

Updates in the Use of Bone Grafts in the Lumbar Spine

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Abstract

There has been a rapid increase in the number of lumbar fusion procedures performed in the last 10 years. Many of these procedures involve the use of bone grafts and specifically bone graft extenders and substitutes. Fusion depends on host and surgical factors including the selection of an appropriate graft. Bone grafts have osteoconductive, osteoinductive, and osteogenic properties. Iliac crest autograft has long been considered the gold standard for bone graft procedures as it inherently imparts all three. However, its use is associated with significant disadvantages including donor site pain, increased operative time, and insufficient availability. Allograft has been used to avoid the complications of donor site morbidity but has increased risks of rejection, disease transmission, and slower incorporation into the host bone. The use of alternative bone grafting options, such as demineralized bone matrix, synthetics (ceramics), bone morphogenetic proteins, collagen-based matrices, autogenous growth factors, and bone marrow aspirate, have become routine in some institutions. This review paper highlights the different bone grafting options currently available, discusses their pros and cons, and briefly reviews the relevant literature.

A growing number of lumbar spinal fusions are performed every year.¹ The choice of the appropriate bone graft needed to achieve a successful fusion can be an intimidating task. Currently, there are over 200 different commercial types of bone graft extenders, enhance-

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ers, and substitutes available from which to choose. Many surgeons still believe that iliac crest bone autograft (ICBG) is the gold standard for lumbar spinal fusion. Successful fusion has been demonstrated following iliac crest bone grafting in various applications in lumbar spine surgery.^{2,3} However, the morbidity rates associated with the use of ICBG remain high, with some studies reporting up to a 50% rate of persistent donor site pain, paresthesias, hematoma, and infection.⁴ This has led to an increasing push for the use and development of bone graft substitutes in spine surgery. Local autograft, allograft, demineralized bone matrix (DBM), synthetic bone grafts (ceramics), bone morphogenetic proteins (BMPs), autogenous growth factors (AGFs), bone marrow aspirate (BMA), and collagen based matrices are gaining popularity and being increasingly used in the lumbar spine. This paper will describe each graft type, evaluate the pros and cons of its use, and briefly review the relevant literature.

Autograft

Iliac crest bone graft has remained the gold standard for use as an adjunct in fusion of the lumbar spine. The massive amounts of cancellous bone that can be obtained from the inner table of the pelvis provide all the desired properties of osteoconduction, osteoinduction, and osteogenicity. Its large surface area has the optimal chemistry, structure, and porosity to serve as an excellent scaffold for new bone formation. Similarly, it contains all the necessary bone-forming growth factors and is inherently osteoinductive. Active and dormant osteoblasts give it osteogenicity. Furthermore, cancellous bone is easily re-vascularized and rapidly incorporated at the host site. There are no concerns for disease transmission and no risks of immunogenicity.

The use of ICBG has been well-supported in the literature with fusion rates as high as 93%.^{2,3,5,6} Unfortunately, morbidity associated with its use is also well-reported.

Donor-site morbidity can be attributed to the harvesting procedure of the ICBG. This procedure is associated with longer operative times, increased estimated blood loss, and a longer hospital stay.^{7,8} Elderly patients with increasing medical co-morbidities may have less ICBG available for harvest, and often the quality of this bone is poor. These concerns have led to the increasing body of research focused towards developing an ideal bone graft substitute.

Local Autograft

Similar to ICBG, local autograft is composed of the optimal chemistry, structure, and porosity desired in a bone graft and contains all bone forming growth factors to be osteoinductive, osteoconductive, and osteogenic. It is harvested from the lamina, spinous processes, facets, or ribs that are often resected during the lumbar decompression procedure. Because the bone is obtained locally, it is associated with less morbidity compared to ICBG (less blood loss and shorter operative time). Disadvantages include its relatively limited quantity and its greater composition of cortical bone compared to cancellous bone.

Some investigators are touting local autograft as the new "Gold Standard." Recent studies have shown equivalent fusion results for local autograft and ICBG in single level posterolateral fusion. Ohtori and associates prospectively examined single-level instrumented posterolateral fusion at L4-L5 with a local bone graft versus an ICBG for degenerative spondylolisthesis.⁹ Eighty-two patients were randomized into a local autograft group (N = 42) and an ICBG group (N = 40). Rate and time to fusion were equivalent (90% fusion at 8.5 months in the local bone graft group, and 85% fusion at 7.7 months in the ICBG group.) Sengupta and colleagues retrospectively compared 76 patients undergoing instrumented posterolateral fusion with local autograft (40 patients) or ICBG (36 patients).¹⁰ He reported similar fusion rates for single level fusions (80% at 28 months) but noted worse results in the local autograft group for multi-level fusions (20% fusion local autograft versus 66% ICBG). Schizas and coworkers prospectively reviewed 59 patients undergoing instrumented posterolateral fusion and at 12 months found equivalent fusion rates (76% local versus 68% ICBG).¹¹ Lee and associates reviewed a case series of 182 patients undergoing posterolateral instrumented fusion with local autograft only and found a fusion rate of 93%.¹²

Allograft

Allograft bone is harvested from cadaveric tissue donors and has been used for many years due to its osteoconductive and osteoinductive properties. It comes in a variety of forms including freeze-dried, fresh-frozen, cancellous chips, structural, and demineralized bone matrix (DBM). Compared to many of the bone graft substitutes in use today, it is relatively cheap and readily available. Depending on its form, it can have substantial structural strength. Its

use carries no associated donor-site morbidity. However, allograft incorporation into the host bone is slower and less complete compared to autograft.¹³ There is also a theoretical risk of disease transmission and immune rejection. Reported rates of disease transmission are 1 in 1.6 million with fresh frozen and 1 in 2.8 billion with freeze dried allograft. In spine surgery, there is only one reported case of HIV transmission.¹⁴

An and colleagues prospectively reviewed a cohort of 20 patients undergoing instrumented posterolateral fusion.¹⁵ Fusion rates for ICBG, frozen allograft, freeze-dried allograft, and a mixture of allograft and autograft were examined. He demonstrated a 0% fusion rate for freeze-dried allograft, and an 80% fusion rate with ICBG at 24 months. Gibson and coworkers also compared fresh frozen allograft to ICBG for posterolateral instrumented lumbar fusion.¹⁶ They did not report fusion rates instead citing the importance of clinical outcomes in determining the success of a lumbar fusion. Their cohort of 69 patients were followed up at 6 years, and no differences in clinical outcomes were seen with 33% of patients in both groups doing the same or worse and 36% requiring further surgery.

Freeze dried allograft is more commonly used to achieve posterolateral fusion. Much of the evidence supporting its use is reported in the adolescent idiopathic scoliosis fusion literature. Knapp retrospectively reviewed 111 patients at 5 years postoperative and using a combination of freeze-dried allograft chips and local autograft consistently achieved a 97% fusion rate with an average 5.9° loss of curve correction.¹⁷ Jones and colleagues also demonstrated excellent fusion rates of 93% in 55 patients with use of freeze-dried allograft chips and local autograft at 3-years follow-up.¹⁸

Allograft is also used as a structural interbody graft in the lumbar spine. Both fresh frozen and freeze-dried forms are used. Thalgott and coworkers compared fresh frozen and freeze-dried allograft used as a structural interbody graft in 50 patients undergoing circumferential lumbar fusion.¹⁹ At 24-months follow-up, using plain radiographs and CT scans, there was a greater fusion rate seen with fresh frozen allografts (65% freeze-dried versus 77% fresh frozen). Overall clinical outcomes were also equivalent, but a closer analysis found that nonsmoking patients fused with fresh frozen grafts had a significantly better clinical outcome.

Demineralized Bone Matrix

Demineralized Bone Matrix (DBM) has emerged to enhance, and often supplant, the use of freeze-dried allograft in posterolateral fusion. Through chemical processing, DBM is created from cadaveric bone. DBM retains the same properties as freeze-dried allograft but without the mineral content. It serves as an effective osteoconductive scaffold and contains type I collagen and non-collagenous proteins. Its osteoinductivity can be attributed to a small concentration of growth factors. It is manufactured in

Table 1 Demineralized Bone Matrix Products in Clinical Use

Product	Carrier
Grafton	Glycerol
Osteofil	Porcine collagen-based hydrogel
DBX	Hyaluronic acid
Allomatrix®	Calcium sulfate/carboxymethyl-cellulose

powder, fiber, pellet, gel, putty, and sheet forms (Table 1). Its advantages include its excellent handling characteristics and lack of donor morbidity. Much like allograft it is relatively inexpensive and unlimited in quantity compared to ICBG. Its main disadvantage is the inherently variable osteoinductive properties. This variability is present between the different manufacturing companies as well as by the same manufacturer. Another potential concern stems from animal studies that have shown DBMs to be nephrotoxic. Bostrom and associates implanted rats with very high doses of Grafton DBM and on autopsy found that the rats had died from hemorrhagic nephrotoxicity.²⁰ The glycerol carrier has been implicated as the nephrotoxic agent, but no adverse effects have been seen thus far clinically in humans.

Wang and colleagues used a rat model to show that commercially available DBMs have highly variable osteoinductive potentials.²¹ They compared Osteofil, Grafton, Dynagraft, and ICBG. After a posterolateral fusion was performed, the rats were sacrificed at 2, 4, 6, 8 weeks postoperative, and fusions were assessed with plain radiographs, manual palpation, and histology. Osteofil and Grafton showed significantly higher rates of fusion at all-time points compared to Dynagraft and ICBG. Bae and coworkers tested a single DBM product and used ELISA to quantify concentrations of BMP-2 and BMP-7.²² He found significant lot-to-lot variability in BMP concentrations and in vivo rates of fusion. Fusion rates correlated positively with BMP-2 and BMP-7 concentrations and predicted in a dose-dependent manner the in vivo fusion performance in rats. They also found that the concentrations of BMP-2 and BMP-7 were one million times less than concentrations required for fusion clinically.

Cammissa and associates prospectively reviewed their use of Grafton DBM gel composite in 120 patients undergoing instrumented posterolateral fusion.²³ At 24 months,

fusion results were equivalent between patients receiving both Grafton and ICBG compared to ICBG alone (52% versus 54%). Although the investigators concluded that the combined use of Grafton with ICBG helped to reduce the total volume of ICBG needed for fusion, their study had a 30% rate of lost to follow-up. Vaccaro and coworkers also prospectively reviewed 73 patients undergoing posterolateral fusion and reported that DBM Grafton Putty and bone marrow aspirate (BMA) combined produced fusion rates similar to ICBG (63% Grafton Putty and BMA versus 67% ICBG).²⁴

Synthetic Bone Graft Substitutes

Synthetic bone graft substitutes are osteoconductive agents that consist of coralline hydroxyapatite, β -tricalcium phosphate, silicate-substituted calcium phosphate, calcium sulfate, or a combination of these minerals. They have different fabrication techniques, crystallinity, pore dimensions, mechanical properties, and resorption rates (Table 2). Commonly referred to as “ceramics,” they have the desired properties of being non-immunogenic, unlimited in supply, easily sterilized, and readily stored. Disadvantages include their brittle structure and low tensile strength. Ceramics must be protected from excessive loading forces until a solid fusion has taken place. Early generations of ceramics were criticized for their extremely slow resorption times.

Coralline hydroxyapatite is synthesized from sea coral. Coral in its native form is calcium carbonate, which through a series of chemical reactions is processed to become coralline hydroxyapatite (Fig. 1). Pro Osteon 200 and 500R (Biomet, Warsaw, Indiana) are commercially available and have an interconnectivity and porosity similar to cancellous bone. It is available in granular or block configurations and in differing pore sizes. Korovessis and colleagues prospectively reviewed their 57 patients undergoing posterolateral fusion.²⁵ They compared ICBG, coralline hydroxyapatite, and BMA. At 12-months follow-up, they found that only ICBG had achieved fusion and recommended that coralline hydroxyapatite not be used alone for posterolateral fusion in the lumbar spine. Lee and coworkers reviewed their 32 patients undergoing combined posterolateral and posterior lumbar interbody fusion with coralline hydroxyapatite and local autograft or ICBG alone.²⁶ They found no differences in the rate of posterolateral fusion (87% fusion for Coralline HA and local autograft versus 89% fusion for ICBG).

Table 2 Synthetic Bone Graft Substitutes

Product	Trade Name
Coralline Hydroxyapatite	Pro Osteon 200/500R (Interpore Cross International, Irvine, CA)
Silicate-substituted calcium phosphate	Actifuse (Apatech, Foxborough, MA)
Calcium sulfate	Osteoset (Wright Medical Technologies, Arlington, TN)
Beta tricalcium phosphate	Vitoss (Orthovita, Malvern, PA)

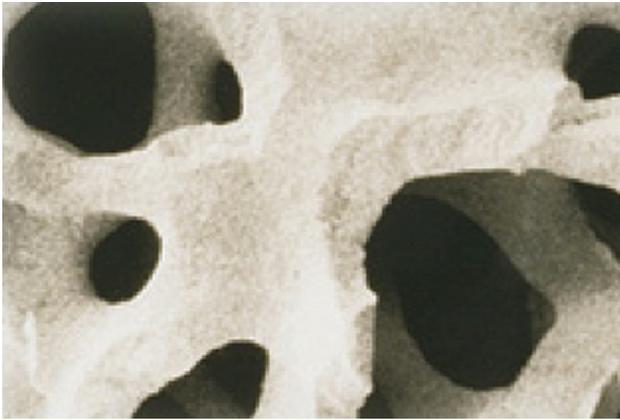


Figure 1 Scanning electron micrograph of coralline hydroxyapatite. Image courtesy of Integrated Optics International, San Diego, CA.

Silicate-substituted calcium phosphates have recently gained more attention as an effective bone graft enhancer. Actifuse is composed of 0.8% silica substituted hydroxyapatite and calcium phosphate (Fig. 2). Silicone has been shown in vitro studies to have osteogenic properties.²⁷ It has a 35% to 50% porosity, and the silicone allows for a different composition, geometry, and surface charge. Jenis and colleagues published a case series of 42 patients undergoing instrumented posterolateral fusion. Actifuse was combined with BMA obtained from iliac crest, and fusion rates of 35% at 6 months postoperative and 77% at 24 months postoperative were reported.

Calcium sulfate was first used in orthopaedic trauma patients to serve as a carrier for antibiotics and to function as a void filler in long bones. It has slowly gained use in the lumbar spine as a completely resorbable and biocompatible bone graft extender. It is quickly resorbed, usually within 6 to 8 weeks and has been implicated in causing postoperative wound drainage problems due to an excessive inflammatory reaction. This notoriety has been well documented in the orthopaedic trauma literature. Ziran and associates reported a 51% wound drainage and 30% infection rate



Figure 2 Silicate-substituted calcium phosphate.

following use of calcium sulfate in treating nonunions.²⁸ Chen and coworkers prospectively reviewed 74 patients who underwent posterolateral fusion with calcium sulfate and local autograft. At 33-months follow-up, they showed equivalent fusion rates with ICBG (87% calcium sulfate and local autograft versus 90% ICBG).²⁹ Niu and associates had far worse results with the use of calcium sulfate in 43 patients undergoing posterolateral fusion. At 12-months follow-up, there was a 45% fusion rate with calcium sulfate and BMA compared to ICBG alone.³⁰

Beta tricalcium phosphate (β -TCP) has a mineral structure similar to bone and is also very porous. It has a relatively quick resorption rate of 12 to 24 months but has not been associated with excessive postoperative wound drainage. Linovitz and colleagues reported on seven patients that underwent either anterior or posterior lumbar interbody fusion (ALIF/PLIF). A combination of β -TCP, freeze-dried cancellous allograft, and venous blood was used to obtain 100% fusion rates in the 12 levels that were fused. Dai and coworkers prospectively studied 62 patients undergoing posterolateral fusion with β -TCP and local autograft and found 100% fusion rates on plain radiographic assessment at 3-years follow-up in both groups.³¹ Ransford and associates reviewed a large cohort of 341 patients undergoing posterolateral fusion for adolescent idiopathic scoliosis (AIS) and demonstrated excellent success with average loss of correction of only 2° in the β -TCP group versus 4° in the ICBG group at 18-months follow-up.³¹ They also noted less wound healing issues with the β -TCP group compared to the ICBG group. Lerner and coworkers also reviewed β -TCP use in 40 AIS patients and at average of 20-months follow-up noted a loss of correction of 2.6° for the β -TCP group versus 4.2° for ICBG.³² Roughly 20% of the patients in the ICBG group complained of persistent donor site pain.

Bone Morphogenetic Proteins

With reported fusion rates of 95% to 98%, bone morphogenetic proteins have revolutionized the ability to achieve successful fusion in the lumbar spine. First discovered in 1965 by Dr. Marshall Urist, BMP belongs to the TGF- β superfamily of growth factors. BMP induces bone formation by influencing mesenchymal stem cells through a complex signaling pathway to stimulate osteoblasts to produce bone. Clinically, rhBMP-2 (Infuse) and rhBMP-7 (OP-1) are used in the lumbar spine.

BMP is relatively soluble and therefore requires the use of a carrier. The carrier plays the important role of delivering BMP to the fusion site, retaining it locally at an effective concentration and providing an environment compatible for fusion with the host bone. Therefore, the structure, biomechanical strength, and porosity of the carrier play an integral role in successful fusion. Common carriers include an absorbable type I collagen sponge (ACS), ceramics (hydroxyapatite, tricalcium phosphate),

synthetic polymers (polylactic acid, polyglycolic acid), and allograft.

Minamide and colleagues studied the biomechanical properties of three different BMP carriers in a rabbit model. They compared alpha-tricalcium phosphate cement, sintered bovine bone coated by type I collagen, and a type I collagen sheet. Alpha-tricalcium phosphate cement achieved the earliest solid spinal fusion followed by sintered bovine bone coated by type I collagen. Incidentally, the most widely utilized carrier for rhBMP-2, type I collagen, performed the worst. The investigators concluded that an effective BMP carrier requires sufficient biomechanical strength and possess a bony or porous structure.³³

The successful use of BMP is well-demonstrated in all types of lumbar spinal fusion. rhBMP-2 (Infuse, Medtronic) is FDA approved for use with metallic tapered cages in ALIF. It is widely utilized for a variety of applications in the lumbar spine, and these are considered "off-label." Burkus and coworkers demonstrated in a level I study with 279 patients undergoing ALIF for degenerative disc disease that rhBMP-2 had equivalent fusion rates to ICBG at 24-months follow-up.³⁴ rhBMP-2 on an absorbable collagen sponge was placed into two tapered threaded fusion cages, and the success of fusion was evaluated both by plain films and CT. Functional scores and neurologic status improved in both treatment groups. At 24 months, the investigational group's fusion rate (94.5%) remained higher than that of the control group (88.7%). At 2-years follow-up, 32% of patients reported graft site discomfort, and 16% were bothered by its appearance.

Boden and colleagues reported their initial results with the use of rhBMP-2 with a ceramic granule carrier in posterolateral lumbar fusions in 25 patients. Using plain radiographs and CT, they demonstrated higher fusion rates in the rhBMP-2 group than in controls (100% versus 40%) at 1-year follow-up. This included nine patients in the rh-BMP group who did not have any instrumentation. However, their results were limited by a higher proportion of workman's compensation, diabetics, and smokers in the ICBG group. Dimar and associates prospectively looked at 98 patients undergoing instrumented posterolateral fusion at 24 months with rhBMP-2 and a tricalcium-hydroxyapatite-collagen carrier and showed significantly higher fusion rates at 24-months follow-up for the rhBMP-2 group compared to ICBG (91% versus 73%).

Mummaneni and coworkers performed a TLIF in 40 patients, and at 9-months follow-up demonstrated a higher and quicker fusion rate for rhBMP-2 using plain radiographs (91% fusion at 3 months for rhBMP-2 versus 73% fusion at 4 months for ICBG).³⁵ This compound was FDA approved for revision posterolateral lumbar fusion in 2009. It is combined with a carboxymethyl-cellulose carrier to create a putty-like graft that has excellent handling characteristics. Johnsson and associates performed a prospective, randomized study of 20 patients who underwent single

level uninstrumented posterolateral fusion at L5/S1.³⁶ They used radiostereometric analysis to make 3-dimensional measurements of vertebral motion. At 12-months follow-up, they found no significant differences in fusion rates between rhBMP-7 and ICBG.

Vaccaro and colleagues performed a randomized multicentered study comparing rhBMP-7 to ICBG in 335 patients who also underwent uninstrumented posterolateral fusion. The investigators did not quantify fusion rates but instead noted the presence of new bone on CT scans. Seventy-five percent of the rhBMP-7 patients versus 77% of the ICBG patients had presence of new bone on CT scan. This was not statistically significant, but the presence of bridging bone across the intertransverse process region was dissimilar. Bridging bone was noted in 56% of the rhBMP-7 patients versus 83% of the ICBG patients. According to the investigators, this did not affect the stability of the fusion and clinical outcomes for both were equivalent at 3 years.

The multitude of studies demonstrating comparable fusion rates between BMP and ICBG is readily apparent. However, the large availability and viability of potent growth factors can have untoward effects as well. Although there are only a few documented cases of adverse events related directly to BMP use, there are certain safety issues and complications related to the use of BMP in the lumbar spine.

Ectopic bone formation has been described to occur in the neural foramen and the central canal after BMP use. The risk of forming ectopic bone is unknown, but postoperative hematoma and the use of hemostatic agents have been associated with its development. Ectopic bone tends to form along the anterior epidural space and along the track of BMP insertion. Haid and colleagues performed single-level PLIF on 67 patients with degenerative disc disease. They used either rhBMP-2 on a collagen sponge carrier or ICBG. On postoperative CT scans, they discovered that 71% of the patients in the rhBMP-2 group had formed ectopic bone in the canal. The patients were not symptomatic; the investigators noted that this was only a radiographic finding and not associated with any adverse clinical outcome.³⁷ Joseph and coworkers performed minimally invasive PLIF or TLIF on 33 patients and noted that 21% of the patients in the rhBMP-2 developed ectopic bone. Again these investigators noted no clinical sequelae associated with the heterotopic bone formation.³⁸

Radiculitis, occurring just days after surgery, is also a known complication of BMP use. Often imaging does not reveal evidence of neural compression. Mindea and associates retrospectively reviewed 43 patients who underwent minimally invasive TLIF and found an 11% rate of new postoperative radiculitis in the rhBMP-2 group. This occurred between 2 to 4 days postoperatively.³⁹ Rihn and coworkers also noted a 17% rate of radiculitis occurring on average 12 weeks postoperative on 75 patients undergoing single level TLIF with rhBMP-2.⁴⁰

Vertebral osteolysis is also a serious complication following BMP use. This phenomenon is associated with allograft resorption, cage migration, and subsidence. Although the etiology is unknown, end plate violation during disc space preparation has been cited as a possible cause. Lewandrowski and colleagues reviewed a series of 68 patients who underwent minimally invasive TLIF with rhBMP-2 and PEEK cages and had a 7% rate of vertebral osteolysis. All cases developed between 1 to 3 months postoperatively at the L5-S1 level and presented with worsening back pain with variable radicular pain. The defect developed in the L5 vertebral body in all five patients and spontaneously filled in 3 months later with resolution of symptoms.⁴¹ McClellan and coworkers noted a 69% (22 of the 32 levels reviewed) rate of osteolysis in 26 patients undergoing TLIF with rhBMP-2. They perform 1 mm cut CT scans at an average of 4.4 months post-operative. Fifty percent of these bone resorption defects were characterized as mild with less than 25% of the area of the interbody implant involved or less than 3x3 mm on any CT scan cut. However, 31% (7 of 22 levels) of the defects were described as severe with greater than 75% of the area of the interbody graft or greater than 1x1 cm on CT scan. The investigators noted that these bone resorption defects were associated with graft subsidence and lack of radiographic evidence of progression toward fusion in multiple cases. However, they did not comment on the clinical significance of these findings or overall fusion rates.⁴²

Wound dehiscence and infection have been reported in multiple studies with use of both rhBMP-2 and rhBMP-7. Boden and colleagues noted a wound dehiscence in 1 of his 11 patients that underwent an ALIF with rhBMP-2.⁴³ Luhmann and coworkers had a 3% rate of wound infection with use of rhBMP-2 after ALIF or posterior fusion.⁴⁴ One patient developed a deep wound infection after posterior fusion that required operative management for irrigation and debridement, and another patient developed a superficial wound dehiscence after ALIF that was managed non-operatively. Vaccaro and associates reported wound infections in 4 of 24 patients who underwent uninstrumented posterolateral fusions with rhBMP-7.⁴⁵ Although none required operative management, there were no such complications in the control allograft group.

Retrograde ejaculation (RE) associated with rhBMP-2 use during ALIF surgery has garnered more attention recently. Carragee and coworkers retrospectively compared the rate of RE in male patients after one- and two-level ALIF procedures with or without rhBMP-2.⁴⁶ They reported that patients who had fusions with rhBMP-2 had a 7.2% (5/69 patients) rate of RE compared with 0.6% in control patients (1/174). RE is a known complication of ALIF procedures as the superior hypogastric plexus crosses the lumbosacral junction in the retroperitoneal space directly anterior to the lower lumbar disc spaces. The Food and Drug Administration (FDA) documents reported higher

rates of RE after ALIF in the rhBMP-2 groups (8%) compared to controls (1.4%) but did not indicate if this finding was related to rhBMP-2 use.⁴⁷ A number of studies have shown higher rates of RE after transperitoneal compared to retroperitoneal approaches during ALIF.^{34,48} However, Carragee's study is the first to strongly suggest that rhBMP-2 use during ALIF is associated with an increased rate of RE. Based on these results, it may be advisable to counsel male patients about increased risks of sterility with rhBMP-2 use in ALIF procedures.

Autogenous Growth Factors

Autogenous growth factors (AGFs), which are obtained by the ultra-concentration of platelets, have had numerous reported uses in the lumbar spine. These AGFs include important growth factors like platelet-derived growth factor (PDGF) and transforming growth factor (TGF- β) that are known to promote chemotaxis and proliferation of mesenchymal stem cells and osteoblasts to enhance bone healing. AGFs are then combined with thrombin and either ICBG, local autograft, or allograft to form a cohesive graft material. Advantages of AGF include its osteoinductive capabilities and its lack of immunogenicity. The disadvantages include the need for pre-operative blood draw and platelet processing and the increased costs of a longer anesthesia and operating time. Blood is drawn on the day of surgery, and a two-stage pheresis is performed using a cell saver to separate out three fractions. The buffy coat, consisting of platelets and white blood cells, is processed to obtain the AGF concentrate, which has platelet concentrations 6 to 10 times the patient baseline. The fractions containing platelet-poor plasma and red blood cells are returned to the patient.

Initial results of AGF were encouraging when Lowery and coworkers reported the results of their first 19 patients treated with AGF for posterolateral and anterior lumbar interbody fusion. AGF was used with ICBG and or local autograft and coralline hydroxyapatite in all fusions. The investigators noted no pseudoarthrosis among the 23 levels they fused posterolaterally. However, the investigators were unable to draw any conclusions about the efficacy of AGF because ICBG or local autograft was used at every level of fusion.⁴⁹ Hee and associates prospectively examined 23 patients who underwent TLIF and at 2 years noted 90% to 100% fusion rate. Jenis reviewed 37 patients who received AP interbody fusion. At 2-years follow-up, they assessed interbody fusion by CT and noted equivalent fusion rates for both groups (89% AGF and allograft versus 85% ICBG). Clinical outcomes were similar for both groups.

However, more recent studies have been less encouraging. Weiner and colleagues retrospectively reviewed their experience with 59 patients who underwent single level uninstrumented posterolateral fusion.⁵⁰ The control group received ICBG only, and the AGF group received ICBG augmented

Table 3 Summary of Lumbar Bone Grafting Options

	Advantages	Disadvantages
Graft		
Iliac crest	Gold standard	Donor morbidity
Local autograft	Osteoinductive Osteoconductive Osteogenic	Limited quantity 
Allograft		
Fresh-frozen	Large availability, low cost, growth factors	Disease transmission
Freeze-dried	Large availability, low cost	No growth factors
DBM	Large availability, low cost	Few growth factors
Ceramics	Structurally sound, No immunogenicity	Requires osteoinductive cells
β-TCP	Porosity; mineral structure like bone	Structurally weak
CHA	Structurally sound	Slow resorption
Silicate-substituted Calcium phosphate	Structurally sound	Cost
Calcium sulfate	Resorbable; biocompatible	Wound drainage
rhBMP-2/7	Growth factors	Cost
AGF	Growth factors	Cost; efficacy?
BMA	Live cells, growth factors, low cost	Osteoinductive only
Vitoss	Structurally sound, Osteoinductive w/ BMA	Cost; bovine antigenicity?
Healos	Structurally sound, Osteoinductive w/ BMA	Cost; bovine antigenicity?

with AGF. Fusions were assessed by plain radiography, and at 2-years follow-up, there was a 62% fusion rate for the AGF group compared to 91% for the ICBG group. Castro and coworkers reported their results with AGF in TLIF and showed that at 3-years follow-up patients who had received AGF and ICBG had a 19% decreased fusion rate compared to those who had received ICBG only.⁵¹ Carreon and associates also showed disappointing results with use of AGF in their series of 76 patients undergoing instrumented posterolateral fusion. At 2-years follow-up, there was a 25% nonunion rate in the ICBG and AGF group compared to a 17% nonunion rate in the ICBG only group.⁵² Although the reasons for AGF failure are not entirely clear, possible theories for decreased efficacy include; poor concentrating techniques; platelet clumping; platelet gel fibrinolysis; and an inadequate platelet gel carrier for posterolateral arthrodesis.

Collagen-Based Matrices

Collagen-based matrices combine a bovine-based type I collagen with an osteoinductive agent, such as bone marrow aspirate (BMA), local autograft, or ICBG. Disadvantages include its lack of structural strength and theoretical risk of hypersensitivity to bovine collagen or disease transmission. Vitoss (B-TCP: OrthoVita, Malvern

PA, USA) and Healos (DePuy Orthopaedics, Inc.) are two of the more commonly used matrices. Vitoss is composed of a type I bovine collagen and β-Ca₃ PO₄ in a 50:50 ratio. It is very porous and when added to BMA, forms an osteoinductive and osteoconductive bone graft substitute. There are multiple case series reporting its use. Epstein and colleagues reported on 40 patients who underwent instrumented posterolateral fusion. Using Vitoss, BMA, and local autograft, they demonstrated a 96% fusion rate for single level and 85% fusion rate for two level fusions at 6-months follow-up.

Healos is composed of a type I bovine collagen and hydroxyapatite in an 80:20 ratio. Ploumis and associates demonstrated equivalent fusion rates for Healos with BMA and local autograft compared with allograft and local autograft in patients with lumbar degenerative scoliosis. Twenty-eight patients underwent posterolateral fusion, and at 2-years follow-up, similar fusion rates were observed in both groups (92% fusion for HEALOS/BMA/local autograft versus 94% fusion for allograft and local autograft). Clinical outcomes in regards to pain and function were no different. However, there was a significantly slower fusion rate in the Healos group.⁵³ Neen and coworkers reported a single surgeon's results of 50 patients who underwent

posterolateral fusion, PLIF, or circumferential fusion with Healos and BMA. The same procedures performed during an earlier three-year span served as the ICBG comparison group. Equivalent fusion rates (93% for both groups) were demonstrated in posterolateral fusions for the two groups with no significant difference in the subjective and objective clinical outcomes. However, fusion rates were significantly lower when Healos and BMA were used for lumbar interbody fusion compared to ICBG. There were no lasting complications associated with Healos compared with a 14% persistent donor site pain complication in the ICBG group. The investigators concluded that Healos was effective for posterolateral fusion but did not recommend using HEALOS alone for interbody fusion.⁵⁴

Bone Marrow Aspirate

Bone marrow aspirate (BMA) is both osteoinductive and osteogenic. It is typically used with a structural graft to give it mechanical strength. Its inherent advantages are the minimal harvest site morbidity associated with its use and the tremendous number of osteogenic mesenchymal cells that can be delivered to the fusion site. However, potential drawbacks include the fact that it requires an osteoconductive agent and that the amount of osteoinductive factors derived from the BMA are variable depending on the quality of the donor bone marrow. Curylo and associates used a rabbit posterolateral fusion model to show improved fusion rates with the concomitant use of BMA and ICBG. They reported 61% fusion rates with BMA and ICBG versus 25% fusion with ICBG only. Niu and coworkers prospectively evaluated 43 patients who underwent posterolateral fusion and at 12 months showed equivalent fusion rates for BMA and local autograft versus ICBG alone (86% versus 91%).

Conclusions

The wide array of available bone grafting options can make choosing the appropriate bone graft a daunting task (Table 3). Although numerous studies supporting the use of each of the graft types presented in this review are in the literature, much of the evidence is of low quality or is simply insufficient. Leading researchers have termed the quest to find justification for use of these new and expensive bone graft substitutes as the “burden of proof.” As such, ICBG remains the gold standard of all bone grafts. There is ample evidence to support the effectiveness of BMPs in achieving successful fusion in the lumbar spine. The use of local autograft is well supported for single level posterolateral fusion. There are several animal studies supporting the efficacy of ceramic bone grafts and initial clinical studies show ceramics and collagen matrices to be promising. However, with the current lack of high-level studies supporting the use of many of the bone graft enhancers and substitutes, future research will be critical to further evaluate the merits of each product.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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