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The Role of Osteobiologics in Spinal Deformity

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The estimated number of bone graft procedures in the United States per year approaches 500,000, and nearly half of these are for spinal fusion [1]. Unfortunately, the rate of nonunion for spinal fusion surgery has been reported to be between 5% and 35% [2]. Metabolic factors, host-specific factors, and surgeon technique have all contributed to disappointing fusion rates. Additionally, the finite availability of autogenous bone combined with the significant reported morbidity leaves the patient and surgeon lacking enthusiasm for harvesting autogenous iliac crest bone graft (ICBG). Although ICBG represents the "gold standard" in bone grafting material, recent developments in the understanding of osteobiology and the basic science behind bone healing have provided surgeons today with an abundance of bone graft options.

The process of graft incorporation can be divided into five stages:

1. Inflammation
2. Vascularization
3. Osteoinduction
4. Osteoconduction
5. Remodeling

The first is inflammation, which lasts for approximately 14 days. The decrease in fusion rates seen with the use of anti-inflammatory medications in the perioperative period points to the importance of this inflammatory phase [3]. The second stage is vascularization, during which capillary buds invade the graft. The third stage is osteoinduction, which begins 2 to 3 weeks after transplantation. The hallmark of osteoinduction is the differentiation of stem cells into osteoblasts. The fourth stage is osteoconduction, characterized by ingrowth into host bone and creeping substitution, the simultaneous creation of new bone by osteoblasts and resorption of graft bone by osteoclasts. The fifth stage is remodeling, which is a dynamic combination of the first four stages. Remodeling is typically complete by 1 year [4,5].

Autograft

Autogenous bone graft, usually from the iliac crest, remains the gold standard by which all alternatives are measured. Autograft bone possesses all the properties desired in a bone graft option, namely, osteoconductivity, osteoinductivity, osteogenesis, and mechanical strength (Table 1).

Disadvantages of ICBG can include donor site pain (3%–50%), neurovascular injury (2%), infection (2%–6%), hematoma (5%), seroma (5%), cosmetic deformity (3%), blood loss, bowel herniation (1%–5%), and iatrogenic fracture (1%) [6–9]. The cost of obtaining the ICBG and treating the morbidity associated with the harvest of ICBG can exceed $5000 per patient [10].

In spinal deformity surgery, the use of autograft has its limitations. Long fusions often require substantial amounts of graft material and can exceed the available amounts in the iliac crest. Instrumentation to the pelvis can also prohibit the extent to which the crest can be used without loss of fixation. In addition, the iliac crest is frequently a poor source of bone in revision cases, in which extensive or multiple harvests leave a paucity of

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Table 1
Bone-graft alternatives and their relative biologic properties

Grafting material	Osteoconduction	Osteoinduction	Osteoprogenitor cells	Immunogenicity	Donor site morbidity	Immediate torque strength
Cancellous autologous graft	++++	++	+++	−	+	−
Cortical autologous graft	+	±	±	−	+	++
Fresh allograft	+	±	−	++	−	++
Frozen allograft	+	±	−	+	−	++
Freeze-dried allograft	+	±	−	±	−	+
Ceramics	+	−	−	−	−	±
Demineralized bone matrix	+	++	−	−	−	−
Bone marrow	−	±	++	−	−	−
Particulate ceramic with bone marrow	++	±	++	−	−	−

From Gazdag AR, Lane JM, Glaser D, et al. Alternatives to autogenous bone graft: efficacy and indications. J Am Acad Orthop Surg 1995;3:3; with permission. © 1995 American Academy of Orthopedic Surgeons.

cancellous bone. In cases of neuromuscular scoliosis, the pelvis is often small and osteoporotic, yielding poor quantities of bone.

Even in cases in which abundant autograft is available, adult deformity cases can present a challenging environment in which to attain fusions. In the adult patient, the pseudarthrosis rate is substantial, especially if a long fusion (ie, T3 to sacrum) is being attempted, particularly in patients older than the age of 55 years [11]. To prevent postoperative pseudarthroses in long fusions to the sacrum, most spine surgeons recommend an anterior surgical procedure to increase stability and the likelihood of solid union. This anterior operation is typically a fusion of T11 to the sacrum done through a thoracoabdominal approach or a paramedian approach for fusion of the lower two to four lumbar levels. When performing a thoracoabdominal approach, a rib can be harvested for bone grafting; however, a single rib does not usually fill more than two disc spaces in the adult patient. With a paramedian approach, accessing a rib is not straightforward and other sources of bone graft are required (ie, anterior iliac crest). Use of fresh-frozen or freeze-dried femoral rings has gained some popularity in the anterior spine but is not universally accepted.

Allograft

Allograft bone is the second most commonly transplanted tissue, second only to blood [12]. There are many advantages to using allograft bone, and one of the most important is its availability in nearly unlimited quantities. It can be used alone or as an adjunct to autograft bone. Further, it saves the operative time associated with harvesting of autograft and avoids donor site morbidity. Allograft bone does not require human leukocyte antigen (HLA) cross-matching, because most of the antigenic stimuli are removed during processing, sterilization, and preservation [13].

Disadvantages include the possibility of disease transfer. The rate of HIV transfer from allograft bone is estimated at less than 1 in 1 million, although there has never been a documented case using freeze-dried bone. The risk of disease transmission of HIV or hepatitis is reportedly higher with fresh-frozen allografts [14]. The processing and sterilization procedures can lead to other changes in graft properties, such as a decrease in mechanical strength and osteoinductive potential.

Bone is a composite of organic proteins and minerals providing structural strength. The

mineral phase is composed mostly of crystalline calcium phosphate analogs. The organic phase consists of collagen and noncollagenous matrix proteins providing a scaffold for new bone growth. Thus, mineralized allograft, such as fresh-frozen or freeze-dried cancellous chips or cortical bone, is primarily osteoconductive in nature. Few growth factors and no cells survive processing and transplantation, leaving allograft with little osteoinductive and no osteogenic traits. The graft depends on contributions from the host bed for these. Fresh-frozen allografts retain their mechanical properties, whereas freeze-dried allografts can lose up to 50% of their original mechanical strength [13].

Cortical allografts provide significant mechanical strength, allowing for structural support. They incorporate slowly, however, by means of a process of periosteal new bone formation around the allograft. Cortical allografts do not fully incorporate and remain a mixture of necrotic and viable bone. Cancellous preparations, in contrast, lend little mechanical strength but have a much faster rate of incorporation. They incorporate with new bone forming on the surfaces of trabeculae, a much larger surface area than the edges of a cortical graft; further, they remodel completely with time with more rapid and complete revascularization [5].

These differing mechanical and biologic properties make each type of allograft suitable for different applications. Cortical allografts, such as femoral rings or fibular rings, can be useful in applications that require structural support in compression, such as anterior lumbar interbody fusions. Allograft can be useful in anterior spinal column reconstruction. Bridwell and colleagues [15] followed 24 patients prospectively who underwent thoracolumbar anterior column reconstruction with fresh-frozen allograft combined with posterior autogenous fusion and instrumentation with a minimum follow-up of 2 years. The allograft used anteriorly included eight tricortical iliac crests (five plus autogenous rib), three autogenous packed tibia, one autogenous packed femur, one femoral head, and one full-thickness ilium. Grafts maintained their position in 22 of 24 patients; only 1 patient had a nonunion.

Cancellous allograft, such as cancellous chips or particulate grafts, would be more suitable used alone or as autograft extenders in areas that need little mechanical strength but high osteoconductivity, such as posterolateral fusions [16]. These applications need faster incorporation, remodeling, and revascularization of bone graft. Knapp and colleagues [17] retrospectively studied the use of allograft in adolescent idiopathic scoliosis for posterior fusions with instrumentation in 111 patients with a minimum follow-up of 5 years. There were three pseudarthroses (2.7%) and 5.9% loss of correction, numbers comparable to those in previous studies using autograft. Bridwell and colleagues [18] analyzed 40 patients with neuromuscular scoliosis with an average 3- plus 9-year follow-up using allograft in combination with local bone graft for posterior fusions with instrumentation. Twenty-eight of 40 patients attained solid radiographic fusion with three definite pseudarthroses (7.5%). Nine patients were difficult to assess but did not have any obvious instrumentation failure.

Demineralized bone matrix

Demineralized bone matrix (DBM), as the name implies, is allograft material that has been stripped of its mineral phase, leaving behind the organic phase, an osteoconductive composite matrix of collagen and noncollagenous proteins. Because osteoinductive growth factors are contained within the organic phase, DBM has a higher potential for osteoinductive new bone formation. In fact, bone morphogenetic proteins (BMPs) were first isolated by Marshall Urist in 1965 from extracts of demineralized bone. These glycoproteins are the primary osteoinductive components of DBM. DBM is available in multiple forms, including putty, gel, flexible sheets, or mixed with cortical chips [13].

The quantity of BMPs in DBM, however, is questionable. Peterson and colleagues [19] showed the variability in effectiveness among different manufacturers of DBM. Their study in athymic rats found that fusion rates were highest with Grafton (Osteotech, Eatontown, New Jersey), less so with DBX (Musculoskeletal Transplant Foundation [MTF]; available through Synthes, Paoli, Pennsylvania), and lowest with AlloMatrix (Wright Medical, Arlington, Tennessee). Histologic analysis of the spines in groups I, II, and III demonstrated varying amounts of residual DBM and new bone formation. Subsequently, Bae and colleagues [20] showed by means of ELISA the high variability in BMP-2, BMP-7, and BMP-4 content among different manufacturers of DBM, and even among different lots of DBM from the same manufacturer. In addition, the absolute

quantity was on the order of 1×10^{-9} g of BMP per gram of DBM.

Despite the potential for osteoinductivity, clinical studies of DBM used in spinal fusion have failed to show success rates similar to those of autograft. In the lumbar spine, results are mixed, with some studies showing enhancement of arthrodesis when mixed with allograft or autograft and other studies showing similar or inferior results to autograft. A prospective study by Cammisa and colleagues [21] with posterolateral autograft on one side and autograft plus Grafton DBM on the contralateral side demonstrated no difference in fusion rates between groups, with 54% being judged as fused on the autograft side and 52% judged as fused on the Grafton side. This implies that the use of allograft with Grafton DBM as a bone graft extender does not significantly affect fusion rates. Thus, although DBM may be useful as a bone graft extender or enhancer, it may be questionable in stand-alone situations.

Ceramics

During the 1990s, the ceramic class of osteobiologics first came into widespread use. Chiroff and colleagues [22] were the first to discover that marine invertebrate corals shared a strikingly similar microscopic porous structure with bone, and they postulated the use of these corals as a bone graft substitute. Composed of calcium sulfate (hydroxyapatite [HA] and tricalcium phosphate), bovine collagen, natural coral, calcium carbonate, or a combination thereof, these materials are named for the genera of marine corals after which they are fashioned. Classification as an applicable ceramic requires the following four qualities: (1) tissue and mechanical compatibility, (2) stability in bodily fluids, (3) ability to withstand sterilization, and (4) capability to be molded into functional shapes.

All the ceramics act as an osteoconductive scaffold when placed next to bone. Alone, they are neither osteogenic nor osteoinductive. Their pore size between 100 and 500 μm is critical for the fibrovascular ingrowth of osteoid matrix (Fig. 1). Mineralization of osteoid proceeds over the scaffold in a manner more consistent with intramembranous than enchondral ossification, and remodeling by means of multinucleated giant cell–like cells begins only when the surgeon provides the graft with stability, viability, and proximity, the so-called ''triad'' of osteoconduction [23].

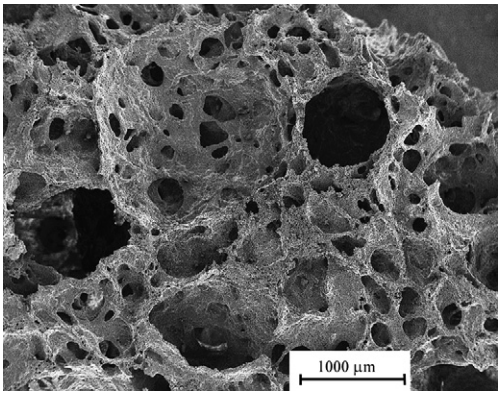

Fig. 1. High-power scanning electron micrograph of β-tricalcium phosphate (TCP) bone graft substitute (Vitoss) demonstrating an interconnecting porosity of between 100 and 500 μm. (*Courtesy of* OrthoVita, Malvern, PA; with permission).

Unlike allograft, ceramics usually do not induce an inflammatory response in the host organism. The ability to sterilize ceramics lowers the risk of infection greatly compared with allograft as well. Ceramics may be fashioned into blocks or granules to fit specifically into bony voids, and the overall cost tends to be less than that of other bone graft substitutes.

Coralline ceramics are patterned after naturally occurring corals, containing endoskeletons with interconnecting porosity [24]. Work by Chapman and colleagues [25] and Holmes and colleagues [26] demonstrated unequivocally that porous HAs undergo a process of extensive fibrovascular ingrowth mimicking that of autograft in vivo. This interconnecting porosity seems to be the key physical property to ensure bony ingrowth, but it comes at the cost of reduced graft mechanical properties. The mechanical strength and porosity of the coralline ceramics are roughly equivalent to those of cancellous bone and provide minimal immediate structural support. Ceramics are anisotropic with high compressive strength, low tensile strength, and relatively low fracture toughness [27].

There is a paucity of literature on the clinical use of coralline blocks in the thoracolumbar spine. Thalgott and colleagues [28] retrospectively analyzed the use of Pro Osteon 200 (Interpore Cross International, Irvine, Calfornia) anteriorly in circumferential lumbar fusions supplemented with posterior autograft and pedicle screw fixation. Twenty patients were followed for a minimum

of 3 years; 30 (94%) of 32 levels were deemed to be fused anteriorly. Posteriorly, the utility of coralline blocks as a graft extender was demonstrated by Delecrin and colleagues [29] in adolescent idiopathic scoliosis. Using Triosite (Zimmer, Warsaw, Indiana) combined with autograft in 28 patients with a minimum 24-month follow-up, all patients demonstrated incorporation of the graft. In 1 patient requiring revision surgery for proximal implant failure and eventual removal instrumentation, sequential biopsies showed ingrowth of new bone into the macropores of the ceramic block (Fig. 2).

Another form of ceramics, tricalcium phosphates (TCPs) are readily absorbed in vivo and create a surface layer of locally enriched calcium phosphate as they dissolve. These regions seem to enhance the interface between the implant and host bone. Injectable calcium phosphate (Norian-SRS, Cupertino, California) is a carbonated apatite with a compressive strength between 4 and 10 times that of cancellous bone. A powder composed of α-TCP, calcium carbonate, and monocalcium phosphate monohydrate is mixed with a sodium phosphate solution to form an injectable paste that hardens in an isothermic manner at neutral pH. The material reaches 50% of its ultimate compressive strength within 10 minutes of implantation. By 24 hours after implantation, the cement reaches 90% of its ultimate compressive strength. As with all ceramics, there is little local inflammatory phase associated with its implantation [30]. Unlike other ceramics, this calcium phosphate formulation is a true load-sharing bone graft. Although injectable TCP has shown some utility in vertebroplasty [31], its effectiveness in fusions remains to be seen.

TCP also may be used in its noninjectable form (Vitoss; OrthoVita, Malvern, Pennsylvania). Early animal studies by Ohyama and colleagues [32] compared histologic microradiographic and biomechanical data of TCP versus autograft in an interbody cage canine fusion model at 16 weeks after surgery. They found no significant differences in functional unit stiffness between the autograft and the TCP levels, a 50% fusion rate for the TCP levels contrasted with a 41.7% fusion rate for autograft levels, and a virtually identical mean percentage of trabecular bone area within interbody cages. Human spinal applications of the noninjectable TCP formulation focused on its efficacy as a bone graft extender. Using a 50:50 ratio of lamina autograft and Vitoss, Epstein [33] showed CT and dynamic radiographic evidence of fusion in 26 of 27 single-level and 11 of 13 double-level posterolateral lumbar fusions up to 12 months after surgery. Linovitz and Peppers [34] showed 100% radiographic fusion using a combination of allograft and Vitoss with venous blood in 12 levels of anterior and posterior lumbar interbody fusions at 6 months in seven patients.

Bone morphogenetic protein

BMPs were first discovered in 1965. Urist [35] described the properties of bone-derived proteins

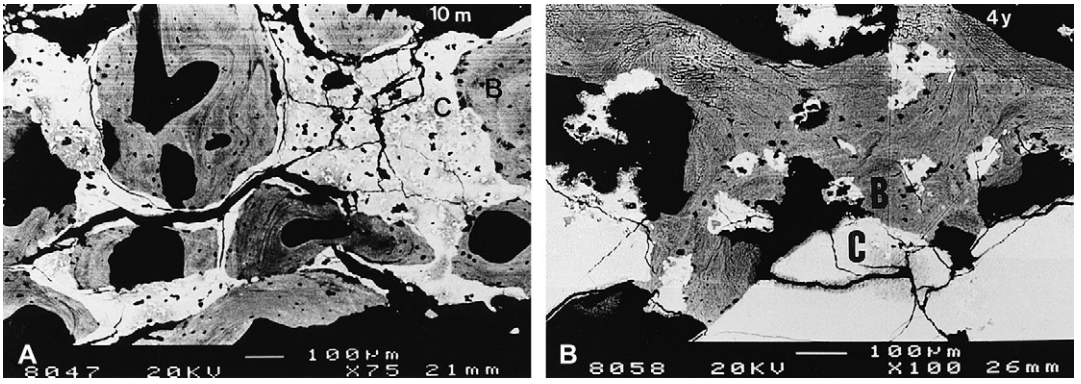

Fig. 2. Scanning electron microscopy shows the incorporation of bone (B) into macroporous ceramic (C) from the same patient at two different times: at 10 months (revision surgery because of superior grip dislodgement) (*A*) and at 4 years (removal of all the implants because of localized inflammatory reaction) (*B*). (*From* Delecrin J, Takahashi ST, Gouin F, et al. A synthetic porous ceramic as a bone graft substitute in the surgical management of scoliosis: a prospective, randomized study. Spine 2000;25(2):568; with permission.)

to induce bone formation in animals. BMPs are a member of the transforming growth factor-β (TGFβ) superfamily of proteins [36–39]. Currently, three such proteins have undergone clinical trials. They are recombinant human bone morphogenetic protein (rhBMP)-2, rhBMP-7 (also called osteogenic protein-1 [rhOP-1]), and growth and differentiation factor-5 (rhGDF-5).

BMPs act as local signaling molecules. In addition to involvement in bone and cartilage formation, BMPs create an environment for red bone marrow formation and contribute to systemic hematopoietic production.

Of the commercially available BMPs, BMP-2 has been most extensively studied in human and animal models. Boden and colleagues [40] described the first successful human trials of anterior interbody spinal fusion using rhBMP-2. Subsequently, larger trials showed similar promising results for anterior interbody and posterior interbody fusions, with fusion rates higher than those for autograft bone [41–43].

Luhmann and colleagues [44] recently published a prospective analysis of radiographic outcome using rhBMP-2 anteriorly and posteriorly in 95 adult patients with deformities with a minimum 2-year follow-up. In the anterior group, in which an average of 10.8 mg per level was used with no additional bone graft, operative levels were deemed to be fused in 96% (89 of 93 levels). A combination of local bone with an average of 13.7 mg per level was used in the posterior group, and 93% (110 of 118 levels) were judged to be fused. In 8 patients with compassionate use, the median dose was 40 mg per level with a separate compression-resistant matrix (CRM), and 100% (52 of 52 levels) were determined to be fused (Fig. 3).

In another study by Dimar and colleagues [45], 463 patients were randomized to ICBG or rhBMP-2/CRM (AMPLIFY; Medtronic Sofamor Danek, Memphis, Tennessee) at a dose of 40 mg per level in single-level posterolateral fusions for degenerative disc disease. These investigators found lower blood loss and a higher fusion rate (94.9% versus 86.8%) in the rhBMP-2 group at 24 months, with no differences in adverse events. Although this much higher dose formulation of rhBMP-2 is not yet commercially available, it shows promise with use posteriorly. Cost, however, may still be prohibitive for routine use.

Another member of the BMP family, rhBMP-7 or rhOP-1, has shown success in treating fractures and nonunions [46,47], but its effectiveness in the

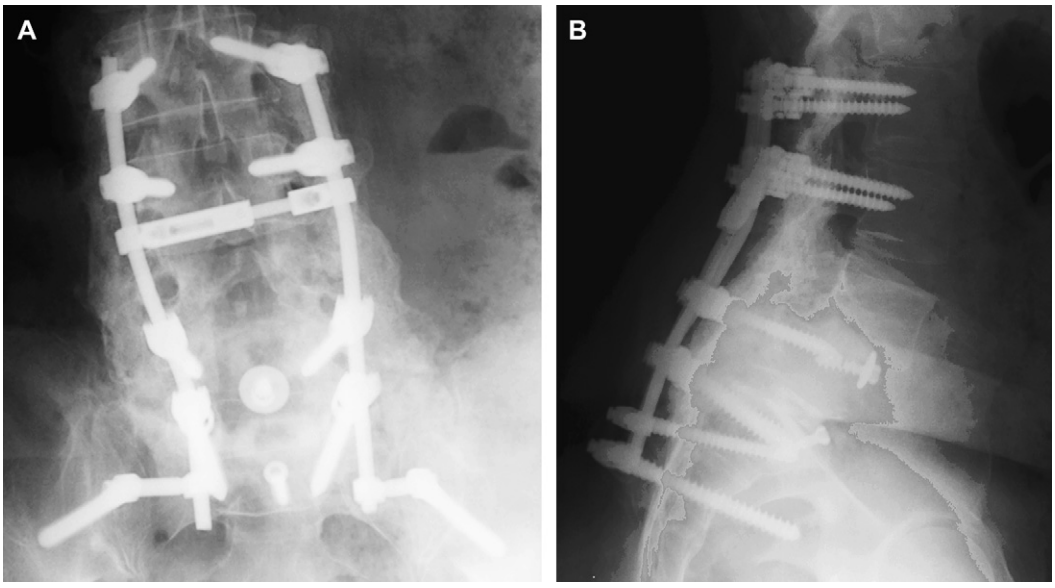

Fig. 3. A 50-year-old patient 14 months after L2-ilium revision posterior spinal fusion (rhBMP-2, 40 mg per level, with CRM) for L4-L5 and L5-S1 pseudarthroses after index L4-S1 anteroposterior spinal fusion (for postlaminectomy spondylolisthesis). Standing long-cassette coronal (*A*) and lateral (*B*) radiographs at 14 months after surgery show an impressive posterior fusion mass from L2 to the sacrum. (*From* Luhmann SJ, Bridwell KH, Cheng I, et al. Use of bone morphogenetic protein-2 for adult spinal deformity. Spine 2005;30(17 Suppl):S113; with permission.)

spine has not been as convincing to date. Vaccaro and colleagues [48] studied OP-1 for posterolateral fusion in 27 patients at 24 months. Clinical success, defined as a 20% improvement in the preoperative Oswestry score, was achieved by 85% of patients in whom OP-1 putty was used and in 64% of patients in whom autograft was used, but a successful posterolateral fusion was achieved in only 55% of patients in whom OP-1 putty was used and 40% of patients in whom autograft was used. Kanayama and colleagues [49] observed 19 patients who underwent posterolateral lumbar fusion using pedicle screw instrumentation and were randomized to receive OP-1 putty (OP-1, 3.5 mg/g of collagen matrix per side) alone ($n = 9$) or local autograft with HA-TCP granules ($n = 10$). Based on surgical exploration of 16 patients, new bone formation was macroscopically observed in the posterolateral lumbar region in all cases; however, solid fusion was observed in only 4 of 7 patients in whom OP-1 putty was used and in 7 of 9 patients in whom HA-TCP/autograft was used.

Another recombinant protein, rhGDF-5, has been studied in lumbar fusion. Thus far, rhGDF-5 has been able to produce 100% posterolateral lumbar fusion in white rabbits [50] in combination with a cross-linked type I collagen carrier with HA coating. In sheep [51], no difference was demonstrated between autograft and rhGDF-5 by manual, radiographic, or histologic analysis. Although fusion rates with GDF-5 seem promising in animal models, no human studies have been published to date.

Summary

In an effort to eliminate the morbidity associated with bone graft harvest from the iliac crest as well as to reduce the incidence of nonunion, the search for the optimal bone graft extender and substitute has intensified. With the myriad of various bone graft substitutes currently on the market, a balance must be struck between fusion rates, clinical outcomes, and cost-effectiveness.

References

[1] Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002;27:S26–31.

[2] Ludwig S, Kowalski J, Boden S. Osteoinductive bone graft substitutes. Eur Spine J 2000;9(Suppl 1): s119–25.

[3] Dahners LE, Mullis BH. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. J Am Acad Orthop Surg 2004; 12(3):139–43.

[4] Malloy KM, Hilibrand AS. Autograft versus allograft in degenerative cervical disease. Clin Orthop Relat Res 2002;394:27–38.

[5] Ehrler DM, Vaccaro AR. The use of allograft bone in lumbar spine surgery. Clin Orthop Relat Res 2000;371:38–45.

[6] Khanna G, Lewonowski K, Wood KB. Initial results of anterior interbody fusion achieved with a less invasive bone harvesting technique. Spine 2006;31(1):111–4.

[7] Arrington ED, Smith WJ, Chambers HG, et al. Complications of iliac crest bone graft harvesting. Clin Orthop Relat Res 1996;329:300–9.

[8] Schnee CL, Freese A, Weil RJ, et al. Analysis of harvest morbidity and radiographic outcome using autograft for anterior cervical fusion. Spine 1997; 22(19):2222–7.

[9] Sawin PD, Traynelis VC, Menezes AH. A comparative analysis of fusion rates and donor-site morbidity for autogenetic rib and iliac crest bone grafts in posterior cervical fusions. J Neurosurg 1998;88: 255–65.

[10] Shors C. Coralline bone graft substitutes. Orthop Clin North Am 1999;30(4):599–613.

[11] Kim YJ, Bridwell KH, Lenke LG, et al. Pseudarthrosis in long adult spinal deformity instrumentation and fusion to the sacrum: prevalence and risk factor analysis of 144 cases. Spine 2006;31(20): 2329–36.

[12] Prolo DJ, Rodrigo JJ. Contemporary bone graft physiology and surgery. Clin Orthop 1985;200: 322–42.

[13] Berven S, Tay BK, Kleinstueck FS, et al. Clinical applications of bone graft substitutes in spine surgery: consideration of mineralized and demineralized preparations and growth factor supplementation. Eur Spine J 2001;10(Suppl 2):S169–77.

[14] Tomford WW. Bone allografts: past, present and future. Cell Tissue Bank 2000;1(2):105–9.

[15] Bridwell KH, Lenke LG, McEnery KW, et al. Anterior fresh-frozen structural allografts in the thoracic and lumbar spine. Spine 1995;20:1410–8.

[16] Martin GJ, Haid RW, MacMillian M, et al. Anterior cervical discectomy with freeze-dried fibula allograft. Spine 1999;24:852–9.

[17] Knapp DR, Jones ET, Blanco JS, et al. Allograft bone in spinal fusion for adolescent idiopathic scoliosis. J Spinal Disord Tech 2005;18(Suppl 1): S73–6.

[18] Bridwell KH, O'Brien MF, Lenke LG, et al. Posterior spinal fusion supplemented with only allograft bone in paralytic scoliosis. Does it work? Spine 1990;19:2658–66.

[19] Peterson B, Whang PG, Iglesias R, et al. Osteoinductivity of commercially available demineralized

bone matrix. Preparations in a spine fusion model. J Bone Joint Surg Am 2004;86(10):2243–50.
[20] Bae HW, Zhao L, Kanim LE, et al. Intervariability and intravariability of bone morphogenetic proteins in commercially available demineralized bone matrix products. Spine 2006;31(12):1299–306 [discussion: 1307–8].
[21] Cammisa FP Jr, Lowery G, Garfin SR, et al. Two-year fusion rate equivalency between Grafton DBM gel and autograft in posterolateral spine fusion: a prospective controlled trial employing a side-by-side comparison in the same patient. Spine 2004;29(6):660–6.
[22] Chiroff RT, White EW, Weber KN, et al. Tissue ingrowth of replamineform implants. J Biomed Mater Res 1975;9:29–45.
[23] McAndrew MP, Gorman PW, Lange TA. Tricalcium phosphate as a bone graft substitute in trauma: preliminary report. J Orthop Trauma 1988;2(4):333–9.
[24] White E, Shors EC. Biomaterial aspects of Interpore-200 porous hydroxyapatite. Dent Clin North Am 1986;30:49–67.
[25] Chapman MW, Bucholz R, Cornell CN. Treatment of acute fractures with a collagen-calcium phosphate graft material: a randomized clinical trial. J Bone Joint Surg Am 1997;79(4):495–502.
[26] Holmes R, Money V, Bucholz R, et al. A coralline hydroxyapatite bone graft substitute. Clin Orthop 1984;188:252–62.
[27] Jarcho M. Calcium phosphate ceramics as hard tissue prosthetics. Clin Orthop 1981;157:259–78.
[28] Thalgott JS, Klezl Z, Timlin M, et al. Anterior lumbar interbody fusion with processed sea coral (coralline hydroxyapatite) as part of a circumferential fusion. Spine 2002;27(24):E518–27.
[29] Delecrin J, Takahashi ST, Gouin F, et al. A synthetic porous ceramic as a bone graft substitute in the surgical management of scoliosis: a prospective, randomized study. Spine 2000;25(2):563–9.
[30] Kurashina K, Kurita H, Hirano M, et al. In vivo study of calcium phosphate cements: implantation of an alpha-tricalcium phosphate/dicalcium phosphate dibasic/tetracalcium phosphate monoxide cement paste. Biomaterials 1997;18:539–43.
[31] Hong SJ, Park YK, Kim JH, et al. The biomechanical evaluation of calcium phosphate cements for use in vertebroplasty. J Neurosurg Spine 2006;4(2):154–9.
[32] Ohyama T, Kubo Y, Iwata H, et al. Beta-tricalcium phosphate as a substitute for autograft in interbody fusion cages in the canine lumbar spine. J Neurosurg 2002;97(3 Suppl):350–4.
[33] 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(6):424–9.
[34] Linovitz RJ, Peppers TA. Use of an advanced formulation of beta-tricalcium phosphate as a bone extender in interbody lumbar fusion. Orthopedics 2002;25(5 Suppl):s585–9.
[35] Urist MR. Bone: formation by autoinduction. Science 1965;150:893–9.
[36] Wozney JM. Overview of bone morphogenetic protein. Spine 2002;27(16 Suppl 1):S2–8.
[37] Mehler MF, Mabie PC, Zhang D, et al. Bone morphogenetic proteins in the nervous system. Trends Neurosci 1997;20:309–17.
[38] Heldin CH, Miyazono K, ten Dijke P. TGF-beta signaling from cell membrane to nucleus through SMAD proteins. Nature 1997;390:465–71.
[39] Ebara S, Nakayama K. Mechanism for the action of bone morphogenetic proteins and regulation of their activity. Spine 2002;37(16 Suppl 1):S10–5.
[40] Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000;25(3):376–81.
[41] Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine 2002;27(21):2396–408.
[42] Burkus JK, Sandhu HS, Gornet MF. Influence of rhBMP-2 on the healing patterns associated with allograft interbody constructs in comparison with autograft. Spine 2006;31(7):775–81.
[43] Haid RW Jr, Branch CL Jr, Alexander JT, et al. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J 2004;4(5):527–38 [discussion: 538–9].
[44] Luhmann SJ, Bridwell KH, Cheng I, et al. Use of bone morphogenetic protein-2 for adult spinal deformity. Spine 2005;30(17 Suppl):S110–7.
[45] Dimar JR, Glassman SD, Burkus JK, et al. A large-scale, level I, clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine fusion. Presented at the 41st Annual Scoliosis Research Society. Monterey (CA), September 13–16, 2006.
[46] Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. J Bone Joint Surg Am 2001;83(Suppl 1(Pt 2)):S151–8.
[47] Johnson EE, Urist MR, Finerman GA. Distal metaphyseal tibial nonunion. Deformity and bone loss treated by open reduction, internal fixation, and human bone morphogenetic protein (hBMP). Clin Orthop Relat Res 1990;(250):234–40.
[48] Vaccaro AR, Anderson DG, Patel T, et al. Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. Spine 2005;30(24): 2709–16.
[49] Kanayama M, Hashimoto T, Shigenobu K, et al. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. Spine 2006;31(10):1067–74.

[50] Magit DP, Maak T, Trioano N, et al. Healos/recombinant human growth and differentiation factor-5 induces posterolateral lumbar fusion in a New Zealand white rabbit model. Spine 2006;31(19): 2180–8.

[51] Jahng TA, Fu TS, Cunningham BW, et al. Endoscopic instrumented posterolateral lumbar fusion with Healos and recombinant human growth/differentiation factor-5. Neurosurgery 2004;54(1): 171–80.