The Role of the Osteoconductive Scaffold in Synthetic Bone Graft

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Abstract

Autogenous bone is regarded as the gold standard for bone graft materials as it provides 3 elements necessary to generate and maintain bone: scaffolding for osteoconduction, growth factors for osteoinduction, and progenitor cells for osteogenesis. Allograft is more limited than autograft in these essential elements and yields more variable clinical results. Composite synthetic grafts offer an alternative that can potentially unite the 3 salient bone-forming properties in more controlled and effective combinations than can be obtained in many clinical situations, without the disadvantages found with autograft. This article examines the underemphasized but crucial role of the osteoconductive scaffold in the composite synthetic bone graft.

Bone is used annually in > 450,000 graft procedures in the United States and in 2.2 million procedures worldwide to repair bone defects caused by either trauma or tumor resection and to achieve spinal arthrodesis.[1,2] To date, autogenous cancellous bone remains the gold standard for these procedures; it provides all 3 interdependent elements necessary to maximize bone-forming ability: scaffolding for osteoconduction (bone mineral and collagen), growth factors for osteoinduction (noncollagenous bone matrix proteins), and progenitor cells for osteogenesis.[3] The osteogenic potential of autograft is limited, however, by logistic and functional disadvantages. The acquisition of autogenous bone increases operative time and the donor site, generally the iliac crest, may not have sufficient bone of suitable quality to meet the need. Donor site complications and procurement morbidity can result in increased patient recovery time, disability,[4] and chronic pain at the bone graft donor site (9% incidence of chronic pain following lumbar spinal fusions).[5] The efficacy of autogenous graft is further limited because most viable cells taken from the harvest site die when they are separated from their blood supply and processed in the surgical suite.[6,7] The incidence of nonunions in posterolateral lumbar fusions, the most commonly performed spinal arthrodesis, varies from 5%-44%,[6] and a rate of pseudarthrosis as high as 68% in anterior lumbar fusion has been reported.[8]

Allograft is the preferred substitute when autografting is not a realistic option. However, allograft tissue is expensive, yields more variable clinical results than autograft, and has known risks of bacterial contamination, viral transmission, and immunogenicity.[9,10] To lessen the potential risks to the recipient, allograft bone is intensively treated prior to preservation for storage; these processes contribute to increased costs and diminished mechanical and biologic properties.

A variety of synthetic bone grafts have been tried, including ceramics, collagen, noncollagenous proteins, bioactive glasses, and biodegradable polymers; they are used in approximately 10% of bone graft procedures performed worldwide.[1] The perceived drawbacks of some substitutes include poor resorbability, inclusion of processed animal components, inferior handling characteristics, and cost. The combination of osteoconductive matrices with osteoinductive growth factors and osteogenic cells may potentially surpass the functionality of autograft and allograft; composite grafts comprise the most rapidly expanding category of autograft substitutes.[11] One of the primary barriers that has slowed development of an ideal composite graft has been the considerable challenge of finding the optimal scaffold vehicle for

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delivering osteogenic cells and osteoinductive growth factors.[12-14] The carrier must have the appropriate 3-dimensional (3-D) structure to serve as an osteoconductive matrix for bone-forming cells; it should be biocompatible to minimize interference with bone induction from an inflammatory reaction; it must be biodegradable to minimize the effects of residual carrier on the biomechanical properties of the repair, yet it must persist in vivo long enough to maintain bioactive elements at the site of implantation and optimize their release profile. Reconciling these sometimes competing requirements is difficult. Issues of binding, bioavailability, and diffusibility have not been resolved.[14] The role of the osteoconductive component of a composite graft is more than that of a passive scaffold. Its role is pivotal as a dynamic delivery system for bioactive agents.[6]

SYNTHETIC OPTIONS

Ceramics

Calcium phosphate ceramics are synthetic scaffolds that have been used in dentistry since the early 1970s and in orthopedics since the 1980s.[11,15-17] Tricalcium phosphate (TCP) ceramic has a stoichiometry similar to amorphous biologic precursors to bone, whereas hydroxyapatite (HA) has a stoichiometry similar to bone mineral. Neither of these synthetic calcium phosphate bone substitutes exists naturally, but they have been shown to evoke a biologic response similar to that of bone.

When these synthetic materials are immobilized next to healthy bone, osteoid is secreted directly onto the surfaces of the ceramic in the absence of a soft tissue interface. Subsequently, the osteoid mineralizes and the resulting new bone undergoes remodeling. Both TCP ceramic and HA are highly biocompatible. They differ, however, in the biologic response engendered at the host site: porous TCP ceramic is removed from the implant site as bone grows into the scaffold; HA is more permanent. These ceramics are known to be osteoconductive but lack intrinsic osteogenic potential as is found with autograft. Synthetic ceramics are readily available and are without infectious or immunogenic potential. They reduce patient morbidity significantly by reducing the need for a second operative site.

The mechanical properties of calcium phosphate scaffolds are not suited to withstand torsional and tensile forces imposed on the skeleton; their clinical use is limited to nonweight bearing sites. Their mechanical properties resemble those of ceramics because the inorganic compounds are processed (sintered for thermal consolidation) at temperatures higher than 1000∞C. The sintering process can be modified to form either a single phase or multiple principal phases of calcium phosphate. After the material has been sintered, residual minor impurities and secondary phases can exert a measurable effect on mechanical properties. Calcium phosphate ceramic bone substitutes are more brittle and have less tensile strength than bone.[11] The eventual mechanical properties of a ceramic implant (eg, compressive strength) will surpass the initial values, especially because the construct is porous so as to encourage tissue penetration and flow of nutrients through the structure following surgery. Once the scaffold has incorporated with surrounding hard tissue, its mechanical strength approaches that of cancellous bone.[11,18]

Subtle differences in chemical composition and crystalline structure of various calcium phosphates may have a major impact on their physical characteristics in vivo. Constructs with higher density and crystallization have greater mechanical strength but undergo slower resorption. Although calcium phosphate–based products have been studied for bone repair for 80 years, principally the so-called high-temperature calcium phosphates, such as β-tricalcium phosphate (β-TCP), HA, or some combination of the 2, have predominated in recent medical studies.[17]

The porosity of the ceramic structure is a major determinant of the amount of surface area exposed to the biologic milieu. As such, greater porosity can accelerate physical processes, such as dissolution, and biologic processes, such as cellular attachment and osteoid deposition. Factors associated with porosity become the primary physical determinants of the speed and completeness of incorporation of bone-forming tissue and subsequent bone remodeling. Pore sizes in the range of 150-500 µm are optimal for interface activity, bone ingrowth, and implant resorption.[11] Interconnected porosity, found only in some calcium-based scaffolds, allows viable cellular components to permeate throughout the matrix to facilitate rigid fixation in surrounding bone. The most commonly used bone graft substitutes made from TCP are approximately 35%-50% porous, with pores ranging from 100-300 µm.[10]

A variety of commercial bone substitutes are made of HA, for example, Pro Osteon 500R (Interpore Cross, Irvine, Calif), Endobon (Merck, Darmstadt, Germany), and Pyrost (Stryker Howmedica Osteonics, Rutherford, NJ).[17] Hydroxyapatite is essentially nondegradable, with resorption rates of only 5%-15% per year.[10]

Hydroxyapatite may also be made from natural coral exoskeletons by hydrothermal conversion of calcium carbonate into calcium phosphate. Coral has an interconnected pore structure (trabecular pattern) similar to that of cancellous bone, containing only 20% matrix.[11] Longitudinal pores within the Goniopora genus measure 500-600 µm across with porous interconnections measuring 220-260 µm in diameter and a wall thickness of approximately 130 µm.[19] One calcium-based material derived from coral, Pro Osteon 500R, is converted incompletely so that the outer surfaces of the scaffold contain HA while the underlying portion retains more resorbable calcium carbonate.[11] Interporous HA has been compared with cancellous autograft in filling metaphyseal defects in a study of 40 patients with displaced tibial plateau fractures. Clinical and

radiographic assessments at follow-up periods averaging 15.4 months (autograft) and 34.5 months (HA) demonstrated no noteworthy differences between the groups in maintenance of reduction, time required to (radiologic) union, and range of knee motion.[20]

The initial mechanical limitations of ceramic scaffolds do not confer an advantage to either autograft or allograft, because these biologic scaffolds do not provide adequate early mechanical support. When any bone graft is used in a body weight-bearing site, it requires stress shielding support by means such as plates or screws. Ceramic scaffolds are typically used to fill cystic defects, repair fractures of the tibial plateau, and extend autogenous bone grafts.[21]

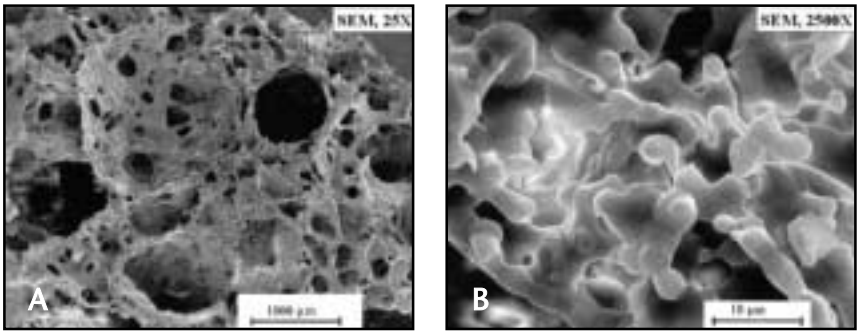

Figure 1: Scanning electron microscopy images showing the ultraporous β-tricalcium phosphate scaffold.

Calcium Phosphate Cements

Another class of calcium phosphate, the so-called low-temperature variant, is calcium phosphate cement (CPC). Calcium phosphate cements are made from dissolving 1 or more calcium phosphates in aqueous solution at room temperature. The calcium phosphates precipitate into a less soluble structure. Most CPCs have precipitated hydroxyapatite (PHA) or carbonated PHA as the end product of the setting reaction. Although the biodegradability of apatite CPC is greater than that of HA, it is slow, with CPC still present after 2 years.[22,23] Hardening of the end-product via precipitation rather than polymerization (as with PMMA cements) has the advantage of releasing little heat. During the precipitation reaction, the calcium phosphate crystals grow and become entangled; the entanglement provides a mechanical rigidity to the cement.[17] Nevertheless, most commercial CPCs have a porosity of approximately 50%, with a fragility profile similar to traditional calcium phosphates; the compressive strength of most commercial CPCs (10-100 mPa) is much higher than the tensile strength (1-10 mPa).[11,17] This necessitates their use in either low or nonload bearing applications or in combination with metal implants. Moreover, CPCs have a small pore size (1 μm), another drawback compared with open-macroporous calcium phosphate. This is too small to allow fast bone ingrowth and, therefore, the CPC degrades from the outside in, layer by layer.[17] However, any alteration of the cement matrix to incorporate macropores would compromise its mechanical properties.

The discovery of CPC has caused a much wider use of low-temperature calcium phosphates in medicine.[17] Injection-hardening ceramics have been used in bone screw augmentation, maxillofacial surgery, space-filling internal fixation (eg, metaphyseal fractures and other bone defects), and augmentation of osteoporotic vertebral bodies.[10,11,17,24-26] The initial compressive strength of the hardened material is similar to that of cancellous bone (55 mPa), yet the filled region undergoes remodeling over the long term, ultimately being replaced by host tissue.[27] Vascular channel invasion, osteoclastic activity, and new bone formation are visible within a few weeks of implantation, with minimal foreign body reaction.[10]

In a prospective, randomized study of 40 patients with redisplaced distal radial fractures, treatment with injectable CPC (Norian SRS Cement, Norian Corp, Cupertino, Calif) and cast immobilization for 2 weeks was compared with external fixation alone for 5 weeks.[28] Comparable functional outcomes were attained for the 2 groups except for more rapid recovery of grip strength and wrist mobility in the patients treated with cement. However, neither treatment was able to fully stabilize the fracture; progressive redislocation was shown radiographically.[21] A prospective, randomized study compared CPC injection (and 2 weeks of cast immobilization) with conservative treatment in 110 patients with distal radial fractures.[24] The rate of malunion was 41.8% in patients treated by immobilization alone compared with 18.2% in those injected with cement prior to immobilization. Patients with the CPC implants had less pain and earlier restoration of movement and grip strength. Injectable CPC has also shown potential when used to augment hip fracture treatment.[29]

However, low-viscosity injectable cements are not highly porous. Therefore, the material remains inert for long periods with insubstantial resorption.[11] The initial liquid state can lead to difficulties during placement, such as extrusions into intra-articular regions.[30]

Ultraporous β-Tricalcium Phosphate

An ultraporous scaffold (Vitoss, Orthovita, Malvern, Pa) processed from β-TCP particles averaging 100 nm in size[31] more closely resembles the structure of natural cancellous bone (Figure 1A). Smaller particles improve osteoconductive performance (Figure 1B)[32] and facilitate osteoclastic digestion during remodeling. This new material has a broad range of pore size (1 μm-1 mm) and interconnected microporosity, both associated with

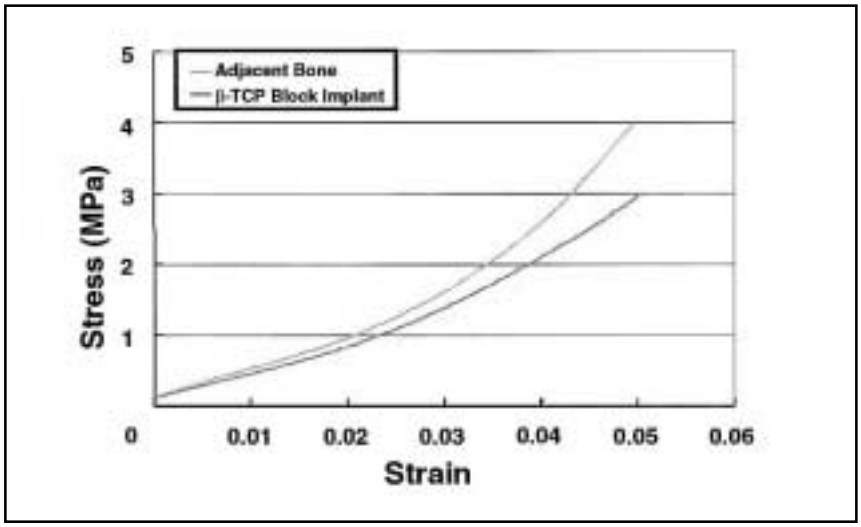

Figure 2: Results of compression testing of the ultraporous β-tricalcium phosphate (b-TCP) implant compared with adjacent bone at 52 weeks.

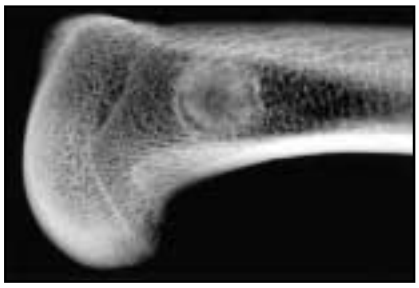

Figure 3: Radiograph of ultraporous β-tricalcium phosphate implant in canine metaphyseal defect at 3 weeks showing resorption (clearing) and some immature bone formation in the interior region of the implant.

better osteoconduction. The scaffolding is supplied as block pieces that may be shaped at the time of surgery and tamped into position, or as morsels for packing into irregularly shaped bone voids.

When placed into cylindrical canine metaphyseal defects, ultraporous β-TCP implants were essentially removed and replaced with new bone in 6-12 weeks.[33] Approximately 82% of the implanted ultraporous scaffold resorbed at 12 weeks compared with 34% of the HA-coated calcium carbonate scaffold ($P < .05$). Histologically, radiographically, and mechanically, bone within defect sites repaired with ultraporous β-TCP was comparable to adjacent original bone at 12, 24, and 52 weeks (Figures 2 and 3).[34]

Biologic Processed Scaffolds

Cadaveric cortical bone can be decalcified and additionally treated to reduce the potential for transmissible infection and immunogenic host response. The altered material, demineralized bone matrix (DBM), retains the trabecular structure of the original tissue and can serve as a biologic scaffold[11] despite the loss of structural strength once contributed by the preexisting bone mineral.[35] The process of demineralizing bone does not eliminate all bone growth factors, which are now more bioavailable with the mineral phase removed. Thus, DBM can impart more osteoinductive potential than standard mineralized allograft.[6,10] Clinical results have not been uniformly favorable, however, and variable clinical response is attributed partly to nonuniform processing methods found among numerous bone banks and commercial suppliers.[11,21] Other concerns relate to the effectiveness of processing on immunogenicity and disease transmission.[3] If, after extensive processing, DBM still retains some beneficial proteins (ie, those that induce or accelerate bone production), then what assures the full elimination of more problematic proteins? Demineralized bone matrix, nonetheless, is widely used to extend autogenous bone graft.[6,21,36]

Composite Scaffolds

The purpose of using a composite scaffold is to amplify and control the concentration of elements that are found naturally in autogenous bone to provoke a stronger, quicker bone repair response. Separately, ceramic scaffolds may supply a structural underlay, whereas processed or biologic grafts may offer the osteoinductive and osteogenic elements; however, no single synthetic matrix has yet effectively combined all 3 capabilities. A graft material that contains any 1 of these features can be effective in specific circumstances, but the more elements are brought together and the greater their concentration, the greater the potential is for speedy repair and long-term maintenance of the graft.[3] Autograft naturally contains osteoinductive, osteoconductive, and osteogenic components, but often in amounts more limited than would be potentially available in an engineered composite graft.[3]

In a composite, the proteinaceous osteogenic or osteoinductive components (eg, mesenchymal stem cells from bone marrow or growth factors) can be concentrated and delivered to the graft site by way of an osteoconductive carrier. Carrier resorbability must match the expected rate of progressive bone replacement at the defect site. In this manner, the osteoconductive matrix acts as a delivery system for bioactive agents[6]; the matrix function exceeds that of a passive scaffold as its chemical surface shows a direct effect on wound cells as well as serving as the attachment site for bioactive molecules such as growth factors and adhesion molecules.[10] The elusive search for the appropriate vehicle has so far confounded the task of evaluating specific composite grafts that include bone morphogenetic proteins or osteoprogenitor cells from bone marrow.[12-14]

Composites with Collagen

Collagen, the most pervasive protein

in the extracellular bone matrix, provides a physical and chemical milieu favorable to bone regeneration.[27] When collagen is introduced into a composite scaffold, it does not enhance its mechanical properties; however, it can improve the handling characteristics of certain mixtures. As most collagen used for graft is animal derived, collagen is associated with potential immunogenicity. The primary use of collagen in bone graft preparations has been as a delivery system for osteoconductive, osteoinductive, or osteogenic factors. Results have been mixed,[10] but some combinations of collagen sponges with osteoinductive proteins have shown promise.

Studies to supplement autograft with collagen have reported mixed results. In a canine study of posterior segmental spinal fusion by Muschler et al,[37] autograft added to a composite of bovine dermal collagen with ceramic granules of 60% HA and 40% TCP was less satisfactory than a smaller volume of autograft alone. In a canine anterior spinal fusion model, however, the collagen/ceramic composite was found to be an effective autograft extender.[38]

Composites with Bone Marrow Aspirate

Bone marrow and bone marrow aspirate (BMA) have been identified as sources of osteogenic factors; their effectiveness in healing smaller, well-defined bone defects and treating delayed unions and nonunions in tibial fractures has been documented.[3,39] It has been postulated that an osteoconductive scaffold can limit the diffusion of bone marrow away from the defect site and improve efficacy in larger defects.[11,21] Tricalcium phosphate and HA have been used as carriers for BMA in canine radius defects; combinations of these ceramic scaffolds with BMA have been as effective as autogenous bone.[32,40,41]

In a multicenter, randomized study of 213 patients treated for long bone fractures and followed for 2 years, patients treated with a combination of autogenous BMA and a composite of mixed phases of calcium phosphates and bovine collagen had union rates and functional measures that were comparable to those of patients treated with autogenous bone alone.[42] Additionally, the incidence of infection was reduced in the BMA/composite group relative to the autograft group: 4.9% versus 13% incidence at the fracture site (P= .008), and 4.9% versus 14.2% when the donor site (iliac crest) was accounted for (P= .003). Infection seen in patients receiving autograft was unexpectedly more frequent at the host site than at the donor site.[42] Although the absence of a bone marrow-only group makes determining the contribution of synthetic composite versus bone marrow difficult, there was no evidence of inhibition as was seen in Muschlerís animal study with a collagen composite (no added BMA) cited previously.[37]

The osteoinductive properties of the combination scaffold of BMA with ultraporous β-TCP have been shown to be superior to the biologic scaffold of DBM alone. In a 56-day study with athymic nude rats, a composite of ultraporous β-TCP infused with isologous bone marrow was compared with DBM (Grafton DBM Flex, Osteotech Inc, Eatontown, NJ) implanted bilaterally in axillary muscle (n= 24 for each material). Significantly more new bone was formed within the marrow-augmented ultraporous β-TCP sites than in the sites filled with DBM at days 14 and 28 (P< .05). The proportion of bone filling the implants, assessed histomorphometrically, was 0%, 1%, and 14% for DBM-treated animals versus 3%, 9%, and 17% for animals treated with the composite at days 14, 28, and 56, respectively. Bone formation induced by DBM was not significant until day 56.[43]

Composites with Bone Morphogenetic Protein

Bone morphogenetic protein (BMP) was first identified in 1976 by Urist, who began his search for the osteoinductive component of bone by processing large, kilogram quantities of bovine bone to extract a few milligrams of biologically active material. Several members of the BMP family have since been identified, some of which can now be produced in commercial quantities by molecular cloning.[35] The BMP most actively studied, the recombinantly produced human protein rhBMP-2, is under evaluation in combination with a bovine collagen sponge in a composite scaffold for promotion of spinal union and for repair of defects in the iliac crest created when autogenous bone was removed to supply bone graft.

In a multicenter pilot study approved by the US Food and Drug Administration, spinal fusions were attempted in 14 patients with lumbar degenerative disk disease using threaded interbody metal cages filled with rhBMP-2/collagen sponge (11 patients) or autograft (3 patients). By 6 months, vertebrae were fused in all 11 patients who received the composite scaffold versus 2 of 3 patients who received autogenous graft; these results were maintained at 1 year.[44] The rhBMP-2/collagen sponge composite graft is currently being used in 45 patients to repair defects in iliac crests generated by the removal of autogenous bone used to fuse cervical vertebrae following diskectomy.

In the United States, Europe, and Australia, the combination of recombinant human osteogenic protein-1 (rhOP-1) and collagen has been used in spondylolisthesis cases as a replacement for iliac crest autograft in posterolateral spinal fusion. In a US Investigational Device Exemption (IDE) pilot study by Patel et al[45], this putty-like material has shown bone bridging in 21 of 24 treated patients, comparable to 11 of 12 autograft control patients, who also had 90% bridging bone. In addition, the rhOP-1 patients have shown approximately twice the success rate of autograft (> 20% Oswestry score improvement), and radiographic success (stability on flexion/extension films and bridging bone). No product-related adverse events have been reported.

TABLE

Summary of Osteoconductive Scaffolds*

Graft	Osteoconduction	Osteoinduction	Osteogenesis	Advantages
Autograft	3	2	2	"Gold standard" for biocompatibility and fusion
Allograft	3	1	0	Any available forms (eg, dowels, etc)
DBM	1	2	0	Supplies osteoinductive BMPs,bone graft extender
TCP, hydroxyapatite	1	0	0	No supply constraints, biocompatible
Calcium phosphate cement (CPC)	1	0	0	Injectable, no supply constraints, some initial structural support
β-TCP/BMA composite	3	2	2	Ample supply
Collagen	2	0	0	Good delivery vehicle for other graft materials
BMP/synthetic composite	—	3	—	Potentially limitless supply

**References 6, 10, 11, 27, 30, 47, 48.*
Score range: 0 (none) to 3 (excellent).
Abbreviations: DBM = demineralized bone matrix, TCP = tricalcium phosphate; BMA = bone marrow aspirate, BMP = bone morphogenetic protein, and R&D = research and development.

The combination of collagen and rhOP-1, also identified as BMP-7, has also been used to treat tibial nonunions. In a multicenter, randomized study of 124 patients treated for tibial fractures and followed for 2 years, patients treated with a combination of rhOP-1 and bovine collagen had clinical and radiographic assessments comparable to patients treated with autogenous bone alone.[46] Additionally, the incidence of postoperative osteomyelitis at the nonunion site was reduced in the rhOP-1/collagen group relative to the autograft group, 3% versus 21% (P= .002).

SUMMARY

Advances in bone grafting are progressing with the evolution of biomaterials that permit the incorporation of osteoinductive and osteogenic proteins into osteoconductive composite scaffolds (Table). Accompanying these developments has been a reduction of patient morbidity (commonly associated with secondary surgery for bone procurement) and alleviation of patientsí concerns about transmission of diseases and viruses (from processed cadaveric or xenogenic materials). Although the past decade has emphasized mechanical factors in orthopedic surgery, the next decade will focus more on biologic factors, such as recombinant human growth factors and composite autogenous alternatives.[11]

More progress has been made in the isolation and synthesis of growth factors than in the evaluation of the osteoconductive carrier, the role of which has been underestimated as merely a static matrix. This perception among clinicians and researchers is rapidly changing. Increasingly, the carrier will function as a dynamic element to optimize the release kinetics for osteoinductive and osteogenic elements; the carrier must immobilize osteoinductive growth factors and osteogenic cells and resorb in a timely fashion.[12-14] Nuances of scaffold chemistry and structure are now understood as crucial to establishing this delicate balance, prompting the development of second generation carriers, such as resorbable ultraporous β-TCP constructs of nanometer-size particles. Technological and conceptual advances may ultimately lead to a number of ideal autograft substitutes, with graft materials and composites becoming increasingly specialized.[7]

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Disadvantages	Clinical Results
Procurement morbidity, limited availability	56%-100% in spinal fusion[6]
Immunogenic, disease transfer risk	60%-90%[49]
No structural support, variable osteoinductivity	Equivalent to pure autograft when used as extender[36]
Little initial structural support	Equivalent to autograft, but decreased complications[20,50-52]
Lack of placement control, incomplete resorption	Equal or superior to conventional treatment[24,28,29]
Little initial structural support	Preclinical only
Minimal structural support, potentially immunogenic	Combined with bone marrow, equivalent to autograft in treatment of long bone fracture[4]
R&D and commercialization costs	Ongoing clinical studies using rhBMP-2 combined with either ceramic or collagen sponge show results comparable to autograft[46]

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