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## Clinical application of ceramics in anterior cervical discectomy and fusion: A review and update

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# Clinical Application of Ceramics in Anterior Cervical Discectomy and Fusion: A Review and Update

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## Abstract

**Study Design:** Narrative review.

**Objectives:** Anterior cervical discectomy and fusion (ACDF) is a reliable procedure, commonly used for cervical degenerative disc disease. For interbody fusions, autograft was the gold standard for decades; however, limited availability and donor site morbidities have led to a constant search for new materials. Clinically, it has been shown that calcium phosphate ceramics, including hydroxyapatite (HA) and tricalcium phosphate (TCP), are effective as osteoconductive materials and bone grafts. In this review, we present the current findings regarding the use of ceramics in ACDF.

**Methods:** A review of the relevant literature examining the clinical use of ceramics in anterior cervical discectomy and fusion procedures was conducted using PubMed, OVID and Cochrane.

**Result:** HA, coralline HA, sandwiched HA, TCP, and biphasic calcium phosphate ceramics were used in combination with osteoinductive materials such as bone marrow aspirate and various cages composed of poly-ether-ether-ketone (PEEK), fiber carbon, and titanium. Stand-alone ceramic spacers have been associated with fracture and cracks. Metallic cages such as titanium endure the risk of subsidence and migration. PEEK cages in combination with ceramics were shown to be a suitable substitute for autograft.

**Conclusion:** None of the discussed options has demonstrated clear superiority over others, although direct comparisons are often difficult due to discrepancies in data collection and study methodologies. Future randomized clinical trials are warranted before definitive conclusions can be drawn.

## Keywords

ceramics, discectomy, hydroxyapatites, intervertebral disc degeneration, tricalcium phosphate

## Introduction

Anterior cervical discectomy and fusion (ACDF) is a reliable and well-accepted procedure, commonly used for cervical degenerative disc disease. Since its introduction in the 1950s by Smith and Robinson,<sup>1</sup> and later by Cloward,<sup>2</sup> different graft materials including autograft, allograft and bone substitute have been used for the fusion. For decades, autograft (mostly harvested from the iliac crest) was the most commonly used material and the gold standard, owing to high fusion rate, good biocompatibility, and nonimmunogenicity.<sup>3,4</sup> However, limited availability and donor site morbidities such as

pain, hematoma, infection, fracture, visceral herniation and meralgia paresthetica, as well as increased blood loss and operation time, have prompted surgeons to pursue new

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alternatives.<sup>5-9</sup> Allograft (mostly freeze-dried graft made from cadaveric bone) and xenograft (animal allograft) have been used with satisfactory results, although pseudarthrosis, immune-compatibility issues, and risk of infection with transmissible diseases remained concerning.<sup>10</sup>

Another alternative is development of synthetic bone graft substitutes such as ceramics, poly-methyl-methacrylate (PMMA) and biocompatible osteoconductive polymer (BOP).<sup>3</sup> Ceramics are crystalline structures of mineral salts produced at high temperature with various structural and physiological properties related to different processing methods. The calcium phosphate ceramics, including hydroxyapatite (HA) and tricalcium phosphate (TCP), are the most investigated bone substitutes and have been used for nearly 30 years in dental and reconstructive surgeries.<sup>11-17</sup> Both HA and TCP are fragile materials, although various preparation methods can yield a variety of compositions ranging from amorphous porous to densely crystallized, which consequently vary in compression strength and other properties.<sup>17,18</sup> The porous structure resembles that of cancellous bone, which enhances the ingrowth of host bone, while higher density and crystallization produce a greater mechanical strength.<sup>17</sup> Of the fundamental properties of a bone graft (osteoconduction, osteoinduction, and osteogenesis), ceramics provide osteoconduction, while the autograft is osteoconductive, osteoinductive, and osteogenic, due to numerous surviving bone marrow cells.<sup>16,19,20</sup> Although there have been a growing number of clinical studies investigating the application of ceramics in ACDF during the past few years, the superiority of ceramic materials over autograft is not definitive. The purpose of this article is to review the clinical evidence on application of ceramics in ACDF and to highlight the current state of the art.

## Hydroxyapatite

HA [ $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ] is a hydroxyl compound of calcium phosphate and is the main component of natural mineralized bone. The synthetic form is highly crystalline, produced through a high-temperature reaction and is similar to the natural HA chemically and crystallographically. Such chemical similarity to natural bone and the subsequent biocompatibility and osteoconductivity is the exceptional property of HA.<sup>19,21</sup> Formation of direct chemical bonding between the bone and HA has been demonstrated by electron microscopy.<sup>22</sup> Also, the newly formed bone at the surface of the ceramic was similar to normal bone, confirming the osteoconductivity of HA.<sup>22</sup> Unlike autograft, allograft and TCP, the absorption rate of HA is very low and with progression of the osteoconduction, the newly produced bone encompasses the implant. Even though the implant eventually fuses with the adjacent vertebrae without absorption, it generally does not provoke foreign body reaction.<sup>22,23</sup> However, there is limited evidence of foreign body reaction to the HA implants in cervical discectomy.<sup>24,25</sup>

Since the first clinical use of HA in ACDF by Koyama and Handa<sup>26</sup> in 1986, its utility has been evaluated in many studies. In general clinical results were promising, demonstrating that the graft was generally stable and formation of bridging

bone was observed without noticeable inflammatory reactions.<sup>8,9,27-29</sup> Senter et al<sup>8</sup> used synthetic, dense, non-resorptive HA spacers on 84 patients (Supplemental Table S1). In their study, although the HA spacer was similar to iliac crest autograft in terms of symptom relief, spinal alignment and stability, superiority was demonstrated in terms of long-term relief of symptoms, lower need for reoperation and the absence of resorption with subsequent collapsed disc space.<sup>8</sup> Kim et al<sup>9</sup> used a 30% porous HA spacer with convex top and bottom surfaces and a double pore structure (smaller pores of 2-5  $\mu\text{m}$  and larger pores 200-500  $\mu\text{m}$  in diameter). They reported equivalent improvements in neurological status, 100% graft stability, formation of bridging bone 1 to 2 years after surgery, no collapse of the vertebral body, and preserved normal cervical lordosis in most cases.<sup>9</sup> In another study the same authors used a rectangular HA spacer with a threaded design combined with rigid anterior cervical spine plating. Complete fusion was achieved in all cases and no graft extrusion, deterioration, subsidence, or fracture was observed. Improvements in clinical outcomes, formation of bridging bone on the surface of the grafts in all patients, and preserved intervertebral space were reported.<sup>27</sup> Suetsuna et al<sup>28</sup> used an open-pore structure HA implant (100-500  $\mu\text{m}$ ), with 40% to 45% porosity in 36 patients. This open-pore structure preserves the continuity between pores, which is conducive to tissue ingrowth and enhances the access of living cellular constituents into the implant; therefore, it is postulated that open-porosity improves the regeneration processes.<sup>30,31</sup> The authors found that the radiographic results were not inferior to those of the same procedure using autologous bone graft and no collapse or displacement was observed.<sup>28</sup> HA grafts with plate fixation were used by Bruneau et al<sup>32</sup> in 54 patients and demonstrated satisfactory clinical and radiological results with 99% fusion rate after a mean follow-up of 14.9 months. In their series, no pseudarthrosis or dislocation was detected. There was graft collapse or fracture in 4 of 68 fused levels which had no effect on the fusion or clinical outcome.<sup>32</sup> In the study by Vukić et al,<sup>29</sup> HA graft was used in 86 patients with or without plating. The clinical outcome was good or excellent in 94% of patients with radiculopathy, while it was less favorable in myelopathic patients, of whom 54% had poor or fair results. No graft collapse was detected and newly formed bone deposits, which could enlarge over time and make a complete bony bridge between the 2 endplates, were seen behind the graft in all patients. However, 1-year fusion rates did not reach 100% (86% for 2-level discectomy, 81% for 3-level discectomy, and 70% for 4-level discectomy). There were 8 graft fractures which did not require surgery and 2 graft extrusions, which occurred in noninstrumented patients and required revision surgery.<sup>29</sup>

Although greater porosity of the HA enhances the osteoconductivity and bony ingrowth, it is associated with more fragility and fracture.<sup>33</sup> To overcome this, Yoshii et al<sup>34</sup> designed a new synthetic HA block with a dense layer at the center for load bearing covered by a porous layer, with 40% porosity and 100- to 300- $\mu\text{m}$  pores. To enhance osteoinduction and osteogenesis,

the composite HA with small cancellous bone chips (trephine bone) was used. Fifty-one patients underwent ACDF and anterior plating. Fusion rates and preservation of the cervical lordosis at 2-year follow-up were comparable in the HA and the iliac crest autograft groups. No major collapse or fragmentation of the HA graft occurred.<sup>34</sup>

ACDF with HA and metallic cages such as titanium has been used based on satisfactory long-term outcomes of titanium cages.<sup>35</sup> Papavero et al<sup>36</sup> used a rectangular fenestrated titanium cage filled with a porous HA cylinder (porosity of 30%-80% and mean pore diameter of 451  $\mu\text{m}$ ) soaked with vertebral bone marrow aspirate (BMA) in 78 patients. Because the radiopaque implant limits the radiographic assessments, quantitative computed tomography (qCT) was performed to evaluate the graft. They did not detect any slippage or fracture and the HA mass in the core of the implant increased up to 24% with a steady state over 2 years, which supports coverage of the HA by a newly formed bone layer. Seventy-one patients benefited from the surgery with symptom alleviation and no revision surgery was performed.<sup>36</sup> Sugawara et al<sup>37</sup> applied a cylindrical titanium cage filled with HA granules (1-2 mm granules, 50% porosity) in 48 patients. The 2-year fusion rate was 90% and no material-related adverse effects were observed.<sup>37</sup>

Unlike metallic cages, radiolucent materials such as polyether-ether-ketone (PEEK) and carbon fiber-reinforced polymer eliminate the difficulties of determining the degree of fusion.<sup>20,38-41</sup> In a clinical study on 45 patients, Chang et al<sup>20</sup> compared the preliminary outcomes of cervical fusion using PEEK cages containing either autologous bone or HA. During 2- to 10-year follow-up, they found no radiographic complications and the same fusion rate for both groups, suggesting that ACDF with PEEK cage containing HA is a safe and suitable alternative to autograft.<sup>20</sup> Mashhadinezhad et al<sup>39</sup> performed a similar study on 236 patients. Improvement in neurological deficit, radicular pain, and recovery rate was the same between PEEK cages filled with autograft and HA granules during 12-month follow-up and no additional surgeries were required.<sup>39</sup> During 54 to 90 months, Marotta et al<sup>38</sup> followed 132 patients who underwent ACDF with stand-alone carbon fiber cage filled with HA and reported a significant improvement in clinical evaluations. The fusion rate was 87.1%. Adjacent segment degeneration was observed in 24 (18.1%) patients, of whom 13 (9.8%) required a new surgery.<sup>38</sup> The term *adjacent segment degeneration* (ASD) has been used to describe radiological changes seen at levels adjacent to a previous spinal fusion site that do not necessarily correlate with any clinical findings. In contrast, "adjacent segment disease" is associated with new clinical symptoms.<sup>42</sup> It is postulated that the unique anatomy of the cervical spine and a highly mobile upper cervical region make this region vulnerable to ASD and after cervical fusion procedures, the motion closely transfers to the upper cervical spine.<sup>42</sup> Still, the risk factors directly correlated with ASD are not adequately reported. Although it seems that the incidence of ASD is lower in disc arthroplasty compared with fusion procedures such as ACDF, the high-quality evidence so far have failed to demonstrate a statistically significant difference.<sup>43,44</sup>

In a recent clinical trial, Yi et al<sup>45</sup> implanted PEEK cages filled with a mixture of HA/TCP or a mixture of HA/demineralized bone matrix (DBM). One year after the operation, complete bone fusion was achieved in 87% of patients in both groups as demonstrated on dynamic radiographs. The fusion rate on the CT scan was 87% for the HA/TCP mixture and 72% for the HA/DBM mixture. Both groups were the same in terms of clinical and radiological outcomes.<sup>45</sup>

## Sandwiched Hydroxyapatite

In 1994, Isu et al<sup>46</sup> modified an ACDF technique developed by Williams, using bone grafts obtained from cervical vertebral bodies (Williams-Isu method). Based on this, a sandwich method was proposed by Suzuki et al<sup>47</sup> in 1997 and a year later by Takayasu et al,<sup>48</sup> to be used when adequate amounts of bone could not be harvested from the vertebral body. In this method, HA is placed between 2 layers of the bone grafts. Kim et al<sup>49</sup> conducted a radiological case-control study in 40 patients to examine the efficacy of the sandwiched HA compared with the Williams-Isu method. The alignment and height of the fused segment were significantly better in the sandwich method. In contrast, the whole spine alignment was the same.<sup>49</sup> To facilitate the technique and eliminate the need for special equipment such as a microsurgical saw and to decrease the risk of cervical kyphosis in patients with preoperative kyphosis, Kogure et al<sup>50</sup> modified the Williams-Isu method. They used a conventional high-speed drill instead and reduced the size of the grafted bone. Five patients underwent surgery and were followed for 3 years. Evaluations showed all patients had achieved solid fusion. Two of the 4 patients with preoperative cervical kyphosis were free of kyphosis postoperatively.<sup>50</sup>

## Coralline Hydroxyapatite

Sea coral is mainly composed of calcium carbonate. In a synthetic process, all proteins are removed from the coral and the calcium carbonate is converted to calcium HA. This method preserves the geometric integrity of the biologic structure and eliminates immunogenic proteins.<sup>51</sup>

In 1999, Thalgot et al<sup>51</sup> used coralline HA implants with rigid anterior plating in 26 patients. Although the authors could not document the complete fusion by plain radiograph, all disc spaces showed total incorporation at the end of 2-year follow-up. Cracks were detected in four patients, without any evidence of disc space collapse, plate migration or detrimental clinical outcomes. Also, there were 2 plate migrations caused by falling after surgery. The authors found the implant to be a promising replacement for bone graft in the cervical spine.<sup>51</sup> A prospective randomized trial was conducted by McConnell et al<sup>52</sup> in 29 patients to compare coralline HA implants with conventional iliac autograft. Although graft fragmentation and settling were significantly higher in HA-implanted patients, the clinical outcomes and final graft fusion rates were similar. The authors were obligated to terminate further enrollment of participants in the clinical trial due to the high percentage of fragmentation

and collapse in the HA group. They concluded that the coral-line HA implants did not possess adequate structural integrity to resist axial loading during cervical interbody fusion.<sup>52</sup> In contrast, Mastronardi et al<sup>53</sup> performed ACDF with PEEK cages containing granulated coralline HA or a gel solution composed of deantigenated pig bone. The fusion rate was 100% in both groups at 12-month follow-up and no major complications such as breaking, collapse, angular deformation, subsidence, or inflammatory reaction were noted.<sup>53</sup>

## Tricalcium Phosphate

TCP [ $\text{Ca}_3(\text{PO}_4)_2$ ] is a bioabsorbable and biocompatible compound that exists in either  $\alpha$  or  $\beta$  crystalline forms.<sup>54</sup> TCP is more soluble and degradable than HA, with a higher bone regeneration rate and lower mechanical strength.<sup>54-57</sup>

In 2009, Dai and Jiang<sup>55</sup> evaluated the effectiveness of interbody cages containing  $\beta$ -TCP for treatment of cervical radiculopathy and myelopathy in a randomized clinical study (Supplemental Table S2). Sixty-two patients received discectomy and fusion with interbody cages (carbon fiber or PEEK) containing granulated  $\beta$ -TCP were randomly assigned to receive plate fixation or not. At 3 months, the fusion rate in patients without plating was significantly lower. However, successful bony fusion was achieved in all patients across both groups at 6-month follow-up assessment. Superior and/or inferior cage immigration into the endplates was significantly higher in patients without plating; yet there was no significant difference in clinical improvement between 2 groups. No early or late implant-related complications occurred and no additional surgeries were required. They found the  $\beta$ -TCP implant with or without anterior plating an appropriate option for cervical fusion.<sup>55</sup>

Acharya et al<sup>58</sup> used stand-alone cervical cages filled with  $\beta$ -TCP soaked in autologous bone marrow aspirate in 15 patients with a single-level cervical discopathy and followed them for 12 months. At 6 months, 14 out of 15 patients had bridging bony fusion on CT scan and the 1 patient who did not have signs of union at 6 months, showed fusion at the final follow-up. The clinical outcomes were excellent in 11 patients and good or satisfactory in 4.<sup>58</sup>

In a study by Zagra et al,<sup>59</sup> 33 patients underwent implantation of a stand-alone PEEK cage augmented with  $\beta$ -TCP and were compared with 2 other groups: (1) iliac autograft with plate fixation and (2) iliac graft with titanium cage. All patients achieved a solid fusion at the last follow-up. In patients treated with PEEK cages and  $\beta$ -TCP no graft-related complications, subsidence or migration of the cage was observed. In titanium cage-implanted patients, subsidence and migration of the cage into the vertebral body was observed in 7 patients (35%). The authors proposed that the rigidity of titanium cages may predispose the implant to subsidence into the superior or inferior adjacent vertebral body. The authors did not find any statistical differences in clinical outcomes (pain and disability) at a minimum 5-year follow-up. Nevertheless, ACDF with PEEK cage and  $\beta$ -TCP was not only clinically effective but also resulted in

a better fusion rate.<sup>59</sup> Sugawara et al<sup>37</sup> used cylindrical titanium cages packed with  $\beta$ -TCP in 57 patients and found no dislocation or material-related complications, in contrast to the study by Zagra et al<sup>59</sup> They reported that the fusion rate was significantly higher in the  $\beta$ -TCP compared with HA at 6-month (46% vs 24%) and 1-year follow-up (69% vs 49%); however, the fusion rate was similar between groups at 2-year follow-up (94% vs 90%).<sup>37</sup> Park and Roh<sup>60</sup> compared the efficacy of iliac autograft with PEEK cages filled with  $\beta$ -TCP. After 24 months, fusion had occurred in 22 of 24 patients treated with  $\beta$ -TCP and in 22 of 23 patients with iliac autograft. The fusion rate and clinical outcomes of ACDF using PEEK cages filled with  $\beta$ -TCP versus iliac autograft were similar; however, in patients treated with PEEK cages and  $\beta$ -TCP the fusion was somewhat delayed, there was more prevalent cage subsidence, and some patients experienced segmental kyphosis.<sup>60</sup>

Two studies used a composite material containing  $\beta$ -TCP and resorbable poly-L-lactic acid (PLLA) to produce an implant that could endure high biomechanical stresses with lower risk of rupture. Debusscher et al<sup>61</sup> used a composite material with 45% porosity containing 60%  $\beta$ -TCP and 40% resorbable PLLA to increase both strength and elasticity. The fusion rate was 96% without mobility of the grafted levels for all patients at 6 months after surgery. At a follow-up time beyond 36 months, complete resorption of cages was found only in 19%, while extensive (>50%) resorption was present in 48% and partial (<50%) resorption in 33% of patients. Clinical outcomes and the average overall and segmental lordotic angles significantly improved over the follow-up period. No measurable implant displacement or other material complications, cysts or lysis were detected on CT scan analysis at the last follow-up.<sup>61</sup> Brenke et al<sup>62</sup> used a similar resorbable cage in a larger group of patients with cervical disc degeneration ( $n = 33$ ), but because of the observation of cage dislocations in 4 patients (2 dorsal and 2 ventral), the study was discontinued prematurely. Postoperative radiographic morphology of the cages showed changes within 3 months; 22 cages (71%) had anterior and/or posterior eroded edges, 2 cages (6.7%) had a central crack in the  $\beta$ -TCP core and 4 cages (13%) showed signs of ventral or dorsal breakage of the composite part. The authors concluded that the  $\beta$ -TCP/PLLA cage is inappropriate for use as a stand-alone device due to unacceptably high rates of implant dislocations.<sup>62</sup>

## Biphasic Calcium Phosphate

Biphasic calcium phosphate (BCP) is a composite of HA, which is less soluble, and  $\beta$ -TCP, which has greater solubility.<sup>54,63</sup> Thus the factor determining solubility in the biphasic ceramics is the HA/ $\beta$ -TCP ratio; the lower the ratio, the greater the solubility and osteoclastic resorption.<sup>63,64</sup> However, osteoclastic resorption does not always enhance as solubility increases. Yamada et al<sup>63</sup> demonstrated that, although pure  $\beta$ -TCP had the highest solubility in acidic solution, a biphasic ceramic calcium with HA/ $\beta$ -TCP ratio of 25/75 was more extensively resorbed with osteoclasts than pure  $\beta$ -TCP.

In the clinical setting, the biphasic ceramic used for ACDF is commonly composed of 60% HA and 40%  $\beta$ -TCP.<sup>65-67</sup> The study by Cho et al<sup>65</sup> involving 100 patients showed that PEEK cages containing BCP or autograft had 100% fusion rate at 6-month follow-up (Supplemental Table S3). Of note, the fusion rate was lower with cages containing BCP than autograft during the first 5 months after the operation. Spinal curve correction, neuroforamen enlargement, and neurological recovery were the same in both groups.<sup>65</sup> Chou et al<sup>66</sup> compared the results of BCP implants (9 with PEEK and 27 with titanium cages) with autograft (n = 19). After 1 year, the fusion rate was 100% in patients treated with PEEK cages or autograft and no subsidence or subluxation was reported in either, while the titanium cage fusion rate was as low as 46.5% and led to subsidence and subluxation in 26% and 3.7% of patients, respectively. The PEEK cage containing BCP was demonstrated to be a viable alternative to autograft.<sup>66</sup> Another study using PEEK cages containing BCP was conducted by Mobbs et al<sup>67</sup> involving 58 patients. They reported that the fusion rate was 100% at 6 months with anterior plating and 96.2% without plate fixation. In the nonplated group, delayed fusion, nonunion, graft subsidence, and graft migration occurred.<sup>67</sup>

## Conclusion

This review was intended to discuss the current status of the use of ceramic materials in ACDF procedures. Many options are available including HA, coralline HA, sandwiched HA, TCP, BCP, as well osteoinductive materials such as BMA and various cages composed of PEEK, fiber carbon, and titanium. None of these options has demonstrated clear superiority over others, although direct comparisons are often difficult due to discrepancies in data collection and study methodologies. Stand-alone ceramic spacers have been associated with fracture and cracks. Metallic cages such as titanium endure the risk of subsidence and migration. PEEK cages in combination with ceramics were shown to be a suitable substitute for autograft. PEEK is radiolucent, more elastic and has better capacity for load distribution between the cage and bone; also, when filled with ceramics, the spacer is osteoconductive. Plate fixation was shown to be beneficial due to the lower risk of subsidence and migration and possibly earlier fusion. However, more accurate evaluations concerning the higher complication rate is necessary.

The relative dearth of high-quality evidence in this arena hinders decision making and the diversity of assessments in different studies makes comparisons difficult. Traditionally, the most widely accepted prognostic factor in ACDF has been fusion status which was evaluated with various methods and radiological modalities. Patient-related outcomes, which are considered to be of critical importance, are neglected in some studies. More homogeneity in the assessments and data presentation is necessary for a good body of evidence. Future randomized clinical trials are warranted before definitive conclusions can be drawn.

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