-up visit.

Efforts have been made to create composite ceramic grafts, often a combination of  $\beta$ -TCP and HA, in an attempt to maximize fusion rates. Multiple studies have used them as standalone bone substitutes as well as bone graft extenders. Parker et al. compared the use of AttraX (95%  $\beta$ -TCP + 5% HA) with rhBMP-2 in 135 patients undergoing extreme lateral interbody fusion (XLIF). Fusion rate at the 2-year postoperative visit was 80% for  $\beta$ -TCP group compared with 96% for rhBMP-2 group [19]. However, this difference was only

significant when  $\beta$ -TCP was used as a standalone graft. No difference in fusion rate was seen when both groups were supplemented by instrumented fusion. Conversely, Malham et al. used Mastergraft (85%  $\beta$ -TCP + 15% HA) as a bone graft extender by combining it with rhBMP-2 in patients undergoing XLIF [20]. Supplemental fixation was used to avoid subsidence, maintain stability, or correct any deformities. Authors reported a fusion rate of 95.2% for standalone group vs 80% for supplemental fixation group at 1-year follow-up.

## Calcium Sulfate

Calcium sulfate has long been used as a bone substitute, particularly in orthopedic trauma, and has been praised for its availability, low-cost, and osteoconductive properties [21]. The crystalline structure of calcium sulfate is similar to that of cancellous bone, providing architecture for the introduction of capillaries and mesenchymal stem cells [22]. The lack of osteoinductive or osteogenic properties, as well as quick resorption time (1–3 months), hinders the use of calcium sulfate as a standalone graft and mandates the use of additional substances such as demineralized bone matrix or local allograft for maximized effect [21, 23].

Owing to the traditional use of calcium sulfate in trauma, a handful of recent studies have shown that pedicle screw fixation is improved with calcium sulfate augmentation in unstable thoracolumbar burst fractures [24–26]. Calcium sulfate injections have also been shown in sheep models to reduce fracture risk in osteoporotic vertebral bodies [27].

Previous reviews have demonstrated similar results between calcium sulfate and autologous graft for lumbar fusion across multiple studies [23]. However, more recent clinical investigations of calcium sulfate for spinal fusion are limited. In a prospective study of 68 patients with cervical degenerative disc disease being treated with one- or two-level discectomy, Xie et al. showed comparable results between polyether-ether-ketone (PEEK) interbody cages with calcium sulfate/demineralized bone matrix (CS/DBM) and those with autogenous iliac cancellous bone [28]. At 12-month follow-up, the CS/DBM group showed 94.3% fusion compared with 100% in the ICBG group. Both groups had 100% fusion at final follow-up (24 months). No significant difference was found in follow-up clinical symptom score or lordotic angle between the two groups. The complication rate for the ICBG group (18.2%) was significantly higher than the CS/DBM group (8.6%) [28].

## PMMA

Polymethylmethacrylate (PMMA) has been a staple of orthopedic surgery for years. Traditionally utilized as a cement in total joint replacement, PMMA was subsequently expanded into uses such as vertebroplasty and kyphoplasty. The methylmethacrylate monomer is capable of polymerizing at room temperature, is

low-cost, and has good biocompatibility, although it is bioinert and thus has minimal bone remodeling capacity [29, 30].

Studies comparing PMMA against other materials for use in cages for anterior cervical fusion have yielded variable results. A review by Noordhoek et al. compared PEEK cages, titanium cages, cage-screw-combinations (CSC), and PMMA cages. Of the seventy-one studies included, only 6 looked at PMMA, but a significantly higher incidence of subsidence occurred in PMMA vs PEEK or CSC (30.2% vs 23.5% and 15.1%) [31]. A recent single-blind randomized controlled study by Farrokhi et al. comparing PEEK cage with a novel PMMA cage enrolled 64 patients that were randomly assigned to undergo ACDF using either the acrylic cage ( $n = 32$ ) or PEEK cage ( $n = 32$ ). At 12-month follow-up, there was a statistically significant difference in the disc space height between acrylic and PEEK ( $5 \pm 0.9$  mm and  $4.25 \pm 1$  mm, respectively), as well as intervertebral angle correction ( $3.38 \pm 1.9$  and  $3.16 \pm$  degrees, respectively) [32].

Recently, PMMA has been utilized for pedicle screw augmentation to increase pull-out strength and resistance to failure in osteoporotic patients [33]. Low-quality bone has increased risk for implant failure, and while a number of techniques have been assessed to improve fixation in these patients, PMMA-augmented screws have demonstrated to be most successful [34]. Four retrospective studies (ranging from 28 to 313 osteoporotic patients) examined the safety and efficacy of lumbar fusion using cement injectable cannulated pedicle screws (CICPS) [34–37]. Three studies utilized Visual Analog Scale and Oswestry Disability Index to assess efficacy and showed statistically significant decreases in low back and lower leg pain [35–37]. They also examined complications and found leakage rates between 6.46 and 10.3%, with all cases of leakage being clinically insignificant. The fourth retrospective study, by Martín-Fernández et al., was the largest (313 patients) and showed a leakage rate of 62.3%, none of which showed major clinical complications [34]. The same study found a revision rate of 17.9%, mostly in patients with  $> 4$  level reconstruction.

A prospective study by Cao et al. prospectively compared unilateral transforaminal lumbar interbody fusion using traditional pedicle screws and PMMA-augmented screws in osteoporotic patients [38]. The fusion rate with PMMA was significantly higher (91.3% vs 79.2%), and at 2-year follow-up, there was a significant difference in disc height in the PMMA group vs non-PMMA ( $10.7 \pm 1.6$  mm vs  $8.7 \pm 2.3$  mm).

### Bioactive Synthetics: Si-CaP and Bioactive Glass

Silicate-substituted calcium phosphate (Si-CaP) is a new generation of ceramics formed by a partial substitution of phosphate with silicate (usually around 0.8% by weight) [39]. Silicate has been shown to have a role in bone metabolism and can upregulate osteoblast proliferation and differentiation, promote osteoinductive gene expression, and increase type I

collagen synthesis [40, 41]. Adding silicate to the ceramic increases negative surface charge leading to increased osteoblast attraction to the surface of the material and additionally induces porosity, making it an osteoinductive material [42]. Wheeler et al. compared Si-CaP to iliac crest autograft and found fusion mass to be higher with Si-CaP, while bony bridging was equivalent when compared with autograft treatment [40]. A study by Jenis et al. showed a fusion rate of 76.5% at 24 months of follow-up following posterolateral lumbar fusion [43]. In two separate studies, Alimi and et al. found fusion rates of 90% and 82.9% following spinal fusion (cervical, thoracic, and lumbar procedures included) [39, 44]. Licina et al. compared Si-CaP with rhBMP-2, and fusion was observed in 9/9 and 8/9 patients, respectively, following posterolateral lumbar fusion with similar alleviation of pain and improvement in quality of life [45]. A prospective study by Pimenta et al. compared Si-CaP with rhBMP-2 bone graft [46]. Pimenta et al. reported complete fusion with both graft materials with rhBMP-2 resulting in more rapid early postoperative fusion following XLIF. More recently, Mokawem et al. found a combined fusion rate of 98.9% following TLIF and LLIF using SiCaP-packed 3D-printed lamellar titanium cages, while Bolger et al. found the use of Si-CaP to have a fusion rate of 86.3% at 12 months following PLF surgery [47, 48]. Additionally, Lerner et al. found Si-CaP augmented with BMA to be an effective and safe bone graft extender in scoliosis surgery [49].

Bioactive glass is an osteoconductive bone substitute that is composed of 46.1 mol% SiO<sub>2</sub>, 24.4 mol% Na<sub>2</sub>O, 26.9 mol% CaO and 2.6 mol% P<sub>2</sub>O<sub>5</sub> (45S5 bioactive glass) [50]. Bioactive glass bonds strongly to bone due to the formation of an HCA layer which interacts with collagen fibrils of damaged bone [50]. Once this HCA layer is formed, dissolution of calcium and silica ions stimulates attachment of osteoblasts, cell division, and up-regulation of osteogenic genes that is dose dependent to ion release [51, 52]. Early animal model studies found bioactive glass to induce either comparable rates of fusion or higher volumes of fusion mass than autograft [53–55]. Ilharberborde et al. conducted a comparative study of bioglass vs iliac crest autograft for spinal fusion in adolescent idiopathic scoliosis and found complete fusion with both graft materials in 88 patients [56]. A study by Frantzen et al. found a higher fusion rates with bioglass with a higher silica content than 45S5 BAG (53.9 vs 46.1 mol% for 45S5) in patients undergoing L4/5 and L5/S1 spinal fusion for spondylolisthesis [57]. A recent study by Barrey et al. assessed 30 patients with a wide range of degenerative and traumatic conditions of the cervical or lumbar spine who underwent spinal fusion with bioactive glass and found an overall fusion rate of 93% at 1-year postop [58].

### P-15

Recently, P-15, a synthetic 15-amino acid polypeptide that mimics the cell-binding domain of type-I collagen, has emerged



as a bone graft alternative in the setting of spinal fusion. Serving as an attachment site for osteogenic cells to type I collagen, P-15 also stimulates osteoblastogenesis by promoting the differentiation of bone marrow stromal cells to osteoblasts. Furthermore, it enhances the cellular production and subsequent secretion of various growth factors, cytokines, and bone morphogenetic proteins that signal for further osteoblastogenesis [59, 60]. i-Factor Bone Graft (Cerapedics, Inc., Westminster, CO) is a bone graft substitute which consists of P-15 bound to an anorganic bone material (ABM); it therefore contains both osteoconductive and osteoinductive properties. To date, favorable fusion rates with use of P-15 have been demonstrated in a limited number of clinical studies in the setting of cervical fusion [61, 62].

In a single-blinded randomized controlled IDE trial, Arnold et al. demonstrated non-inferiority of i-Factor when compared with local autograft bone in the setting of single-level ACDF utilizing a cortical ring allograft. At 12-month follow-up, fusion rates with use of i-Factor were comparable to that of autograft (88.97% compared with 85.82%, respectively;  $P = 0.0004$ ) with no significant differences in adverse events or patient reported clinical outcomes between the two groups [61]. In the 2-year follow-up study, overall fusion rates had improved with no significant differences between groups (94.87% vs 93.79% in autograft group;  $P = 0.2513$ ). However, use of i-Factor was associated with overall improved clinical outcomes when utilizing study defined endpoints of success (fusion, Neck Disability Index > 15, neurological success, and absence of reoperations; 69.83% in the i-Factor group vs 56.35% in the autograft group;  $P = 0.0302$ ) [62].

In the setting of lumbar fusion surgery, preliminary animal studies have additionally shown P-15 to be a useful fusion adjunct [59, 63]. While high-quality clinical data is limited, in their series of 110 patients who underwent either single or multi-level ALIF utilizing ABM/P-15, Mobb et al. demonstrated high fusion rates (97.5%, 81%, and 100% in single-level, two-level, three-level fusions, respectively) and favorable patient-reported outcome measures at 2-year follow-up [64].

While P-15 may prove to be a useful adjunct in the setting of spinal fusions, additional high-quality and independently conducted clinical studies are warranted to further delineate its clinical utility.

## Conclusions

Ceramics have been present in the spine fusion arena for several decades; however, their use has been limited. The major obstacles in published literature are small sample size and different physical and chemical properties resulting in low evidence and a potential risk for bias. Although non-inferiority with the use of ceramics as a bone graft extender when compared with ICBG

has been demonstrated, many published studies were not adequately powered to show a significant difference. Even with limitations ceramics hold a promise as a value-based graft material being easily available, relatively inexpensive, and non-immunogenic. Chemical modifications and addition of various elements have a potential to not only enhance cell differentiation and growth factor production but also stimulate vascularization and help prevention of surgical site infection. In patients with risk factors such as osteoporosis, bioactive synthetics can play an important role with addition of strontium which has a potential of inhibiting osteoclast activity. Finally, cost is one of the key variables when it comes to spine conditions and their treatments. Studies have shown that ceramics are less expensive than other graft materials [65]. Well-designed prospective studies on new ceramics and hybrids are warranted to solidify the clinical impact and utility in various spine fusion procedures.

## Compliance with Ethical Standards

**Conflict of Interest** No conflicts of interest for the current study. Disclosures outside of submitted work: Brandon Ortega, Carson Gardner, Sidney Roberts, and Andrew Chung have no disclosures. Jeffrey Wang: royalties—Biomet, Seaspine, Amedica, DePuy Synthes; investments/options—Bone Biologics, PearlDiver, Electrocore, Surgitech; board of directors—North American Spine Society, AO Foundation (20,000 honorariums for board position, plus travel for board meetings), Cervical Spine Research Society; editorial boards—Spine, the Spine Journal, Clinical Spine Surgery, Global Spine Journal; fellowship funding (paid directly to institution)—AO Foundation. Zorica Buser: consultancy—Cerapedics, The Scripps Research Institute, Xenco Medical (past), AO Spine (past); research support—SeaSpine (past, paid to the institution), Next Science (paid directly to institution), Motion Metrics (paid directly to institution); North American Spine Society—committee member; Lumbar Spine Society—co-chair research committee; AOSpine Knowledge Forum Degenerative—associate member; AOSNA Research Committee—committee member.

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