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

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### **COMMITTEE ON BIOLOGICAL IMPLANTS**

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## A REALITY CHECK

Estimates of over 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)

**Donors**

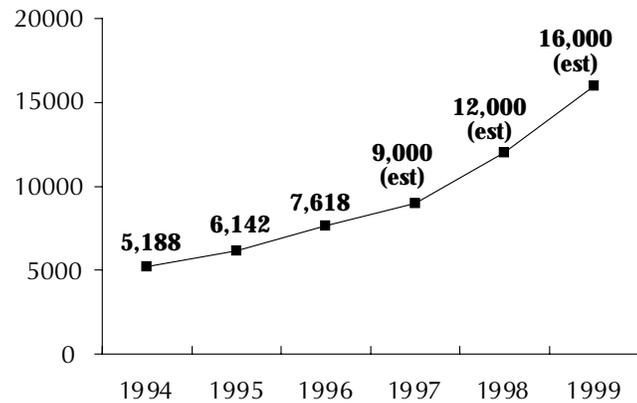


Figure 1: U.S. trends in musculoskeletal tissue donors  
Source: United Network for Organ Sharing & MTF

**U.S. Sales**  
(\$millions)

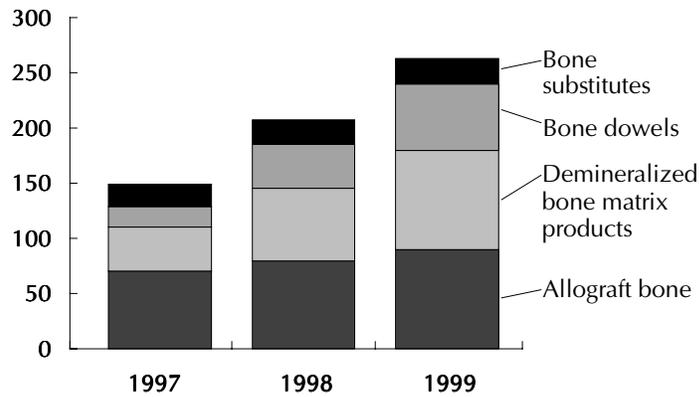


Figure 2: U.S. sales of bone graft and bone substitutes  
Source: Orthopedic Network News, industry estimates

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 have 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 transplant 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.

Through these processes all bone graft and bone graft substitute materials may be described.

## BONE AUTOGRAFTS

Fresh autogenous cancellous and to a lesser degree cortical bone are benchmark graft materials that both allograft and bone substitutes strive to match in *in vivo* performance. They incorporate all of the above properties, are harvested at both primary and secondary surgical sites and are viral transmission free. Further they offer structural support in combination with device hardware and ultimately become mechanically efficient structures as they are incorporated into surrounding bone through creeping substitution. Autograft availability is, however, limited and often associated with donor site morbidity.

# BONE ALLOGRAFTS

In contrast, the advantages of bone allograft harvested from cadaver sources lie in its ready availability in various shapes and sizes, which avoids sacrificing host structures as well as donor site morbidity. They are distributed through regional tissue banks. However, they are not without controversy particular to their association with the transmission of infectious agents, a concern virtually eliminated through tissue processing and sterilization. Both freezing and irradiation modify the processes of graft incorporation and affect structural strength. Comparative properties of both allo- and autograft bone are appreciated in Figure 3. Often in complex surgical reconstructions these materials are used in tandem with implants and fixation devices. (Figure 4)

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

Figure 3: Comparative properties of bone grafts

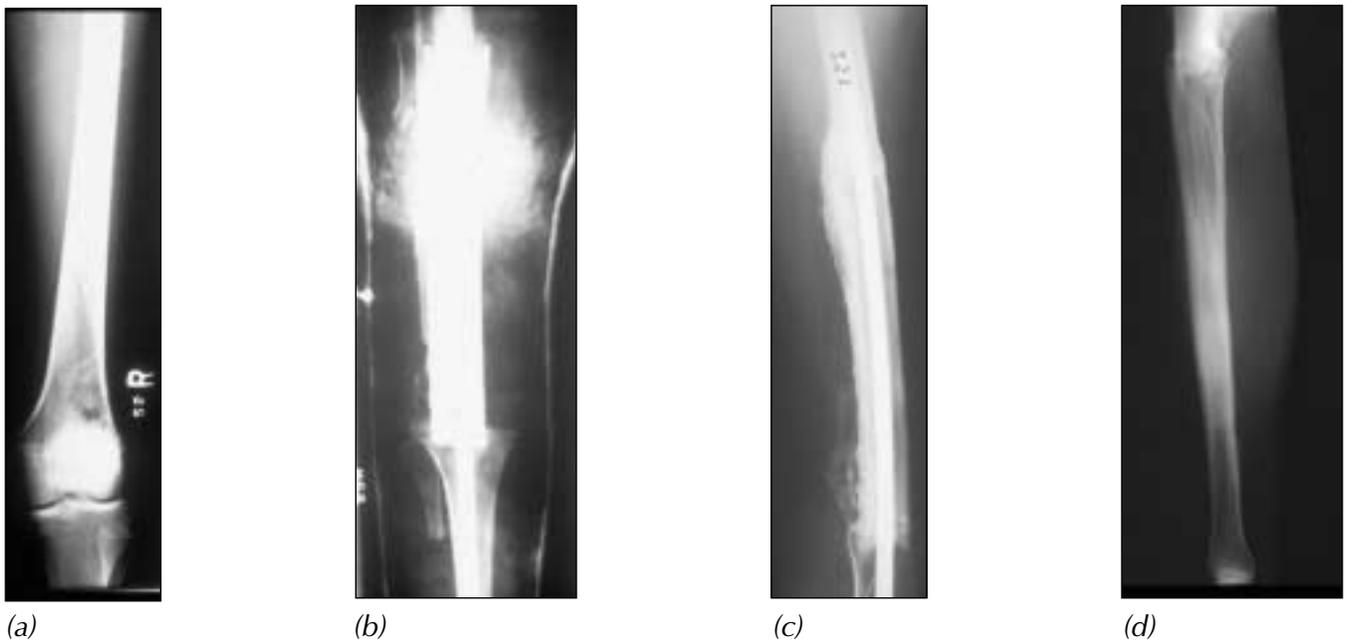


Figure 4: (a) 17-year old patient with osteosarcoma of the distal femur with no extra-osseous extension or metastatic disease. Following chemotherapy, (b) limb salvage with wide resection was performed. Femur reconstruction consisted of an autogenous cortical fibular graft, iliac crest bone chips, morselized cancellous autograft and structural allograft combined with internal fixation. (c) At 3 years graft incorporation and remodeling. (d) At 10 years following resection, with IM rod removal at 5 years, limb restoration is noted.

# 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 inclusive of cavitory bone deficiency, as an augment in situations of segmental bone loss and interbody spine fusion. They are variable in their consistency, mechanism of action and claims. Figure 5 typifies a sampling of these 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 seeks to demonstrate their mechanisms of action through the healing process. (Figures 6, 7 and 8)

Company	GenSci OrthoBiologics		Interpore Cross International	Osteotech	Wright Medical Technology		Zimmer
Commercially available product	OrthoBlast™	DynaGraft®	ProOsteon® 500R	Grafton®	OSTEOSET®	AlloMatrix™	Collagraft™
Composition	Heat sensitive copolymer with cancellous bone chips and DBM	Heat sensitive copolymer with DBM	Coral HA Composite	Deminerzalized bone matrix (DBM) combined with Glycerol	Surgical grade calcium sulfate	DBM with surgical grade calcium sulfate powder	Mixture of hydroxyapatite, tricalcium phosphate, and bovine collagen
Commercially available forms	Injectable paste or putty	Injectable gel, matrix or putty	Granular or block	Gel	Various sized pellets	Injectable or formable putty	Strip configurations
Claimed mechanisms of action	<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> </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> </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>
Burdens of proof	<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>	<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>Case reports</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>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>
FDA status	<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 510K	<ul style="list-style-type: none"> <li>Minimal manipulation</li> <li>Non-regulated</li> </ul>	Approved 510K	<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

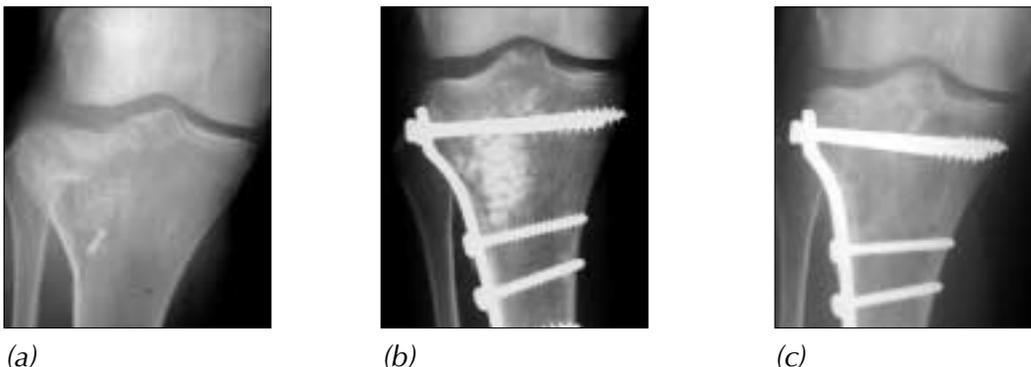


Figure 6: (a) 60-year old female with a comminuted depressed lateral tibial plateau fracture. (b) ORIF was performed and the resulting defect filled with OSTEOSET® pellets, post-op is noted at 3 weeks. (c) At 7 months post-op, restoration of trabecular bone is noted with complete dissolution of the graft material.



(a)



(b)



(c)

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



(a)



(b)



Figure 8: (a) AP and lateral films of a 12-year old active male patient with a spiral diaphyseal fracture of the right distal humerus through a unicameral bone cyst after 4 weeks in a Sarmiento brace, callus around the fracture site is noted. The cyst was aspirated and DynaGraft® gel in combination with bone marrow aspirate from the iliac crest 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. metaphyseal defect, long bone fracture, interbody spine fusion, posterolateral spine fusion) have differing 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 environment will not tolerate the use of purely osteoconductive materials as a stand alone substitute, and will only sometimes permit their use as a bone graft extender. Thus, validation of any bone graft substitute in one clinical site may not be predictive of 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 pre-clinical studies to justify the use of an osteoinductive graft material or the choice of one brand over another. Although not commonly recognized, evidence clearly suggests that it is much harder to make bone in humans than in cell culture or rodent models with a progressive hierarchy of difficulty in more complex species. Only human trials can determine their efficacy in humans and are site specific in their effectiveness.

A third principle requiring burden of proof specifically pertains to products that are not subject to high regulatory levels of 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 for safety and effectiveness required before these products are marketed and used in patients. While these products may satisfy the technical definition of "*minimal manipulation*", there is a risk that they may not produce the expected results in humans where there has been little or no animal testing in relevant models.

## FUTURE

Ongoing human trials involving a number of BMP derived growth factors (particularly BMP2 and OP1) describe impressive osteoinductive capacity in tibial fracture healing and spine fusion. Their methods of administration have been direct to the surgical site but more promising in combination with substrates to facilitate timed release delivery and/or provide a material scaffold for bone formation. FDA regulatory imperatives will determine their availability and 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 which regenerate and restore tissue to its functional state. These are likely to encompass further families of growth factors, evolving biological scaffolds and the incorporation of mesenchymal stem cells. Ultimately, the evolution of *ex vivo* bio-reactors capable of bone manufacture with the appropriate biomechanical cues will provide tissue engineered constructs for direct use in the skeletal system. The future is now!

## 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 whose makeup include natural, synthetic, human and animal derived materials.
  - Fresh autogenous cancellous and to a lesser degree cortical bone are the benchmark graft materials that both allograft and bone substitutes must strive to match in *in vivo* performance. Their short comings lie in limited availability and donor site morbidity.
  - In contrast, the advantages of allograft bone lie in size and shape availability, the avoidance of host structure sacrifice and donor site morbidity. Tissue processing however modifies graft incorporation as well as structural strength. Infectious disease transmission, particularly viral 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 consistency, mechanism of action and claims.
  - 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* in processing and manufacture are not subject to the same 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 pre-clinical and human studies in site specific locations where they are to be utilized in surgery.
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