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Alternatives to Autologous Bone Harvest in Spine Surgery

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Abstract: Spine fusion remains a common means of achieving stability in spinal surgery. Methods for obtaining fusion involve decortication of the host bed and introduction of a grafting material. Autologous bone has served as the standard material for these procedures in that its three cardinal properties encourage effective bone healing: osteogenic cells, an osteoconductive structure, and an osteoinductive matrix. Further, both cancellous bone with its increased surface area and osteogenic potential and cortical bone with its structural properties may be harvested. However, autologous bone suffers certain drawbacks, particularly a high rate of donor site morbidity, limited amounts of available bone, and the additional operative time required for harvest. For these reasons, intensive efforts have been directed toward developing alternative substances to either augment or substitute for autologous bone in spinal surgery. In this paper, we will examine some of the commonly used and emerging materials and their indications in spinal surgery.

Introduction

Spinal arthrodesis attempts to eliminate motion by achieving bony union (fusion) between mobile elements of the spine. In 1983, an estimated 180,000 procedures were performed to confer stability on various segments of the spinal column [41]. However, the complete process to achieve union remains incompletely understood. Even in ideal circumstances, pseudarthrosis remains a significant clinical problem. To increase fusion rates, the emphasis of the past 10 years has been on mechanical factors, such as internal fixation. The next 10 years promise increased attention to the biological factors influencing fusion. The development of various alternatives to autologous bone graft, particularly growth factor-containing and composite materials, is an example of this trend.

In 1942, Abbott [2] provided an early description of bone harvest from the ilium. Since that time, iliac and other autologous sources have been used extensively in spine surgery [29]. Autologous bone offers the three cardinal properties conducive to bony fusion. Its hydroxyapatite (HA) crystals and collagen serve as an osteoconductive framework for new bone formation. A number of lining cells in the graft bone marrow cavity are directly osteogenic. Cancellous bone and adjacent hematoma express growth factors to induce regenerative processes.

Alternatives now in use, or soon to be in use, include allograft demineralized bone matrix (DBM), autologous bone marrow, ceramics, and growth factors. None of these materials offers all three fusion-inducing properties. Although the literature contains many conflicting reports, the majority of the available data suggest that fusion rates are higher and clinical results are improved with the use of autograft in either the structural or cancellous settings. While composite grafts with recombinant bone morphogenic proteins (BMPs) may provide increased fusion rates in the future, autologous bone remains the gold standard.

Autologous bone has certain shortcomings, however. Principally, these include limited amounts available and complications associated with harvest. Given that most spinal procedures, indeed most orthopaedic procedures, are intended to improve function, the search for alternative graft sources with decreased functional morbidity has been intense. In considering alternatives, a strict comparison of biologic properties as well as clinical results is required. However, these clinical data are limited for most of the materials presented.

Biology of Grafting

Although much more is known about the phases of fracture healing, bone graft incorporation apparently represents a similar cascade of events (Fig. 1) [8]. In one model, three major steps have been identified [12,15,16]. First, recruitment of undifferentiated progenitors from the host bed, and in autograft from the marrow cavity of the bone graft, occurs. Surgical trauma and decortication lead to bone necrosis of fracture fragments with cell death and release of intracellular by-products. These products, along with a low oxygen tension and pH, serve as chemoattractants to undifferentiated osteoprogenitor cells from the host bed. A graft material may also contain osteogenic cells capable of directly forming bone. In early stages of healing, these cells will graft with host bone. However, they must be protected during the graft procedure to ensure viability. The only known osteogenic grafts are fresh autogenous bone and bone marrow cells.

Second, the undifferentiated progenitors give rise to chondroblasts and osteoblasts in a cascade mediated by other chemical factors. This process is known as osteoinduction. As prostaglandins serve as significant mediators of

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Table 1. Growth factors involved in musculoskeletal repair processes

Factor	Location	Principle actions
TNF	Macrophages	1. Increase bone resorption 2. Increase cell replication
FGF	Inflammatory cells Osteoblasts, chondrocytes	1. Increase cell replication 2. Indirectly increase collagen production 3. Angiogenic 4. Regulates cell differentiation
PDGF	Platelets, monocytes Endothelial cells	1. Increase osteoblast/chondrocyte proliferation 2. Increase collagen and NCP synthesis
IGF	Bone and cartilage	1. Stimulates cartilage growth
TGF beta	Platelets, osteoblasts Chondrocytes, bone Matrix	1. Increase osteoblast/chondrocyte proliferation 2. Increase proteoglycan synthesis 3. Decrease collagen synthesis
BMP	ECM of bone	1. Induces bone formation

Abbreviations: NCP, noncollagen proteins; TNF, tumor necrosis factor; IGF, insulin-like growth factor (or somatomedin).
(Modified from OKU 5: General Knowledge, p. 22, and Trippel et al. [68].)

this cascade, inhibitors such as NSAIDs should be avoided in patients undergoing fusion [42].

Osteoinduction also involves several families of local growth factors. These factors influence migration, differentiation, and the activity of bone-forming mesenchymal cells (Table 1). BMP, the most famous of these, is actually a family of at least 15 growth factors originally identified for their ability to stimulate de novo formation of bone [68]. Osteogenic protein 1 (OP-1, also known as BMP-7) is a member of this family. Pure BMPs are very potent; subcutaneous injection of only 50–100 ng will cause heterotopic bone formation in rats. BMP represents 0.1% by weight of all bone protein and is most abundant in diaphyseal cortical bone. Immunolocalization studies have noted increased cellular expression of BMP as enchondral ossification progresses to early woven bone. Then, during callus maturation, BMP expression drops off [9]. BMPs are also found in the extracellular matrix (ECM). Here, they are not accessible for osteoinduction until the bone matrix has been demineralized. Once exposed, however, they induce formation of cartilage and bone.

Outside of the family of BMPs are other related growth factors. These proteins include transforming growth factor-beta (TGF-b), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Although TGF-b cannot induce ectopic bone formation alone, it is closely related in structure to BMP. The exact roles of TGF and BMP in bone morphogenesis and repair are not understood. However, TGF seems to have an earlier role in granulation tissue development.

FGF has been noted to have an angiogenic effect and appears to be important in neovascularization and wound healing. In a rat fracture model, FGF increased the size of the fracture callus [68]. PDGF is believed to be a local tissue growth regulator. In a rabbit model, PDGF increased the density and volume of the fracture callus. The role of platelets as a major source of PDGF underscores the importance of the blood clot in bony healing scenarios. Graft material may contain osteoinductive molecules as well (e.g., DBM, certain recombinant growth factors, and autogenous and allograft bone).

In the third phase of bony incorporation, osteoconduction, a scaffold is established on which active progenitors can produce new bone. During this phase, bony continuity is achieved across the desired space, allowing for ingrowth of neovasculature and osteogenic precursors. Then, new bone remodels along lines of stress in accordance with Wolff's law. A graft may assist in osteoconduction by providing a

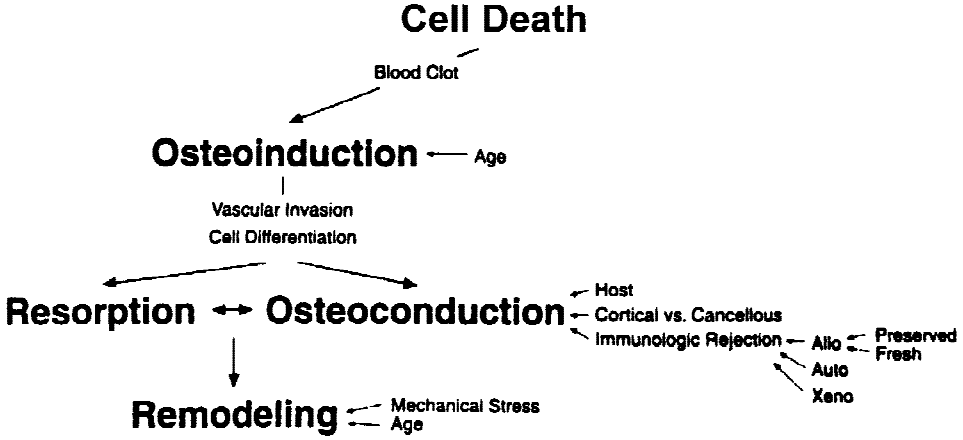

Fig. 1. A flow chart of fusion incorporation. (From Simon [63] by permission American Academy of Orthopaedic Surgeons.)

favorable, although nonviable, infrastructure on which bone may form via creeping substitution. Solely osteoconductive materials confer no active cells or inductive stimuli. There are many examples of osteoconductive grafts, including autogenous and allograft bone and calcium phosphate ceramics.

Although not central to the present discussion of alternatives to autogenous bone, local and systemic factors are critical in terms of ultimate clinical results. As such, these factors should be addressed in conjunction with the selection of a graft material. Systemic factors, such as cigarette smoking, have long been suspected of decreasing bone formation [8] (Table 2). Head injury, on the other hand, tends to increase peripheral bone formation [31]. There are no systemic therapies available to capitalize on these factors.

The surgeon has more control over local factors in the fusion bed. The physiologic milieu may, in fact, be a major determining factor in the type of graft material selected. For example, injured muscle does not supply the neovasculature required to achieve fusion. Further, macrophage activity in soft tissues increases the release of cytotoxic products and growth factors that promote fibrous tissue rather than bone formation. Also, inflammation from bacterial invasion also destroys molecular signals in the osteoinduction process [8].

The amount of graft available and its placement in the fusion bed are believed to have a profound impact on the quantity and quality of the subsequent fusion. A gap between fragments inhibits the passage of molecular signals and the creation of an osteoconductive framework [35]. Electromagnetic fields (EMF) and ultrasound (US) have also been proposed as means of enhancing the local fusion milieu and achieving higher rates of fusion. Animal models have had mixed results and human clinical studies have suffered from design flaws. Some clinical information suggests that EMFs and US may have a role in the promotion of bony union in pseudarthrosis. However, the data are limited and no clear clinical recommendations can be made at this time [8,31].

Autograft

Autograft (formerly called homograft) refers to bone taken from one anatomic site and transplanted to another site in the same individual. As this transfer contains live osteocytes, autograft is the most osteogenic material. Although autograft is the material most likely to encourage fusion, pseudarthrosis rates in spinal surgery still range from 5 to 35% [64]. Autograft offers complete histocompatibility and virtually no inflammatory encapsulation of the graft material. However, although these benefits are striking, the major shortcomings of autologous bone harvest have fueled the intensive search for alternatives (Table 3).

Harvest of autologous bone engenders a fairly significant rate of donor site morbidity and complications. Complications rates vary significantly by series and depend on the source (rib, fibula, iliac crest). Complications can be major or minor. Minor complications such as superficial infections, seromas, and minor hematomas are treated with aggressive nonoperative management (e.g., aspiration, antibiotics). Minor complications range from 3.1 to 39% [3,4,34,70]. Altered sensation at the harvest site (including hyperesthesia, dyesthesia, or hypesthesia) is directly related to the amount of soft tissue dissection. Seen in 10–25% of patients, altered sensation is the most common complication reported [27,66].

Major complications require a change in treatment, prolonged hospitalization, or a return to the operating room. With iliac crest bone harvest, major complications range from 0 to 17.9% [3,4,34,70] and include muscle herniations, vascular and nerve injuries, deep infections or hematoma, and iliac fractures [34,40]. Major vascular or urethral injuries are also reported [17,20,26]. In posterior spinal surgery, the overall complication rate was higher with the same incision harvest [70].

Structural autograft recovery often involves greater soft tissue dissection than cancellous bone. In the ilium, exposure of both tables of the crest is required and a palpable

Table 2. Local and systemic factors affecting bone healing

Local factors		Systemic factors	
Positive	Negative	Positive	Negative
Good vascular supply	Radiation	Growth hormone	Osteoporosis
Large surface area	Tumor	Thyroid hormone	Vitamin D deficiency
Mechanical stability	Local bone disease	Somatomedins	Corticosteroids
Growth factors	Infection	Vitamin A	NSAIDs
BMP	Mechanical instability	Vitamin D	Chemotherapy
Electrical stimulation	Bone wax	Insulin	Smoking
Mechanical loading	Denervation	Parathyroid hormone	Anemia
		Calcitonin	Rheumatoid arthritis
		Anabolic steroids	Sepsis
			Diabetes
			SIADH
			Malnutrition
			Sickle cell disease
			Thalassemia major

(Modified from Boden and Schimandle [8].)

defect may remain. After fibulectomy, many report that the leg remains slightly weak and painful. Yet, harvest of small tricortical pieces of iliac crest for anterior cervical discectomy and fusion (ACDF) may have a lower associated complication rate [34] than large exposures for cancellous bone grafting.

Autograft harvest engenders increased surgical time and cost [56]. However, the alternatives can also be quite expensive (Table 4). The amount of autogenous bone available for harvest may be insufficient for long, multisegment fusion, especially in patients with previous harvests. Alternative graft material are particularly important as autograft extenders. The autograft is divided into three main categories: cancellous, cortical, and vascularized cortical (Table 5). Cancellous bone remains the most successful material for posterior spinal fusion. Cancellous grafts offer more surviving bone cells as well as the greatest connectivity. Connectivity refers to the large trabecular surface area, which is readily incorporated during new bone formation.

Cancellous bone does not offer initial structural support. However, this quickly changes, due to augmentation and union (osteointegration) with host osseous structures. Strength increases as bone mass increases and as the construct remodels along lines of stress. Cancellous autograft tends to become completely incorporated. Careful attention to sizing is critical to preserve osteogenesis. In large pieces, diffusion of nutrients limits graft cell survival. Ideally, cancellous autograft should be prepared in small, flat strips of slabs about 5 mm across. Remember that antibiotic powder exposure inhibits osteogenesis.

Cortical autograft is predominantly used for large defects (7.5–25 cm) that require immediate structural support. Unlike cancellous bone, however, cortical bone may lose up to one third of its strength during incorporation [24]. Cortical bone remodels over a 6–18 month period. Osteoclast tunneling and resorption remove nonviable bone, but significant islands of nonviable bone remain through life. Fibular struts demonstrate the greatest structural integrity, but stress fractures are a problem in longer grafts (12–25 cm). Some authors recommend protecting these grafts for 2 years.

Aside from initial strength, cortical grafts are less desirable than cancellous grafts. Fewer marrow spaces yield fewer osteogenic cells. Those cells present are less likely to survive (<5%) because they are embedded in matrix and thus, shielded from nutrient diffusion. Cortical grafts present less surface area onto which new bone can form and are more resistant to vascular ingrowth and remodeling [8].

Vascularized cortical grafts are harvested with an artery and vein. This pedicle is reanastomosed at the fusion site. The fibula, iliac crest, and rib may be used for this purpose. The continued arterial supply and venous drainage allow for improved incorporation and less necrotic bone remains after the remodeling process. The graft will increase in girth with compressive loads. The procedure is technically demanding and requires increased operating room time and larger exposures with increased donor site morbidity.

Vascularized grafts are indicated in select cases for anterior fusion, particularly with highly traumatized tissues, after radiation-induced fibrosis, or when radiation or chemotherapy is given postoperatively. They are clearly supe-

Table 3. Pros and cons of various grafting materials

Pros	Cons
Autograft	
Most osteogenic	Pseudarthrosis rates still up to 35%
No disease transmission	Morbidity and complication rates up to 35%
Complete histocompatibility	Increased blood loss and risk of transfusion
	Increased surgical time and cost
	Limited supply
Bone marrow	
Nonmorbid harvest technique	Limited amounts available
Osteogenic material	Must be used immediately (limited viability)
Allograft	
Avoids morbidity of autograft harvest	Slower incorporation rate
Both osteoconductive and inductive	Increased infection rate
	Greater resorption rate
	Disease transmission possible (rare)
	Immunogenic
	Decreased mechanical strength*
Demineralized Bone Matrix (DBM)	
Osteoinductive	No osteoconductivity
Easy to mold/implant	No structural strength
Less disease transmission risk than allo*	
Less immunogenic than allo*	
Ceramics	
No inflammatory response	Difficult to follow ingrowth on X-ray
No disease transmission	Brittle, low fracture resistance
Available in multiple forms	Limited bony replacement potential

*After processing.

Table 4. Hospital cost data for bone graft substitutes commonly used at William Beaumont Hospital

Material	Size	Cost
Pro-osteon (Interpore)	10-cc block	$ 998
	7.5-cc block	860
	30-cc small granules	662
	20-cc small granules	575
	30-cc large granules	675
MTF*		
Corticocancellous chips		
Small	30 cc	310
Large chips	30 cc	310
Granules	30 cc	310
Crushed cancellous bone	30 cc	475
Cancellous chips	30 cc	340
Cancellous powder	4 cc	82
Cortical bone dowel	11 mm	432
Cancellous, unicortical dowel	13 mm	438
Endodowel	18 mm, >1.8 cm long	633
Iliac crest wedge	8 mm	468
Fibular shaft	4.0 × 14–18 cm	360
DBM (Grafton)		
Gel	10 cc	754
Flex	10 × 25 cm	768
Putty	210 cc	798

*Prices are for freeze-dried materials. Frozen materials are also available at slightly higher cost from the Musculoskeletal Transplant Foundation (MTF). Comparison with two other tissue banks (Central Florida Tissue Bank and Allosource) revealed only minor price differences.

rior when defects to be bridged are greater than 12 cm [25]. In these cases, significantly decreased stress fracture rates are reported (25% versus 50%). Further, vascularized grafts are better able to heal any stress fractures that do occur. Ultimately, though, vascularized grafts have demonstrable superiority for only the first 6 months. Thereafter, no differences in biomechanical testing to torque, bending, or torsion can be detected.

Alternatives to Autograft

The following alternatives will be compared to autologous bone. Although they share the common advantage of avoiding the morbidity of autologous bone grafting, fusion-inducing properties vary (Table 6).

Recombinant growth factors

Recombinant growth factors may soon be available for human use. Prior to use, efficacy, lack of immunogenicity, side effects, and toxicity must be demonstrated [68]. As in future healing, recombinant growth factors are believed to be osteoinductive in the setting of fusion incorporation.

Bone marrow cells

An alternative source of autogenous osteoprogenitor cells lies in the bone marrow. In young individuals, 1:50,000 nucleated cells is an osteoprogenitor. This ratio falls to 1:2,000,000 in the elderly [16]. However, this proportion can be increased by using by centrifugation techniques [58]. Bone marrow is harvested in 2-ml aliquots [59] from the ilium (occasionally, the proximal humerus) in a nonmorbid manner with a syringe. The material must be used immediately or cell viability declines. A mechanism for growing mesenchymal stem cells out of culture is under development [10].

Allograft

Allograft (formerly termed heterograft) refers to bone transplanted from one member of a species to another. The use of allograft has expanded recently due to improved methods of procurement, preparation, and storage; better implant techniques; and the desire to avoid autograft complications. Allograft is available in various shapes useful in spine surgery. These include iliac crest bicortical and tricortical strips, cancellous and cortical dowels (in anterior lumbar interbody fusion), and fibular and femoral shafts and wedges (in anterior lumbar corpectomy with fusion and anterior cervical corpectomy with fusion). Cancellous and corticocancellous pieces (croutons) are also available.

Allograft is both osteoinductive and osteoconductive, but to a lesser degree than autograft. Allografting is associated with slower fusion, greater resorption, and increased infection rates. Infectious disease transmission is the most feared allograft complication. Sterilization is not a substitute for meticulous screening and a sterile harvest. Further, sterilization may interfere with the biologic and mechanical integrity of the graft.

The Food and Drug Administration (FDA) mandates that both member and nonmember institutions meet American Association of Tissue Banks (AATB) requirements, including meticulous donor selection criteria; repeated testing; la-

Table 5. Properties of autologous bone grafts

Property	Cancellous	Nonvascularized cortical	Vascularized cortical
Osteoconduction	++++	+	+
Osteoinduction	++	+/−	+/−
Osteoprogenitor cells	+++	−	+
Immediate strength	−	+++	+++
Strength at 6 months	++	++	+++
Strength at 1 year	+++	+++	++++

(From Gazdag et al. [30].)

beling requirements; long-term tracking of the graft; and facility inspection [1]. If these requirements are met, risk of human immunodeficiency virus (HIV) transmission should be less than 1 per million uses [13]. In fact, risks may be even lower with the advent of HIV testing via DNA polymerase chain reaction (PCR) technology. There are only two documented cases of HIV seroconversion after 3 million cases of allograft bone usage. Both of these followed unprocessed fresh-frozen grafting [30].

Several types of allograft are available (Table 7). The immunogenicity and maintenance of osteoinductive and osteoconductive properties are related to the method of graft processing and preservation. This processing may destroy HIV and other viruses [30]. Fresh allograft engenders an intense immune response in the host. Further, the need for rapid transfer decreases the time available for host pathogen testing. As a substrate for bony fusion, it is clearly inferior to autograft. Fresh allograft is used mainly in joint-resurfacing procedures and has no role in spine surgery.

Fresh-frozen allograft is prepared by chilling to −70°C. Freezing decreases enzymatic degradation without decreasing biomechanical properties and provides a graft intermediate in immunogenicity between fresh and freeze-dried allograft.

Freeze-dried, or lyophilized, allograft is processed by removing water from tissue and vacuum packing. This process is very effective in decreasing immunogenicity and allows the graft to be stored for 5 years. On rehydration, however, both hoop strength and compression strength are diminished. This decrease is not clinically significant in the context of rigid internal fixation.

Allograft is used to fill defects and to serve a structural role as an intercalary support. It may also be used as a graft expander. However, little clinical data are available concerning its effectiveness in this role. Some authors [23] recommend that allograft replace autograft in individuals with very high bone formation propensity (e.g., children).

DBM

DBM represents an extreme form of allograft processing. It is available commercially as Grafton allogenic bone matrix (Osteotech, Shrewbury, NJ). DBM is prepared by decalcification (acid extraction) of cortical bone. This process leaves collagen, noncollagenous proteins, and growth factors in continuity as a composite. In disrupting cell membrane proteins, DBM processing provides the least immunogenic variety of allograft bone.

DBM is available in powder form, as crushed granules, putty, chips, and in a gel- packed syringe (using a glycerol carrier). While its osteoinductive capacity is well established, it appears that the primary active components are mainly BMPs. The amount of BMP present is not known, but the concentrations are believed to be much lower than seen in recombinant BMP preparations. DBM is not classified by the FDA as a device, but as a graft tissue source. Therefore, its use is regulated as are other sources of allogenic bone.

Xenograft

Xenograft is bone transplanted from one species to another. There is a long history of xenografting in orthopaedics including ivory, cow horn, and bovine bone. However, xenografts invoke an intense immune response. The graft may become encapsulated, resulting in obstruction of microanatomoses between graft and recipient tissues. Xenografting is not recommended.

Ceramics

Ceramics comprise another large family of bone graft alternatives. Although there are several types of ceramic implants available, they share certain characteristics. Common requirements include tissue, mechanical, and physical compatibility with host tissues, stability in bodily fluids, and the ability to withstand sterilization. Implanted ceramics do not induce an inflammatory or foreign body response [12]. Further, they can be formed into compact or porous form and harbor no risk of infectious disease transmission. Disadvantages include the difficulty of assessing ingrowth on x-rays.

Ceramics are brittle, with low fracture resistance and ten-

Table 6. Properties of bone graft alternatives

Material	Osteoconduction	Osteoinduction	Osteoprogenitor cells	Immunogenicity	Donor site morbidity	Immediate torque strength
Cancellous autograft	++++	++	+++	−	+	−
Cortical autograft	+	+/−	+/−	−	+	++
Fresh allograft	+	+/−	−	++	−	++
Frozen allograft	+	+/−	−	+	−	++
Freeze-dried allograft	+	+/−	−	−	−	+/−
DBM	+	++	−	−	−	−
BMPs	−	++++	−	−	−	−
Bone marrow	−	+/−	++	−	−	−
Ceramic alone	++	−	−	−	−	−
Ceramics with marrow	++	+/−	++	−	−	−
Xenograft	++	−	−	+++	−	+/−

(Modified from Gazdag et al. [30] and Boden and Schimandle [8].)

sile strength. Therefore, they must be shielded from loading until bone ingrowth has occurred. In long bones, this shielding includes rigid stabilization and nonweight-bearing status. Once ingrowth is complete, the mechanical properties of the construct are similar to cancellous bone.

Although ceramics are biodegradable and compatible with new bone remodeling, the resorbing cell is a foreign body giant cell, not the osteoclast [41]. True cutting cone formation does not occur and bony replacement is limited to the outer 2–10 μm of the implant. Large segments of ceramic may remain in place for up to 10 years [36]. There are four main types of ceramics available today: sintered, replamiform, collagen mesh, and injection hardening. The first two are commonly used while the latter two are in development.

High-temperature sintered ceramics are created with pressure compaction. While porous, there is no interconnectivity of pores. Therefore, bony resorption is required to access inner pores [41]. HA and tricalcium phosphate (TCP), the two most common forms of sintered ceramics, vary in their chemical and structural (crystalline) composition. HA ($Ca_{10}[PO_4]_6[OH_2]$) is resorbed slowly, if at all. TCP ($Ca_3[PO_4]_2$) is more porous than HA and degrades 6–12 times faster. Most TCP is resorbed within 6 weeks after implantation [36]. TCP is weaker mechanically, however, and therefore mixtures of HA and TCP are often used.

Ceramics can be formed into compact or porous structures. The shape and architecture of the resulting crystal are key to strength and incorporation time. Higher density and crystallization yield greater mechanical strength and better resistance to dissolution. Sintered ceramics have an amorphous ultrastructure and porosity. Optimal pore size, 150–500 m, enhances interface activity, bone ingrowth, and biodegradation of the implant.

Replamiform ceramics are made from natural coral. Coral is composed of 97% calcium carbonate, but is structurally similar to bone. Two common types of coral, by genus, have structures that emulate cancellous and cortical bone, respectively [12,60]. *Gonipora* creates a structure with 500–600-μm pores and 220–260-μm interconnections. This "trabecular pattern" is similar to cancellous bone, with 20% matrix and the rest "marrow space" [41] (Fig. 2). *Porites*, on the other hand, is similar to cortical bone with 200–250-μm pores and parallel channels connected by 190-μm fenestrations. Unlike the random pore structure of sintered ceramics, the unique structural geometry of coralline promotes rapid resorption and reossification. One form of replamiform ceramic employs hydrothermal exchange to replace calcium carbonate with calcium phosphate [43]. This material, marketed as Pro-Osteon (Interpore, Irvine, CA), is essentially coralline HA. Both forms are extremely biocompatible. An incompletely converted, calcium phosphate and calcium carbonate material, termed Pro-Osteon 500R, is being investigated for a potentially more predictable resorption profile.

A new form of ceramic is being developed in which an early collagen mesh network is lightly covered with carbonate-enriched HA. This form also allows for interconnection of the pores [41]. Injection-hardening ceramics (e.g., Norian Skeletal Repair System) [16,38,41,62] are also being developed for use in metaphyseal fractures. Nonorganic calcium and phosphate are mixed to form a paste that is injected into the fracture. The paste hardens to form a ceramic mass (dahllite) within hours. At 12 hours, the material reaches its peak compressive strength of 55 Mpa. However, there is little control over porosity and the material remains inert for long periods of time. Ultimately, there may be a role for injection of this material in fractures of the thoracolumbar spine.

Composites

Composites comprise the most rapidly expanding category of autograft alternatives. With composites, the favorable properties of different materials are incorporated in a single compound. An early example of this concept is marketed as Collagraft (Zimmer, Warsaw, IN; Collagen Corp, Palo Alto, CA). Collagraft is a mixture of porous beads of 60% HA, 40% TCP, and bovine deantigenated fibrillar collagen. The material has 70% porosity with a pore diameter of 500–1,000 μm. It is available in paste and soft strip form. Collagraft is associated with some inflammation at the insertion site. Although collagraft confers no structural support when implanted, it may be combined with antineoplastics and antibiotics.

Table 7. Types of allograft bone

Type	Processing and storage	Sterilization
Frozen	Frozen and stored at −80°C	Aseptic acquisition
	Suited for large allografts	Gamma irradiation
	Shelf life of at least 2 years	
Freeze dried	Usually frozen to −30°C	Gamma irradiation
	Exposed to low atmospheric pressure	Ethylene oxide exposure
	Suited for small amounts of material	
	Indefinite shelf life	
Demineralized	Exposure to strong acids	Gamma irradiation
	Suited for powders and small amounts of material	Ethylene oxide exposure
Fresh	Refrigerated, not frozen	Aseptic acquisition

(From: OKU 5: General Knowledge, page 24, AAOS, Rosemont Ill, 1996.)

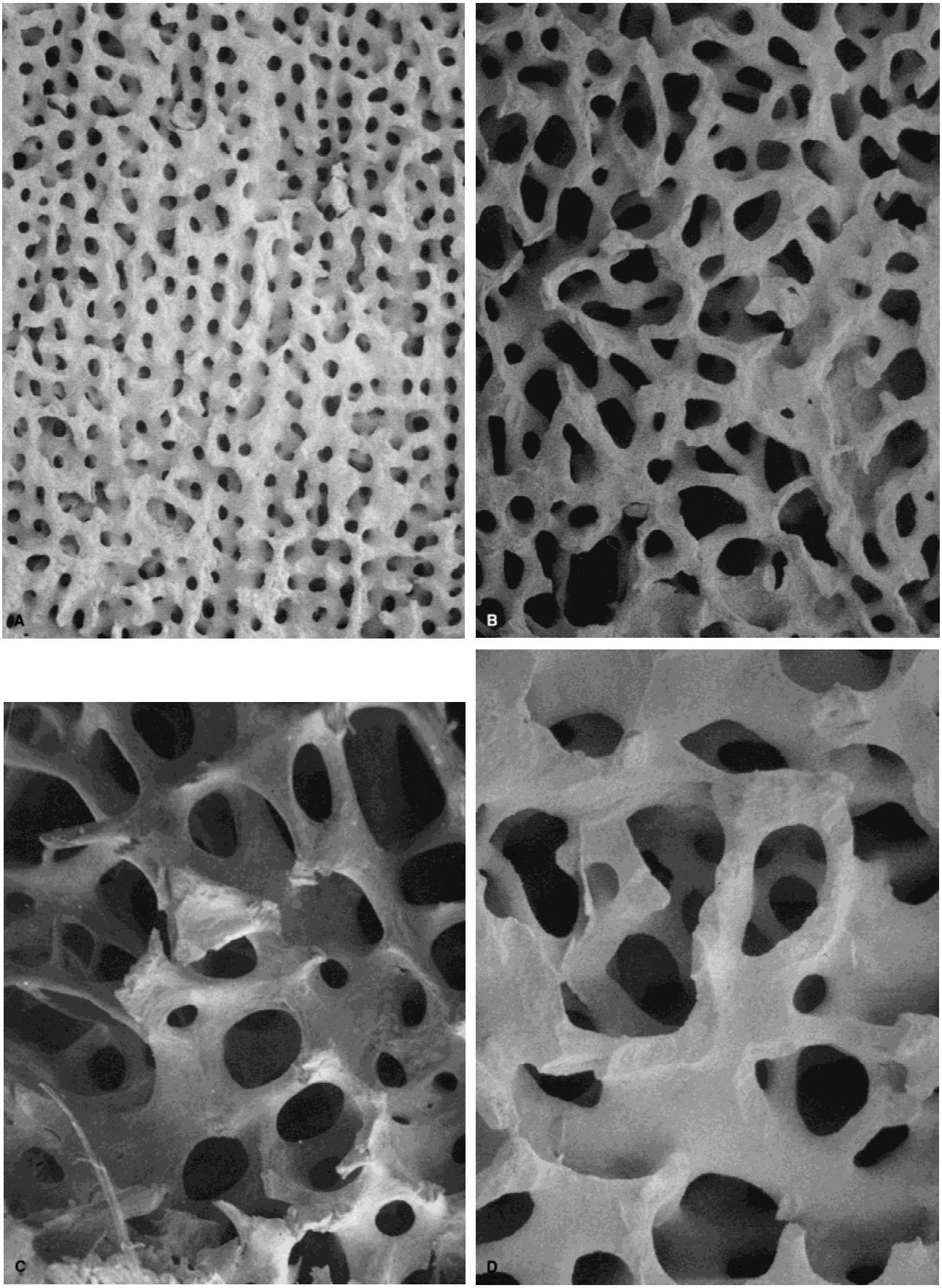

Fig. 2. Low and high-power micrographs of Pro-osteon. (From Gazdag et al. [30] by permission Interpore, Inc.)

Comparative Clinical Results

Valid recommendations for use of autologous bone alternatives require convincing clinical efficacy data. However, in most cases, the literature offers conflicting or limited reports. Few randomized, prospective trials are available. The majority of human studies suffer from a number of limitations (e.g., heterogenous diagnoses, patient ages and comorbidities, surgical techniques). Therefore, many use recommendations based on animal studies. Several animal fusion models have been developed (rabbit, dog, and cat) in which different types of spine fusions have been studied (anterior/posterior interbody, spinous process, laminar, facet, posterolateral intertransverse). How well these models predict clinical results remains controversial.

The results of allograft fusion techniques in spine surgery are also controversial. There are a number of studies comparing allograft with autograft. These include several well-designed animal reports, but few clinical studies with adequate design are available.

In tumor cases, major structural allograft has been associated with high complication rates [24]. Yet, use of allograft for bone tumors is associated with an overall 80% success rate. Most failures occur in the first 3 years. These failures include fractures (5–19%), nonunions (14%), and infections (10–15%).

Overall, allograft is more successful when placed in the anterior column under compression [8]. After ACDF, some authors report identical results with allograft, while others cite an increased rate of pseudarthrosis [44,71]. In a dog anterior column model, allograft demonstrated slower incorporation, increased resorption, and increased infection rates when compared with autograft [69].

In general, allograft placed on the tension side of the spine is associated with inferior results [37,45]. Yet, in scoliosis surgery, some authors [65] report acceptable fusion rates with allograft in children. Also, one group [39] reported excellent fusion rates (98%) with allograft and noted that fusion technique was more important than the material used. Yet another series [46] reported a 66% nonunion rate with allograft versus 36% for autograft.

Studies reporting the use of DBM have reported excellent clinical results in the promotion of bone regeneration in well-supported, stable skeletal defects [54]. Other series have been less optimistic. Some authors report variable effectiveness of DBM in bone induction, possibly due to denaturation of protein during FDA-mandated sterilization. In one rabbit model, DBM was a better autograft substitute than frozen allograft [53]. In spine surgery, DBM is most successful as an adjunct with other grafting materials.

A number of studies have examined the clinical results associated with the use of ceramic implants. TCP has been reported comparable to autogenous bone when filling defects secondary to trauma, tumors, and cysts [12]. In a study of Ray fusion cages in a goat model, equal bone ingrowth was achieved with autograft or granular TCP [47]. Passutti et al. [55] used HA-TCP alone or mixed with autograft in 12 patients with scoliosis. At 15 months, all had fused. Biopsies of the fusion mass were performed in two cases and revealed new bone directly bonded to the ceramic implant. In other studies [12,36,43,48], autologous bone has demonstrated consistently superior performance when compared with ceramic implants alone.

Coralline implants have yielded equal functional outcomes when used as a defect filler in proximal tibial defects in both dogs and humans [11,33]. In these scenarios, histologic analysis demonstrates cortical and cancellous ingrowth at appropriate locations. FDA approval of Pro-Osteon is limited to the filling of long bone metaphyseal defects. There are no approved uses in spinal surgery. However, in some cases Pro-Osteon 500 granules are being used as a graft extender. The use of ceramics to fill voids under compression is limited to certain anterior column applications (e.g., tumors and compression fractures). In these cases, careful protection of the weight-bearing column is needed to prevent shattering of the implant block [21]. One sheep study [67] demonstrated better fusion performance of ceramics of various porosities versus autograft. In this study, collapse and peri-implant mineral density were similar to autograft.

Successful use of autogenous bone marrow has been described alone [16] or in combination with other bone graft substitutes [5,58]. Thus far, clinical trials have demonstrated good results in long bone nonunions [20]. Increased use of bone marrow as an adjunct to some graft materials is being recommended. Its bone-forming ability is sustained or augmented with bone extracts containing BMP.

The next several years promise an explosion of data regarding the use of recombinant human (rh) growth factors. A number of animal studies are available. Zdeblick et al. [72] fused goats with BAK cages loaded with BMP. They achieved higher fusion rates and accelerated bone formation with BMP than with autologous bone. A similar cage study [6] in rhesus monkeys reported a 100% fusion rate with low and high doses of rh-BMP-2 placed in collagen sponges. In a dog posterolateral fusion model, 100% fusion rates were achieved in decorticated spines fused with BMP. An 89% fusion rate was reported when no decortication was performed [59]. Boden et al. [7] demonstrated increased fusion rates with bovine BMP versus autograft in a rabbit posterolateral intertransverse fusion model (100% versus 62%).

Early clinical trials are underway. These are likely to reveal significant differences in fusion rates and may prove superior to present autograft techniques. Work by Urist et al. [41] in 70 patients have revealed no side effects or tumorigenic activity. They described a 100% success rate in spine fusion using a nonrecombinant mix of BMPs and osteocalcin. However, we are at least 2–3 years away from widespread clinical availability of recombinant BMP.

Increasingly, composites incorporating the profusion properties of several graft substitutes are described. Ultimately, many of these composites will include BMP and other growth factors. Collagraft represents one available commercial preparation. Its use has mainly been focused on expansion of available autogenous bone volume. When mixed with patient's marrow, collagraft provides both its

Table 8. Clinical applications of autologous bone and bioalternative grafts*

Augmentation of autologous bone graft
1. Bone marrow mixed with ceramics or allograft
2. Ceramics or morcellated allograft
3. DBM or bone marrow
Expander to fill anterior column defects
1. Cancellous autograft or ceramics mixed with bone marrow
2. Ceramics or morcellated allograft alone
3. DBM or bone marrow
Reconstruct anterior column defects, such as anterior cervical disc/corpectomy with fusion
1. Cortical autograft†
2. Frozen cortical allograft‡
3. Freeze-dried allograft
4. Ceramics
Posterior spine pseudarthrosis
1. Cancellous autograft‡
2. DBM
3. Bone marrow
4. Morcellated allograft

*Options listed in order of efficacy.
†Consider cortical autograft for irradiated beds, defects >12 cm.
‡This option much preferable to the following option.
(Modified from Gazdag et al [30].)

own osteoinduction potential with the osteogenic potential of marrow osteoprogenitor cells. In one series [5], this use yielded better results than either agent alone or allograft alone. In one series of trauma patients [22], collagraft results were comparable with autograft results.Yet, operating room time was decreased and harvest site morbidity was eliminated. When using collagraft as a graft material near exposed neural elements, its placement is crucial in that it has the potential for flow in the presence of postoperative bleeding [41].

DMB's osteoinductive properties have been combined with the osteogenic properties of marrow cells. Muschler et al. [50] used a dog segmental posterior spinal fusion model to compare autograft, a collagen-ceramic composite, a collagen-ceramic-autograft composite, and a collagen-ceramic-BMP composite with no graft. While autograft was the most effective graft material, the addition of BMP to a collagen-ceramic composite improved union scores to near composite with autograft levels. Ceramic alone was no better than no graft.

Because coralline bonds well with bone, but lacks osteoinduction properties, it will not encourage fusion in the context of nonunion or a deficient soft tissue bed. Yet, osteogenic and osteoinductive potential may easily be added. Ceramic blocks have a demonstrated chemical affinity for growth factors [68]. Moreover, marrow grows well in these blocks forming a true composite [51]. Ultimately, these ceramics are likely to be used as a carrier for marrow or recombinant factors [52].

In an animal model, Ragni and Lindholm [57] described earlier bone formation with BMP-impregnated HA blocks than with BMP or HA alone or with autograft. At 6 months, however, results between HA-BMP were similar to autograft. While these results are promising, no human reports are available.

Summary

There are a number of graft materials available as alternatives to autologous bone. No one graft type is appropriate in all cases, however. The specific clinical need must be clearly defined so that the graft with the appropriate biologic characteristics can be chosen.

In spinal surgery, grafting is most often performed for one of the following reasons: structural support, defect or void filling, grafting for fusion in a favorable bed, grafting for fusion in an unfavorable bed, and grafting in the presence of infection. The various alternative materials described above are increasingly used to fill these needs (Table 8). Allograft remains a reasonable choice as a structural graft in the anterior column. In the presence of a deficient fusion bed, scarred or radiated tissue, or infection, strong consideration should be given to autologous structural bone, in particular, vascularized grafts. Many of the materials described function well as void fillers in the anterior column, provided adequate structural support is available. With the exception of certain classes of patients with exceptional bone-healing capacity, posterior spinal fusion should be carried out with autogenous, cancellous bone. Augmentation of this graft for long fusions, however, may be undertaken with several of the materials above.

Increasingly, composites of alternative materials will be used to fulfill several bone- healing requirements. The use of recombinant growth factors in these composites is very promising and may ultimately replace the routine harvest of autogenous bone. However, more clinical data are required for reasonable comparison of these materials with autologous bone. As clinical data become available, the methods of fusion assessment are critical in determining results. Roentgenograms may not accurately detect pseudarthrosis. The only reliable assessment of fusion is by exploration. Therefore, before autologous bone may be supplanted as the standard graft material, a careful assesment of both the data themselves and their source is mandatory.

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