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# BONE-GRAFT SUBSTITUTES: *FACTS, FICTIONS & APPLICATIONS*

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## COMMITTEE ON BIOLOGICAL IMPLANTS

Prepared by:

A. Seth Greenwald, D.Phil.(Oxon)  
Scott D. Boden, M.D.  
Victor M. Goldberg, M.D.  
Yusuf Khan, M.S.  
Cato T. Laurencin, M.D., Ph.D.  
Randy N. Rosier, M.D.

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## A REALITY CHECK

It is estimated that more than 500,000 bone-grafting procedures are performed annually in the United States, with approximately half of these procedures related to spine fusion. These numbers easily double on a global basis and indicate a shortage in the availability of musculoskeletal donor tissue traditionally used in these reconstructions. (Figure 1)

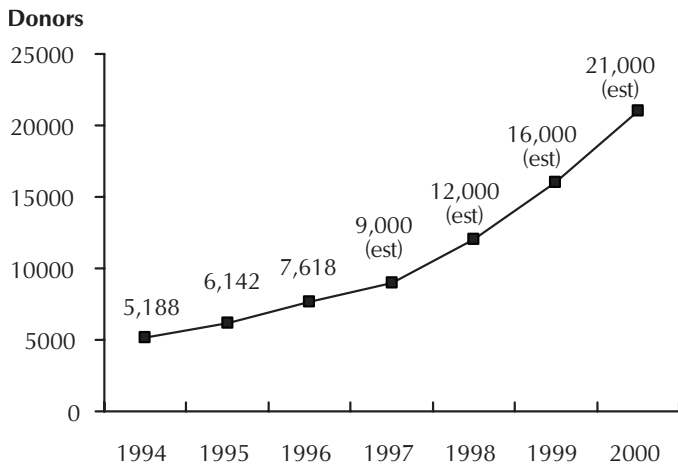


Figure 1: U.S. trends in musculoskeletal tissue donors  
Source: United Network for Organ Sharing & MTF

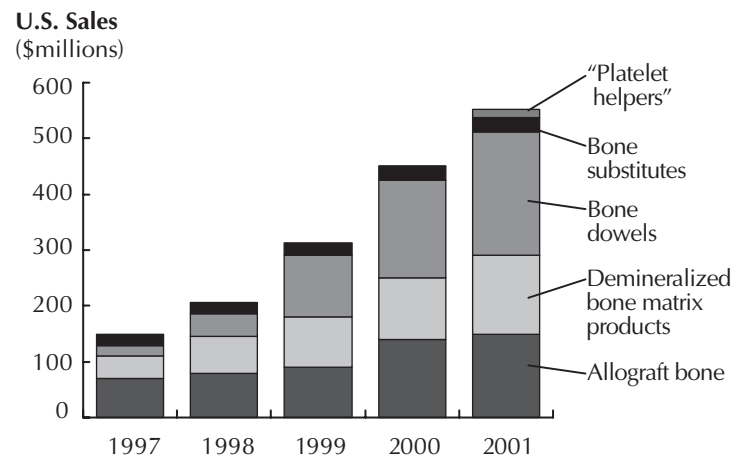


Figure 2: U.S. sales of bone graft and bone substitutes  
Source: Orthopedic Network News, industry estimates

This reality has stimulated a proliferation of corporate interest in supplying what is seen as a growing market in bone-substitute materials. (Figure 2) These graft alternatives are subjected to varying degrees of regulatory scrutiny, and thus their true safety and effectiveness in patients may not be known prior to their use by orthopaedic surgeons. It is thus important to gain insight into this emerging class of bone-substitute alternatives.

## THE PHYSIOLOGY OF BONE GRAFTING

The biology of bone grafts and their substitutes is appreciated from an understanding of the bone formation processes of *Osteogenesis*, *Osteoinduction* and *Osteoconduction*.

**Graft Osteogenesis:** The cellular elements within a donor graft, which survive transplantation and synthesize new bone at the recipient site.

**Graft Osteoinduction:** New bone realized through the active recruitment of host mesenchymal stem cells from the surrounding tissue, which differentiate into bone-forming osteoblasts. This process is facilitated by the presence of growth factors within the graft, principally bone morphogenetic proteins (BMPs).

**Graft Osteoconduction:** The facilitation of blood-vessel incursion and new-bone formation into a defined passive trellis structure.

All bone graft and bone-graft-substitute materials can be described through these processes.

## BONE AUTOGRAFTS

Fresh autogenous cancellous and, to a lesser degree, cortical bone are benchmark graft materials that allograft and bone substitutes attempt to match in *in vivo* performance. They incorporate all of the above properties, are harvested at both primary and secondary surgical sites, and have no associated risk of viral transmission. Furthermore, they offer structural support to implanted devices and, ultimately, become mechanically efficient structures as they are incorporated into surrounding bone through creeping substitution. The availability of autografts is, however, limited and harvest is often associated with donor-site morbidity.

## BONE ALLOGRAFTS

The advantages of bone allograft harvested from cadaver sources include its ready availability in various shapes and sizes, avoidance of the need to sacrifice host structures and no donor-site morbidity. Bone allografts are distributed through regional tissue banks. Still, the grafts are not without controversy, particularly regarding their association with the transmission of infectious agents, a concern virtually eliminated through tissue-processing and sterilization. However, both freezing and irradiation modify the processes of graft incorporation and affect structural strength. A comparison of the properties of allograft and autograft bone is shown in Figure 3. Often, in complex surgical reconstructions, these materials are used in tandem with implants and fixation devices. (Figure 4)

Bone Graft	Structural Strength	Osteo-Conduction	Osteo-Induction	Osteogenesis
Autograft				
Cancellous	No	+++	+++	+++
Cortical	+++	++	++	++
Allograft				
<i>Cancellous</i>				
Frozen	No	++	+	No
Freeze-Dry	No	++	+	No
<i>Cortical</i>				
Frozen	+++	+	No	No
Freeze-Dry	+	+	No	No
Demineralized Allogeneic Cancellous Chips	No	+	++	No

Figure 3: Comparative properties of bone grafts

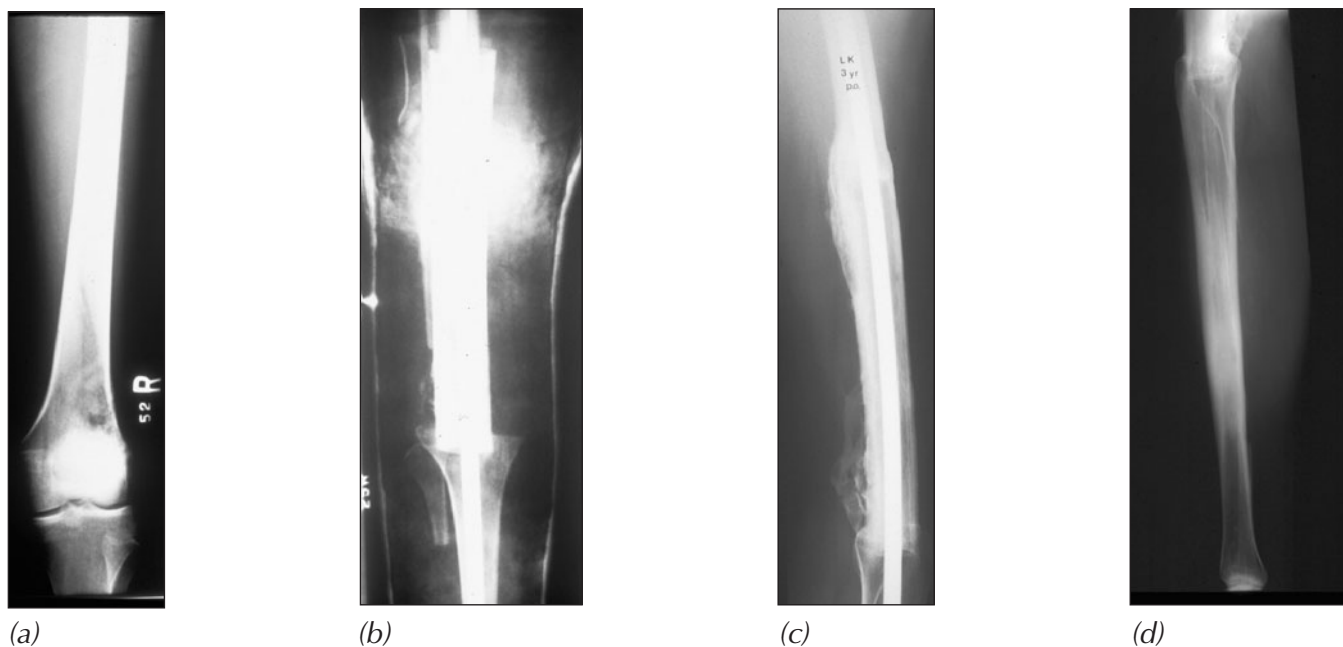


Figure 4: (a) A 17-year old patient with osteosarcoma of the distal part of the femur with no extraosseous extension or metastatic disease. Following chemotherapy, (b) limb salvage with wide resection was performed. Femoral reconstruction with the use of an autogenous cortical fibular graft, iliac crest bone chips, morselized cancellous autograft and structural allograft combined with internal fixation. (c) Graft incorporation and remodeling are seen at 3 years. (d) Limb restoration is noted at 10 years following resection. (The intramedullary rod was removed at 5 years.)

# BONE GRAFT SUBSTITUTES

The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective. Within these parameters a growing number of bone alternatives are commercially available for orthopaedic applications, including reconstruction of cavitory bone deficiency and augmentation in situations of segmental bone loss and interbody spine fusion. They are variable in their composition, their mechanisms of action and the claims made against them. Figure 5 shows a sampling of bone-graft-substitute materials. It is important to note that they all are osteoconductive, offer minimal structural integrity and possess little, if any, ability to facilitate osteoinduction. A series of case examples demonstrate their mechanisms of action through the healing process. (Figures 6, 7 and 8)

Company	GenSci OrthoBiologics	Interpore Cross International	Medtronic Sofamor Danek	Osteotech	Regeneration Technologies	Wright Medical Technology	Zimmer
<b>Commercially available product</b>	OrthoBlast™	ProOsteon® 500R	InFUSE™	Grafton®	OSTEOFIL®/ REGENAFIL®	AlloMatrix™	Collagraft™
<b>Composition</b>	Heat sensitive copolymer with cancellous bone chips and DBM	Coral HA Composite	rhBMP-2 protein with absorbable collagen sponge	Deminerlized bone matrix (DBM) combined with Glycerol	DBM combined with non-toxic natural gelatin carrier	DBM with surgical grade calcium sulfate powder	Mixture of hydroxyapatite, tricalcium phosphate, and bovine collagen
<b>Commercially available forms</b>	Injectable paste or putty	Granular or block	Freeze-dried powder and sponge in several sizes	Gel	Injectable paste Injectable putty, strips and blocks with cortical cancellous chips	Injectable or formable putty	Strip configurations
<b>Claimed mechanisms of action</b>	<ul style="list-style-type: none"> <li>• Osteoconduction</li> <li>• Bioresorbable</li> <li>• Limited osteo-induction</li> </ul>	<ul style="list-style-type: none"> <li>• Osteoconduction</li> <li>• Bioresorbable</li> </ul>	<ul style="list-style-type: none"> <li>• Bioresorbable sponge</li> <li>• Osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>• Osteoconduction</li> <li>• Bioresorbable</li> <li>• Limited osteo-induction</li> </ul>	<ul style="list-style-type: none"> <li>• Osteoconduction</li> <li>• Bioresorbable</li> <li>• Limited osteo-induction</li> </ul>	<ul style="list-style-type: none"> <li>• Osteoconduction</li> <li>• Bioresorbable</li> <li>• Limited osteo-induction</li> </ul>	<ul style="list-style-type: none"> <li>• Osteoconduction</li> <li>• Bioresorbable</li> <li>• Limited osteo-induction when mixed with bone marrow</li> </ul>
<b>Burdens of proof</b>	<ul style="list-style-type: none"> <li>• Case reports</li> <li>• Animal studies</li> <li>• Cell culture</li> </ul>	<ul style="list-style-type: none"> <li>• Human studies</li> <li>• Case reports</li> <li>• Animal studies</li> </ul>	<ul style="list-style-type: none"> <li>• Human studies</li> <li>• Animal studies</li> </ul>	<ul style="list-style-type: none"> <li>• Human studies</li> <li>• Case reports</li> <li>• Animal studies</li> </ul>	<ul style="list-style-type: none"> <li>• Human clinical study data available March 2002</li> <li>• Case reports</li> <li>• Animal studies</li> <li>• Every lot <i>in vivo</i> tested for osteoinduction</li> </ul>	<ul style="list-style-type: none"> <li>• Case reports</li> <li>• Animal studies</li> <li>• Cell culture</li> </ul>	<ul style="list-style-type: none"> <li>• Human studies</li> <li>• Case reports</li> <li>• Animal studies</li> <li>• Cell culture</li> </ul>
<b>FDA status</b>	<ul style="list-style-type: none"> <li>• Minimal manipulation</li> <li>• Non-regulated</li> </ul>	Approved 510K	PMA approval pending (FDA Advisory Panel voted 1/10/02 to recommend approval)	<ul style="list-style-type: none"> <li>• Minimal manipulation</li> <li>• Non-regulated</li> </ul>	<ul style="list-style-type: none"> <li>• Minimal manipulation</li> <li>• Non-regulated</li> </ul>	<ul style="list-style-type: none"> <li>• Minimal manipulation</li> <li>• Non-regulated</li> </ul>	Approved PMA

Figure 5: Summary of typical bone-graft substitutes that are commercially available

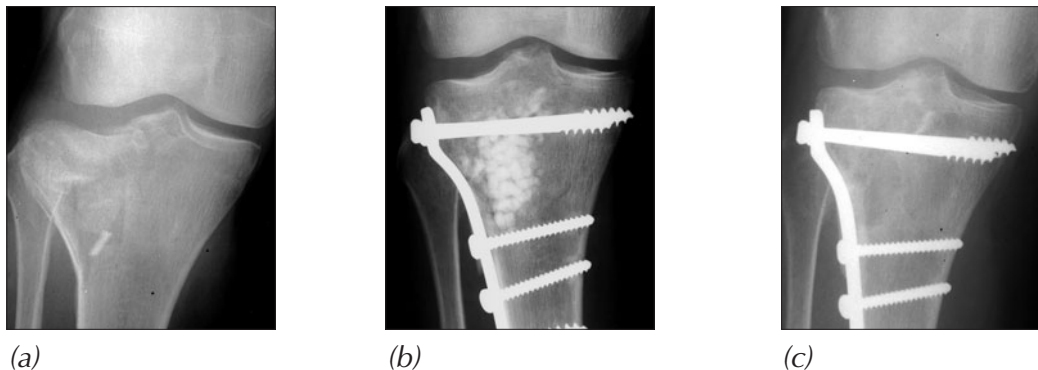


Figure 6: (a) A 60-year old female with a comminuted depressed fracture of the lateral tibial plateau. (b) 3 weeks after ORIF with filling of the resulting defect with OSTEOSET® (Wright Medical Technology, Inc., Memphis, TN) pellets. (c) At 7 months post-op, restoration of trabecular bone with complete dissolution of the graft material is noted.



(a)



(b)

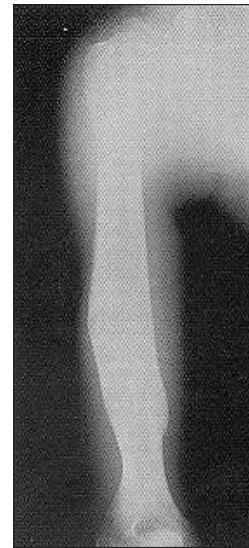


(c)

Figure 7: (a) A 37-year old male with an open, comminuted fracture of the distal part of the left femur. (b) ORIF was performed with use of Collagraft™ mixed with iliac crest bone-marrow aspirate. (c) At 18 months post-op, healing with graft incorporation is confirmed radiographically.



(a)



(b)



Figure 8: (a) AP and lateral radiographs of an active 12-year old male patient with a spiral diaphyseal fracture of the distal part of the right humerus, through a unicameral bone cyst. After 4 weeks of treatment with a Sarmiento brace, callus around the fracture site was noted. The cyst was aspirated, and DynaGraft® (GenSci OrthoBiologics, Inc., Irvine, CA) gel in combination with bone-marrow aspirate from the iliac crest was injected. (b) At 6 weeks marked radiopacity of the cyst is noted.

## BURDEN OF PROOF

It is reasonable to assume that not all bone-substitute products will perform analogously. Thus, a quandary of choice confronts the orthopaedic surgeon. As a first principle, it is important to appreciate that different healing environments (e.g., a metaphyseal defect, a long-bone fracture, an interbody spine fusion, or a posterolateral spine fusion) have different levels of difficulty in forming new bone. For example, a metaphyseal defect will permit the successful use of many purely osteoconductive materials. In contrast, a posterolateral spine fusion will not succeed if purely osteoconductive materials are used as a stand-alone substitute. Thus, validation of any bone-graft substitute in one clinical site may not necessarily predict its performance in another location.

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## BURDEN OF PROOF (Cont'd.)

A second principle is to seek the highest burden of proof reported from preclinical studies to justify the use of an osteoinductive graft material or the choice of one brand over another. Whether it is more difficult to make bone in humans than it is in cell-culture or rodent models, with a progressive hierarchy of difficulty in more complex species, has not been clearly determined. Only human trials can determine the efficacy of bone-graft substitutes in humans as well as their site-specific effectiveness.

A third principle requiring burden of proof specifically pertains to products that are not subjected to high levels of regulatory scrutiny, such as demineralized bone matrix (DBM) or platelet gels containing “autologous growth factors”. Such products are considered to involve minimal manipulation of cells or tissue and are thus regulated as tissue rather than as devices. As a result, there is no standardized level of proof of safety and effectiveness required before these products are marketed and are used in patients. While these products may satisfy the technical definition of “*minimal manipulation*”, there is a risk that they will not produce the expected results in humans when there has been little or no testing in relevant animal models.

## FUTURE

Ongoing human trials involving a number of BMP-derived growth factors (particularly BMP-2 and OP-1) have demonstrated impressive osteoinductive capacity in tibial fracture-healing and spine fusion. Their methods of administration have included direct placement in the surgical site, but results have been more promising when the growth factors have been administered in combination with substrates to facilitate timed-release delivery and/or provide a material scaffold for bone formation. Food and Drug Administration regulatory imperatives will determine their availability and they are likely to be costly, which will influence specific clinical use.

Further advances in tissue-engineering, “the integration of the biological, physical and engineering sciences”, will create new carrier constructs that regenerate and restore tissue to its functional state. These constructs are likely to encompass additional families of growth factors, evolving biological scaffolds and incorporation of mesenchymal stem cells. Ultimately, the development of *ex vivo* bioreactors capable of bone manufacture with the appropriate biomechanical cues will provide tissue-engineered constructs for direct use in the skeletal system.

## TAKE HOME MESSAGE

- The increasing number of bone-grafting procedures performed annually in the United States has created a shortage of cadaver allograft material and a need to increase musculoskeletal tissue donation.
  - This has stimulated corporate interest in developing and supplying a rapidly expanding number of bone substitutes, the makeup of which includes natural, synthetic, human and animal-derived materials.
  - Fresh autogenous cancellous and, to a lesser degree, cortical bone are the benchmark graft materials that, ideally both allograft and bone substitutes should match in *in vivo* performance. Their shortcomings include limited availability and donor-site morbidity.
  - The advantages of allograft bone include availability in various sizes and shapes as well as avoidance of host-structure sacrifice and donor-site morbidity. Tissue-processing, however, modifies graft incorporation as well as structural strength. Transmission of infection, particularly the human immunodeficiency virus (HIV) has been virtually eliminated as a concern.
  - The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective. Currently marketed products are variable in their composition, their mechanism of action and the claims made about them.
  - It is reasonable that not all bone-substitute products will perform the same. Tissue or cellular-derived products that satisfy the technical definition of *minimal manipulation* with regard to processing and manufacture are not subject to a high level of regulatory scrutiny. Their true *safety and effectiveness* may not be known.
  - A quandary of choice confronts the orthopaedic surgeon. *Caveat emptor!* Selection should be based on reasoned *burdens of proof*. These include examination of the product claims and whether they are supported by preclinical and human studies in site-specific locations where they are to be utilized in surgery.
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