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Bone grafting options for lumbar spine surgery: a review examining clinical efficacy and complications

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Abstract

Background: Iliac crest harvest has been considered the "gold standard" at producing successful arthrodesis of the lumbar spine but is also associated with many donor-site morbidities. Many alternatives have been used to avoid iliac crest harvest, including autologous bone from other donor sites, allogeneic bone, ceramics, and recombinant human bone morphogenetic proteins (rhBMPs). This review will highlight the properties and preparations of these graft types and their potential complications and reported clinical efficacy.

Methods: A Medline search was conducted via PubMed by use of the following terms in various combinations: lumbar fusion, freeze-dried allograft, fresh-frozen allograft, autograft, iliac crest, demineralized bone matrix, rhBMP-2, rhBMP-7, scoliosis, bone marrow aspirate, HEALOS, coralline hydroxyapatite, beta tricalcium phosphate, synthetic, ceramics, spinal fusion, PLF, PLIF, ALIF, and TLIF. Only articles written in English were assessed for appropriate material. Related articles were also assessed depending on the content of articles found in the original literature search.

Conclusions: Although iliac crest remains the gold standard, reported success with alternative approaches, especially in combination, has shown promise. Stronger evidence with limited sources of potential bias is necessary to provide a clear picture of their clinical efficacy.
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Keywords: Lumbar fusion; Bone graft; Iliac crest

The choice of bone graft for lumbar spinal arthrodesis takes many factors into consideration. Achieving a successful fusion is the primary goal when selecting a graft; however, other considerations that contribute to bone graft selection include patient morbidity related to autograft harvest at various sites, the status of the graft bed and local tissues, patient biological status, primary or revision status, mechanical environment, supplemental fixation, comorbidities and habits, cost of the graft, and patient expectations of surgical outcome. In selecting an appropriate graft, 3 important properties should be considered: osteoinductivity, osteoconductivity, and osteogenicity. Osteoinductivity is the ability of the graft to promote the migration of new bone precursor cells that can differentiate into osteoblasts and osteocytes to produce new bone. Osteoconductivity is the ability to allow bone growth and vascularization within and on the surface of the graft material. Osteogenicity is the presence of bone cells that can produce and maintain the growing bone.[1,2] Some materials that are not applied in a standalone fashion can be used as graft enhancers or graft extenders. Graft enhancers are materials that produce a stronger fusion mass when compared with primary graft material alone, whereas graft extenders are agents that produce the desired fusion result with less primary graft material.[3]

For fusions of the lumbar spine, iliac crest bone graft (ICBG) has been considered the "gold standard" for arthrodesis.[4,5] Although the fusion rates and time to fusion are generally excellent for ICBG, increased operating time and donor-site morbidity are major concerns with the use of this graft type.[6–8] As a result, alternative methods and techniques have been used to minimize donor-site morbidity. Avoiding the use of ICBG altogether has become more common with the proliferation of reports showing the effectiveness of other graft options such as bone marrow aspirate, local autogenous bone, allografts, synthetic materials, and recombinant human bone morphogenetic proteins (rhBMPs). Each of these alternatives has certain advantages

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and disadvantages when considering the overall clinical outcome for a patient.

In addition to ICBG, there are other autologous bone graft options including the rib, fibula, and vertebral body, but they also share the problem of donor-site morbidity, increased operative time, and blood loss.[4] Local autologous bone harvested during neurologic decompressive laminectomy is also a viable source of bone graft material. Usually, the quantity of bone graft available when using local autologous bone is much less than the potential quantity of ICBG and contains fewer live cells and channels for vascularization because of its predominantly cortical nature.[9]

Allograft bone is in relatively abundant supply and provides an ideal matrix for osteoconduction.[10] Fresh-frozen allograft also contains growth factors necessary for osteoinduction, but it carries the risk of disease transmission and potential immunologic reactivity.[11] Freeze-dried allograft minimizes these concerns, but it is brittle and more susceptible to fracture if used as a structural graft.[12] Demineralized bone matrix (DBM) is not useful as a structural graft material because of its amorphous consistency, but it can act as an osteoinductive and osteoconductive graft extender.[2]

Ceramic graft materials have recently become more popular. They are in abundant supply without any concerns of disease transmission and have low immunologic reaction. However, synthetic materials have not been shown to match human autograft or allograft as an ideal matrix for osteoconduction.[13]

This review will focus on the relative merits and disadvantages of autologous, allogeneic, and synthetic grafting options as well as rhBMP in lumbar spine procedures. It will also cover some grafting options used in scoliosis correction because these procedures can also involve the lumbar spine and may provide more evidence for or against the use of certain graft options.

Methods

A Medline search was conducted via PubMed by use of the following terms in various combinations: lumbar fusion, freeze-dried allograft, fresh-frozen allograft, autograft, iliac crest, demineralized bone matrix, rhBMP-2, rhBMP-7, scoliosis, bone marrow aspirate, HEALOS, coralline hydroxyapatite, beta tricalcium phosphate, synthetic, ceramics, and spinal fusion. Only articles in English were assessed for appropriate material, and related articles were also found through the search. The primary search for “graft lumbar fusion” yielded over 800 results. The most recent material was evaluated first for appropriateness, and further material was assessed for up to 15 years previously for the specific graft material and procedure. Animal studies were assessed when lack of clinical data was available to highlight future clinical directions. The majority of publications fell into the level II category of evidence—generally, retrospective reviews and nonrandomized trials. Level III evidence was assessed when limited or no level II evidence was available regarding a specific graft material; this included histologic and clinical case reports.

Discussion

Autograft

Autograft from the iliac crest has distinct advantages in producing a successful fusion. Harvested at the time of the procedure, ICBG contains many intact cells with osteoinductive growth factors. This is particularly true of the cancellous component of ICBG, which also contains readily available channels for vascularization.[14,15] Unfortunately, it has also been found that harvesting ICBG is associated with complications including hemorrhage, hematomas, herniation, infection, nerve damage, pelvic fracture, and chronic pain.[4,6,7,16,17] Significant life-threatening bleeding can result from damage to the superior gluteal artery in the greater sciatic notch.[17] Lumbar and abdominal hernias have been reported, and damage to the superior cluneal nerve, lateral femoral cutaneous nerve, and ilioinguinal nerve has been cited as a source of intractable neuralgic pain.[17–19] Donor-site pain is the most common morbidity associated with ICBG harvest, and many studies have shown that there is an appreciable intensity of chronic pain after the procedure. Kim et al[8] reported that the mean visual analog scale pain scores for 104 patients at 1 year of follow-up was 16.1 out of 100 (SD, 24.6). In addition, 16.5% of patients reported that donor-site pain at the time was worse than pain at the surgical site. Sasso et al[6] noted that 31% of 141 patients who received ICBG for an anterior lumbar fusion reported donor-site pain and 16% of the same pool also reported fair or poor appearance of their graft site at 2 years’ follow-up. Schwartz et al[7] found that patients who had donor-site pain at 3 years’ follow-up had difficulty in daily activities including household chores (19%), recreational activities (18%), walking (16%), sexual intercourse (16%), work (10%), and wearing clothing (9%).

Because of ICBG’s effectiveness at producing solid fusions, techniques have been developed to reduce morbidity at the donor site. Kurz et al cited many different techniques to avoid common complications with ICBG harvest. They recommended that the incision for a posterior approach be within 8 cm of the posterior superior iliac spine to avoid injury to the superior cluneal nerves. They also advised against harvesting near the sciatic notch to avoid injury to the superior gluteal artery and nerve, the sciatic nerve, and the ureter. The authors stated that use of a suction drain at the harvest site greatly reduced the incidence of significant hematoma formation, although there is some evidence that suction drainage of the harvest site does not significantly improve patient outcomes.[19–21] Singh et al[22] reported that patients who received a continuous infusion of 96 mL of 0.5% Marcaine (2 mL/h for 48 hours) at the harvest site reported significantly less donor-site pain and greater satisfaction after posterior spinal fusion at 4 years’ follow-up. Of the 9 patients who received an infusion, none had chronic

dysesthesia develop compared with 7 of 10 cases in the control group. In cases where synthetics and allograft were not available, Bapat et al[23] attempted to prevent iliac crest donor-site pain by using rib from a concurrent thoracotomy to reconstruct large iliac crest defects. The 30 patients in this study had significantly less intense and less frequent donor-site pain and fewer cosmetic complications at the donor site compared with the 24 patients in the control group.

Autologous bone from alternate sites is also available for grafting. Sawin et al[24] found successful fusion in 296 of 300 posterior cervical cases (98.6%) using rib autograft, whereas iliac crest successfully fused 49 of 52 cases (94%). Donor-site morbidity and other major complications were significantly less common in the rib autograft group compared with the iliac crest group. No study has directly compared the use of rib with ICBG in lumbar spine procedures, probably because lumbar procedures do not readily expose the ribs as they would for the thoracic spine.

Local bone is often preferred as a substitute to ICBG. It is readily available without the need for a separate harvest site. Lee et al[25] found that local bone from spinous processes and laminae was effective for instrumented posterolateral lumbar and lumbosacral fusion and produced good to excellent clinical results in 76% of 182 patients. Miura et al[26] reported using laminar bone in posterolateral lumbar interbody fusion. At 3 months' follow-up, 5 of 30 levels (16.7%) had evidence of radiographic arthrodesis. At 1 year of follow-up, all of the 25 levels available for evaluation had radiographically fused with significantly improved clinical outcomes. Although the results are promising, the loss to follow-up of nearly one-fifth of the levels in the study may have skewed the results.

Local bone may also serve as a graft extender. Hsu et al[27] reported that when combining equal parts ICBG and local bone for posterolateral fusion (PLF), patients had comparable fusion rates to those who received ICBG alone. One group reported that high-speed bur shavings collected from the lamina during decompression remained histologically viable.[28] Local bone has also been used for correction of the spine because of scoliosis. A retrospective study of 25 scoliosis corrections by Violas et al[29] found that the use of local bone alone with Cotrel-Dubousset instrumentation produced successful radiographic fusion in all cases over an average of 10 levels. All cases had a loss of correction of less than 5° after a minimum of 5 years' follow-up and improved clinical outcomes.

Stem cells have been proposed as another alternative to the use of autologous bone cells. Use of stem cells could potentially reduce the need for high doses of rhBMPs and improve overall fusion by introducing live bone precursor cells to a fusion site as opposed to inducing bone formation from a limited pool of preexisting cells.

Currently, only animal studies have been performed using stems cells that are purified and isolated before implantation. In a rat study by Miyazaki et al, stem cells derived from both bone marrow and adipose tissue that had been transfected with a bone morphogenetic protein (BMP) 2 gene from an adenovirus were implanted. Rats in these groups were compared with rats that had received rhBMP-2 alone, as well as rats that received stem cells without transfection of the BMP-2 gene. It was found that all 20 rats that received transfected stem cells produced solid spinal fusion and 15 of the 20 rats also produced fusion beyond the level of implantation and greater bone formation than the 10 rats that received just rhBMP-2. Rats that received stem cells without transfection did not show evidence of fusion, highlighting the importance of bone-inducing factors for arthrodesis.[30] Although experiments like these are extremely promising, the clinical applications of these studies may be somewhat farther off because of potential remnant virus infection from transfection and the involved preparation of the graft material required.

Currently, the use of bone marrow aspirate in the clinical setting has shown promise. Although aspirate, the liquid portion of marrow, does not provide as high a concentration of stem cells as the isolated and purified forms seen in animal studies, evidence suggests that there may be enough to induce bone formation.[31] The method for obtaining aspirate through insertion of a needle into the iliac crest, vertebral bodies, or anteromedial surface of the tibia is minimally invasive and has few complications.[32] A comparison of bone marrow obtained from both the iliac crest and vertebral body through posterior aspiration of 21 patients by McClain et al[33] found that the vertebral body had a much higher concentration of bone progenitors than iliac crest, making it a more useful site for aspiration. BMA can be mixed with allograft or autologous bone for delivery to the graft site. In a retrospective study of 88 patients undergoing posterior spinal fusion with dual rods and hooks or pedicle screws for adolescent idiopathic scoliosis by Price et al,[34] patients received either ICBG, freeze-dried corticocancellous bone, or BMA with DBM. Failure was defined as a loss of correction of 10° or more. The authors found that BMA mixed with DBM and ICBG had comparable failure rates (11.1% and 12.5%, respectively). Freeze-dried allograft had a failure rate of 28%. The authors also reported no incidence of pseudarthrosis with BMA and DBM but one each with both ICBG and freeze-dried allograft. Aspirate can also be delivered to the graft site via mineralized hydroxyapatite bovine collagen sponge (HCS) (HEALOS; DePuy Orthopaedics, Raynham, Massachusetts) that provides some structural support, an osteoconductive medium laced with cells, and osteoinductive growth factors. It can also be mixed with local bone or allograft. Carter et al[35] found that in transforaminal lumbar interbody fusion and PLF, 95% of 22 levels receiving HCS with BMA produced a radiographically successful fusion. Neen et al[36] found that HCS with BMA was comparable to ICBG for PLF procedures but ineffective for use in interbody fusions. They reported an 84% fusion rate in 25 patients compared with a fusion rate of 94% with autograft in 25 patients at 2 years' follow-up. They stated that when interbody fusions were not

taken into account, arthrodesis rates were comparable to autograft. In a study by Kitchel[37] patients had HCS and BMA placed on one side for PLF and ICBG on the contralateral side. The author reported that radiographic outcomes on both sides of the arthrodesis were comparable. Patients had a fusion rate of 84% over 25 levels with autograft and 80% of 25 levels fused with HCS/BMA along with significant improvements in patient outcomes at 1 and 2 years' follow-up.

Cases of osteomyelitis present more of a challenge with respect to graft materials that can be used without promoting persistent infection. Lu et al[38] reported using rib autograft in a titanium cage for treatment of osteomyelitis of the thoracolumbar spine, with 1 pseudarthrosis occurring in 8 cases by use of either anterior or posterior approaches for thoracic and thoracolumbar fusions. In a retrospective study, Moran et al[39] reported that use of a vascularized fibular graft was the most successful for reconstruction and fusion of complex spinal cases in which tumor resection or osteomyelitis had occurred. Of the 14 grafts that were used, 12 (86%) produced successful results with a healing time between 3 and 10 months. A study by Weinstein et al[40] found that removing all bone graft and instrumentation before fusion may not be indicated if the graft still appears viable, although they did recommend aggressive debridement with delayed closure.

Allograft

Allograft bone is an abundant source of material for spinal fusions. Allograft bone provides an ideal matrix for new bone formation and does not have the drawbacks that come with the use of ICBG: increased operating time, increased blood loss, and donor-site morbidity.[4]

In all cases of allograft, cellular debris from dead cells in the allograft can lead to an immune response, resulting in slower incorporation of the graft and inflammation at the fusion level. The specific preparation of allograft can diminish or eliminate BMPs available for osteoinduction.[11] There are 3 commonly used forms: fresh-frozen allograft, freeze-dried allograft, and DBM.[4]

Fresh-frozen allografts involve the simplest preparation method of all the allograft types. After the allograft is harvested, it is treated with an antibiotic solution and frozen at −70 °C.[11] Fresh-frozen grafts have been shown to have the greatest strength of any type of structural allograft, but they also carry a risk of disease compared with freeze-dried bone, although disease transmission can be minimized with proper screening and harvesting techniques. The risk of contracting HIV from properly screened and harvested allograft bone is approximately 1 in 1.6 million, less than the chance of contracting HIV from a blood transfusion.[12] According to Mroz et al,[41] 2 cases of hepatitis C transmission and 1 case of hepatitis B have been reported for fresh-frozen allograft bone, although they believed that the risk of transmission may be understated. Storage of allograft is also a concern. Laitinen et al[42] reported that fresh-frozen allograft stored at −40 °C, the current recommendation, had much higher rates of lipid oxidation relative to grafts stored at −70 °C over a period of 3 years, decreasing both the viability and quality of the graft.

Freeze-dried allografts are also treated with an antibiotic solution and frozen. Ninety-five percent of the water is then removed, allowing it to be stored at room temperature.[11,12] Not only are freeze-dried grafts easier to maintain, but they are also associated with an even smaller risk of infection and immunologic compromise; the chances of contracting HIV from a freeze-dried allograft are 1 in 2.8 billion, and no cases of HIV transmission have ever been reported with freeze-dried grafts.[11,43] The downside to the use of structural freeze-dried bone is potentially decreased mechanical stability relative to fresh-frozen bone, making freeze-dried allograft more susceptible to fracture. Compared with fresh-frozen bone, Cornu et al found that freeze-dried bone had a significant but small reduction in ultimate stress (18.9%) and stiffness (20.2%).[44] A contradictory study by Brantigan et al found that there was no significant difference between the compressive strength of fresh-frozen, freeze-dried, and ethylene oxide–treated allograft bone.[45] Irradiation of freeze-dried allograft is also common to enhance sterility, but this has been shown to degrade graft strength.[12] A study by Hamer et al found that a graft with a standard irradiation dose of 28 kGy had a 64% reduction in energy to failure compared with fresh-frozen allograft.[46] Another study, by Currey et al, found that grafts irradiated with 29.5 kGy had a considerable decrease in the work required for graft fracture compared with fresh-frozen graft (0.3-0.6 kJ/m^2 compared with 6.8–12.6 kJ/m^2).[47] The study by Cornu et al also found a 71% reduction in work to fracture when irradiated with 25 kGy.[44] Aside from the potential reduction in mechanical stability, freeze drying and irradiation also denature endogenous BMPs, rendering them ineffective in the induction of bone formation.[11]

DBM is bone that has been acid treated to have the mineralized portion removed while maintaining the organic matrix and growth factors.[4] During the treatment process, BMPs that were once coupled to the mineral bone matrix and unavailable to induce bone formation are freed by the acid and make DBM weakly osteoinductive. As a result of its preparation, DBM is weakly osteoconductive because the organic portions of bone, such as collagen, remain. Approximately 93% of DBM consists of collagen, whereas only 5% consists of other growth factors, a fraction of which are BMPs.[2] Osteoinductivity may be variable within a single manufacturer's product and between manufacturers because of differences in graft production processes and inconsistencies in other parameters such as the source of the bone, which depends on the individual donor and the site of harvest. In a study using rat model by Wang et al,[48] 3 different commercial DBM preparations were compared. Fusion rates were 14 of 18 levels (78%) for Osteofil (Medtronic Sofamor Danek, Memphis, Tennessee), 11 of 17 levels (65%) for Grafton (Osteotech, Eatontown, New Jersey), and 0 of 17 levels for Dynagraft (GenSci Regeneration

Sciences, Irvine, California). There was no statistically significant difference in fusion rates between Osteofil and Grafton. Schizas et al[49] found that DBM was useful as a graft extender for both local bone and ICBG. They compared 33 patients who had local bone or ICBG augmented with DBM with 26 patients who received ICBG or local bone alone. The groups were equivalent with respect to radiographic fusion and self-reported outcomes. Although the literature has supported the use of DBM as a potential graft extender, there was no clinical evidence to support its use as a standalone graft material.

The literature has shown mixed results on the use of allograft alone. In a study by Gibson et al,[50] clinical outcome scores from a total of 69 patients who had PLF were similar between allograft- and autograft-treated individuals. Patients were evaluated by use of a questionnaire but were not assessed radiographically. In a prospective randomized trial comparing fresh-frozen and freeze-dried structural femoral ring allograft in anterior lumbar interbody fusion (ALIF), Thalgott et al[51] also reported no significant difference in 40 patients' self-reported outcomes between the use of freeze-dried and fresh-frozen allograft. Radiologic evaluation showed that 40 of the 56 levels (71%) using allograft of either kind fused, although 10 of the 16 pseudarthrosis patients were smokers. Of the 15 patients who required a revision for pseudarthrosis, 10 had received freeze-dried grafts, although the increased incidence was not statistically significant. In a prospective study of 144 patients undergoing PLF, Jorgenson et al[52] compared ICBG alone, ICBG mixed with ethylene oxide–treated allograft, and ethylene oxide–treated allograft alone. Patients served as their own controls by placing ICBG on one side of the spine and the composite on the other side. The authors found that ICBG was significantly superior at producing fusion radiographically compared with allograft alone and allograft mixed with ICBG.

Because of the extensive fusion requirements for correction of scoliosis, allograft bone is a readily available alternative to iliac crest. In an early study of allograft use in place of iliac crest, Dodd et al[53] randomized 40 patients to receive either ICBG or femoral head allograft. At 6 months' follow-up, the groups were clinically and radiographically comparable. Various other retrospective studies using freeze-dried allograft have also been performed more recently, with reported pseudarthrosis rates ranging from 1.1% to 7.3% and loss of correction ranging from 3.4% to 10%.[54–57] A recent prospective study was performed by Nakazawa et al[58] with 36 patients undergoing correction for scoliosis due to Duchenne muscular dystrophy. Patients were randomized to receive either ICBG or allograft bone. Radiologic loss of correction and clinical outcomes were similar between the 2 groups.

Generally, the literature indicates that fresh-frozen structural allograft for interbody indications is preferred. Despite the small chance of disease transmission and potential immunogenic complications, the structural integrity and presence of growth factors make it superior to both freeze-dried and DBM allografts.

Synthetic grafting options

Synthetic materials avoid the complications of the use of autologous and allogeneic bone, but currently, they cannot provide an optimal osteoconductive and osteoinductive environment without another graft material because they only mimic the mineral portion of bone.[13] The most popular options for synthetic grafting material are coralline hydroxyapatite (CHA) (Pro Osteon; Biomet Spine, Parsippany, New Jersey) and β-tricalcium phosphate (β-TCP) (Vitoss [Orthovita, Malvern, Pennsylvania] and OSferion [Arthrex, Naples, Florida]).[13] Although there have been no clinical data available, silicated ceramic graft materials (Actifuse; ApaTech, Foxborough, Massachusetts) have also shown promise in animal studies.[59,60]

β-Tricalcium phosphate

β-TCP has a mineral structure similar to normal bone leading to few immunologic complications.[13] Consisting of 39% calcium and 20% phosphate, dissolution of the graft through phagocytic resorption creates a medium rich in substrates for osteogenesis. However, there can be an inflammatory reaction due to remaining debris from the graft if it is broken down too quickly.[13,61] Not osteoinductive on its own, β-TCP can be augmented with bone marrow aspirate, rhBMP-2, or traditional bone autografts and allografts.

Although there are no clinical or animal studies for β-TCP dissolution and bone incorporation in the lumbar spine, a rat study by Fujita et al in the ENT literature found that bone deposition occurred on the surface of parietal bone β-TCP block implants at 2 weeks after implantation. At 24 weeks' follow-up, β-TCP blocks showed evidence of fracture and resorption.[62]

Ogose et al[63] performed a histologic analysis on a series of patients undergoing revision spine fusion. Specimens were removed 12 days to 160 weeks after implantation. It was found that 2 of 5 specimens had capillary proliferation and collagen formation within the micropores of the material along with bone formation on the surface of the graft and osseous integration into the native trabecular bone at 4 weeks and 72 weeks after implantation. A specimen removed at 2 weeks after implantation was found to have osteoclast precursors, along with collagen and microvascular proliferation within the material, although there was no reported bone deposition on the surface of the material. Patients whose grafts were removed at 12 days and 160 weeks after implantation showed minimal bone deposition and cellular proliferation. The case study shows evidence for the osteoconduction of β-TCP and provides a potential timeline for graft incorporation and bone formation in the absence of in vivo clinical studies. Epstein[61,64,65] has reported multiple studies combining β-TCP and local bone. A preliminary study reported that 91% of 53 instrumented PLF levels were successfully fused with a 50:50 mixture of

β-TCP and local bone.[61] Only 1 case required surgical revision. A subsequent report by the same author found that using β-TCP to augment ICBG or local bone for PLF resulted in a 15% pseudarthrosis rate in 60 patients at 2 years' follow-up in non-instrumented cases.[64] Pseudarthroses occurred mostly in older patients (mean age, 76 years vs 70 years), women (7 female patients vs 2 male patients), and patients with a past history of smoking (4 of 9 vs 23 of 60). The most recent study by Epstein[65] reported that 76 of 79 levels (96%) fused in single-level cases and 19 of 21 cases (90%) completely fused over 2 levels when β-TCP augmented local bone in instrumented PLF cases. Pseudarthrosis only occurred in smokers. Although the reports show some promise, the lack of a proper control group using ICBG may only confirm that further study into the use of β-TCP is warranted, not necessarily that it is superior to, or even equivalent to, ICBG. Dai and Jiang[66] found equivalent self-reported outcome scores and radiographic assessments for 62 patients undergoing instrumented PLF with β-TCP and local bone or ICBG.

Use of ceramics, especially β-TCP, has also been reported in scoliosis correction. The first report came from Ransford et al[67] in a multisite prospective study of 341 patients comparing ICBG and/or rib autograft with β-TCP (Triosite; Zimmer, Swindon, England). At 18 months' follow-up, the autograft group had an 8% (4°) loss of correction compared with 3% (2°) in the experimental group. Miyazaki et al[68] conducted a meta-analysis of the literature and found that Ransford et al was the only group to present level I evidence for the use of β-TCP in the scoliosis literature. In a prospective study by Delecrin et al[69] comparing ICBG and local bone with a mixed block of β-TCP and HA, 28 patients in the experimental group had less intraoperative blood loss and similar radiographic and clinical outcomes at a minimum of 2 years' follow-up. They recommended use of ceramic material alone only in patients aged between 13 and 25 years because their age favored better healing. Use of β-TCP as a graft extender for scoliosis correction has also been tested. Muschik et al[70] found comparable results between patients who received allograft mixed with autologous bone and patients who received β-TCP (chronOS; Mathys Medical, Ltd, Brussels, Belgium) with autologous bone. The most recent report, from Lerner et al,[71] found that loss of curve correction after a minimum of 2 years' follow-up was 2.6° in a study group of 20 patients who received β-TCP compared with 4.2° in 20 patients who received ICBG. The authors reported 1 case of pseudarthrosis in the experimental group. There was no evidence of β-TCP remaining at the pseudarthrosis site when it was histologically evaluated.

Coralline hydroxyapatite

Hydroxyapatite (HA) forms the mineral component of human bone and can be synthesized from sea coral for use in bone grafting. Depending on the type of coral used, CHA grafts can be made with different porosities and different pore diameters changing the nature of the graft. Because of its rigid structure, CHA can function well as a structural graft. HA can coat an internal structure of calcium carbonate, the calcium salt of which coral normally consists. These grafts are typically resorbed over the course of 6 to 18 months. Grafts that consist completely of HA are typically resorbed at a rate of 2% to 5% per year and can provide structural support for the lifetime of a patient if necessary.[13] The same animal study by Fujita et al cited earlier also tested CHA blocks in rat parietal bone, finding bone deposition at 2 weeks after implantation and stability with minimal signs of resorption and no signs of fracture at 24 weeks' follow-up, providing more evidence of the long-term stability of solid CHA.[62] Although graft material stability is important, interference with bone formation due to inadequate dissolution must be taken into account when considering the optimal graft for a patient because solid fusion is the ultimate goal.

CHA, like β-TCP, can serve as a graft extender but is not effective as a standalone material because it does not have an osteoinductive component. Although it has shown success in animal models,[72] CHA has shown mixed results in the literature. Lee et al[73] found that use of CHA with local bone was comparable to iliac crest in patients undergoing posterolateral lumbar interbody fusion. Although the short-term outcome scores of the group using iliac crest were better, at 1 year postoperatively, there was no statistical difference in both fusion rates (39 of 47 levels [83%] for CHA compared with 40 of 47 levels [85%] for ICBG) and self-reported outcome scores. The study showed patient satisfaction, but it was not able to prove radiographic superiority and was therefore not helpful in determining the true effectiveness of CHA. A study by Korovessis et al[5] found that the 20 patients who had undergone PLF with a graft consisting of CHA, local bone, and BMA had significantly less operating time, blood loss, and pain than patients who received ICBG alone or ICBG augmented with CHA, local bone, and BMA. All 3 groups achieved adequate fusion. They reported that CHA was least effective when used with small amounts of local bone and emphasized the important of fusion bed preparation for producing a successful arthrodesis. In a review of a broad range of grafting options, Miyazaki et al[68] found that Korovessis et al presented level I evidence for CHA use. Despite this, the authors believed that the report of results may have been unclear at times, especially with respect to the somewhat ambiguous report of outcome assessment scores of the patients. Although this study showed some success with the use of local bone combined with CHA, another study, by Hsu et al,[27] found that CHA was only successful at augmenting ICBG and not local bone. They reported that when compared with a contralateral ICBG graft, 15 of 19 levels (79%) fused when ICBG was combined with CHA whereas only 10 of 19 levels (53%) fused with the use of local bone augmented with CHA.

Bone morphogenetic protein

rhBMPs have garnered attention because of their osteoinductive capabilities. rhBMPs have been shown to be effective with graft extenders but have also proven to be effective as a bone graft substitute. However, their cost and recent reports of complications in the literature have tempered enthusiasm for their use. rhBMP molecules have been developed through molecular cloning techniques. Although several types of rhBMP molecules are believed to induce bone formation, rhBMP-2 (Infuse; Medtronic Sofamor Danek) and rhBMP-7 (OP-1; Stryker Biotech, Hopkinton, Massachusetts) have been marketed for clinical application. Of these, only rhBMP-2 has been Food and Drug Administration (FDA) approved for use in ALIF within a titanium cage.[74] However, numerous other off-label applications of rhBMP in spine surgery have been reported.[1,65,75–86] rhBMP molecules are thought to interact with other signaling molecules to promote osteoblast differentiation and osteogenesis.[87,88] Carriers are used to hold the rhBMP in place until osteoblast differentiation and osteogenesis are initiated, which typically occurs over several weeks. Carriers include synthetic polymers, calcium phosphate ceramics, and type I collagen. Although the carriers differ in terms of structural properties, type I collagen is often used with rhBMP within an interbody cage to promote interbody fusion. PLF, however, requires a carrier with adequate structural integrity that allocates space for fusion mass formation around transverse processes. For this purpose, calcium phosphate ceramics including CHA and β-TCP have been used successfully.[89–91] Although much of the literature has provided high levels of evidence, the strong presence of industry funding in the following studies may call into question the complete objectivity of the results.

Clinical trials evaluating the efficacy of rhBMP-2 were first performed for ALIF, and this remains the only FDA-approved indication for rhBMP. In a prospective randomized study, 279 patients with single-level lumbar disc disease underwent ALIF with either 12 or 18 mg of rhBMP-2 on a type I collagen carrier or ICBG. Both grafting options were placed within a titanium cage.[74] The authors reported a fusion rate of 94.5% in the rhBMP group as compared with 88.7% in the ICBG group without the morbidities typically associated with ICBG. In another ALIF study of 77 patients, the use of rhBMP-2 within a machined allograft spacer was compared with allograft alone.[77] At 6 months' follow-up, patients receiving rhBMP-2 with allograft had a 100% fusion rate as compared with 98% with allograft alone. However, graft height subsidence was 27% in the rhBMP-2 group as compared with 4.6% in the allograft-only groups. A histologic study found no subsidence in rhBMP-2–enriched allograft recovered after revision of an anterior interbody release, and the authors argued that rhBMP-2 osteoinductivity and structural allograft biomechanical stability were both important for promoting new bone formation.[10] In a prospective study anterior interbody fusion rates with rhBMP-2–enriched allograft were 94%, 100%, and 100% at 6, 12, and 24 months' follow-up.[92] In comparison, fusion rates of 66%, 84%, and 89% were observed with allograft alone at identical time points. In a prospective nonblinded study using allograft dowels with either autograft or rhBMP-2 for ALIF, the authors found that 100% of patients in the rhBMP-2 group showed new bone formation at 12 and 24 months.[82] In comparison, 89% and 81.5% of patients in the autograft group showed fusion at 12 and 24 months, respectively. The authors noted, however, that 18% of patients in the investigational group showed radiographic and computed tomographic evidence of bone resorption within the vertebral body outside the allograft dowel. This was of no clinical consequence, however. In contrast, in a European cohort of 36 patients, rhBMP-2 was found to show a trend toward higher nonunion rates (56%) than ICBG (36%) for ALIF performed with a femoral ring allograft in standalone fusions.[81] The authors also noted early radiographic and computed tomographic evidence suggestive of aggressive resorption and resulting instability in the rhBMP-2 group, possibly accounting for the increased pseudarthrosis rate. Toth et al[93] found that the increase in resorption may be dose dependent based on a study in which they found markedly increased sheep osteoclast activity with increasing concentrations of rhBMP-2 when delivered to bone voids.

Although the use of rhBMP-2 is currently off-label for posterior-based procedures, the literature supports its use over ICBG.[65,80,88] In a prospective randomized study comparing rhBMP-2 and ICBG in PLF for single-level lumbar degenerative disease, the fusion rate was significantly higher for the rhBMP-2 group (88% vs 73%).[80] Clinically, however, the authors did not find the use of rhBMP-2 to correlate with improved performance on outcome measures. However, conflicting results have been reported. In a retrospective European study rhBMP-2 had equivocal but not superior performance compared with ICBG for primary single-level PLF.[78] The authors stressed the importance of including a cost-benefit analysis and clinical correlations with radiographic findings in such studies.

Recently, the literature has reported complications with the increased use of rhBMP-2 in spine procedures. The majority of reports come from off-label use of rhBMP-2 in the cervical spine and include dysphagia, swelling anterior to the vertebral body, and inflammatory response to the product.[94–98] In the lumbar spine there have been few reports of complications with the use of rhBMP-2, the most common complaint being radiculitis, although osteolysis, ectopic bone formation, and wound complications have also been reported.[99–101] For 102 randomized patients aged over 60 years undergoing lumbar spine fusion, rhBMP-2 was determined to be a viable replacement for ICBG in terms of safety, clinical efficacy, and cost-effectiveness.[65,78] Patients receiving rhBMP-2 had a total cost of care over a period of 2 years of $42,572 compared with $40,131 for ICBG. Glassman et al[102] also performed a cost-effectiveness study and

found that the hospital cost burden associated with the use of rhBMP-2 was higher ($24,736 vs $21,138) but that the total cost to the patients aged over 60 years was ultimately lower at 3 months after surgery because of the lower cost of inpatient care and rehabilitation for the rhBMP-2 group (overall, $33,860 on average for rhBMP-2 group and $37,227 on average for ICBG group).

Another rhBMP that has been used is BMP-7. Also referred to as OP-1, its FDA approval has been limited to treatment for nonunion of long bone fracture, and any use for lumbar spine procedures is considered off-label.[103] Cunningham et al[104] showed in a dog model that rhBMP-7 combined with autologous bone led to an accelerated rate of fusion at 4 weeks' follow-up compared with autologous bone alone and a greater rate of fusion at 6 months' follow-up (14 of 18 levels compared with 8 of 18 levels). Vaccaro et al[105] performed a randomized controlled study in which patients received either rhBMP-7 or ICBG in a PLF procedure. At 1 year of follow-up, 18 of 21 patients in the rhBMP-7 group reported improvements compared with 8 of 11 receiving ICBG. Radiographically, 14 of 19 patients who received rhBMP-7 had successful fusion compared with 6 of 10 who received ICBG. At 2 years' follow-up, self-reported outcome scores had improved in 17 of 20 patients (85%) receiving rhBMP-7 and successful radiographic fusion had occurred in 11 of 20 patients (55%).[106] In a study by Vaccaro et al[76] with a longer 3-year follow-up, 335 patients receiving either rhBMP-7 or autograft for non-instrumented PLF had equivalent outcomes both radiographically and clinically.

Because of promising results, Stryker Biotech sought FDA approval for OP-1 use in PLF procedures. An FDA advisory panel found that the pivotal study was too flawed to recommend device approval. Although the statistical analysis showed no evidence of inferiority on radiographic and clinical assessment for 160 patients receiving OP-1 compared with 58 patients receiving autograft, the panel had multiple concerns with the study. The most glaring concern was the change of the measure of radiographic success from the presence of bridging bone in PLF to just the presence of bone. Other concerns included inconsistent time measures for analysis of patient outcome, lack of blinding outside of radiographic assessment, and high exclusion of patients from the control group who may have been successful at 12 months' follow-up that could have raised the threshold for non-inferiority.[107]

Table 1
Funding sources and reported results for use of ceramics in lumbar fusion.

Funding source	Positive results	Negative results	Mixed results	Total
Industry	7	0	0	7
Hospital	0	0	1	1
Foundation	1	0	0	1
Not reported	3	0	1	4

Table 2
Funding sources and reported results for use of rhbmps in lumbar fusion.

Funding source	Positive results	Negative results	Mixed results	Total
Industry	13	2	3	18
Hospital	1	0	0	1
Foundation	0	1	0	1
Not reported	2	2	7	11

Industry's role in the literature

The use of synthetics in lumbar arthrodesis has shown some promise. However, attention has to be drawn to the funding sources for recent literature advocating the use of synthetic graft options over autograft and allograft. Khan et al[108] and Shah et al[109] have reported the influence of industry funding on outcomes in the orthopaedic and spinal literature, respectively. Both reports found that industry-funded studies were significantly more likely to report positive results. In our review of the 13 studies in which a synthetic graft material for lumbar arthrodesis was used, 7 received industry/corporate funding, 1 received hospital funding, 1 received foundation funding, and 4 did not report their source of funding. Of the 7 studies that received corporate funding, all reported positive results with regard to the graft material being used. The article that received foundation funding had positive results. The article that had hospital funding reported mixed results, and of those that did not report their funding source, 1 had mixed results and 3 had positive results. The results are summarized in Table 1.

Thirty-one articles were reviewed regarding rhBMP use. Eighteen had industry involvement; this included direct funding or author disclosure of received benefits. Of the 18 articles, 13 reported positive results with regard to the use of rhBMP, 3 reported mixed results, and 2 reported negative results. Thirteen articles did not receive funding from industry or did not report their source of funding. One received foundation funding and reported negative results, one received hospital funding and reported positive results, and the others did not report a funding source. Of the remaining articles, 7 reported mixed results, 2 reported negative results, and 2 reported positive results. The results are summarized in Table 2.[110]

Conclusions

Table 3 summarizes some of the advantages and disadvantages of each graft type as determined by this review. Although some studies have shown the efficacy of alternative grafting options to be equal or even superior to iliac crest, insufficient evidence exists to abandon its use altogether. In many cases this was because of low-level evidence, as many of the studies conducted did not present level I evidence and were instead retrospective reviews. In many cases the patient populations, though statistically sig-

Table 3
Summary of relative benefits and disadvantages of each type of grafting option.

Graft type	Advantages	Disadvantages
Iliac crest	Large availability, low cost, growth factors, live cells	Donor-site morbidity, increased blood loss, increased operative time
Local bone	Low cost, growth factors, live cells	Limited availability
Bone marrow aspirate	Live cells, growth factors	Needs carrier
Fresh-frozen allograft	Large availability, low cost, growth factors	Disease transmission, inflammation, no live cells
Freeze-dried allograft	Large availability, low cost	Brittle, no growth factors, no live cells
Demineralized bone matrix	Large availability, low cost	Amorphous, few growth factors, no mineral portion
rhBMP	Large availability, potent growth factors	Requires carrier, no live cells, expensive
Ceramics (β-TCP and CHA)	Large availability, structurally sound, low immunogenicity	No live cells, no growth factors, no organic matrix

nificant, were generally small when evaluated prospectively. In the case of β-TCP, much of the literature supporting its use has lacked proper controls, whereas with allograft and CHA, mixed results have been found when compared with iliac crest in the lumbar spine. Much of the evidence presented in favor of the use of BMPs was generally of a high level, but the potential bias that comes with industry involvement may call some results, or the lack of negative results, into question. Despite the drawbacks to some of these past studies, they still provide a great deal of evidence to warrant further investigation into the use of alternative grafting options for lumbar fusion that may provide safer, cheaper, and more efficacious outcomes for patients in the future.

References

1. Boden SD. The ABCs of BMPs. *Orthop Nurs* 2005;24:49–52; quiz 53–44.
2. Lee KJ, Roper JG, Wang JC. Demineralized bone matrix and spinal arthrodesis. *Spine J* 2005;5(Suppl):217S–23S.
3. Lieberman JR, Friedlaender GE. *Bone regeneration and repair: biology and clinical applications*. Totowa, NJ: Humana Press; 2005.
4. Herkowitz HN, International Society for Study of the Lumbar Spine. *The lumbar spine*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
5. Korovessis P, Koureas G, Zacharatos S, Papazisis Z, Lambiris E. Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. *Eur Spine J* 2005;14:630–8.
6. Sasso RC, LeHuec JC, Shaffrey C. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. *J Spinal Disord Tech* 2005;18(Suppl): S77–81.
7. Schwartz CE, Martha JF, Kowalski P, et al. Prospective evaluation of chronic pain associated with posterior autologous iliac crest bone graft harvest and its effect on postoperative outcome. *Health Qual Life Outcomes* 2009;7:49.
8. Kim DH, Rhim R, Li L, et al. Prospective study of iliac crest bone graft harvest site pain and morbidity. *Spine J* 2009;9:886–92.
9. Dempster DW, Ferguson-Pell MW, Mellish RW, et al. Relationships between bone structure in the iliac crest and bone structure and strength in the lumbar spine. *Osteoporos Int* 1993;3:90–6.
10. Lee JY, Zeiller S, Voltaggio L, et al. Histological analysis of a displaced femoral ring allograft spacer filled with a recombinant human bone morphogenetic protein-2-soaked collagen sponge. A case report. *J Bone Joint Surg Am* 2005;87:2318–22.
11. Ehrler DM, Vaccaro AR. The use of allograft bone in lumbar spine surgery. *Clin Orthop Relat Res* 2000;371:38–45.
12. Costain DJ, Crawford RW. Fresh-frozen vs. irradiated allograft bone in orthopaedic reconstructive surgery. *Injury* 2009;40:1260–4.
13. Brandoff JF, Silber JS, Vaccaro AR. Contemporary alternatives to synthetic bone grafts for spine surgery. *Am J Orthop* 2008;37:410–4.
14. Sandhu HS, Grewal HS, Parvataneni H. Bone grafting for spinal fusion. *Orthop Clin North Am* 1999;30:685–98.
15. Rihn JA, Gates C, Glassman SD, Phillips FM, Schwender JD, Albert TJ. The use of bone morphogenetic protein in lumbar spine surgery. *Instr Course Lect* 2009;58:677–88.
16. Chang CH, Lin MZ, Chen YJ, Hsu HC, Chen HT. Local autogenous bone mixed with bone expander: an optimal option of bone graft in single-segment posterolateral lumbar fusion. *Surg Neurol* 2008; 70(Suppl 1):S1:47–9; discussion 49.
17. Arrington ED, Smith WJ, Chambers HG, Bucknell AL, Davino NA. Complications of iliac crest bone graft harvesting. *Clin Orthop Relat Res* 1996;329:300–9.
18. Lipton DE, Nagendran T. A case of lumbar hernia occurring through surgical defect of iliac crest. *Ala Med* 1995;64:6–7.
19. Kurz LT, Garfin SR, Booth RE Jr. Harvesting autogenous iliac bone grafts. A review of complications and techniques. *Spine (Phila Pa 1976)* 1989;14:1324–31.
20. Sasso RC, Williams JI, Dimasi N, Meyer PR Jr. Postoperative drains at the donor sites of iliac-crest bone grafts. A prospective, randomized study of morbidity at the donor site in patients who had a traumatic injury of the spine. *J Bone Joint Surg Am* 1998;80:631–5.
21. Lang GJ, Richardson M, Bosse MJ, et al. Efficacy of surgical wound drainage in orthopaedic trauma patients: a randomized prospective trial. *J Orthop Trauma* 1998;12:348–50.
22. Singh K, Phillips FM, Kuo E, Campbell M. A prospective, randomized, double-blind study of the efficacy of postoperative continuous local anesthetic infusion at the iliac crest bone graft site after posterior spinal arthrodesis: a minimum of 4-year follow-up. *Spine (Phila Pa 1976)* 2007;32:2790–6.
23. Bapat MR, Chaudhary K, Garg H, Laheri V. Reconstruction of large iliac crest defects after graft harvest using autogenous rib graft: a prospective controlled study. *Spine (Phila Pa 1976)* 2008;33:2570–5.
24. Sawin PD, Traynelis VC, Menezes AH. A comparative analysis of fusion rates and donor-site morbidity for autogeneic rib and iliac crest bone grafts in posterior cervical fusions. *J Neurosurg* 1998;88: 255–65.
25. Lee SC, Chen JF, Wu CT, Lee ST. In situ local autograft for instrumented lower lumbar or lumbosacral posterolateral fusion. *J Clin Neurosci* 2009;16:37–43.
26. Miura Y, Imagama S, Yoda M, Mitsuguchi H, Kachi H. Is local bone viable as a source of bone graft in posterior lumbar interbody fusion? *Spine (Phila Pa 1976)* 2003;28:2386–9.
27. Hsu CJ, Chou WY, Teng HP, Chang WN, Chou YJ. Coralline hydroxyapatite and laminectomy-derived bone as adjuvant graft material for lumbar posterolateral fusion. *J Neurosurg Spine* 2005;3: 271–5.

28. Patel VV, Estes SM, Naar EM, Lindley EM, Burger E. Histologic evaluation of high speed burr shavings collected during spinal decompression surgery. *Orthopedics* 2009;32:23.
29. Violas P, Chapuis M, Bracq H. Local autograft bone in the surgical management of adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2004;29:189–92.
30. Miyazaki M. Comparison of human mesenchymal stem cells derived from adipose tissue & bone marrow for ex vivo gene therapy in rat spinal fusion model. *Spine (Phila Pa 1976)* 2008;33:863–9.
31. Ganong WF. Review of medical physiology. 13th ed. Norwalk, CT: Appleton & Lange; 1987.
32. Harrison TR. Harrison's online. New York: McGraw-Hill Health Professions Division; 1998.
33. McLain RF, Fleming JE, Boehm CA, Muschler GF. Aspiration of osteoprogenitor cells for augmenting spinal fusion: comparison of progenitor cell concentrations from the vertebral body and iliac crest. *J Bone Joint Surg Am* 2005;87:2655–61.
34. Price CT, Connolly JF, Carantzas AC, Ilyas I. Comparison of bone grafts for posterior spinal fusion in adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2003;28:793–8.
35. Carter JD, Swearingen AB, Chaput CD, Rahm MD. Clinical and radiographic assessment of transforaminal lumbar interbody fusion using HEALOS collagen-hydroxyapatite sponge with autologous bone marrow aspirate. *Spine J* 2009;9:434–8.
36. Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N. Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. *Spine (Phila Pa 1976)* 2006;31:E636–40.
37. Kitchel SH. A preliminary comparative study of radiographic results using mineralized collagen and bone marrow aspirate versus autologous bone in the same patients undergoing posterior lumbar interbody fusion with instrumented posterolateral lumbar fusion. *Spine J* 2006; 6:405–11; discussion 411–2.
38. Lu DC, Wang V, Chou D. The use of allograft or autograft and expandable titanium cages for the treatment of vertebral osteomyelitis. *Neurosurgery* 2009;64:122–9; discussion 129–30.
39. Moran SL, Bakri K, Mardini S, Shin AY, Bishop AT. The use of vascularized fibular grafts for the reconstruction of spinal and sacral defects. *Microsurgery* 2009;29:393–400.
40. Weinstein MA, McCabe JP, Cammisa FP Jr. Postoperative spinal wound infection: a review of 2,391 consecutive index procedures. *J Spinal Disord* 2000;13:422–6.
41. Mroz TE, Joyce MJ, Steinmetz MP, Lieberman IH, Wang JC. Musculoskeletal allograft risks and recalls in the United States. *J Am Acad Orthop Surg* 2008;16:559–65.
42. Laitinen M, Kivikari R, Hirn M. Lipid oxidation may reduce the quality of a fresh-frozen bone allograft. Is the approved storage temperature too high? *Acta Orthop* 2006;77:418–21.
43. Scarborough RRN. Inactivation of viruses in demineralized bone matrix. Paper presented at: FDA Workshop on Tissue Transplantation and Reproductive Tissue; June 20-21, 1995; Bethesda, MD.
44. Cornu, O, et al. Effect of freeze-drying and gamma irradiation on the mechanical properties of human cancellous bone. *J Orthop Res*, 2000;18(3): p. 426–31.
45. Brantigan, JW, et al. Compression strength of donor bone for posterior lumbar interbody fusion. *Spine (Phila Pa 1976)*, 1993;18(9): p. 1213–21.
46. Hamer, AJ, et al. Biochemical properties of cortical allograft bone using a new method of bone strength measurement. A comparison of fresh, fresh-frozen and irradiated bone. *J Bone Joint Surg Br*, 1996; 78(3): p. 363–8.
47. Currey, JD, et al. Effects of ionizing radiation on the mechanical properties of human bone. *J Orthop Res*, 1997;15(1): p. 111–7.
48. Wang JC, Alanay A, Mark D, et al. A comparison of commercially available demineralized bone matrix for spinal fusion. *Eur Spine J* 2007;16:1233–40.
49. Schizas C, Triantafyllopoulos D, Kosmopoulos V, Tzinieris N, Stafylas K. Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study. *Arch Orthop Trauma Surg* 2008;128:621–5.
50. Gibson S, McLeod I, Wardlaw D, Urbaniak S. Allograft versus autograft in instrumented posterolateral lumbar spinal fusion: a randomized control trial. *Spine (Phila Pa 1976)* 2002;27:1599–603.
51. Thalgott JS, Fogarty ME, Giuffre JM, Christenson SD, Epstein AK, Aprill C. A prospective, randomized, blinded, single-site study to evaluate the clinical and radiographic differences between frozen and freeze-dried allograft when used as part of a circumferential anterior lumbar interbody fusion procedure. *Spine (Phila Pa 1976)* 2009;34: 1251–6.
52. Jorgenson SS, Lowe TG, France J, Sabin J. A prospective analysis of autograft versus allograft in posterolateral lumbar fusion in the same patient. A minimum of 1-year follow-up in 144 patients. *Spine (Phila Pa 1976)* 1994;19:2048–53.
53. Dodd CA, Fergusson CM, Freedman L, Houghton GR, Thomas D. Allograft versus autograft bone in scoliosis surgery. *J Bone Joint Surg Br* 1988;70:431–4.
54. Yazici M, Asher MA. Freeze-dried allograft for posterior spinal fusion in patients with neuromuscular spinal deformities. *Spine (Phila Pa 1976)* 1997;22:1467–71.
55. Grogan DP, Kalen V, Ross TI, Guidera KJ, Pugh LI. Use of allograft bone for posterior spinal fusion in idiopathic scoliosis. *Clin Orthop Relat Res* 1999;369:273–8.
56. Jones KC, Andrish J, Kuivila T, Gurd A. Radiographic outcomes using freeze-dried cancellous allograft bone for posterior spinal fusion in pediatric idiopathic scoliosis. *J Pediatr Orthop* 2002;22: 285–9.
57. Knapp DR Jr, Jones ET, Blanco JS, Flynn JC, Price CT. Allograft bone in spinal fusion for adolescent idiopathic scoliosis. *J Spinal Disord Tech* 2005;18(Suppl):S73–6.
58. Nakazawa T, Takaso M, Imura T, et al. Autogenous iliac crest bone graft versus banked allograft bone in scoliosis surgery in patients with Duchenne muscular dystrophy. *Int Orthop*. 2009 Jun 16. [Epub ahead of print].
59. Hing KA, Wilson LF, Buckland T. Comparative performance of three ceramic bone graft substitutes. *Spine J* 2007;7:475–90.
60. Wheeler DL, Jenis LG, Kovach ME, Marini J, Turner AS. Efficacy of silicated calcium phosphate graft in posterolateral lumbar fusion in sheep. *Spine J* 2007;7:308–17.
61. Epstein NE. A preliminary study of the efficacy of beta tricalcium phosphate as a bone expander for instrumented posterolateral lumbar fusions. *J Spinal Disord Tech* 2006;19:424–9.
62. Fujita, R. Bone augmentation osteogenesis using hydroxyapatite and beta-tricalcium phosphate blocks. *J Oral Maxillofac Surg*, 2003; 61(9): p. 1045–53.
63. Ogose A, Kondo N, Umezu H, et al. Histological assessment in grafts of highly purified beta-tricalcium phosphate (OSferion) in human bones. *Biomaterials* 2006;27:1542–9.
64. Epstein NE. An analysis of noninstrumented posterolateral lumbar fusions performed in predominantly geriatric patients using lamina autograft and beta tricalcium phosphate. *Spine J* 2008;8:882–7.
65. Epstein NE. Beta tricalcium phosphate: observation of use in 100 posterolateral lumbar instrumented fusions. *Spine J* 2009;9:630–8.
66. Dai LY, Jiang LS. Single-level instrumented posterolateral fusion of lumbar spine with beta-tricalcium phosphate versus autograft: a prospective, randomized study with 3-year follow-up. *Spine (Phila Pa 1976)* 2008;33:1299–304.
67. Ransford AO, Morley T, Edgar MA, et al. Synthetic porous ceramic compared with autograft in scoliosis surgery. A prospective, randomized study of 341 patients. *J Bone Joint Surg Br* 1998;80:13–8.
68. Miyazaki, M. An update on bone substitutes for spinal fusion. *Eur Spine J*, 2009;18(6): p. 783–99.
69. Delecrin J, Takahashi S, Gouin F, Passuti N. A synthetic porous ceramic as a bone graft substitute in the surgical management of

scoliosis: a prospective, randomized study. *Spine (Phila Pa 1976)* 2000;25:563–9.
70. Muschik M, Ludwig R, Halbhubner S, Bursche K, Stoll T. Beta-tricalcium phosphate as a bone substitute for dorsal spinal fusion in adolescent idiopathic scoliosis: preliminary results of a prospective clinical study. *Eur Spine J* 2001;10(Suppl 2):S178–4.
71. Lerner T, Bullmann V, Schulte TL, Schneider M, Liljenqvist U. A level-1 pilot study to evaluate of ultraporous beta-tricalcium phosphate as a graft extender in the posterior correction of adolescent idiopathic scoliosis. *Eur Spine J* 2009;18:170–9.
72. Boden SD, Martin GJ Jr, Morone M, Ugbo JL, Titus L, Hutton WC. The use of coralline hydroxyapatite with bone marrow, autogenous bone graft, or osteoinductive bone protein extract for posterolateral lumbar spine fusion. *Spine (Phila Pa 1976)* 1999;24:320–7.
73. Lee JH, Hwang CJ, Song BW, Koo KH, Chang BS, Lee CK. A prospective consecutive study of instrumented posterolateral lumbar fusion using synthetic hydroxyapatite (Bongros(R)-HA) as a bone graft extender. *J Biomed Mater Res A* 2009;90:804–10.
74. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002;15:337–49.
75. Alt V, Chhabra A, Franke J, Cuche M, Schnettler R, Le Huec JC. An economic analysis of using rhBMP-2 for lumbar fusion in Germany, France and UK from a societal perspective. *Eur Spine J* 2009;18: 800–6.
76. Vaccaro AR, Lawrence JP, Patel T, et al. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis: a long-term (>4 years) pivotal study. *Spine (Phila Pa 1976)* 2008;33:2850–62.
77. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD. Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. *J Bone Joint Surg Br* 2007;89:342–5.
78. Glassman SD, Carreon L, Djurasovic M, et al. Posterolateral lumbar spine fusion with INFUSE bone graft. *Spine J* 2007;7:44–9.
79. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Puno RM, Johnson JR. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. *Spine (Phila Pa 1976)* 2005;30:1694–8.
80. Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine (Phila Pa 1976)* 2006;31:2534–9; discussion 2540.
81. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. *Spine (Phila Pa 1976)* 2006;31:E277–84.
82. Burkus JK, Sandhu HS, Gornet MF. Influence of rhBMP-2 on the healing patterns associated with allograft interbody constructs in comparison with autograft. *Spine (Phila Pa 1976)* 2006;31:775–81.
83. Kraiwattanapong C, Boden SD, Louis-Ugbo J, Attallah E, Barnes B, Hutton WC. Comparison of Healos/bone marrow to INFUSE(rhBMP-2/ACS) with a collagen-ceramic sponge bulking agent as graft substitutes for lumbar spine fusion. *Spine (Phila Pa 1976)* 2005;30:1001–7; discussion 1007.
84. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine (Phila Pa 1976)* 2002;27(Suppl 1):S26–31.
85. Glassman SD, Carreon LY, Djurasovic M, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized, controlled trial in patients over sixty years of age. *Spine (Phila Pa 1976)* 2008;33:2843–9.
86. Dimar JR II, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. *J Bone Joint Surg Am* 2009; 91:1377–86.
87. Papakostidis C, Kontakis G, Bhandari M, Giannoudis PV. Efficacy of autologous iliac crest bone graft and bone morphogenetic proteins for posterolateral fusion of lumbar spine: a meta-analysis of the results. *Spine (Phila Pa 1976)* 2008;33:E680–92.
88. Israel DI, Nove J, Kerns KM, et al. Heterodimeric bone morphogenetic proteins show enhanced activity in vitro and in vivo. *Growth Factors* 1996;13:291–300.
89. Zlotolow DA, Vaccaro AR, Salamon ML, Albert TJ. The role of human bone morphogenetic proteins in spinal fusion. *J Am Acad Orthop Surg* 2000;8:3–9.
90. Sandhu HS. Bone morphogenetic proteins and spinal surgery. *Spine (Phila Pa 1976)* 2003;28(Suppl):S64–73.
91. Khan SN, Fraser JF, Sandhu HS, Cammisa FP Jr, Girardi FP, Lane JM. Use of osteopromotive growth factors, demineralized bone matrix, and ceramics to enhance spinal fusion. *J Am Acad Orthop Surg* 2005;13:129–37.
92. Boden, SD, et al. The use of coralline hydroxyapatite with bone marrow, autogenous bone graft, or osteoinductive bone protein extract for posterolateral lumbar spine fusion. *Spine (Phila Pa 1976)* 1999;24(4): p. 320–7.
93. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of interbody fusion rates and clinical outcomes. *Spine J* 2007;7: 301–7.
94. Toth JM, Boden SD, Burkus JK, Badura JM, Peckham SM, McKay WF. Short-term osteoclastic activity induced by locally high concentrations of recombinant human bone morphogenetic protein-2 in a cancellous bone environment. *Spine (Phila Pa 1976)* 2009;34:539–50.
95. Vaidya R, Sethi A, Bartol S, Jacobson M, Coe C, Craig JG. Complications in the use of rhBMP-2 in PEEK cages for interbody spinal fusions. *J Spinal Disord Tech* 2008;21:557–62.
96. Cahill K, Chi J, Day A, Claus E. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA* 2009;302:58–66.
97. Smucker JD, Rhee JM, Singh K, Yoon ST, Heller JG. Increased swelling complications associated with off-label usage of rh-BMP-2 in the anterior cervical spine. *Spine (Phila Pa 1976)* 2006;31:2813–9.
98. Crawford CH III, Carreon LY, McGinnis MD, Campbell MJ, Glassman SD. Perioperative complications of recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge versus iliac crest bone graft for posterior cervical arthrodesis. *Spine (Phila Pa 1976)* 2009;34:1390–4.
99. Shields LB, Raque GH, Glassman SD, et al. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. *Spine (Phila Pa 1976)* 2006;31:542–7.
100. Benglis D, Wang MY, Levi AD. A comprehensive review of the safety profile of bone morphogenetic protein in spine surgery. *Neurosurgery* 2008;62(Suppl 2):ONS423–31; discussion ONS431.
101. Rihn JA, Patel R, Makda J, et al. Complications associated with single-level transforaminal lumbar interbody fusion. *Spine J* 2009;9: 623–9.
102. Rihn JA, Makda J, Hong J, et al. The use of RhBMP-2 in single-level transforaminal lumbar interbody fusion: a clinical and radiographic analysis. *Eur Spine J* 2009;18:1629–36.
103. Glassman SD, Carreon LY, Campbell MJ, et al. The perioperative cost of Infuse bone graft in posterolateral lumbar spine fusion. *Spine J* 2008;8:443–8.
104. Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. *Spine J* 2005;5(6 Suppl): p. 240S–249S.

105. Cunningham BW, Shimamoto N, Sefter JC, et al. Osseointegration of autograft versus osteogenic protein-1 in posterolateral spinal arthrodesis: emphasis on the comparative mechanisms of bone induction. *Spine J* 2002;2:11–24.
106. Vaccaro AR, Patel T, Fischgrund J, et al. A pilot study evaluating the safety and efficacy of OP-1 Putty (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis for degenerative spondylolisthesis. *Spine (Phila Pa 1976)* 2004;29:1885–92.
107. Vaccaro AR, Patel T, Fischgrund J, et al. A 2-year follow-up pilot study evaluating the safety and efficacy of op-1 putty (rhbmp-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. *Eur Spine J* 2005;14:623–9.
108. Tomihara K. Squamous cell carcinoma of the buccal mucosa in a young adult with history of allogeneic bone marrow transplantation for childhood acute leukemia. *Head Neck* 2009;31(4): p. 565–8.
109. Shah RV, Albert TJ, Bruegel-Sanchez V, Vaccaro AR, Hilibrand AS, Grauer JN. Industry support and correlation to study outcome for papers published in Spine. *Spine (Phila Pa 1976)* 2005;30:1099–104; discussion 1105.
110. Khan SN, Mermer MJ, Myers E, Sandhu HS. The roles of funding source, clinical trial outcome, and quality of reporting in orthopedic surgery literature. *Am J Orthop* 2008;37:E205–12; discussion E212.