Biological Approaches to Spinal Instrumentation and Fusion in Spinal Deformity Surgery

Praveen V. Mummaneni, MD, Scott A. Meyer, MD, and Jau-Ching Wu, MD

The use of autografts, allografts, and synthetic materials as bone substitutes in spinal surgery continues to increase as the population ages. Each of these materials has advantages and disadvantages. Autografts have previously been considered the gold standard for their excellent graft incorporation without the risk of rejection or disease transmission. However, their drawback is limited supply and the potential for donor-site morbidity. Allografts are an acceptable alternative because of the relative abundance, availability of desired sizes and shapes, and elimination of procurement-related morbidities. Advances in processing techniques and strict guidelines for allograft donor screening have reduced the risk of disease transmission. However, some manufacturing and sterilization processes can compromise the mechanical strength and biological properties of the allograft. Moreover, allografts may still, albeit rarely, elicit an inflammatory response, be rejected, or transmit disease. Synthetic materials are an emerging and increasingly popular option. However, their ability to incorporate into the host tissue remains uncertain. In addition, the host immune responses are not well elucidated. The biological approaches to spinal instrumentation and fusion must be tailored to meet the specific needs of each clinical scenario.[1]

PRINCIPLES OF BONE FUSION AND BIOMECHANICS

Bone is a biologically dynamic tissue that is always in an active state of deposition, resorption, and remodeling. The process of bone fusion is regarded as a process of healing in which metabolically active cells, matrices, and minerals are integrated into a rigid framework. Hormones, biomechanics, physical activities, nutritional status, and medical comorbidities all exert mutual influences on this process. For example, smoking has been shown to impede bone fusion in spinal surgery.[2,3] Osteoporosis may cause fusion failure owing to unbalanced bone resorption and metabolism. Moreover, patients with diseases such as ankylosing spondylitis often have spontaneously fused spines as a consequence of overreactive inflammation and healing, resulting in brittle deformities.

Bone fusion depends on the biological activities of bone healing. Three major physiological processes directly influence the quality and rapidity of graft incorporation: osteogenesis, osteoinduction, and osteoconduction.

Osteogenesis is new bone formation through cellular proliferation by osteoblastic activity, which requires the presence of bone-forming cells, osteoprogenitor cells or osteogenic precursor cells. Fresh autogenous bone grafts or bone marrow cells have great osteogenic potential because they contain viable cells.

Osteoinduction is the stimulation of precursor cells to differentiate into mature bone cells. Bone grafts usually contain elements with such properties, or supplements can be added. The most powerful osteoinductive effects come from bone morphogenetic proteins (BMPs). Materials like demineralized bone matrix (DBM) also are osteoinductive.

Osteoconduction refers to the appropriate 3-dimensional scaffolds into which viable bone cell growth and neovascularization can take place easily. This process is dependent on the physical properties of the material such as porosity and pore size, architecture, and structural stiffness. Materials like ceramics are designed for this property. One caveat is that osteoconductive materials alone, like ceramics without autograft, have little potential in achieving a solid fusion.

Bone tissue itself adapts to the load it is placed under in a dynamic biomechanical process, as described by the German surgeon Julius Wolff in the 19th century. Wolff's law suggests that certain amounts of loading are helpful to induce bone remodeling to achieve arthrodesis (eg, interbody spinal fusion).[4]

AUTOGRAFTS

Autograft bone provides the 3 properties for successful bone fusion: osteogenesis, osteoinduction, and osteoconduction. Autograft contains viable osteoblasts and osteoprogenitor cells ready for osteogenesis. Endogenous BMPs convey osteoinduction in autografts. Moreover, autografts have similar bone quality and perfect biocompatibility and provide no antigenicity. Autografts remain the gold standard for fusion procedures.[5]

0148-396X

Bone marrow aspirate can also be obtained at the time of iliac crest autograft. Autologous marrow cells aspirated from the iliac wing contain osteoprogenitor cells and osteoinductive growth factors. The bone marrow aspirate can then be mixed with other bone graft extenders such as ceramics for fusion.

In the clinical setting, the anterior iliac crest, posterior iliac crest, fibula, and rib are among the most common sources of autografts.[6] In addition, local autograft can also be used when a laminar decompression is performed, but this local bone contains a relatively high proportion of cortical bone. Cancellous bone allows excellent in-growth of vasculature and matrix; cortical bone provides primarily structural support. The use of autografts incorporates 2 main phases of bone healing. The initial phase of bone resorption and healing is subsequently followed by a late phase of creeping substitution. The entire process usually takes close to 1 year for complete remodeling and incorporation of the bone graft.

The advantages of using autografts include a high fusion rate, availability, no implant cost, and no disease transmission. The use of autografts, however, can have disadvantages, the most notable being donor graft-site morbidity. In 1998, Sawin et al[7] reported donor-site morbidity of 3.7% associated with use of rib graft and 25.3% for iliac crest graft. Complications included pneumonia, persistent atelectasis, wound dehiscence, hematoma requiring evacuation, meralgia paresthetica, iliac spine fracture, and chronic donor-site pain. Other authors[8,9] also reported various complications and morbidity rates between 26% and and 39% for iliac crest bone harvest. Several series report relatively a high rate of morbidity of chronic donor-site pain from 17% to 34% for autograft bone harvested from the iliac crest. Studies also have suggested a discrepancy in the surgeon's assessment of donor-site pain compared with an independent assessment, suggesting that the morbidity may be underestimated.[8] Other major complications from iliac crest harvesting in the literature are bleeding and deep infection.

Moreover, autograft is of limited supply and requires extra surgical time to harvest. Patient age, sex, genetic makeup, systemic diseases, and physical wellness may complicate the quantity and quality of available autologous bone. The associated cost of using an autograft compared with other materials is difficult to estimate and lacks comprehensive analysis. Costs may arise later resulting from treating donor-site morbidities, plus economic loss from prolonged recuperation.

ALLOGRAFTS

Allograft bone is derived from a deceased donor, and the graft either is decontaminated or may undergo a process of sterilization. The methods of processing influence the rate at which a graft will incorporate in the recipient. Autograft surpasses allograft in terms of bone fusion partly as a result of its viable, nonimmunogenic cells and abundance of BMPs that optimize osteogenesis and osteoinduction. Allografts may stimulate localized immune response in the recipient and can cause delayed fusion.

For allografts, balancing clinical efficacy and graft-associated complication is a primary consideration, but there are variables in allograft preparation and preservation. Frozen allografts can be readily available and are stored in freezers colder than $-20°C$, often as low as $-80°C$, and then simply thawed and washed when prepared for use. Grafts can also be provided as freeze-dried (lyophilized); preserving the graft entails cooling to $-70°C$, and under pressure, water is extracted to the point at which the residual moisture content of the graft is generally $< 8\%$. Freeze-dried preparations decrease graft antigenicity, resulting in a reduced incidence of cell-mediated response in the host. Rehydration of lyophilized allografts is recommended before implantation because the low moisture content can result in a brittle graft that should not be subjected to weight-bearing loads until properly reconstituted. Having an inventory of frozen allografts requires that a freezer be purchased and maintained and the storage temperature continuously monitored, whereas an inventory of lyophilized allografts is more easily maintained ''on a shelf.'' Packaging configurations for lyophilized allografts are challenged to maintain a vacuum during their shelf-life while stored.

Fresh-frozen allografts have 10% to to 20% less compression strength but bending strength similar to that of autografts. In contrast, freeze-dried allografts are reduced in bending strength by 50% to to 90% while maintaining their compressive strength. As a consequence, freeze-dried allografts are more susceptible to longitudinal cracks.[10] Some allograft handling processes also involve radiation treatment to sterilize the allograft. Research demonstrates that the use of low-dose radiation has no adverse effect on graft strength.[10]

Various animal and clinical studies compare the clinical efficacy of allograft with autograft. Care must be taken when these results are translated into clinical relevance. The fusion environment must be taken into account. For instance, bone grafts used for interbody fusion in anterior cervical diskectomy and posterior-lateral lumbar fusion have different requirements. For fresh grafts, cortical bone provides better structural support, but cancellous bone provides a better source of osteoblasts and osteocytes. For spinal column interbody fusion, the cortical component provides resilience to the compression force between 2 vertebral endplates. However, its limited surface area and stiffness also hinder vascular in-growth and remodeling. Nevertheless, in circumstances requiring faster new bone formation rather than structural strength such as with posterior lateral lumbar fusion, use of cancellous bone grafts may yield better results.[11]

OTHER BONE SUBSTITUTES FOR SPINAL FUSION

As technology progresses, many materials have come under trial, and some have demonstrated great potential as

substitutes for bone graft. Ceramics, DBMs, and various kinds of spacers have been used.

The DBMs are produced by the pulverization and acidic extraction of allograft bone. Collagen and proteins, including growth factors, with capacity for osteoinduction and osteoconduction are retained after processing; DBMs have no structural strength, and their activity for osteoinduction is not consistent. Their heterogeneity is due to the manufacturing process or quality of donor bone.

The use of DBMs for spinal fusion has been studied in both preclinical and clinical trials. Some results are positive[12,13]; others are not. Current literature recommends using DBMs as bone graft extenders[12,14] to enhance fusion when used in conjunction with autograft. Animal studies suggest that DBMs are inadequate when used alone in posterolateral fusion.[15,16]

Ceramics and synthetic cages or other artificial implantable devices have been marketed for years as bone substitutes, and these synthetic devices eliminate the risk of disease transmission from the deceased donor (Table). They are available in unlimited quantity and can be machined into specified sizes and shapes as desired. Ceramics such as hydroxylapatite and tricalcium phosphate have the capacity for osteoconduction but are brittle and susceptible to shearing force. Thus, ceramics are better as graft expanders but usually need to be used in conjunction with internal fixation because of their lack of structural support strength.[17]

Some clinical studies have demonstrated results that are not favorable for the use of standalone ceramics in anterior interbody fusion in both in the cervical and lumbar spine.[18,19] Their chemical structure is similar to that of mineral bone, facilitating cellular adhesion and vascular in-growth for new bone formation, but ceramics lack osteogenic and osteoinductive activities, so the local host environment will profoundly affect the efficacy of bone fusion. Therefore, appropriate implant site selection, decortication, and the presence of bone marrow or autogenous bone grafts as a source of osteogenic progenitor cells are crucial to the successful incorporation of ceramics into newly formed bone. The rate of resorption and remodeling depends on the composition and porosity of the ceramics. Studies show that ceramics work well with autogenous bone grafts as expanders, so they are potential candidates as vehicles for osteoinductive agents like BMPs.[20]

Cages were first developed by Bagby[21] for interbody spinal fusion in horses.[22] The Bagby cage was a stainless steel basket made as a container for autograft bone. Cages are now available in polyetheretherketone, carbon fiber, and titanium. Initially, they were cylindrical and used in the lumbar spine via the anterior approach. Now, they can be fabricated into variable shapes and can be placed via several routes into different spinal segments.

Cages are used as interbody spacers with the capacity to contain bone graft materials of various kinds.

BONE MORPHOGENETIC PROTEINS

In 1965, Marshall Urist[23] discovered that the degradation products of dead bone, which was referred to as extracellular matrix, had materials capable of inducing new bone formation when implanted in rabbit connective tissue. In 1971, the effective component was called BMP.[24,25] This seminal discovery led to the purification, isolation, and identification

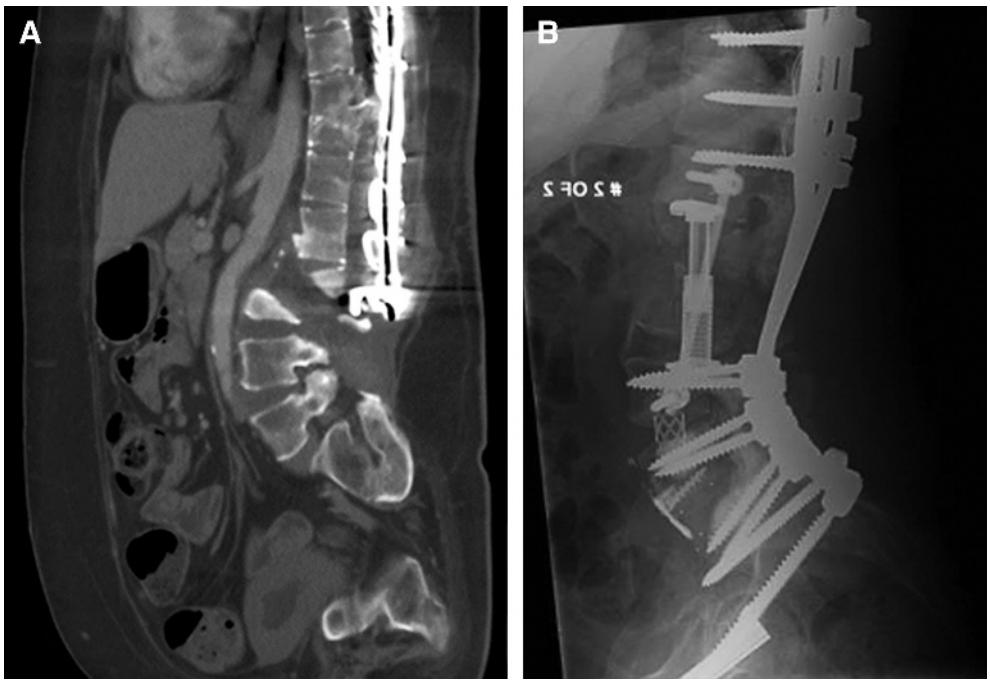

FIGURE 1. A, a paraplegic patient with a Charcot spine with an L3 fracture/dislocation below a Harrington rod fixation. B, spinal reconstruction using anterior (bone morphogenetic protein) and posterior (iliac crest) approaches to achieve appropriate stabilization of the lumbosacral spine.

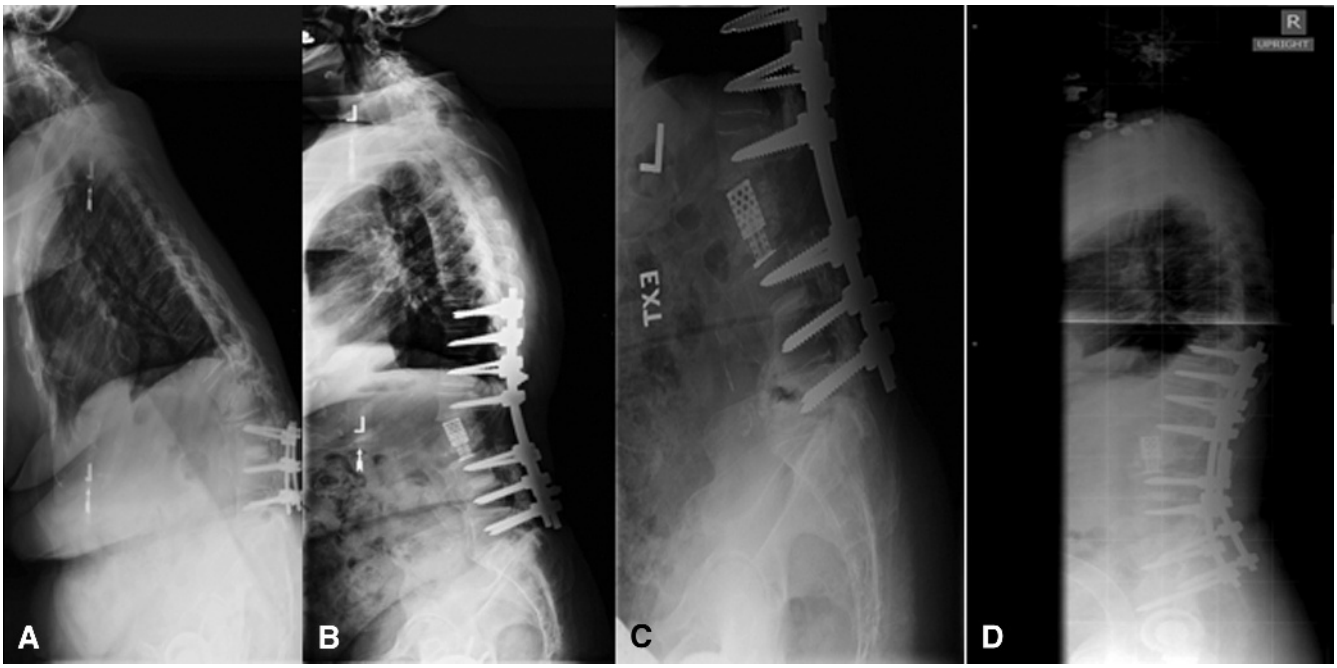

FIGURE 2. A, a 75-year-old woman who had 3 prior lumbar surgeries and L2 proximal junctional kyphosis. B, L2 vertebral column resection with T10 to L5 posterior instrumented fusion using local and iliac crest autograft did not completely restore sagittal balance. C, 6 months later, the patient reported increased back pain and stooped posture. She was found to have distal junctional kyphosis with L5 fracture and screw back-out. D, after a fifth surgery with L5 pedicle subtraction osteotomy and extension of fusion to S1 with iliac screws and iliac autograft.

of BMP peptides. The term BMP now refers to a group of growth factors and cytokines that have the capability to induce bone or cartilage formation. Originally, 7 such proteins, called BMP-1 through BMP-7, were discovered; 13 other BMPs have since been identified.

Initially, it took huge amounts of bone to extract a small amount of BMP. Until the development of recombinant DNA technology, BMPs were very rare and extremely expensive. Today, although still costly, recombinant human BMPs (rhBMPs) are available in high purity and concentration for clinical use. Recombinant BMP-7 and rhBMP-2 have been the most studied and have shown the most potency amongst the BMP family.

Clinical application of rhBMPs requires a carrier. Recombinant BMPs are soluble and dissolve easily in vivo, so they must be placed in high concentration within a vehicle to provide controlled release over time. Otherwise, they become inactivated and lose the capacity for osteoinduction. Boden et al[26] have compared the use of rhBMP-2 in collagen sponge with autograft from the iliac crest filled into threaded cages for lumbar spine interbody fusion. Although there are only a small number of cases, bone fusion is more reliable with rhBMP-2.

Boden et al[27] also conducted a prospective randomized study for use of rhBMP-2 in posterolateral lumbar fusion. Twenty-five patients were randomized into 3 groups: autograft with pedicle screw fixation instrumentation, rhBMP-2 with instrumentation, and rhBMP-2 without instrumentation. The rhBMP-2 was applied in the carrier consisting of 60% hydroxylapatite and 40% tricalcium phosphate granules. There was bone fusion in all (100%) of those who received rhBMP-2, with and without instrumentation. On the other hand, only 40% of patients who received autograft developed a solid fusion. Several other clinical studies also demonstrated the superiority of rhBMP-2 over autografts or allografts in lumbar spine interbody fusion.[28-30] However, a few studies pointed out that rhBMP-2 might cause significant bone resorption of implanted grafts before osteoinduction.[31,32]

Other complications related to BMP use in the lumbar spine include ectopic ossification, seroma formation, and osteolysis.[33]

COSTS

The costs surrounding spinal instrumentation and fusion have been and in the future are likely to be increasingly scrutinized. The cost of instrumentation is well known to have a significant impact on the overall cost related to spinal fusion. However, the cost associated with the use of biologics has become a significant component of the overall cost of instrumented spinal fusion. In 2005, the cost associated with spinal hardware was $1.4 billion, and the cost associated with biologics (BMP) was $800 million. Four years later in 2009, the cost of spinal implants had risen to $1.5 billion, but the cost associated with biologics (primarily BMP) has eclipsed the cost of implants and risen to $1.6 billion.[34]

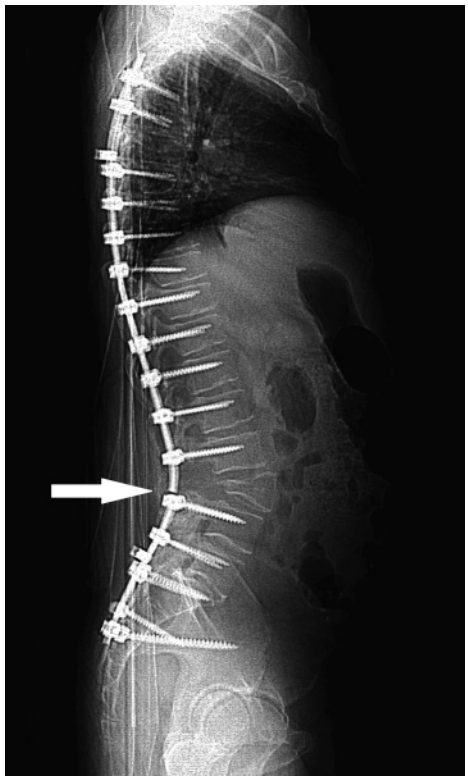

FIGURE 3. L3 pedicle subtraction osteotomy with T4 to the pelvis instrumentation demonstrating pseudoarthrosis and rod fracture at the level of the pedicle subtraction osteotomy. Posteriorly, iliac autograft mixed with allograft bone extender was insufficient to achieve a solid arthrodesis.

SPINAL DEFORMITY

The surgical management of spinal deformity particularly in an aging population presents unique challenges to spinal fusion. Numerous risk factors for the development of pseudoarthrosis have been identified in spinal deformity surgery. Patients > 50 years of age often have osteopenia or osteoporosis, which is a risk factor for the development of pseudoarthrosis. This is important in the surgical planning for those with degenerative scoliosis requiring an instrumented fusion because poor bone quality is frequently present in this patient population. Certain medical comorbidities such as renal failure and rheumatoid arthritis can also negatively affect fusion rates. Multilevel surgeries and fusions extending to the sacrum are especially at increased risk for the development of pseudoarthrosis (Figure 1). The use of certain medications such as nonsteroidal antiinflammatory drugs can limit fusion. Nicotine has also been demonstrated to inhibit bone fusion; thus, it is recommended that patients should quit smoking before multilevel fusion surgery.[35]

Patients undergoing spinal fusion for scoliosis have a significant pseudoarthrosis rate, with a recent systematic review of the literature reporting a pseudoarthrosis rate of 12.9%.[36] The revision rate for primary adult degenerative deformity is high, with 9% of patients requiring a single revision procedure and 2.3% requiring multiple revisions (Figure 2). The most common complication leading to revision surgery is pseudarthrosis.[37] In another series, Bridwell et al[38] reported that 10% of patients undergoing surgery for adult spinal deformity will have delayed implant failure, junctional kyphosis, or nonunion in the 3- to 5-year period, negatively affecting outcome.

The selection of fusion substrate in adult spinal deformity surgery is important given the relatively high risk of pseudoarthrosis (Figure 3). The decision of what graft to use should be based on patient comorbidities and bone stock, in addition to the biomechanics of the planned construct. High pseudoarthrosis rates are seen in adults undergoing surgery for thoracolumbar deformity when allograft is used for posterior constructs or anterior strut graft spanning 4 or more levels.[39] In a recent Maeda et al[40] reported a 72% fusion rate for iliac autografts vs a 96% fusion rate when rhBMP-2 was used. The highest rate of nonunion occurred at the L5-S1 level. Despite the benefits in certain patient populations, debate continues on the use of BMPs because of cost-related issues.

MINIMALLY INVASIVE APPROACHES TO DEFORMITY

Minimally invasive surgical (MIS) approaches to spinal deformity have emerged with the potential to limit pain, blood loss, narcotic requirements, and the length of hospital stay. One significant challenge of minimally invasive approaches is reaching parity in spinal fusion rates with open procedures. Excellent fusion results in adult degenerative scoliosis after MIS trans-psoas interbody fusion with percutaneous pedicle screw fixation using BMP have been reported.[41] To date, only 2 studies on MIS spinal deformity surgery have reported a minimum of 1 year of follow-up. Anand et al[41] reported a retrospective review of 28 patients undergoing a trans-psoas approach supplemented by posterior percutaneous pedicle screw fixation for a minimum of 3 levels; BMP was used for the interbody fusion. The clinical follow-up was a mean of 22 months with a minimum of 13 months. Computed tomography was used to verify fusion, and a 100% fusion rate was reported.

TABLE. Comparison of Bone Substitutes[a]

	Autograft	Allograft	rhBMPs	Ceramics
Clinical efficacy	High	Low	High	Low
Procurement morbidity	High	No	No	No
Cost	Low	Moderate	High	Moderate
Disease transmission	No	Low	No	No
Formation of localized seroma and/or bony overgrowth	No	No	Low	No

[a]rhBMP, recombinant human bone morphogenetic protein.

In the other MIS series with 1 year of follow-up, pseudoarthrosis was reported when posterolateral fusion was used alone without an interbody spacer.[42] Wang and Mummaneni[42] reported a retrospective review on 23 patients undergoing MIS deformity surgery with a mean follow-up of 13.4 months. There were 2 cases of pseudoarthrosis identified in 7 patients who had posterolateral fusion alone without an interbody cage. There were no cases of pseudoarthrosis when an interbody was used as part of the approach to spinal fusion.

THE FUTURE

State-of-the-art advances in science and technology, including rhBMPs, synthetic fusion cages, and minimally invasive instrumentation, have changed the practice of spinal fusion over the past decade. Currently, unsolved issues are optimization of controlled local inflammation induced by cytokines, selection of synergistic vehicles, and cost containment.

Gene therapy may have future clinical applications. Gene transduction in local host cells for the sustainable production of bioactive proteins was originally designed for the treatment of some hereditary diseases. In recent studies, successful genetic transduction of genetic codes for bioactive proteins, which facilitate bone fusion, has also been carried out in animals.[43,44] Developments in gene therapy show the potential for reducing current requirements of high-dose rhBMPs, which may help minimize local adverse reactions. However, concerns for safety when viral vectors are used in gene transduction need further investigation before clinical application can be realized. Transplantation of mesenchymal stem cells for enhancement of bone fusion has already been tried in animal models and in the clinical setting.[45-47]

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article. Dr Mummaneni is a consultant for DePuy Spine and a past consultant for Medtronic. He receives a royalty from DePuy Spine and from Quality Medical Publishers. It should be noted the FDA on-label use of rh-BMP-2 is only for ALIF.

REFERENCES

1. Wu J-C, Mummaneni PV, eds. *Tissue and Cell Transplantation*. Blackwell Publishing Ltd. In press.
2. Bishop RC, Moore KA, Hadley MN. Anterior cervical interbody fusion using autogeneic and allogeneic bone graft substrate: a prospective comparative analysis. *J Neurosurg*. 1996;85(2):206-210.
3. Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR. The effect of cigarette smoking and smoking cessation on spinal fusion. *Spine (Phila Pa 1976)*. 2000;25(20):2608-2615.
4. Frost HM. A 2003 update of bone physiology and Wolff's Law for clinicians. *Angle Orthod*. 2004;74(1):3-15.
5. Mummaneni PV, Lenke L, Haid RW. *Spinal Deformity: A Guide to Surgical Planning and Management*. St. Louis, MO: Quality Medical Publishing, Inc; 2008.
6. Deutsch H, Haid R, Rodts G Jr, Mummaneni PV. The decision-making process: allograft versus autograft. *Neurosurgery*. 2007;60(1)(supp1 1): S98-S102.
7. 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(2):255-265.
8. Heary RF, Schlenk RP, Sacchieri TA, Barone D, Brotea C. Persistent iliac crest donor site pain: independent outcome assessment. *Neurosurgery*. 2002;50(3):510-516.
9. Silber JS, Anderson DG, Daffner SD, et al. Donor site morbidity after anterior iliac crest bone harvest for single-level anterior cervical discectomy and fusion. *Spine (Phila Pa 1976)*. 2003;28(2):134-139.
10. Pelker RR, Friedlaender GE. Biomechanical aspects of bone autografts and allografts. *Orthop Clin North Am*. 1987;18(2):235-239.
11. Urist MR, Dawson E. Intertransverse process fusion with the aid of chemosterilized autolyzed antigen-extracted allogeneic (AAA) bone. *Clin Orthop Relat Res*. 1981;(154):97-113.
12. Girardi FP, Cammisa FP Jr. The effect of bone graft extenders to enhance the performance of iliac crest bone grafts in instrumented lumbar spine fusion. *Orthopedics*. 2003;26(5)(Suppl):s545-s548.
13. Vaccaro AR, Stubbs HA, Block JE. Demineralized bone matrix composite grafting for posterolateral spinal fusion. *Orthopedics*. 2007; 30(7):567-570.
14. 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 (Phila Pa 1976)*. 2004;29(6):660-666.
15. Boden SD, Schimandle JH, Hutton WC. 1995 Volvo Award in basic sciences: the use of an osteoinductive growth factor for lumbar spinal fusion, part II: study of dose, carrier, and species. *Spine*. 1995; 20(24): 2633-2644.
16. Boden SD, Schimandle JH, Hutton WC, Chen MI. 1995 Volvo Award in basic sciences: the use of an osteoinductive growth factor for lumbar spinal fusion, part I: biology of spinal fusion. *Spine*. 1995; 20(24):2626-2632.
17. Miyazaki M, Tsumura H, Wang JC, Alanay A. An update on bone substitutes for spinal fusion. *Eur Spine J*. 2009;18(6):783-799.
18. Thalgott JS, Fritts K, Giuffre JM, Timlin M. Anterior interbody fusion of the cervical spine with coralline hydroxyapatite. *Spine (Phila Pa 1976)*. 1999;24(13):1295-1299.
19. Thalgott JS, Klezl Z, Timlin M, Giuffre JM. Anterior lumbar interbody fusion with processed sea coral (coralline hydroxyapatite) as part of a circumferential fusion. *Spine (Phila Pa 1976)*. 2002;27(24):E518-E525.
20. Autefage H, Briand-Mesange F, Cazalbou S, et al. Adsorption and release of BMP-2 on nanocrystalline apatite-coated and uncoated hydroxyapatite/ beta-tricalcium phosphate porous ceramics. *J Biomed Mater Res B Appl Biomater*. 2009;91(2):706-715.
21. Bagby GW. Arthrodesis by the distraction-compression method using a stainless steel implant. *Orthopedics*. 1988;11(6):931-934.
22. McAfee PC. Interbody fusion cages in reconstructive operations on the spine. *J Bone Joint Surg Am*. 1999;81(6):859-880.
23. Urist MR. Bone: formation by autoinduction. *Science*. 1965;150(698): 893-899.
24. Urist MR. Bone histogenesis and morphogenesis in implants of demineralized enamel and dentin. *J Oral Surg*. 1971;29(2):88-102.
25. Urist MR, Strates BS. Bone morphogenetic protein. *J Dent Res*. 1971; 50(6):1392-1406.
26. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages: definitive evidence of osteoinduction in humans: a preliminary report. *Spine (Phila Pa 1976)*. 2000;25(3):376-381.
27. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine (Phila Pa 1976)*. 2002;27(23):2662-2673.

28. Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine (Phila Pa 1976)*. 2003;28(4):372-377.
29. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine (Phila Pa 1976)*. 2002;27(21):2396-2408.
30. 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(3):301-307.
31. McClellan JW, Mulconrey DS, Forbes RJ, Fullmer N. Vertebral bone resorption after transforaminal lumbar interbody fusion with bone morphogenetic protein (rhBMP-2). *J Spinal Disord Tech*. 2006;19(7): 483-486.
32. 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(10):E277-E284.
33. Mroz TE, Wang JC, Hashimoto R, Norvell DC. Complications related to osteobiologics use in spine surgery: a systematic review. *Spine*. 2010; 35(9)(Suppl):S86-S104.
34. Cahill KS, Chi JH, Day A, Claus EB. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA*. 2009;302(1):58-66.
35. Kanter AS, Asthagiri AR, Shaffrey CI. Aging spine: challenges and emerging techniques. *Clin Neurosurg*. 2007;54:10-18.
36. Yadla S, Maltenfort MG, Ratliff JK, Harrop JS. Adult scoliosis surgery outcomes: a systematic review. *Neurosurg Focus*. 2010;28(3):E3.
37. Pichelmann MA, Lenke LG, Bridwell KH, Good CR, O'Leary PT, Sides BA. Revision rates following primary adult spinal deformity surgery: six hundred forty-three consecutive patients followed-up to twenty-two years postoperative. *Spine*. 2010;35(2):219-226.
38. Bridwell KH, Baldus C, Berven S, et al. Changes in radiographic and clinical outcomes with primary treatment adult spinal deformity surgeries from two years to three- to five-years follow-up. *Spine*. 2010;35(20): 1849-1854.
39. Buttermann GR, Glazer PA, Hu SS, Bradford DS. Anterior and posterior allografts in symptomatic thoracolumbar deformity. *J Spinal Disord*. 2001;14(1):54-66.
40. Maeda T, Buchowski JM, Kim YJ, Mishiro T, Bridwell KH. Long adult spinal deformity fusion to the sacrum using rhBMP-2 versus autogenous iliac crest bone graft. *Spine*. 2009;34(20):2205-2212.
41. Anand N, Rosemann R, Khalsa B, Baron EM. Mid-term to long-term clinical and functional outcomes of minimally invasive correction and fusion for adults with scoliosis. *Neurosurg Focus*. 2010;28(3):E6.
42. Wang MY, Mummaneni PV. Minimally invasive surgery for thoracolumbar spinal deformity: initial clinical experience with clinical and radiographic outcomes. *Neurosurg Focus*. 2010;28(3):E9.
43. Boden SD, Titus L, Hair G, et al. Lumbar spine fusion by local gene therapy with a cDNA encoding a novel osteoinductive protein (LMP-1). *Spine (Phila Pa 1976)*. 1998;23(23):2486-2492.
44. Helm GA, Alden TD, Beres EJ, et al. Use of bone morphogenetic protein-9 gene therapy to induce spinal arthrodesis in the rodent. *J Neurosurg*. 2000;92(2)(Suppl):191-196.
45. Gan Y, Dai K, Zhang P, Tang T, Zhu Z, Lu J. The clinical use of enriched bone marrow stem cells combined with porous beta-tricalcium phosphate in posterior spinal fusion. *Biomaterials*. 2008;29(29):3973-3982.
46. Minamide A, Yoshida M, Kawakami M, et al. The use of cultured bone marrow cells in type I collagen gel and porous hydroxyapatite for posterolateral lumbar spine fusion. *Spine (Phila Pa 1976)*. 2005;30(10): 1134-1138.
47. Wang T, Dang G, Guo Z, Yang M. Evaluation of autologous bone marrow mesenchymal stem cell-calcium phosphate ceramic composite for lumbar fusion in rhesus monkey interbody fusion model. *Tissue Eng*. 2005;11(7-8):1159-1167.