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Bone substitutes and expanders in Spine Surgery: A review of their fusion efficacies

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Abstract

Study Design
A narrative review of literature.

Objective
This manuscript intends to provide a review of clinically relevant bone substitutes and bone expanders for spinal surgery in terms of efficacy and associated clinical outcomes, as reported in contemporary spine literature.

Summary of Background Data
Ever since the introduction of allograft as a substitute for autologous bone in spinal surgery, a sea of literature has surfaced, evaluating both established and newly emerging fusion alternatives. An understanding of the available fusion options and an organized evidence-based approach to their use in spine surgery is essential for achieving optimal results.

Methods
A Medline search of English language literature published through March 2016 discussing bone graft substitutes and fusion extenders was performed. All clinical studies reporting radiological and/or patient outcomes following the use of bone substitutes were reviewed under the broad categories of Allografts, Demineralized Bone Matrices (DBM), Ceramics, Bone Morphogenic proteins (BMPs), Autologous growth factors (AGFs), Stem cell products and Synthetic Peptides. These were further grouped depending on their application in lumbar and cervical spine surgeries, deformity correction or other miscellaneous procedures viz. trauma, infection or tumors; wherever data was forthcoming. Studies in animal populations and experimental in vitro studies were excluded. Primary endpoints were radiological fusion rates and successful clinical outcomes.

Results
A total of 181 clinical studies were found suitable to be included in the review. More than a third of the published articles (62 studies, 34.25%) focused on BMP. Ceramics (40 studies) and Allografts (39 studies) were the other two highly published groups of bone substitutes. Highest radiographic fusion rates were observed with BMPs, followed by allograft and DBM. There were no significant differences in the reported clinical outcomes across all classes of bone substitutes.

Conclusions
There is a clear publication bias in the literature, mostly favoring BMP. Based on the available data, BMP is however associated with the highest radiographic fusion rate. Allograft is also very well corroborated in the literature. The use of DBM as a bone expander to augment autograft is supported, especially in the lumbar spine. Ceramics are also utilized as bone graft extenders and results are generally supportive, although limited. The use of autologous growth factors is not substantiated at this time. Cell matrix or stem cell-based products and the synthetic peptides have inadequate data. More comparative studies are needed to evaluate the efficacy of bone graft substitutes overall.

Keywords: bone substitutes, allografts, demineralized bone matrix (DBM), spine fusion, ceramics, β tricalcium phosphate (β-TCP), hydroxyapatite, rBMP-2, osteogenic protein-1 (OP-1), autologous growth factors, i-factor, synthetic peptides
Introduction

Bone grafts and bone substitutes are indispensable for achieving and maintaining fusion and intersegmental stability in spine surgery. Autologous bone has long been regarded as the gold standard for obtaining reliable spinal fusion, mainly because of its distinctive micro-architecture and biological properties, which provide the perfect blend of osteoconductive, osteoinductive and osteogenic elements. However, the supply of autologous bone graft is limited. Additionally, issues of sub-optimal bone quality in osteoporotic patients and donor site morbidity after graft harvest have compelled the orthopaedic community to look for other options. This need has spawned an industry, marked by the development of numerous bone graft alternatives. The discerning spine surgeon today has a wide array of options, from which to choose. An understanding of the particularities and the published clinical and radiological outcomes in the context of the contemporary spine literature is essential for optimal utilization of bone grafts in spinal surgery.

Materials and Methods

A review of clinical articles on the topic of bone graft substitutes/expanders/extenders was conducted. A PubMed search of English-language articles published through March 2016 was performed. The combination of search terms employed were: bone graft substitutes, bone graft alternatives, fusion extenders/expanders, spinal fusion, lumbar spine, cervical spine, spinal deformity, allografts, demineralized bone matrix, DBM, ceramics, calcium sulphate, β-tricalcium phosphate, hydroxyapatite, autologous growth factors, AGF, stem cells, rhBMP-2, rhBMP-7, and OP-1, synthetic peptides. The following commercial names of bone substitute products were also used to expand the results of the search: Grafton DBM, Accell Connexus, Healos, Polybone, Osferion, BioLu, Triosite, Bongros, Osteofil, Vitoss, Apaceram, Intepore, ChronOS, ProOsteon, Osteoset, Osteocel Plus, ActiFuse, Infuse, Amplify, i-Factor, Ampliplex. Two authors (AK & PM) conducted the search independently and the results were compared. Only studies reporting radiological fusion rates (assessed using X-rays, CT scans and/or isotope bone scans) and/or clinical patient outcomes following the application of bone substitutes in spine surgery were included. Both prospective and retrospective studies were included. Case reports and small case series (n<10) were not reviewed. Studies on animal models were excluded, as were in-vitro studies without reported clinical measures.

All resulting articles were broadly grouped into the following categories: Allografts, Demineralized bone matrix (DBM), Ceramics, Osteogenic growth factors (namely Bone Morphogenic Proteins), Autologous growth factors (AGFs) (Platelet derived growth factors), Stem cell products (Allograft cellular bone matrix) and Synthetic peptides. Additionally, these were sub-categorized according to use in a particular anatomical segment of the spine, where applicable, or for a particular condition, such as spinal deformity. Articles were assigned levels of evidence according to the criteria described by Wright et al. Studies in each category and sub-class are discussed in a manner that places emphasis on higher level of evidence articles first, and in reverse chronological order from recent to remote.

Results

A total of 181 articles met the inclusion criteria (Allograft: 39, DBM: 20, Ceramics: 40, rhBMP-2: 54, rhBMP-7/OP-1: 8, Autologous growth factors: 9, Stem cells based products: 7, Synthetic Peptides 4). More than a third of the studies (62 studies, 34.25%) were related to the use of Bone Morphogenic Proteins (BMP), making this the single largest group of published bone graft substitutes. Studies on ceramics (40) and allografts (39) were the next most extensive-ly published. Autologous growth factors, Stem cell based substitues and Synthetic peptides are relatively novel, and data thereof was less forthcoming.

Allografts

Allograft is bone derived from cadavers. They are highly osteoconductive, variably osteoinductive and lack osteogenic properties due to the loss of cellular elements during processing to reduce immunogenici-
ty. Common processing techniques include freezing and lyophilization (i.e. freeze drying). Lyophilized allografts are processed by dehydration and vacuum packed, facilitating storage at room temperatures. The process of lyophilization reduces immunogenicity more than freezing but results in a greater reduction of mechanical strength on rehydration.

Allografts in cervical spine fusion
Fourteen studies evaluating the use of allografts in surgery for degenerative cervical spine were identified (one level I, two level II, seven level III and four level IV). Graham et al. in a prospective randomized control trial (level I) comparing glycerol preserved versus freeze dried allografts for anterior cervical fusion reported fusion rates greater than 95% in both groups, which were not statistically different (p = 0.2127 and 0.1705 for the 3- and 6-month follow-up, respectively). However, no comparison with autograft was done by the authors in the study. In another prospective semi-randomized comparative study, Suchomel et al. (level II) evaluated freeze-dried fibular allografts versus autologous iliac crest grafts in 80 patients undergoing instrumented anterior cervical fusions. Assessment of fusion was done with AP and lateral radiographs at various time points. In single-level procedures, there was no significant difference in fusion rates (100% vs. 93.3%, p = 0.197) and graft collapse rates (0% vs. 3.4%, p = 0.365) between autograft and allograft, respectively. In two-level procedures the differences were also insignificant: 90.9% vs. 93.5% fusion rate (p = 0.709) and graft collapse incidence of 13.6% vs 4.3% (p = 0.187) for autograft and allograft, respectively; however, fusion took a longer time to occur in the allograft group. The number of levels fused per case did not have any significant effect on outcome measures. More recent level III studies using instrumentation to augment allograft constructs also reported high fusion rates, ranging from 91.9% to 94.3%. Other level III and level IV data similarly related favorable fusion outcomes with allograft use in the cervical spine.

Allograft use for posterior cervical fusion, especially occipito-cervical fusions has been evaluated in level III and level IV studies. Good fusion rates ranging from 89.9% to 95% were reported.

Allografts in lumbar spine fusion
Twelve publications including two level I and four level II studies were found reporting the use of allograft in the lumbar spine. These can be broadly grouped according to use into lumbar interbody fusion or posterolateral fusion. In a prospective randomized study, Putzier et al. (Level I) evaluated the use of allogenic cancellous bone versus cancellous iliac crest autograft for instrumented monosegmental lumbar spondylolisthesis treated with PEEK cages. The surgical technique described was circumferential, consisting of a single-stage anterior procedure followed by posterior instrumentation. Fusion was assessed using plain-films and CT scans for bone formation in the arthrodesed interbody spaces. The authors found no statistically significant differences in the radiological fusion rates between the two groups (85% with autograft versus 80% with allograft) based on 12 month post-operative radiograph assessment (k = 0.90). Clinical outcomes using the Oswestry low back pain Disability Index (ODI) also demonstrated no significant differences in allograft and autograft groups. In another level I study, Thalgott et al. reported that, compared to frozen femoral ring allografts (FRAs), use of freeze dried FRAs for circumferential instrumented lumbar fusion was associated with a higher likelihood of pseudarthrosis (radiographic fusion rates 65.38% vs. 76.67% respectively assessed by periodic AP and lateral radiographs and CT at final follow-up) (p = 0.026). The clinical outcomes between the two groups did not differ significantly. A level III study by Wimmer et al. involved 94 patients with spondylolisthesis treated with anterior interbody fusion using either iliac crest autograft or femoral head allograft supplemented by pedicle screws posteriorly. A 92% fusion rate was reported in the allograft group compared to 95% for autograft (p > 0.05). Four Level IV studies on lumbar interbody fusion, employing either femoral ring or femoral head allografts, similarly demonstrated high radiological fusion rates (ranging from 88 to 98%).

For posterolateral lumbar fusion surgery, two Level II studies by An and Jorgenson et al. demonstrated inferior radiological fusion results for cortico-cancellous allografts (35 - 39.1% fusion rates) compared to autologous iliac crest grafts (up to 80%).
However, two recent level II studies\textsuperscript{18,19} utilizing allografts in combination with bone marrow aspirate (BMA) reported fusion rates up to 80\%\textsuperscript{18} and equivalence with autologous iliac crest grafts.\textsuperscript{19}

**Allografts in Deformity/Scoliosis/Paediatric spine**

No level I or level II studies were found describing the use of allografts in deformity correction surgery. Allograft use in combination with posterior segmental instrumentation was reported to have acceptable fusion rates (ranging from 70\% to 92.7\%) and seemed to be an efficacious and safe substitute for autologous bone in several level III\textsuperscript{30,31} and level IV studies.\textsuperscript{32-36} In one study however, Demirkiran et al.\textsuperscript{36} reported high rates of pseudoarthrosis (13.3\%) in a series of 15 patients with long segment (>6 level) posterior instrumented fusions, with an overall fusion rate of 86.7\% using allograft for instrumented posterior fusions alone. Murphy et al.\textsuperscript{35} showed the safe and effective use of allografts in paediatric subaxial spine surgery with fusion reported in 88\%, in their series of 18 patients.

**Allografts in Spine Trauma, Tumor and Infections**

In a prospective series of 36 patients Finkelstein et al.\textsuperscript{37} (level IV) reported that the use of cortical strut allografts along with instrumented stabilization was a safe and viable alternative to tri-cortical iliac crest autograft, in terms of radiological fusion outcomes (81\% radiologic fusion rate for allografts, no comparator group) for the treatment of thoracolumbar fractures. In another series of 41 patients with large anterior vertebral column defects resulting from various etiologies such as trauma, tumor and infection, Singh et al.\textsuperscript{38} (level IV) found that long segment anterior structural allograft worked well in maintaining vertebral height and structural integrity. A radiological fusion rate of 97.5\% was reported.

The use of structural allograft for the treatment of residual spinal deformity and collapse secondary to tuberculous osteomyelitis was investigated in three different studies (level IV) by Govender et al.\textsuperscript{39-41} The authors concluded that femoral, fibular and humeral allografts were all suitable alternatives to autologous tricortical iliac crest and rib grafts in treating spinal defects, with reported radiological fusion occurring in 94.2\% to 100\% of patients. In a series of 47 patients with vertebral osteomyelitis, Schuster et al.\textsuperscript{42} (level IV) also concluded that the use of structural allografts in combination with aggressive tissue debridement and adjuvant antibiotic therapy was a safe and effective form of treatment.

**Evidence Summary for Allografts**

Use of allografts for cervical fusions is supported in published literature for both anterior (level I, II, III, IV data) and posterior cervical fusions (level III, IV data). The routine supplemental use of anterior cervical plates for instrumentation in recent studies, has resulted in a dramatic increase in fusion rates overall. For lumbar spine applications, the majority of published studies (including level I and II) reported good radiological and clinical outcomes for anterior interbody and circumferential fusions. However allograft use alone for instrumented posterolateral lumbar fusions is not well supported, with two level II studies reporting inferior fusion rates, although there were no differences in clinical outcomes. Allografts in combination with bone marrow aspirates have shown good fusion efficacy for posterolateral lumbar fusions in two recently published level II studies. For use in deformity correction, trauma, tumor and infections, the studies are supportive, although of lower quality evidence (mostly level III and IV).

**Demineralized bone matrix (DBM)**

Demineralized bone matrix (DBM) is derived from human allograft bone. Acid extraction of the bone results in a product that consists of a combination of organic matrix proteins (osteocductive) with small quantities of growth differentiation factors (osteoinductive). A variety of DBM preparations have been made commercially available in the form of powders, granules, gels, putties, and strips.

**DBM use in Cervical Spine**

No level I studies could be identified in this subgroup. A single level II prospective study by An et al.\textsuperscript{41} evaluated the use of DBM (Grafton DBM\textsuperscript{\texttrademark}) in combination with allograft for cervical disc disease. In this study involving un-instrumented fusions, radiologic pseudarthrosis was found in 33.3\% of treated
DBM use in Lumbar fusion

Reports evaluating the use of DBM in lumbar spine fusions are numerous. A total of thirteen articles (one level I, two level II, five level III, and five level IV) were identified in this subclass. In a level I prospective multicenter randomized clinical trial, Kang et al. reported on the efficacy of a DBM preparation (Grafton DBM™) compared with iliac crest autograft for single-level posterior lumbar fusion. Arthrodesis rates evaluated using plain radiographs and computed tomographic scans at 6-month, 1-year, and 2-year time points were 86% for the DBM group versus 92% for the autograft group (p = 1.0). Higher physical function scores were observed in the DBM group at 2 year follow-up, although this also was not statistically significant. The authors concluded that fusion rates and clinical outcomes associated with DBM for lumbar fusion were comparable to the use of iliac crest autograft.

The role of DBM as a fusion extender in conjunction with autograft was investigated by Cammisa et al. (level II) in a 120 patient series undergoing instrumented posterolateral lumbar fusion. Iliac crest autograft was implanted on one side of the spine while a DBM (Grafton DBM™) and autograft composite was used on the contralateral side in the same patient. All subjects were scheduled for anteroposterior radiographs of the lumbar spine at 3, 6, 12, 18, and 24 months. At 12, 18, and 24 months, lateral decubitus flexion-extension films also were included to confirm fusion integrity. After two years of follow-up, fusion rates of 52% on the DBM side and 54% on the iliac crest autograft side were observed. The overall percentage agreement for fusion status between sides reported was approximately 75%, suggesting moderately strong statistical correspondence (k = 0.51, p<0.0001). In another level II prospective study, Vaccaro et al. evaluated DBM (Grafton DBM™) use in instrumented posterolateral lumbarosacral spine fusions. Nineteen patients had supplemental bone grafting with DBM putty enriched with aspirated bone marrow, 27 patients had DBM putty combined with iliac crest autograft, and the control group consisted of 27 patients with autograft. At 24 months after surgery, 63% of levels in the DBM and bone marrow group, 70% of levels in the DBM and iliac crest group, and 67% in the autograft group had radiological fusion as evaluated by anteroposterior, lateral and flexion-extension radiographs (p = 0.875). The remaining studies in this sub-group (level III and IV) similarly provide supportive data for the use of DBM as a graft expander in lumbar fusion surgery.

DBM use in Scoliosis

Two level III reports explored the use of DBM in scoliosis patients. In a retrospective study Weinzapfel et al. compared fusion rates between allograft bone and DBM (Grafton DBM™) following video-assisted thoracoscopic surgery for idiopathic scoliosis. Eighty-two percent of disc levels in the allograft group and 92% in the DBM group were rated as radiologically fused, suggesting superior results for DBM use in scoliosis. Percentage curve correction from before surgery to last follow-up was purportedly similar in both groups. Price et al. also related comparable fusion and failure outcomes for a composite of DBM and autologous bone marrow versus iliac crest autograft in adolescent idiopathic scoliosis.

Evidence summary for DBM

The bulk of the literature on demineralized bone matrix pertains to the lumbar spine, wherein DBM has been shown to be an effective bone extender, when used to augment the volume of autograft (across all evidence level studies). Reports on the use of DBM in the cervical spine along with PEEK cages similarly suggest that DBM is an acceptable alternative to autologous bone (level II, III and IV data). Data regarding the role of DBM in scoliosis is encouraging, although limited to two level III studies. Since demineralized bone matrices lack structural strength, they cannot be used independently in situations where biomechanical stability is required. Utilization of DBM for spine fusion has typically been in combi-
nation with some form of structural bone substitute or interbody cage, with no clinical evidence supporting the use of DBM as a standalone substitute.

Ceramics

Ceramics constitute one of the most extensively studied groups of bone substitutes in spine surgery. Similar to their DBM counterparts, ceramics are mainly used as bone graft extenders in combination with autologous bone or bone marrow aspirates and interbody devices. Ceramics work by providing a scaffold for bone growth and are predominantly osteoconductive. Additional favorable properties of ceramics include the biodegradable nature, feasibility of large scale production and ease of sterilization, non-immunogenicity, and relative lack of toxicity. However, the brittle nature and low shear strength of ceramic grafts limit their use as a standalone bone substitute. Beta-Tricalcium Phosphate (β-TCP), Hydroxyapatite (HA), Calcium Sulphate and more recently Silicate-Substituted Calcium phosphate (Si-CaP) and β Calcium pyrophosphate (β-CPP) are among the most notable ceramic scaffolds that have been studied for use in human spinal fusions.

β-Tricalcium Phosphate (β-TCP)

β-TCP in the lumbar spine

In a prospective randomized clinical study, Dai et al.63 (level I) reported on 62 patients with symptomatic degenerative lumbar spinal stenosis treated with single-level instrumented posterolateral lumbar fusion, with three years follow-up. Patients were randomly assigned to fusion with β-TCP (BioLu™) combined with local bone obtained from the decompression (n = 32) or autologous iliac crest graft (n=30). There were no significant differences in recovery rates using the SF-36 and Japanese Orthopedic Association (JOA) scores at all time intervals. Standard AP and flexion-extension films were obtained at 3, 6, 12 and 24 months, and successful radiographic fusion was documented in all patients in both treatment groups.

Yamada et al.64 conducted a prospective comparative study (level II) in 61 consecutive patients undergoing decompressive laminotomy and single level instrumented posterolateral fusion. Constructs of hybrid bone grafts (β-TCP [Osferion™] + autologous iliac crest bone strips + autologous bone marrow aspirates) were placed on one side of the inter-transverse gutter in all patients. Autologous local bone graft harvested during the laminotomy was placed on the contralateral side as control. Fusion rates assessed with both radiographs and CT scans was higher for the hybrid bone graft side (68.9% at 6 months, 83.6% at 1 year, 93.5% at 2 years) than that for the local bone graft side (49.2% at 6 months, 75.4% at 1 year, 89.1% at 2 years) with a significant difference at 6 months after surgery (p < 0.05). In 2013, Kong et al.65 (level II) reported that the posterolateral fusion rate, using a mixture of β-TCP (PolyBone™) and local bone, was lower than that for local bone alone (57.1% vs 73.8%) at 12 months follow-up (p = 0.092). Lumbar anterior-posterior (AP) and lateral radiograph imaging was done immediately postoperative and at 1, 3, 6 and 12 months. Computed tomography (CT) follow up was also done immediately postoperative and at 12 months. The authors postulated that β-TCP seemed to be counterproductive for fusion in relation to the same amount of autologous bone. A similar opinion was echoed by Thaler et al.66 in a series of 34 patients (level IV) using β-TCP (ChronOS™) in combination with autologous bone marrow aspirate for instrumented posterior lumbar interbody fusion (PLIF). The authors recommended avoiding the use of β-TCP due to high pseudoarthrosis rates. In contrast, five level IV studies67-71 reported acceptable results with the use of β-TCP in combination with autologous bone marrow aspirate for lumbar fusions.

β-TCP in the cervical spine

No published level I studies reported on the use of β-TCP in cervical fusions. By way of a level II prospective study, Dai et al.72 concluded that interbody fusion cages containing β-TCP following one- or two-level discectomy proved to be an effective treatment for cervical spondylotic radiculopathy and/or myelopathy, with successful fusion seen in all patients at 6 months follow-up (p < 0.05), as evaluated using standard AP and lateral flexion-extension radiographs. In a retrospective cohort review, Sugawara et al.73 (level III) reported on the use of β-TCP (Osferion™) (93 segments in 57 patients) compared to Hydroxyapatite (72 segments in 48 patients) packed in cylindrical titanium cages for ACDF procedures.
The complete fusion rate at 6 months and 1 year was significantly superior in the β-TCP group (46% at 6 months and 69% at 1 year) than in the HA group (24% at 6 months and 49% at 1 year) (p < 0.05), and the rates were similar in both groups at two years. Other available Level III and level IV studies report good efficacy and satisfactory outcomes with β-TCP use when compared to autologous bone grafts.

**β-TCP use in scoliosis**

Two level I publications evaluating the application of β-TCP in scoliosis surgeries were identified. Lerner et al. randomized 40 patients with adolescent idiopathic scoliosis (AIS) into two treatment groups undergoing corrective posterior instrumentation; both groups were similar in terms of patient-related and procedure factors. In 20 patients, iliac crest bone graft (ICBG) harvesting was performed whereas the other half received β-TCP (Vitoss™) augmenting local bone graft. Patients were observed clinically and radiologically for a minimum of 20 months postoperatively, with a mean follow-up of four years. Average curve correction was reported at 61.7% in the β-TCP group and 61.2% in the ICBG group at hospital discharge (p = 0.313) and 57.2% and 54.3%, respectively, at follow-up (p = 0.109). The authors concluded that the use of β-TCP as extenders of local bone graft yielded results equivalent to ICBG in the posterior correction of AIS. Delecrin et al. also reported favorable results for the use of porous biphasic calcium phosphate ceramic blocks comprised of β-TCP and hydroxyapatite (Trisite™) in 58 patients with idiopathic scoliosis. In a level II study, Muschik et al. evaluated the utility of β-TCP (ChronOS™) in a granular form to achieve dorsal spondylodesis in 28 patients with AIS. Posterolateral grafting was performed, using either autograft bone mixed with allograft bone (n = 19) or autograft bone mixed with 25 g TCP (n = 9). Radiographically assessed fusion occurred within 6±1 months in both groups (p < 0.87), with no pseudoarthrosis observed. The authors inferred that the use of β-TCP appeared to be a valuable alternative to allograft for deformity surgeries where large amounts of bone are required.

**Evidence summary for β-TCP**

Data on β-TCP use for lumbar spine fusions is inconclusive in view of conflicting results reported across all evidence levels of studies. This is in contrast to its application in cervical spine where all studies report good clinical and fusion outcomes. Similarly, two level I and a single level II study endorse the use of β-TCP for deformity correction in adolescent idiopathic scoliosis.

**Hydroxyapatite (HA)**

Hydroxyapatite is a naturally occurring mineral found in bones and is estimated to contribute up to 50% of the bone by mass. Coralline hydroxyapatite, as the name suggests, is synthesized from sea corals. The material properties of hydroxyapatite are similar to other ceramics; however, compared to the more porous tricalcium phosphate scaffolds, HA products are relatively inert and take longer for biodegradation and resorption.

**Hydroxyapatite (HA) in Lumbar spine**

Level I evidence on the use of HA in cases of intertransverse posterior lumbar fusion does not conclusively support its use over autologous iliac crest bone graft. Korovesis et al. compared coralline hydroxyapatite (Pro Osteon™) (n=19; group A), iliac bone graft (n=18; group B) or both (n=20; Group C) in the setting of instrumented posterolateral and lumbar spinal fusions for patients with degenerative lumbar spinal stenosis. Plain radiographs (standing AP and lateral views, supine oblique right and left, and sitting frontal and lateral bending views) were obtained preoperatively and at 3, 6, 12, 24 and 48 months postoperatively. CT scans were also performed preoperatively and at 12 and 24 months postoperatively to evaluate facet joint arthrodesis. Radiological fusion was achieved at 1 year postoperatively in all groups and vertebral segments. In a prospective case control study involving 58 patients with degenerative spinal stenosis, Hsu et al. (level II) compared coralline hydroxyapatite (CHA) and laminectomy-derived bone as adjuvant graft materials for posterolateral lumbar fusions. Patients were allocated into three groups: laminectomy bone and ICBG (group 1, n = 20), CHA and ICBG (group 2, n = 19), and laminectomy bone and CHA (group 3, n = 19); the respective graft materials were placed in either the right or left inter-transverse space. The best radiological fusion rates were obtained with pure autologous iliac crest graft (95%). After 6 months, CHA...
produced a comparable result to laminectomy-derived bone when combined with iliac crest autograft (group 2) \((p = 0.097)\). However the combination of laminectomy bone with CHA (group 3) failed to yield a satisfactory fusion rate \((57.9\%\)\) up to one year after surgery if no autologous iliac crest graft was added \((p = 0.0217)\). At 1 year postoperatively, the fusion rate difference between groups 1 and 2 remained insignificant \((p = 0.3376)\). For Group 3, the fusion rate \((57.9\%\)\) was markedly lower than that in Groups 1 and 2 \((90.0\%\) and 78.9\%, respectively\). The difference was statistically significant \((p = 0.0217)\) between Groups 1 and 3, but not between Groups 2 and 3 \((p = 0.1627)\). In a level III retrospective study, Hyoungmin et al.\(^8\) concluded that porous hydroxyapatite bone chips (Bongros HA™) were valuable bone graft extenders in PLIFs when used in conjunction with local bone. Three other level IV studies\(^9\),\(^10\),\(^11\) also supported the use of hydroxyapatite as an effective option in combination with other bone graft substitutes such as allograft and autograft.

**Hydroxyapatite (HA) in the Cervical spine**

A single level I study demonstrated that coralline hydroxyapatite was structurally inferior to iliac crest bone for cervical interbody fusion, although clinical results and fusion rates were similar. In this study by McConnell et al.\(^7\), graft fragmentation occurred in 89\% of the hydroxyapatite grafts versus 11\% of the autograft \((p = 0.001)\). Plain AP and lateral radiographs at periodic intervals and CT images for the final status were used to evaluate interbody fusion rates. Significant graft settling was also reported in 50\% of the HA grafts, as compared to 11\% of the autograft patients \((p = 0.009)\). However four level IV studies (using CHA\(^8\), porous HA\(^9\), porous/dense HA composite\(^10\) and nano-HA/polyamide cages\(^11\)) reported good results (fusion rates ranging from 92.5\% to 100\%) and concluded that HA was an effective alternative to autologous iliac crest graft.

**Hydroxyapatite (HA) in Scoliosis**

A single case series of 27 patients (level IV) by Mashoof et al.\(^2\) was identified, concluding that coralline hydroxyapatite was a safe, biocompatible, and effective means of augmenting autogenous bone graft in the treatment of idiopathic adolescent scoliosis with posterior spinal fusion. All patients achieved solid fusion at an average follow-up of 27 months in their series.

**Evidence summary for hydroxyapatite (HA)**

Hydroxyapatite (HA) use in lumbar and cervical spine fusions was not well endorsed by higher evidence level studies, although level III and level IV studies reported good outcomes. Data on the application of HA to scoliosis surgery is also limited to a single case series. Differences in the porosities of ceramic bone extenders may account for these conflicting results in clinical studies. Of note, Wang et al.\(^3\) demonstrated with a clinical study that the porosity of ceramics such as \(\beta\)-TCP had a statistically significant effect on fusion rates, with less porous formulations producing better fusion outcomes. Data such as these may be equally applicable to other forms of ceramic such as hydroxyapatite. The differences in porosities and compositions of commercially available hydroxyapatite products make generalization across the group difficult.

**Calcium Sulphate**

Literature on calcium sulphate products is limited to their use in lumbar fusion surgeries, with two level I\(^4\),\(^5\), one level II\(^6\), and one level III\(^7\) studies included. Niu et al.\(^1\) (level I) evaluated fusion rates using autogenous laminectomy bone chips and calcium sulfate pellets (Osteoset™) augmented with bone marrow aspirates in a prospective randomized study of single-level lumbar posterolateral fusions involving 43 patients. Autologous ICBG was placed on one side in the posterolateral gutter in all patients as a control, and on the other side an equal quantity of laminectomy bone chips mixed with BMA (group 1, \(n = 21\)) or calcium sulfate pellets soaked in BMA (group 2, \(n = 22\)) were used. For the 21 patients in group 1, 18 (85.7\%) exhibited bone fusion on the test side, and 19 (90.5\%) presented evidence of fusion (assessed by follow-up radiographs and/or computed tomograms) on the control side. Thus, the test side with laminectomy bone chips and BMA achieved a fusion rate similar to that on the control side \((p > 0.05)\). For the 22 patients in group 2, 20 (90.9\%) exhibited bone fusion on the control side whereas only 10 (45.5\%) demonstrated complete fusion on the test side \((p < 0.05)\), where calcium sulfate and BMA was applied. The authors concluded that Osteoset™ was...
significantly inferior to ICBG despite the addition of osteoinductive BMA. In contrast, Alexander et al.\textsuperscript{95} found that calcium sulfate pellets plus local decompression bone provided equivalent results compared to autologous ICBG in his preliminary paper on a prospective randomized study sample. In a level II prospective study, Chen et al.\textsuperscript{96} also reported equivalent fusion outcomes for iliac crest bone graft and autograft laminectomy bone with calcium sulfate pellets in 74 patients who underwent one-level (90.8% on test side vs. 89.7% on control side) or two-level lumbar fusions (82.9% on test side vs. 85.7% on control side) (p > 0.05). Comparable results were reported by Chang et al.\textsuperscript{97} in a level III retrospective study of 66 patients who underwent single level posterolateral lumbar fusions with Osteoset\textsuperscript{98}.

**Evidence summary for Calcium Sulphate**

There are discrepancies between the two published level I studies on calcium sulphate use for lumbar spinal fusion, although both utilized the same preparation (Osteoset\textsuperscript{99}). These differences are especially difficult to interpret in light of the fact that the study by Niu et al.\textsuperscript{94} utilizing osteogenic bone marrow aspirates, which should have augmented fusion rates, instead refuted the effectiveness of calcium sulphate pellets. Other studies (level II, III and IV) however are in support of the use of calcium sulphate as a bone graft extender in combination with local autologous bone obtained from decompression.

**Silicate substituted Calcium Phosphate (Si-CaP)**

Silicate substituted calcium phosphates are a novel sub-class of ceramic bone substitutes which, in addition to exhibiting osteoconductive properties, are purported to be osteoinductive as well. This newer generation ceramic material, as the name implies, is prepared by partially substituting silicate for phosphate in a controlled manner. This substitution is typically 0.8% by weight for the commercially available product Actifuse\textsuperscript{\textregistered}. The presence of silicate increases the negative charge of the ceramic scaffold, which is hypothesized to attract more osteoblasts to the material surface, thus conferring osteoinductive effects.\textsuperscript{98} Silicate-substituted calcium phosphate (Si- CaP) has also been shown to exhibit an increased in vivo resorption rate compared to the more traditional hydroxyapatite ceramics.\textsuperscript{99}

**Silicate substituted calcium phosphate (Si-CaP) in lumbar spine and cervical spine**

Level I and level II studies evaluating the efficacy of Si-CaP versus autologous bone grafts are currently lacking, though two level I studies\textsuperscript{100,101} comparing Si-CaP with rhBMP were identified. Level IV retrospective studies by Jenis et al.\textsuperscript{102} and Nagineni et al.\textsuperscript{103} reported fusion rates from 76.5% to 90% with the use of Si-Cap in cervical and lumbar fusion procedures.

**Silicate substituted calcium phosphate (Si-CaP) in scoliosis**

Harshavardhana et al.\textsuperscript{104} in a series of 35 AIS patients (level IV), reported no evidence of pseudarthrosis with the use of Si-CaP (Actifuse\textsuperscript{™}) at 2.9 years of average follow up. No complications were reported in the study. Another level IV publication by Lerner et al.\textsuperscript{105} on the use of SiCap (Actifuse\textsuperscript{™}) for the posterior correction of AIS demonstrated good results in terms of curve correction maintenance, formation of solid fusion masses (100% of cases), and improvements in Visual Analog Scale (VAS) and SRS-22 (Scoliosis Research Society Questionnaire) scores.

**Evidence summary for Si-CaP**

Though level IV data support the use of Si-CaP as a viable alternative to autograft in degenerative lumbar spine fusion and scoliosis surgery, level I studies directly evaluating comparability to autologous bone grafts are not presently available.

**β-calcium pyrophosphate (β-CPP)**

Another novel ceramic substitute, β calcium pyrophosphate (β-CPP) has shown promising results in animal studies in terms of fusion rates and rapid incorporation and resorption characteristics.\textsuperscript{106}

**β-calcium pyrophosphate (β-CPP) in lumbar spine**

A single published report\textsuperscript{107} (level II) was found describing the use of this substitute for short segment lumbar fusions. In this prospective, case matched study, the authors concluded that β-CPP combined with autograft was as effective as autologous bone for instrumented posterolateral interbody fusions. Radiographic evaluation of fusion was done using periodic radiographs and three dimensional thin cut (1 mm) CT images at 12 months postoperatively. The reported fusion rates were 87.0% in the β-CPP group and 89.1% in the autograft group, which were not signific-
significantly different.

Evidence summary for β-calcium pyrophosphate
Although early results suggest efficacy similar to autograft, current data is inadequate to draw conclusions.

Bone morphogenic proteins (BMPs)
No class of bone substitutes/bone graft extenders has been as extensively studied and published as BMPs. Bone morphogenic proteins (BMPs) are osteoinductive molecules belonging to the transforming growth factor beta (TGF-β) superfamily of proteins. Of the more than 20 types of BMPs described, BMP-2 and BMP-7 (also known as Osteogenic protein-1, or OP-1), in their recombinant forms (rh), are the most widely used BMPs in clinical practice. Since BMPs are soluble proteins and may readily diffuse into the surrounding tissues, away from the site of application, they are used in combination with carriers to maintain effective concentrations at the intended fusion sites. Though efforts to identify the ideal carrier are ongoing, absorbable collagen sponges (ACS) and compression resistant matrix (CRM) are frequently used. Autologous and allogenic bone grafts, ceramics, DBMs and polylactic acids are other substrates that have been utilized for rhBMP delivery.

Recombinant Bone Morphogenic Protein-2 (rhBMP-2)
Recombinant BMP-2 has been studied in diverse settings such as degenerative lumbar and cervical spinal fusions, deformity correction, and pediatric spinal fusions as well as in osteomyelitic conditions of the spine. Recombinant BMP-2 in combination with an absorbable collagen sponge (Infuse™) has FDA approval only for anterior lumbar interbody fusions (ALIF) when used within a titanium tapered cage. All other uses of rhBMP-2 are currently physician directed off-label applications.

Recombinant Bone Morphogenic Protein-2 (rhBMP-2) in Lumbar spine
A total of 33 studies (seven level I109-115, eight level II116-123, eight level III124-131, nine level IV132-140, one unclassified141) were identified pertaining to rhBMP-2 use in the lumbar spine alone. The sheer volume of literature on rhBMP-2 reflects its acceptance and popularity as a widely used fusion enhancer, as well as the controversial nature of this compound associated with specific complication profiles.

There are several level I and level II studies describing rhBMP-2 usage in anterior lumbar fusion applications. Burkus et al.114 conducted a prospective, randomized, multicenter study (level I) involving 131 patients to evaluate the safety and efficacy of rhBMP-2 as a replacement for autogenous ICBG in anterior lumbar spinal arthrodesis. The average ODI scores, SF-36 physical component summary scores, and low back and leg-pain scores were significantly better in the study group (p < 0.05). Significantly higher fusion rates (99 % vs. 76%) were also reported in the study group (p < 0.001), assessed with radiographs and CT. Slosar et al.118 reported a 100% fusion rate at 24 months follow-up after anterior lumbar interbody fusions using rhBMP-2 and femoral ring allograft. Similarly high fusion rates (94.5 - 100%) were reported by Burkus et al. in two level II studies121,122 in the context of rhBMP-2 use for anterior lumbar interbody fusions.

There are numerous level I studies describing usage of rhBMP-2 in posterior lumbar applications. After a level I randomized controlled study, Michielsen et al.109 reported results in 40 patients treated with an instrumented single-level posterior lumbar interbody arthrodesis. Interbody arthrodesis was performed using polyether-ether-ketone (PEEK) cages which were filled with 8 mg of rhBMP-2 in the study group and 2.5 mL of autologous bone in the control group. CT scans of the arthrodesed segments were made at three, six, and twelve months postoperatively, as well as bone density measurements. There was a significant difference between the groups with respect to interbody healing on bone densitometry analysis at three, six, and twelve months (p = 0.021, p = 0.004, and p = 0.014, respectively). Fusion on CT scan was ultimately achieved in all patients. The authors also found no significant differences in clinical results (VAS, ODI, and SF-36) between the groups at each postoperative visit. In another level I study wherein 197 patients underwent 1 or 2 level instrumented posterolateral lumbar fusion, Hurlbert et al.110 report-
ed significantly higher radiological fusion rates (assessed via plain radiographs) in patients treated with high doses rhBMP-2 (42 mg/level) compared to those who received autograft (94% vs. 69% respectively) (p = 0.007) at 4 years of follow-up. However, there were no significant improvements in clinical outcomes in the rhBMP-2 group. In a two independent level I studies, Dimar related significantly higher fusion rates for patients in rhBMP-2 groups (using AMPLIFY™, 40 mg rhBMP-2) treated with instrumented posterolateral fusions versus controls in which autologous ICBG was used (96% for the rhBMP group vs. 89% with ICBG, p = 0.014, and 88% with rhBMP vs. 73% in ICBG group, p = 0.051). Clinical outcomes in all groups improved significantly overall; however the increment in outcome measures was not statistically superior for the rhBMP-2 groups in either study. Other level I studies by Glassman et al. and Boden et al. comparing rhBMP-2 to AICBG for posterolateral lumbar fusions reported higher fusion grades, with fusion rates approaching 100% in the study groups.

Eight level II studies on the use of rhBMP-2 in lumbar spine were identified and reviewed. Dawson et al. performed a prospective, randomized, multicenter pilot study investigating the use of rhBMP-2 on an absorbable collagen sponge (12 mg rhBMP-2 dose) combined with a ceramic-granule bulking agent as a replacement for autogenous ICBG in single level instrumented posterolateral lumbar arthrodesis. By 24 months, 95% of patients in the investigational group compared with 70% in the control group had documented fusion (assessed with radiographs and CT scan) (p = 0.120). Significant improvements in clinical outcome measures were also reported in both groups. The authors concluded that the combination of an osteoinductive agent with an osteoconductive matrix may be an effective replacement for autograft in instrumented single-level PLIF. Similarly Katayama et al. concluded that rhBMP-2 can be used as the sole source of osteogenesis with success equivalent to an autologous graft for posterolateral lumbar fusions (82% fusion rate for rhBMP-2 compared to 91% for autologous bone) after a study involving 11 patients who underwent posterolateral L4-5 fusions. In another level II study, Singh et al. reported an overall 97% fusion rate in the rhBMP-2 group (12 mg dose) compared to a 77% fusion rate with ICBG alone (p < 0.05) for instrumented posterolateral fusions. A prospective non-blinded trial (level II) involving 67 patients who underwent PLIF using two cylindrical threaded fusion cages was conducted by Haid et al. Study participants were randomly assigned to one of two groups: investigational (n = 34), who received rhBMP-2 on an absorbable collagen sponge (4-8 mg dose), and the control group (n = 33), who received autologous ICBG. Radiographs and CT scans were used to evaluate fusion at 6, 12 and 24 months. At the last follow up, the 92.3% fusion rate in the investigational group was higher than that of the control group at 77.8%, although this result was not statistically significant.

Multiple level III and level IV studies have been published regarding rhBMP-2 use for lumbar interbody fusions performed with the anterior (ALIF)\textsuperscript{129}, transfemoral (TLIF)\textsuperscript{124-126,131} and posterior (PLIF)\textsuperscript{124} approaches as well as postero-lateral (PLF)\textsuperscript{128-130} and axial (AxiaLIF)\textsuperscript{127} techniques. Almost all of these reports supported the efficacy of rh-BMP-2 for increasing reliable fusion rates. Recent Level III studies by Adams et al.\textsuperscript{124}, Gerszten et al.\textsuperscript{127} and Lee et al.\textsuperscript{128} however failed to document any significant differences in fusion rates with or without the use of rhBMP-2. In fact, after a retrospective cohort study Adams et al.\textsuperscript{124} concluded that rhBMP-2 may unnecessarily increase the risk of complications in routine PLIF and TLIF procedures.

Recombinant Bone Morphogenetic Protein-2 (rhBMP-2) in Cervical spine

Recombinant BMP-2 applications in the cervical region can be broadly grouped into anterior and posterior cervical fusions.

Anterior cervical fusion

Baskin et al.\textsuperscript{142} (level I) compared the safety and effectiveness of Infuse\textsuperscript{20} (rhBMP-2 / ACS) with AICBG placed inside a fibular allograft in a prospective, randomized, clinical pilot trial of anterior cervical discectomy with instrumented interbody fusion. At 24 months follow up, the study group showed mean improvement in neck disability index (NDI) and arm pain scores superior to that of the control group (p = 0.03). One-hundred percent fusion rates
were reported in both groups at 6, 12 and 24 months follow up, assessed with radiographs and CT scans. Buttermann et al.\textsuperscript{143} (level II) also concluded that ACDF performed with rhBMP-2 combined with allograft (0.9 mg BMP per level) was as effective as iliac bone graft in terms of clinical outcomes and fusion rates in a prospective cohort study. Both the study and the control group had similar improvement in all outcome scales (VAS pain, pain drawing, ODI, pain medication use, and opinion of treatment success) and neurological recovery over the 2- to 3-year follow-up period. Level IV studies by Khajavi et al.\textsuperscript{144}, Tumialan et al.\textsuperscript{145}, Boakye et al.\textsuperscript{146} also supported rhBMP-2 use for ACDF.

Posterior cervical fusion
Yan L\textsuperscript{147} recently reported on a prospective, randomized trial (Level II) for the use of ICBG plus rhBMP-2/ACS (Infuse™) vs. ICBG alone in 140 patients who underwent instrumented posterior fusion for the treatment of atlantoaxial instability. The fusion rate was 82.4\% (56 of 68) in the rhBMP-2/ACS group and 78.7\% (52 of 66) in the ICBG group (p = 0.782). Fusion evaluation was done by CT scans performed using 1-mm slices with coronal and sagittal reconstructions. Mean fusion time was 11 days shorter in the rhBMP-2/ACS group than in the ICBG group (p = 0.034). The rest of the data on rhBMP-2 use in posterior cervical fusions is limited at present to four level IV studies,\textsuperscript{148-151} all of which reported good to excellent fusion rates (82.8\% to 100\%) and patient outcomes, mostly pertaining to its application to occipito-cervical fusion.

Recombinant Bone Morphogenic Protein-2 (rhBMP-2) for deformity correction surgery
Two level II\textsuperscript{152,153}, two level III\textsuperscript{154,155} and one level IV\textsuperscript{156} studies investigating the efficacy of rhBMP-2 for adult spinal deformity correction were found. All groups related reliable fusion rates with rhBMP-2, ranging 93.5\% to 100\%, suggesting equivalence to autologous iliac crest bone. A level III study by Kim et al.\textsuperscript{154} further concluded that rhBMP-2 is in fact superior to ICBG in achieving fusion in long constructs for adult spinal deformity.

Recombinant Bone Morphogenic Protein-2 (rhBMP-2) for pediatric spinal surgery
Three level IV studies\textsuperscript{157-159} on the application of rhBMP-2 described excellent outcomes (100\% fusion rates), and supported rhBMP-2 as a successful adjunct to fusion in pediatric patients. However, the complication profile of BMP in this patient population seems to differ from that in adults and is yet to be completely understood.

Recombinant Bone Morphogenic Protein-2 (rhBMP-2) for spinal osteomyelitis
The use of rhBMP-2 in the treatment of pyogenic vertebral osteomyelitis is a relatively novel application. The safety and efficacy of rhBMP-2 in this clinical context is supported by three level IV studies.\textsuperscript{160-162}

Evidence Summary for rhBMP-2
Data of all evidence levels and all areas of application in cervical and lumbar spine fusion support the use of rhBMP-2 for achieving comparable fusion outcome and comparable efficacy to the gold standard autologous ICBG. Data on its use in pediatric spinal fusions and vertebral osteomyelitis, though promising, is presently limited and from lower quality studies.

Recombinant Bone Morphogenic Protein-7 (OP-1)
Osteogenic Protein-1, also known as rhBMP-7, is the only other member of the BMP family whose clinical application has been studied and published in human subjects. This product is available commercially as putty consisting of recombinant OP-1 (rhOP-1) with type I bovine collagen matrix and sodium carboxymethyl cellulose (CMC) as an additive, to be reconstituted with 0.9\% sterile saline solution. In 2004, the US-FDA granted approval of OP-1 putty for humanitarian device exemption (HDE) application as an alternative to autograft in compromised patients requiring revision posterolateral (inter-transverse) lumbar spinal fusions.

Osteogenic Protein 1 (OP-1) in lumbar spine
Delawi et al.\textsuperscript{163} in a prospective randomized study (level 1) evaluated OP-1 for single level instrumented posterolateral fusion surgery for degenerative or isthmic spondylolisthesis. 119 patients undergoing
surgery were randomized 1:1 for bone-grafting (59: ICBG group and 60: OP-1 group). The primary outcome measures were available and evaluated for 113 (56: ICBG group and 57: OP-1 group) of the 119 patients at one year, consisting of a combination of clinical outcomes and evidence of fusion as determined on CT scans. Non-inferiority was not demonstrated in the OP-1 group (40% success rate versus 54% in the ICBG group) in view of lower rate of fusion in the OP-1 group (54% in the OP-1 group versus 74% in the ICBG group, p = 0.03). This was in contrast to the results reported in a previous prospective randomized pilot study involving 36 patients, by the same group of authors. Fusion rates reported in this study were 63% in the OP-1 group and 67% in the autograft group (p = 0.95), with no significant differences in Oswestry scores between the two (p = 0.56). The authors previous conclusions that OP-1 combined with locally obtained autograft was a safe and effective alternative for iliac crest autograft was overturned in the newer study and it was asserted that OP-1 cannot be recommended in instrumented posterolateral lumbar fusion procedures.

Vaccaro et al. reported long term (4 year) outcomes with the use of OP-1 for non-instrumented posterolateral fusions in two independent level I studies, and OP-1 was found equivalent to autograft in terms of safety and efficacy in both. In one of those studies involving 335 patients with degenerative spondylolisthesis and spinal stenosis, a fusion rate of 74.8% for the OP-1 group was obtained compared to 77.4% for the autograft group. Fusion assessment was done by AP and lateral flexion extension radiographs and CT scans. The results were clinically comparable and not significantly different (p = 0.852). In another level I prospective randomized study, Kanayama concluded that OP-1 reliably induced new bone formation, even without autogenous bone graft, but that the fusion rate was not encouraging. The investigation included surgical exploration and histologic assessment of fusion masses. In the OP-1 group radiological fusion was seen in 77.77% of the cases, whereas histological assessment of fusion mass in the patients in this group revealed a fusion rate of 57.1%. In the control group where local autograft mixed with ceramic bone substitute was used, a 90% radiological fusion rate and 77.77% histological fusion rate was reported. The authors suggested that some modification of either the surgical technique or the carrier may be required for extensive use of OP-1 in instrumented posterolateral lumbar fusion. Furlan et al. reported good fusion rates (80%) and improved health related quality of life (HRQOL) outcomes in a level III study using OP-1 and autograft in 30 patients with high risk of spinal pseudarthrosis. The data consisted of cases of lumbar or lumbosacral fusions as well as cervical and occipitocervical fusions for high risk cases such as previous failed fusions, rheumatoid arthritis, systemic lupus erythematosus, Maroteaux-Lamy syndrome, ankylosing spondylitis, steroid use, immunosuppression, heavy smokers and osteopenic or osteoporosis. Level IV publications on a pilot study by Vaccaro et al. support the safety of OP-1 putty when used as an adjunct to autogenous iliac crest bone graft in uninstrumented posterolateral fusions for degenerative spondyloolisthesis. However these studies did not demonstrate improved efficacy of OP-1 combined with autologous bone as compared to autologous bone graft alone.

Evidence Summary for rhBMP-7 (OP-1)
Recently published level I studies suggest provide conflicting data on OP-1 compared to autologous bone grafts in terms of fusion rates and clinical patient outcomes for use in posterolateral lumbar fusions. Of note, rhBMP-7 (OP-1) has only been studied for posterolateral lumbar fusions. Compared to rhBMP-2, the use of rhBMP-7 for other lumbar spine procedures (e.g. ALIF, PLIF, TLIF, MIS) has not been investigated in clinical studies. Data on use in cervical fusions evaluating efficacy as a fusion extender is currently lacking.

Autologous growth factors (AGF)
This group consists of molecules such as Platelet derived growth factors (PDGF) and Transforming growth factor-β (TGF-β) which have been shown to have mitogenic effects on fibroblasts, osteoblasts, and mesenchymal cells. They are obtained from the buffy coat layer formed after centrifugation of whole blood, which is rich in platelets and white cells. The use of these compounds in combination with autologous.
ous bone (either iliac crest or locally derived), allograft or ceramics has been studied in spine fusion procedures.

**Autologous growth factors (AGF) use in lumbar spine**

In a prospective randomized trial (level I) involving 40 patients, Sys et al.¹⁷² studied the application of platelet-rich plasma (PRP) for single level posterior lumbar interbody fusion procedures. The authors reported that adding PRP to autologous bone in posterior lumbar interbody fusion did not lead to a substantial improvement or deterioration when compared to autologous bone alone. There was no difference between both groups in interbody healing on CT-scan reconstructed images at 3, 6, and 12 months (p = 0.741, p = 0.663, p = 0.951). Acebal-Cortina¹⁷⁴ (level II) performed a prospective non-randomized study on the use of autologous platelet concentrate (APC) mixed with local autograft plus tricalcium phosphate and hydroxyapatite for posterolateral lumbar fusions. Significantly lower fusion rates were reported in the study group (74.6 %) compared to the control group (92.5%) where APC was not added (p = 0.021). However in another level II study by Jenis et al.¹⁷⁵ autologous growth factors combined with an allograft carrier was shown to be equivalent in radiographic and clinical outcomes to autograft (89 vs. 85% fusion rates, respectively) in one or two-level instrumented lumbar interbody fusions. Radiographic follow-up at 12 months, 24 months, and longer evaluation included standing lateral flexion and extension dynamic studies. Hee et al.¹⁷⁶ (level II) concluded after a prospective study that autologous growth factors (AGF) in one- and two-level TLIFs did not result in an overall increase in spinal fusion rates compared to autograft, although faster fusions were documented with AGF. Level III¹⁷⁷ and level IV data¹⁷⁸-¹⁸⁰ are contradictory, with two studies¹⁷⁸,¹⁸⁰ supporting use in lumbar fusions and two others¹⁷⁷,¹⁷⁹ questioning efficacy in view of the inferior fusion rates obtained.

**Evidence Summary for Autologous Growth Factors (AGF)**

Autologous growth factor use in either lumbar or cervical spine fusions is not endorsed by the majority of the currently available level I and level II studies. Apart from a few papers (level III and IV data) which report encouraging results, most of the available literature fails to demonstrate any significant benefit with AGF use. The added time and cost involved in obtaining growth factor concentrates intraoperatively further weaken the case for AGFs as a suitable bone graft expander.

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**Allograft cellular bone matrix (ACBM) / Stem cell based products**

These are stem-cell-based allografts which retain their native bone-forming cells, including mesenchymal stem cells and osteoprogenitor cells, along with bone matrix components. ACBM is a novel group of bone graft expanders and, similar to autologous bone, are believed to potentially possess all three physiologic properties involved in normal bone healing; namely osteoconduction, osteoinduction, and osteogenesis.¹⁸²

**Allograft cellular bone matrix (ACBM) / Stem cell based products in lumbar spine**

The clinical use of ACBM products has been reported for lumbar spine fusions in five case series (level IV) publications.¹⁸²-¹⁸⁶ Three of these reported on the
use of a commercially available product Osteocel Plus™ (NuVasive Inc., San Diego, CA) whereas one study$^{185}$ used enriched autologous mesenchymal stem cells (MSCs) harvested from iliac crest bone marrow in combination with porous β-TCP granules. All of these studies reported good fusion rates (ranging from 90.2% to 92.3%) and supported the safety profile of this novel bone extender.

Allograft cellular bone matrix (ACBM) / Stem cell based products in cervical spine

Literature on use of allograft cellular bone matrix (ACBM)/ Stem cell based products for anterior cervical discectomy and fusion procedures is very recent. In a retrospective review of a matched cohort patient population (level III), Mc Anany et al.$^{187}$ evaluated 57 patients who underwent a one- or two-level instrumented ACDF procedure using interbody allograft, and Osteocel™ (NuVasive, San Diego, CA, USA). The patients were matched to a control group of 57 patients, where only interbody allograft spacer was used. At the 1-year follow-up, 50 of 57 (87.7%) patients in the Osteocel cohort demonstrated a solid fusion compared with 54 of 57 (94.7%) in the control group ($p = 0.19$). Thus lower fusion rates were found with Osteocel group, though not statistically significant. Another commercially available ACBM that has been studied and recently quoted is Trinity Evolution™ (Musculoskeletal Transplant Foundation, Edison, NJ, USA). Vanichkachorn$^{188}$ in a prospective series (level IV) of 31 patients undergoing single level ACDF, reported a radiological fusion rate of 93.5% at 12 months follow up. Eastlack RK$^{186}$ evaluated the use of Osteocel Plus™ cellular allograft for the anterior cervical disectomy and fusion of 249 levels in 182 patients (level IV). In subjects treated at a single level with a minimum of 24-month follow-up, 92% (79/86) of levels achieved solid bridging and 95% of levels demonstrated range of motion of less than 3°. In combined single and 2-level procedures, 87% (157/180) of levels achieved solid fusion and 92% (148/161) exhibited range of motion less than 3° at 24 months.

Evidence summary for Allograft cellular bone matrix (ACBM)/ Stem cell based products

Literature on the use of allograft cellular bone matrix/Stem cell based products is currently mostly in the form of level IV studies. More evidence on the use of these compounds for spine fusion is required to draw discrete conclusions, though limited available data show good fusion outcomes for both cervical and lumbar applications.

Synthetic Peptides

The combined use of bioactive peptides and porous implants or materials has led to a new generation of fusion extenders.$^{189}$ Perhaps the most well-known, P-15™ is a 15-residue synthetic polypeptide which acts as a binding factor for osteogenic cells on a domain of type I collagen.$^{190,191}$ The P-15™ peptide has been studied in a variety of animal models and is reported to enhance cell migration, induce osteoblast differentiation, and influence a pathway which results in new bone formation.$^{192,193}$ P-15™ gained FDA approval for the treatment of intrabony periodontal osseous defects due to moderate or severe periodontitis. It has been used in dental applications for over a decade and has recently been adopted for use in the spine. I-Factor™ (Cerapedics, Inc., Westminster, CO) is a proprietary composite consisting of P-15 adsorbed to anorganic bovine bone mineral (ABM). ABM consists of smooth, porous particles of “pure” deproteinated hydroxyapatite.$^{190,192}$ This bone graft combination of ABM and P-15, also known as i-Factor™, is claimed to facilitate bone formation.$^{192}$ I-Factor™ is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy. I-Factor™ peptide enhanced bone graft putty must be used inside an allograft bone ring and with supplemental anterior plate fixation.$^{192}$

B2A is another novel synthetic peptide which is similarly purported to increase osteoblast differentiation by interacting with native BMP-2 receptors and amplifying the response to stimulus.$^{194}$ B2A has osteoconductive and osteoinductive properties and animal model studies have demonstrated its superiority over autograft for achieving spinal fusion.$^{189,195}$ BioSET® Amplex™ (Biosurface Engineering Technologies™, Rockville, MD) is a commercially available bone graft kit that combines B2A with bi-phasic hydroxyapatite and β-tricalcium phosphate granules. The ce-
Ceramic granules used in Amplex™ have been FDA cleared for bone graft applications in the skeletal system.

ABM/P-15 in the cervical spine
One report (level 1) was available describing a single-blind randomized non-inferiority control trial. This study compared i-Factor™ (N=165) to iliac crest autograft (N=154) for use in single-level ACDF procedures for cervical radiculopathy. At 12 months follow-up both groups demonstrated a high fusion rate (88.97% for i-Factor and 85.82% for autograft, non-inferiority p = 0.0004) and equivalence with respect to the other clinical outcomes. The authors concluded that i-Factor met all FDA non-inferiority criteria and demonstrated safety and efficacy in this patient group.

ABM/P-15 in lumbar fusion
Two articles were found describing use of i-Factor™ for lumbar fusion procedures. Lauweryns et al. (level III) reported on a prospective clinical and radiological analysis of patients undergoing a PLIF procedure, comparing ABM/P-15 to local autograft. Two cages were placed, one on each lateral side of the interbody space, such that each patient received both the study material and autograft and therefore acted as his or her own control. Fusion was assessed by using CT images. At 24 months intra-cage bridging bone was observed in 95.56% of ABM/P-15 patients and 93.33% of autograft patients (no significant difference). The authors concluded that ABM/P-15 has equal or greater efficacy at 6 and 12 months compared to autograft. Mobbs et al. (level IV) reported on a prospective analysis performed in Australia of a nonblinded cohort of patients who received i-Factor for an ALIF. Evaluation for fusion in coronal, sagittal, and axial CT cuts was performed by two radiologists. At 24 months follow-up, 81-100% of patients who had undergone 3-, 2- or 1-level procedures exhibited fusion at all levels treated. The authors concluded that the ABM/P-15 composite demonstrated promising results for achieving fusion in patients who undergo ALIF for degenerative spinal diseases.

Evidence summary for ABM/P-15
Limited available data indicate non-inferiority of ABM/P-15 compared to autograft for single-level cervical fusion surgery. It is difficult to draw conclusions for use in the lumbar spine, although very recent level III and IV data suggest ABM/P-15 may be beneficial for lumbar fusion.

B2A in the cervical spine
No reports were found describing the clinical use of B2A in cervical spine surgery.

B2A for lumbar fusion
One article (level II) was available reporting initial results from a clinical trial comparing autograft to B2A. Twenty-four patients undergoing single-level TLIF were randomized to receive 150 mg/cm$^3$ of B2A, 750 mg/cm$^3$ granules of B2A, or ICBG. At 12-month follow-up there were non-significant differences (p = 0.08) in the rates of fusion, with the 750 group achieving the highest (100%) and the 150 group the lowest (50%). The author’s concluded that a 750 mg/cm$^3$ quantity of B2A appears to be superior to autograft when used for TLIF, acknowledging that no significant difference was demonstrated.

Evidence summary for B2A
Although initial clinical reports are promising, no recommendations can be made currently based on the limited data available regarding the use of B2A in spine surgery.

Discussion and conclusions
Despite the remarkable advancements in the field of bone graft alternatives for spinal fusion, no graft substitute/expander to date has demonstrated clear superiority over autologous iliac crest graft. Autograft, although mired by issues such as donor site morbidity and limited availability, remains the gold standard for spinal fusion. The ideal bone graft substitute with equal or superior efficacy combined with a minimal complication and risk profile does not appear to exist at this time. Allograft works well as an osteoconductive scaffold with some degree of osteoinductive properties. Demineralized bone matrix is associated with variable outcomes and is dependent upon the formulation used and differences in factors such as product batch. Ceramics appear to be a promising group of bone graft extenders, especially when com-
bined with bone marrow aspirates. The most published and extensively studied group of rhBMPs likely came closest to dethroning iliac crest autograft, when promising early reports emerged over a decade ago. However their complication profile, which was beyond the scope of discussion of this review, as well recent studies re-evaluating the risks/benefits with BMP use, require physicians to reconsider their routine application in spinal fusion procedures. Autologous growth factors and platelet gels have failed to demonstrate any advantage in terms of fusion efficacy. Lastly, data on stem cell based products and the synthetic peptides is currently very limited, having only recently popped up on the horizon. More better quality studies are required comparing these substitutes and extenders not just with autografts, but also with each other. Nevertheless, with such a plethora of available options, and with such diversity in the data on their application under different scenarios and in different combinations, it becomes necessary for spine surgeons to scrutinize all options carefully before adopting them in clinical practice.

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**Disclosures & COI**

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