Biologic substitutes in spinal arthrodesis
Substitutos biológicos en arthrodesis vertebral
Substitutos biológicos em artrodese vertebral

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ABSTRACT
The authors present in this article a revision on the use of bone graft and other biological substances for the accomplishment of vertebral arthrodesis, discussing the individual characteristics, the basics of performance, the advantages, the disadvantages, and the clinical applicability of the different alternatives.

KEYWORDS: Arthrodesis; Spinal fusion/methods; Bone transplantation/utilization; Bone substitutes/therapeutic use

INTRODUCTION
The use of iliac crest bone graft for spinal arthrodesis continues to remain the gold standard in the induction of a solid fusion mass. However, despite the use of internal fixation, pseudarthrosis still occurs in 10% to 15% of all spine fusion surgeries. Moreover, approximately 500,000 autogenous bone grafting procedures are performed annually, of which nearly 50% are used for spine fusion. Iliac crest bone graft harvest involves a separate incision, increased operative time and blood loss, and significant donor site morbidity. Studies have shown that up to 30% of all patients who have undergone autogenous iliac crest bone grafting experience significant postoperative complications including hernia formation, infection, hematoma, and fracture.

The unacceptable rates of pseudarthroses and documented operative morbidity from the harvest of autograft can confound patient outcomes from primary spine fusion in many clinical situations. In addition, the stringent biological environment created from pseudarthrosis formation presents a more complicated array of problems and unpredictable outcomes after further surgical intervention. Because the success rates of fusion in this poor osteoinductive environment are relatively low, recent studies have been directed towards the development of new biologic substitutes to improve outcomes after spine surgery. The arena of biologic substitutes in spinal arthrodesis has expanded to include allograft, autologous cells, demineralized bone matrix (DBM), ceramic carriers, recombinant growth factors, and tissue engineering therapies. Continued research has been conducted to identify the ideal bone graft substitutes for spine surgery, which should be osteogenic, biocompatible, user-friendly, cost-effective,
and provide structural support. This article reviews the pre-clinical and clinical data regarding the use of bone graft substitutes in the induction of spine fusion.

**AUTOGRAPH**

Autogenous cancellous bone graft remains the gold standard material for bone grafting for orthopaedic procedures because it alone offers three of the four necessary components for bone repair: osteoinductive signals from associated growth factors, osteogenic cells, and an osteoconductive matrix. Animal models have shown the incorporation of cancellous grafts into host bone. Both autogenous cortical and cancellous bone grafts are currently used in spine fusion procedures. The majority of autografts harvested contain cancellous bone. Although without compressive strength, cancellous grafts have a large trabecular area, which encourage the consolidation of the fusion mass. The bone graft ultimately becomes denser than surrounding host bone.

The use of autologous bone graft in spine arthrodesis typically presents a number of problems for the surgeon. The elderly patient population presents unique clinical conditions such as osteoporosis, poor bone stock, and anesthetic risks of increased operative time. Many studies have demonstrated that the harvest of autogenous graft leads to clinically significant perioperative and postoperative anesthetic risks of increased operative time. Many studies have demonstrated variable rates of fusion, amount of new bone formation, and presence of residual DBM. This wide variability of biologic activity of DBMs is likely influenced by the associated donor, carrier, and the assorted demineralization and sterilization methods used.

**DEMINERALIZED BONE MATRIX**

Demineralized bone matrix (DBM) is created through the acid extraction of the mineralized phase of bone. The preparation of DBM was originally characterized by Urist et al and then modified by Reddi and Huggins. Allogeneic bone is crushed to a particle size of 74 to 420 μm followed by demineralization in 0.5N HCL mEq/g for three hours. Methods of processing follow the same initial steps, however, additives and refining techniques are different depending on the source and company involved. Over forty different commercial preparations available on the market also use different carriers such as glycerol, hyaluronic acid, gelatin, and calcium sulfate powder. This has led to wide biologic variability in terms of osteoinductive potential in vivo.

DBMs have been found to have rich osteoconductive capabilities but questionable osteoinductive activity. DBMs have been shown to induce rapid revascularization, serving as an excellent osteoconductive scaffold. However, osteoinductive capacity of DBM is dependent on a number of factors such as the bone quality of the original donor, and the different commercial sterilization and handling methods. Sterilization by ethylene oxide and use of gamma irradiation, for example, have been found to significantly reduce osteoinductivity.

For example, a large number of DBMs have been combined with glycerol to help convert the allograft to a putty form which may impart unpredictable biologic effects. A previous study in our laboratory showed that large quantities of DBM material are lethally toxic to athymic rats in a dose-dependent manner. Other studies have confirmed the toxicity of glycerol in large doses. However, despite these findings, in more than 10 years of use of these DBMs in humans, there have been no reported cases of renal toxicity related to the glycerol carrier.

Despite their wide use in spinal arthrodesis, DBMs have been evaluated in few animal models and laboratory studies. DBMs, like allograft bone, are not subject to the rigorous testing of the FDA because they are classified as minimally manipulated tissue for transplantation. Recent studies have demonstrated the variability of these preparations in inducing osteogenic activity in an intramuscular animal model, a rat femoral defect, and a rat spine fusion model. In a study using a rat spine fusion model, widely variable osteoinductive potential was demonstrated using different commercially available DBM preparations. Histologic analysis of the spines eight weeks after DBM implantation demonstrated variable rates of fusion, amount of new bone formation, and presence of residual DBM. This wide variability of biologic activity of DBMs is likely influenced by the associated donor, carrier, and the assorted demineralization and sterilization methods used.

DBMs have been used successfully as bone graft extenders to promote spinal fusion and the healing of long bone nonunions. Certain formulations have also induced successful spine arthrodesis when used alone or in conjunction with autograft, bone marrow, or ceramic carriers. Additional studies have combined the use of autologous bone marrow and DBM in healing osseous defects.

Morone & Martin reported the efficacy of DBM in a rigorous rabbit posterolateral lumbar intertransverse process model in a number of studies. The body of evidence from these studies suggests that when used alone, DBMs are unable to induce posterolateral spinal fusion in rabbits. However, certain formulations of DBMs, when added to iliac crest autograft, increased fusion rates. These authors concluded that although certain DBMs are inadequate as graft substitutes, they may be useful as a viable graft extender in posterolateral spine fusion procedures.

There is a need for further study of the influence of donor age and sex, processing, and success of DBMs. A number of reasons such as the lack of FDA oversight and the wide variety of donors to supply the graft contribute to outcome variability from the use of DBM. It is important to note that DBMs are used clinically solely as bone graft extenders and not substitutes. Since all DBMs do not have the same biologic potential, the optimal DBM for each clinical situation needs to be determined. To date, no studies have analyzed the capability of DBMs to integrate into an in vivo environment.

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CERAMICS

Ceramic carriers are derived from a process called sintering, which uses high temperatures to extract individual crystals that fused together at crystal grain boundaries\(^{14}\). Commercial calcium phosphate materials are produced with pore diameters between 200 and 500 μm, approximating the structure of human trabecular bone\(^{36}\). The osteoconductive matrices used in conjunction with these carriers are comprised of hydroxyapatite, tricalcium phosphate, and/or calcium sulfate\(^{31}\). Klawitter et al. concluded that the size and interconnectedness of the pores of an implant are important in allowing bony ingrowth and blood vessels to integrate within the carrier\(^{32}\). However, other investigators have indicated that the degree of interconnectivity porosity (12-80%) and pore size (range < 1 μm to 1500 μm) do not inhibit bone formation\(^{3}\). Ceramics possess a number of attractive qualities as a biologic substitute in spinal arthrodesis. They have been found to be safe, osteoconductive, and biocompatible with biologically active cells such as autologous bone marrow\(^{14}\). Furthermore, the material properties of these carriers such as compression resistance are advantageous in orthopaedic procedures. Calcium-collagen graft, which is comprised of hydroxyapatite, tricalcium phosphate (TCP), and both Type I and III collagen, has been used clinically to augment fracture healing in acute long-bone fractures\(^{34}\). When compared to autologous bone graft, there were no differences between the two groups in terms of union rate or outcome measures\(^{34}\). TCP is another porous ceramic that undergoes partial conversion to hydroxyapatite once it is metabolized in the body\(^{33}\). However, because it is resorbed faster than hydroxyapatite and poses a more unpredictable biodegradation profile, TCP is rarely used in the clinical setting\(^{36}\).

The use of ceramics alone has been evaluated in preclinical and clinical models of spinal surgery; however, because they serve exclusively as an osteoconductive matrix, these carriers are usually combined with osteoinductive factors in the clinical setting. Walsh et al. reported the formation of a denser fusion mass with the use of a ceramic composite comprised of 65% hydroxyapatite, and 35% TCP, and type I bovine dermal collagen (Collagraft, Zimmer) when compared to autogenous bone graft in a ovine lumbar fusion model\(^{37}\). However, studies using ceramic carriers in posterior lumbar\(^{38}\) and anterior interbody thoracic spine fusion models\(^{39}\) in canines, have reported inferior union rates and biomechanically weaker fusion masses when compared with autograft. Reports using sea coral have shown it to be of limited clinical utility in the enhancement of spinal fusion\(^{40}\). Ceramic composites have also successfully enhanced spinal fusion in clinical investigations using anterior cervical fusion and posterior spinal fusion for adolescent idiopathic scoliosis\(^{41}\).

Although favorable evidence exists supporting the use of ceramics in spine fusion, these carriers also have significant limitations. Interporous hydroxyapatite has brittle handling properties and minimal tensile strength. Subsequently, rigid fixation of the surrounding region is necessary to protect the ceramic from shear and torsional stresses\(^{35}\). The resorption characteristics of ceramics also vary depending on the preparation. Newer commercial fabrications may display more rapid resorption \textit{in vivo}, thereby permitting more complete bone remodeling\(^{41}\). The definitive role of ceramic composites in spine surgery has yet to be delineated, however, early results have been promising. Ceramics have been shown to support vascular ingrowth, promote cellular adhesion, and enhance new bone formation\(^{32}\). The use of these carriers combined with an osteoinductive stimulus may one day replace the use of autogenous bone grafting.

AUTOLOGOUS CELLS

Autologous human bone marrow cells provide osteogenic capability through the action of secreted cytokines and growth factors. Bone marrow contains osteoprogenitor cells and growth factors that actively recruit host mesenchymal stem cells (MSCs) to undergo osteoblastic differentiation. Recent research has reported the ability of bone marrow to stimulate bone formation\(^{41}\). \textit{In vitro} expansion of MSCs with a ceramic carrier comprised of hydroxyapatite and beta-tricalcium phosphate in canines promoted superior healing of a critical-sized femoral defect compared with autologous bone marrow alone\(^{44}\). Autologous cells provide significant osteoinductive capabilities through osteogenic cells, however, when used alone, they lack localized structural support. For this reason, the combination of an osteoconductive matrix and autologous marrow has been assessed in tibial nonunions, bone cysts, and comminuted fractures associated with bone loss\(^{24,45}\). Autologous cells, with or without matrix, have also been used to treat nonunions of carpal bones, tibia, femur, and humerus\(^{14}\). MSCs in autogenous bone marrow are capable of developing into mature osteoblasts when exposed to the appropriate growth factors. Furthermore, culture expansion of MSCs has been shown to amplify the number of osteoprogenitor cells in vitro\(^{46-47}\). In a pre-clinical critical-sized defect model in canines, culture-expanded MSCs exhibited superior healing rates when compared to bone marrow\(^{46}\). These results show promise for the use of MSC therapy in lumbar spinal fusion, particularly in the elderly patient population. In patients where autogenous bone graft is limited, less invasive bone marrow harvest procedure through the same lumbar incision may provide a supply of osteoprogenitor cells that may promote spinal fusion.

Bone marrow cells are easily accessible through aspiration from the posterior iliac wing, and a recent study has recommended the harvest of smaller volumes (2 cc) of bone marrow in order to obtain a higher concentration of osteoblast progenitor cells\(^{47}\). Muschler et al. reported the efficacy of concentrating bone-marrow-derived cells from bone marrow aspirates using a selective cell attachment technique in a canine posterior segmental spine fusion model\(^{44}\). Their results suggest that when used with a bone
marrow clot, an enriched cellular composite graft of concentrated bone marrow cells induced a greater spine fusion mass volume \textit{in vivo} than cancellous bone matrix alone\textsuperscript{48}. Early evidence in animals supports further investigation into the use of autologous bone marrow with an osteoconductive carrier in the induction of spine fusion. With the addition of a suitable carrier, the combination offers three of the four necessary elements for bone repair: osteogenic bioactive factors, responding cells, and a matrix to encourage ingrowth of host capillaries. Together, the use of autologous cells with a carrier offers components for bone repair akin to that of autogenous bone graft. Complications are subsequently avoided, such as those associated with bone graft harvesting and the low risk of infection. However, there are concerns about the potential variability in human bone marrow cellularity as well as an age-related decline in progenitor cells\textsuperscript{49}. Although the benefits are supported by a strong theoretical basis and success in animal models, further studies into using autologous cells as a bone graft substitute in spine fusion are needed.

**ALLOGRAFTS**

Allograft bone offers advantages over autogenous bone graft in the setting of spinal arthrodesis because there is an abundant supply of graft material and the morbidity associated with autograft harvest is avoided. Allografts are either preserved through frozen or freeze-dried processes, or offered as fresh specimens. The process of freeze-drying decreases antigenicity which aims at reducing the host’s cell-mediated immune response. This ultimately leads to increased graft incorporation\textsuperscript{50}, however, freeze-drying also decreases osteogenic activity and hinders host vascular invasion. The loss of osteoinductive capabilities leads to a higher incidence of nonunion and delayed union in comparison to autografts\textsuperscript{15}. Furthermore, resorption of cancellous allograft proceeds at a slower rate than autogenous graft leaving necrotic tissue at the surgical site. Necrotic allograft bone has been reported at the site of implantation even years after surgery\textsuperscript{51}. The risk of disease transmission from musculoskeletal tissue donors exists from the use of allografts, however, this has been found to be low. New standards in screening donor tissue enforced by the American Association of Tissue Banks have reduced the risk of HIV disease transmission to no greater than one in 1.5 million\textsuperscript{53}. In the past five years, no cases of HIV transmission have been reported (78-90% fusion). Clinical evidence involving multi-level cervical fusion or corpectomies show a significantly higher fusion rate with the use of autograft versus allograft\textsuperscript{2,55,59}. For this reason, allograft bone is not currently recommended in cervical spine fusion involving multiple levels.

In summary, cortical allografts provide structural support to the anterior column and have been used successfully in interbody fusions and result in comparable outcome and fusion rates to those with autogenous bone graft in the lumbar spine. Cortical allograft also provides adequate fusion rates at single levels in the cervical spine when autograft is undesirable. Based on the body of evidence available, cancellous allograft bone should only be used as a bone graft extender in posterolateral arthodesis and anterior instrumented procedures of the thoracolumbar spine.

**GROWTH FACTORS**

The discovery of bone morphogenetic proteins (BMP) by Urist in 1965\textsuperscript{50} has led to a diverse area of research dedicated to the identification and characterization of osteoinductive growth factors. Members of the TGF-\beta superfamily, BMPs have been proposed for a number of applications in orthopaedic surgery\textsuperscript{61}. Recombinant BMP-2 (rhBMP-2) and BMP-7 (or osteogenic protein-1, rhOP-1) have been evaluated in numerous pre-clinical models\textsuperscript{61-62}. Studies demonstrating successful spinal arthrodesis have been reported in animals\textsuperscript{63-64}. In fact, FDA approval has been granted for the use of rhBMP-2 to enhance anterior spinal fusion\textsuperscript{65} and rhOP-1 to treat recalcitrant long bone nonunions\textsuperscript{66}.

The efficacy of recombinant BMPs has been evaluated in a number of pre-clinical models of spine fusion. Recombinant BMP-2 has been shown to reproducibly heal the lumbar spine in rodents and nonhuman primates\textsuperscript{67-70}. Furthermore, rhOP-1 has also demonstrated consistent bone...
healing properties in rodent and sheep models. Results from these studies suggest that the use of rh-BMP results in similar if not superior fusion rates with biomechanically stronger fusion masses when compared to autogenous bone grafts.

The first clinical pilot study using BMP in an anterior interbody fusion cage reported high rates of radiographic fusion with more rapid improvement in clinical outcome. Fourteen patients with single-level degenerative disc disease were randomized to receive anterior lumbar interbody arthrodesis with a cylindrical fusion cage packed with either with the combination of rh-BMP-2 and collagen sponge or iliac crest autogenous bone graft. Fusion rates were higher (11/11 fusions versus 2/3 fusions) and clinical outcomes were better at the 3-month timepoint with rh-BMP-2 than with autograft. At 6 months, both study groups demonstrated similar levels of clinical improvement. This subsequently led to the FDA approval for the use of rhBMP-2 for human subjects in anterior spinal fusion. Since then, further studies have expanded the potential clinical indications of recombinant BMPs.

Boden et al. reported the clinical use of rhBMP-2 on a biphasic calcium phosphate carrier in the healing of a posterolateral spine fusion in a comparison study involving 25 patients. Radiographic fusion rates were significantly greater in the 20 patients treated with rh-BMP-2 (20 out of 20 fused), compared to the autograft group (2 out of 5 fusions). Moreover, clinical improvement as defined by the mean Oswestry Disability Index score (6 weeks postoperatively) was greatest in the rhBMP-2 treatment only group.

Vaccaro and colleagues demonstrated the efficacy of rhOP-1 putty (3.5 mg rhOP-1 with 1 g Type I collagen) in the enhancement of posterolateral lumbar arthrodesis. In a randomized, prospective, multicenter study, a total of 36 patients with degenerative spondylolisthesis were treated with either rhOP-1 or autogenous iliac crest bone graft in an instrumented posterolateral fusion following a decompressive laminectomy. At the one-year timepoint, comparable rates of clinical and radiographic posterolateral arthrodesis were found between the autograft and rhOP-1 study groups. These authors concluded that fusion rates in the absence of internal fixation with the use of rhOP-1 putty was safe and yielded comparable results to that of iliac crest bone graft.

Modifications in the accompanying carrier can enhance the efficacy and local delivery of BMP. Previous research has shown the requirement of high doses of BMP-2 when used with a plain collagen sponge in animal models. One study has reported the advantages of carrier modifications involving the addition of fast-resorbing biphasic calcium phosphate granules or allograft chips. Using these carrier modifications, the amount of rh-BMP2 required to heal a nonhuman primate spine model was decreased significantly. The authors concluded that simple cost-effective alterations in carrier composition may decrease the amount of recombinant BMP used to induce spine arthrodesis.

The continued research into the efficacy of recombinant BMPs in the augmentation of spinal arthrodesis offers promising results. Evidence from early clinical trials indicate that the use of rh-BMPs results in fewer side effects, more rapid clinical improvement, and fusion rates that are as good as, if not better than iliac crest autograft. However, there remains uncertainty in regards to the cost-effectiveness of rh-BMPs and for which clinical indications they are most applicable. Furthermore, identification of appropriate carriers for different clinical scenarios is essential in order to reduce both dose and cost of recombinant proteins.

**GENE THERAPY AND TISSUE ENGINEERING**

Tissue engineering remains an attractive potential option for spinal arthrodesis because of its ability to closely approximate the biology of autologous bone graft. Gene therapy involves the in vitro transfer of genetic material to cells to stimulate in vivo expression of a targeted protein. Gene therapy systems are comprised of the DNA sequence, a vector, such as a virus, to mobilize the genetic material in question, and target cells to express the protein. There are a number of theoretical advantages with the use of genetic transfer systems over the use of recombinant protein. First, gene transfer strategies offer greater availability of a growth factor such as bone morphogenetic protein at the intended site of fusion. Gene delivery vehicles are available to continually deliver a protein to a local area, thereby compensating for the rapid biodegradation of recombinant growth factors. Secondly, target cells have osteoinductive capabilities that increase the potential for bone formation. These differences may prove to be critical in a stringent biological environment where sustained BMP production is required for osseous repair.

Early results using BMP gene transfer via an in vivo technique revealed successful fusion only in immunocompromised animals. Since then, a number of immunocompetent animal studies have demonstrated the efficacy of gene therapy in the healing of long bone defects and spinal fusion. A study in our laboratory reported successful results with the use of ex vivo adenooviral gene transfer in a posterolateral spine fusion model in immunocompetent rats. BMP-2-producing target cells were created from syngeneic rat bone marrow cells and implanted with DBM and collagen sponge between the transverse processes of L4 and L5. All spines treated with BMP-2-producing bone marrow cells and recombinant BMP fused at four weeks postoperatively regardless of the carrier used, while none of the control groups fused. Histologic analysis revealed that coarse trabecular bone had formed from cells generated by adenooviral gene transfer whereas thin, lace-like bone formed from that of recombinant BMP.

A separate group of investigators reported the use of adenooviral gene transfer with a construct containing the cDNA for BMP-7 in a rat spine fusion model. Syngeneic bone marrow cells modified with BMP-7 were combined with...
freeze-dried allograft bone and implanted into immunocompetent rats. Successful fusion, deemed by manual palpation, was seen in 8/10 rats of the treated groups as compared to 0/10 of the control groups. Using an adenoviral construct coding for the reporter gene ß-galactosidase, the authors found maximal protein expression on postoperative day 3, and observed a progressive decline to background levels by postoperative day 14. This endpoint suggests that due to the episomal nature of the adenovirus genome, genetically modified cells are not permanently altered.

The success of gene therapy has also been reported in higher animal models. Harvested mesenchymal stem cells from pigs were used as targets for adenoviral-mediated transfer of the BMP-2 gene. The transduced cells were then used to successfully heal the thoracic disc spaces of three pigs through an anterior thoracoscopic injection. Radiographic and histologic examination confirmed bridging bone in all six disc spaces treated with adenovirus while little bone formation was seen in the control injections.

Studies reporting the use of gene therapy systems in animal models in the spine literature have most often involved the use of the adenoviral vector. In addition to BMP-2 and BMP-7, recent reports have shown the successful use of other bone morphogenetic protein genes, such as BMP-6 and BMP-9. Despite the widespread use of adenoviral vectors for the transfer of BMP genes, several limitations exist regarding its use in clinical trials. First, adenovirus has been found to offer short-term production of protein. In vivo data suggests that the delivery of growth factor falls to background levels 14 days after implantation. Adenoviral vectors have also been found to induce a significant host immune response. Studies suggest that this immunogenicity may interfere with spine arthrodesis rates, especially if the host has been previously exposed to the vector. For this reason, the development of alternative vectors in the induction of bone formation has been made. Lentiviral vectors impart minimal immunogenicity and have been found to result in the long-term production of BMP-2 in vitro for over 12 weeks. The successful transfer of the BMP-4 gene using an adeno-associated viral vector has also been reported.

Studies in preclinical models reporting the use of gene therapy to enhance bone repair in animal models show promise in its future use to treat spinal arthrodesis in humans. The sustained local production of growth factor remains attractive in the research of bone repair and may become even more important in the treatment of pseudarthroses or other conditions of unfavorable bony healing. With additional investigation into its safety profile in humans, the use of gene therapy within the realm of tissue engineering may soon become a reality in the field of spine surgery.

DISCUSSION

Spine arthrodesis often presents a number of difficulties including osteolytic bone defects, poor biological environment, and compromised bone stock. Bone graft and bone graft substitutes are vital to a spine surgeon’s armamentarium in dealing with issues of bone loss, solid fusion, and clinical outcome. These substances vary widely in regards to available data, and careful evaluation is necessary to identify the appropriate use of various bone graft agents.

Currently established treatment options including the use of allograft or autograft may soon be supplemented with recombinant growth factors or products from tissue engineering. Although its cost-effectiveness must be assessed, use of these novel biologic substitutes may be used to enhance bone repair in more stringent biologic environments such as those in revision procedures. Further study into the efficacy of bone graft substitutes will hopefully lead to improved clinical outcomes in primary and revision spine fusion.

The body of evidence reporting the efficacy of recombinant BMP in clinical studies has grown considerably over the past three years. Since the first report of BMP-induced osteoinduction in a clinical trial, additional studies have reported the superiority of rh-BMP2 to the use of autogenous bone graft. Recent studies have shown that with adequate dosing of recombinant protein in patients without spinal instability, the use of rhBMP may decrease the need for instrumentation. Furthermore, multiple investigators have demonstrated the osteoinductive versatility of recombinant BMP using multiple approaches. Future uses of rhBMP may lead to higher success rates in minimally invasive procedures and lessen surgical exposures. Despite excellent clinical results, many concerns still exist for the regular use of recombinant growth factors. Clinical studies which confirm the safety from the use of rh-BMP2 in humans fall short in evaluating possible long-term effects. Furthermore, the current cost of rhBMP precludes its routine use in spine arthrodesis.

The investigation into the use of tissue engineering to deliver the sustained production of BMP may soon present an additional bone graft option for the spine surgeon. Delivery of protein through gene expression may be better suited in a biologically stringent environment than recombinant BMP which may be degraded quickly. However, safety concerns have hindered the progress of tissue engineering in the clinical setting. Recent interest has been dedicated to the characterization of the lifespan of transduced cells, duration of gene expression, and systemic effects on the host genome after the use of gene therapy. Additional studies in higher pre-clinical models are needed to assess the long-term effects of gene therapy before its clinical use in humans is widely accepted.

The future of the use of bone graft substitutes to enhance spine arthrodesis remains bright. Multiple avenues of research exist in the development of biologic substitutes for the enhancement of spine fusion. The continued laboratory and clinical characterization of spinal biologics will ultimately offer spine surgeons multiple options in the arena of spine fusion.
REFERENCES


