CHAPTER 6

BONE GRAFT SUBSTITUTES

D. Scot Malay, DPM, FACFAS
W. Aaron Broyles, DPM

The purpose of this paper is to review the available bone graft substitutes that can be employed in podiatric reconstructive surgery. Bone graft substitutes (BGS) are readily available materials that can be used to eliminate or diminish the need to harvest autogenous bone graft, while satisfactorily repairing osseous defects and enhancing bone healing related to the treatment of bone defects secondary to osteotomy, fracture, osteomyelitis, and nonunion.

FUNDAMENTAL PROCESSES OF BONE HEALING

In order to better understand the use of BGS, it is necessary to review the basic processes involved in bone regeneration. The three fundamental processes of bone regeneration include: 1. osteogenesis, 2. osteoinduction, and 3. osteoconduction. Osteogenesis requires the presence of functional chondrocytes (for enchondral bone formation), osteocytes, and undifferentiated stems cells (osteoprogenitor cells) that have the ability to convert to chondrocytes and osteocytes. Osteoinduction effects differentiation of osteoprogenitors into chondrocytes and osteoblasts.

Osteoconduction requires the presence of suitable mineralized scaffolds along which osteoprogenitor cells can produce new bone and osteoclasts can remove dead bone remnants and remodel existing bone, and along which revascularization can occur. Of equal importance to these fundamental processes, are the presence of satisfactory vascularity and mechanical stability (Figure 1).

AUTOGENOUS BONE GRAFT: "THE GOLD STANDARD"

Traditionally, autogenous bone has been thought of as the "best" bone source for bone graft material. The reasons for this are numerous, including the fact that autogenous bone provides osteogenic, osteoinductive, and osteoconductive properties to the graft. Moreover, there is no risk of antigenicity or exogenous disease transmission[1] from the donor to the recipient. Furthermore, the autogenous bone can be harvested to contain both cortical as well as cancellous bone (Figures 2, 3). However, the fact that autogenous bone must be harvested from either a local or distant anatomical site, or both, persists to be the greatest drawback to use of this technique. In fact, donor site morbidity related to chronic pain, blood loss, infection, and nerve injury, as well as complications related to additional surgical and anesthesia time, are commonly associated with autogenous bone graft use. Banwart and colleagues[2] evaluated iliac crest (Figure 4) donor site morbidity by means of meta-analysis, and identified a 25-45% complication rate, and 40% of the patients related donor site pain that persisted for at least five years into the postoperative phase. When large grafts are required, the problem of limited autogenous resources can also be realized. Commonly used autogenous sites (Figures 5, 6, 7, 8) for podiatric surgery, include anterior and posterior iliac crests, proximal and distal tibial metaphyses, and the body of the calcaneus. Within the foot itself, the calcaneus provides the greatest volume and best quality of bone graft, and also provides an ipsilateral site that can be dressed and casted along with the primary operative site. Donor site fracture can occur (Figure 9), and efforts to minimize this complication include avoidance of acute angular stress risers. Essentially all, but especially large, donor site defects should be back-filled with allogeneic bone graft (which eliminates the avoidance of antigenicity and potential for disease transfer advantages of autogenous bone graft) or BGS.

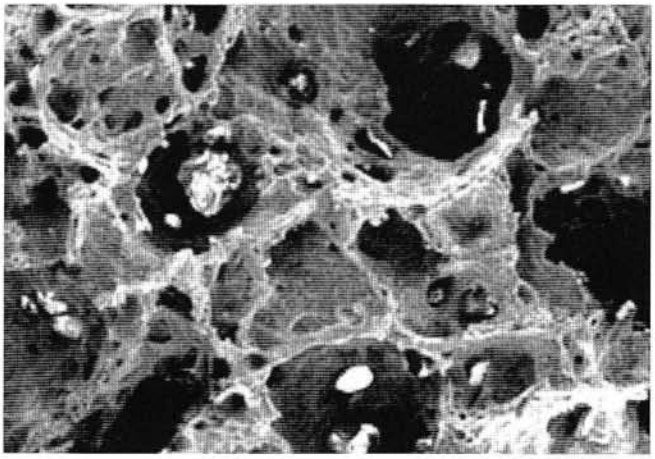

Figure 1. Osteocytes and blood cells within trabecular scaffolds.

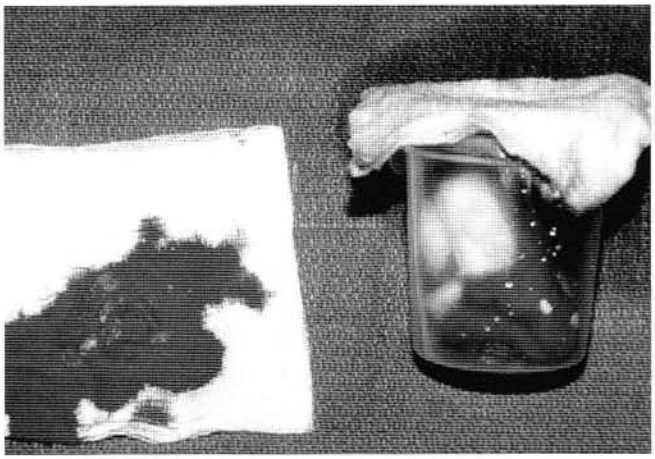

Figure 2. Autogenous cancellous bone chips.

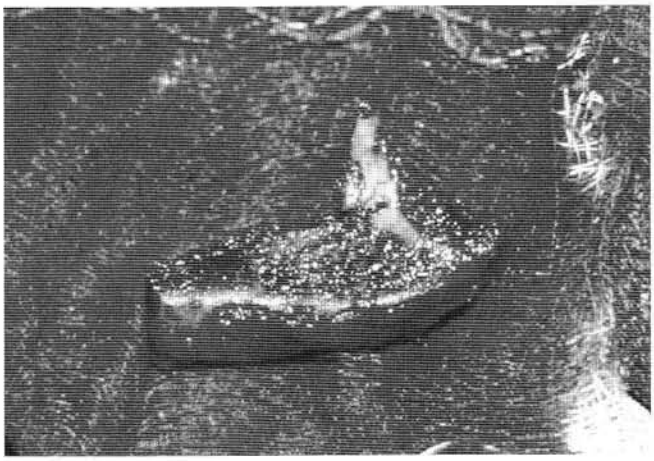

Figure 3. Autogenous corticocancellous iliac crest.

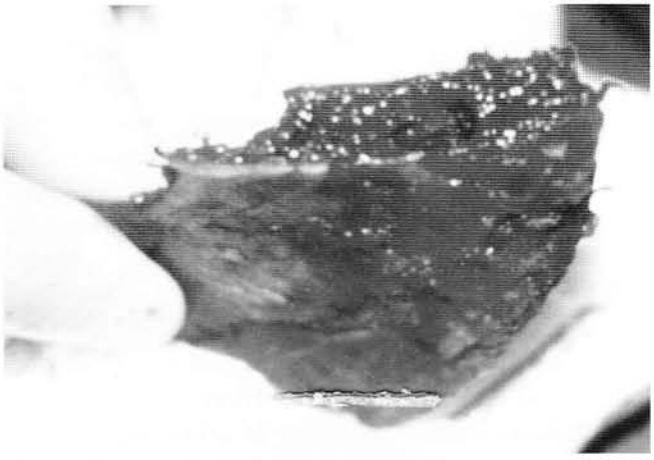

Figure 4. Tri-cortical iliac crest bone graft.

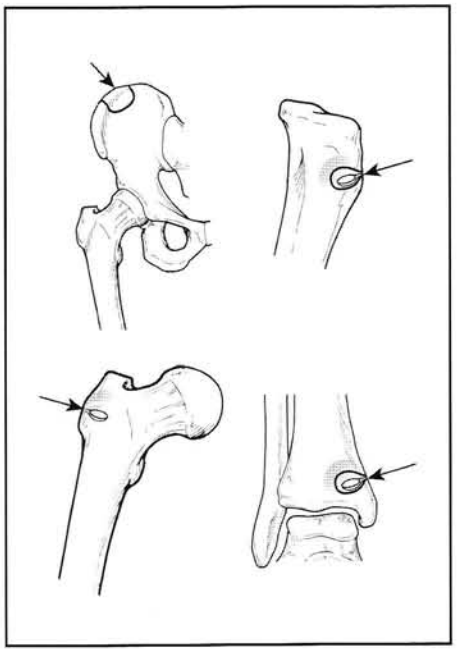

Figure 5. Commonly used autogenous bone graft sources.

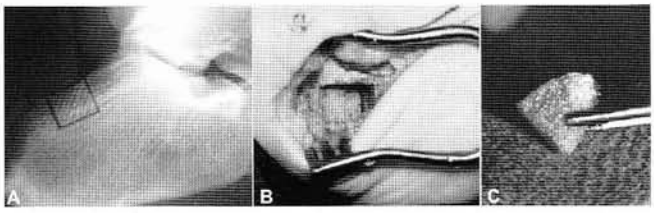

Figure 6. A. Target site for corticocancellous calcaneal donor graft. B. Operative exposure. C. Harvested graft.

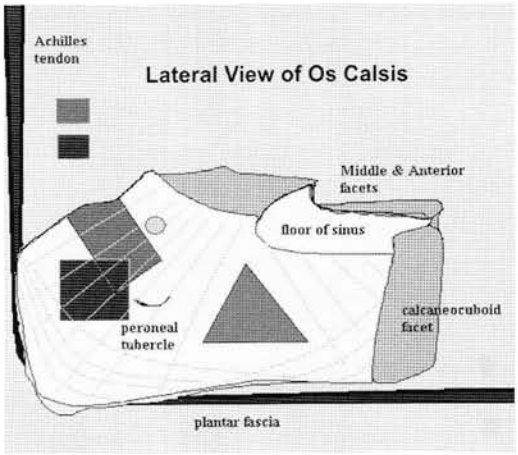

Figure 7. Calcaneal donor sites. Avoid calcaneofibular ligament, neutral triangle, peroneal tubercle, Achilles insertion, STJ and CCJ.

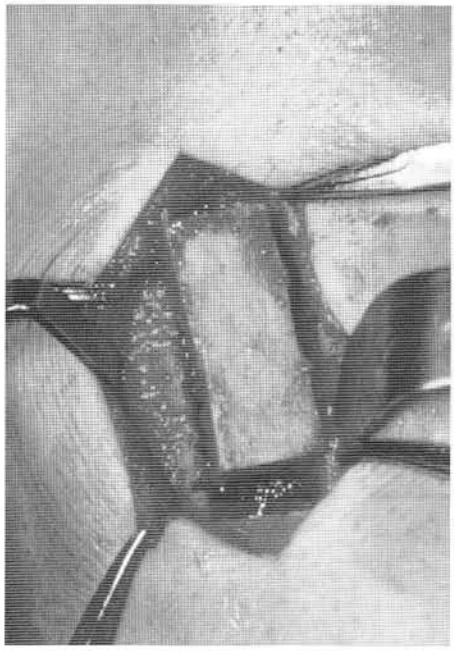

Figure 8. Distal tibial metaphyseal, large corticocancellous donor site.

MOLECULAR BIOLOGY AND BIOENGINEERING OF BGS

BGS are engineered to meet the requirements of bone healing, namely osteogenesis, osteoinduction and osteoconduction. Osteogenic cells, including osteocytes, osteoblasts, and mesenchymal stem cells (MSCs), are found in autogenous bone as well as fresh bone marrow aspirates or cloned bone marrow. Osteoinduction is controlled by a variety of factors, including bone morphogenetic proteins (BMPs) 2 and 7, transforming growth factors (tGFs) derived from platelets and fibroblasts, and are responsible for recruitment and transformation of MSCs. Demineralized bone matrix,[3-9] either allogeneic or recombinant, and autogenous platelet rich plasma serve as sources for these osteoinductive agents. Osteoinductive agents include bioceramics,[10-15] such as tricalcium phosphate (TCP), calcium sulfate (CS), calcium carbonate (CC), and synthetic hydroxyapatite (HA); coralline hydroxyapatite (cHA) produced naturally by corals; extra cellular matrix scaffolds such as collagen or glycosaminoglycan combined with HA and TCP; as well as polymers such as poly-hydroxy acids, polylactide, and polyglycolide, and alloys such as titanium cages.

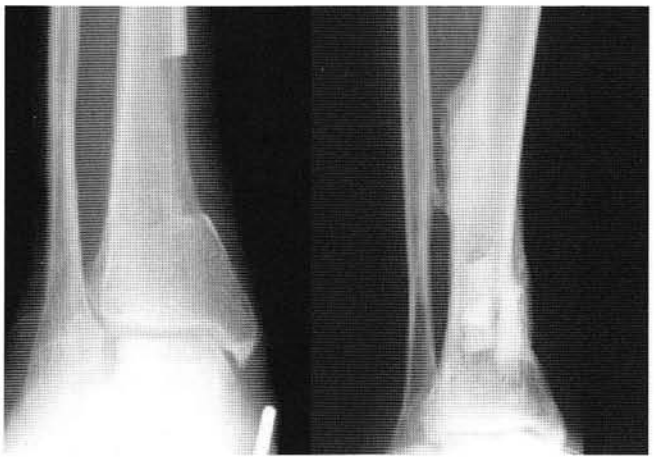

Figure 9. (A) Immediate postoperative and, (B)13 months postoperative. Radiographs of large distal tibial corticocancellous donor site that fractured due to diaphyseal location and large cortical stress riser. Corraline hydroxyapatite backfill persists to be evident long after bone healing.

BONE GRAFT SUBSTITUTES: OPTIONS

Available options for BGS include: 1. demineralized bone matrix, 2. bioceramics, 3. platelet concentrates, and 4. bone marrow aspirates. Each of these materials has advantages and disadvantages that should be taken into consideration prior to use.

Demineralized bone matrix (DBM)

1. Allogeneic (cadaver) demineralized and recombinant human cloned DBM
   a. Batch variability
   b. Potential infection and immunogenicity
2. Osteoinductive, containing bone growth factors
   a. BMPs 2 & 7
      i. Regulate MSC and osteoblasts
      ii. Angiogenic
3. Can be used in conjunction with allogeneic graft, and as a graft expander
4. Available in various forms (Figure 10)
   a. Gel, putty, flexible sheet of demineralized bone collagen fibers
   b. Can combine with demineralized cortical cubes (inductive and conductive)
   c. Grafton*, DBX*, Osteofil, Allomatrix*, DynaGraft

Bioceramics

Bioceramics provide osteoconductive scaffolds (see Figure 14) that invite osteogenic and vascular ingrowth, and frequently used materials include: 1. tricalcium phosphate (TCP), 2. calcium sulfate (CS), 3. calcium carbonate (CC), and 4. hydroxyapatite (HA).

1. Tricalcium phosphate (TCP) scaffold
   a. Osteoconductive (pores)
   b. Mimics cancellous bone
   c. Pores 1-1000 microns
   d. Resorbable calcium phosphate
      i. Beta-TCP resorbed by 24 weeks
   e. Used for over 25 years
   f. Safe (sterile) and nonimmunogenic
   g. Wicks blood and cells into interstices
   h. Orthovita Vitoss (see Figure 15)
      i. Ideal for defect back-fill (see Figure 16)
2. Calcium sulfate
   a. Semi-structural filler with porous
      i. conductive properties similar to TCP
      ii. Dense yet pliable
      iii. Injection system
      iv. Hardens in defect
      v. Can be drilled and fixated
      Resorbs completely (rapid)
   b. Support with internal and or external fixation
   c. Wright Medical AlloMatrix, miniMIIG (CS scaffold with DBM)
   d. CS with antibiotic impregnation
3. Bioceramic combined with allogeneic collagen
   a. Bone graft expander
   b. Osteoconductive
   c. Non-structural paste, soft strip (sponge)
   d. Cryogenically deantigenated bovine fibrillar collagen & porous bioceramic (65% HA, 35% TCP)
   e. Zimmer Collagraft
4. Hydroxyapatite
   a. Natural coralline hydroxyapatite and calcium carbonate (behaves like TCP)
   b. Osteoconductive porous scaffold for back-fill (see Figure 18)
   c. Inorganic, sterile and nonimmunogenic
   d. Minimal structural strength
   e. Slow biodegradation (see Figure 9)
   f. Interpore International Interpore 200 and Pro Osteon 500 (see Figure 19)

Platelet Concentrates

Platelet concentrates, which provide growth factors and clot stability, are readily available in most podiatric cases wherein bone grafting is necessary. Preoperative preparation should include notification of the anesthesiologist, since 55-60 ml of blood must be drawn for harvesting the platelets. The blood can be drawn from either a peripheral access in the upper or lower extremity, or from a central venous line. The blood is centrifuged and the platelets and supernatant are collected. Platelet concentrates are used to augment bone graft stabilization and incorporation.

Features of platelet concentrates:

1. Osteoinduction, clot stability, and chemotaxis
2. Requires at least 55 ml of autogenous blood drawn in the operating room
3. Platelet rich plasma
   a. PDGF, TGF-B, EGF, VEGF
4. Point-of-care "mini lab" (centrifuge, efficient, takes about 15 minutes)
5. DePuy Symphony (see Figure 20) and Smith & Nephew Magellan

Bone Marrow Aspirate

The best source of osteogenic cells is proximal bone marrow in young individuals. As humans age, the peripheral bone marrow, distal to the iliac crest, becomes less osteogenic. Nonetheless, tibial and calcaneal marrow aspirates in generally healthy individuals can enhance the osteogenic and osteoinductive capacity of a bone graft.

Features of bone marrow aspirates:

1. Osteogenic
   a. Osteoblasts
   b. MSCs
2. Combine aspirate with scaffold (Vitoss TCP)
3. Orthovita Imbibe Bone Marrow Aspiration Syringe (see Figure 21)

Other Graft Enhancers and Extenders

1. Acellular allogeneic dermal periosteum replacement scaffold (Wright Medical GraftJacket)
   a. Mimics periosteum
   b. Minimizes fibrous ingrowth
   c. Promotes revascularization
2. Synthetic polymers and permanent bone growth guides
   a. Poly-hydroxy acids, polylactide, polyglycolide
   b. Titanium cages

Figure 10. Two available proprietary forms of demineralized bone matrix: (A) Grafton, and (B) DBX.

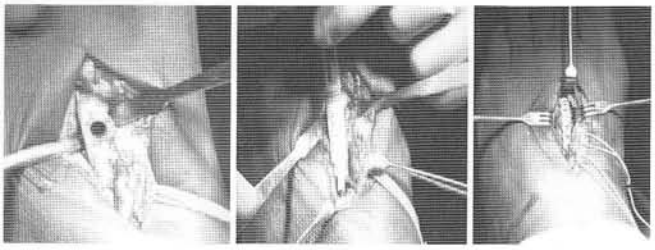

Figure 11 A, B, & C. Repair of third metatarsal nonunion using autogenous calcaneal cancellous bone enhanced with DBX and stabilized with internal fixation.

Figure 12 A, B, & C. Grafton DBM added to autogenous cancellous chips to expand the volume of the graft.

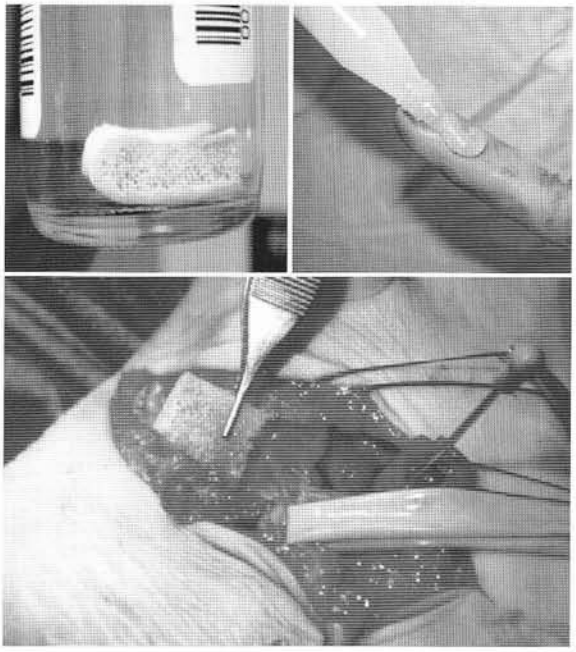

Figure 13 A, B, & C. Allogeneic DBM added to freeze-dried cortico-cancellous bone graft to add osteoinductive properties to the structurally stable and osteoconductive allogeneic graft.

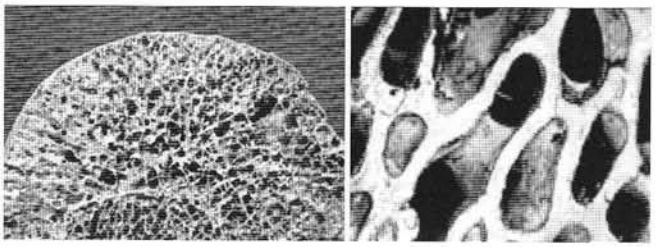

Figure 14. Structural similarity between femoral head trabecular bone (A) and manufactured calcium phosphate (B) scaffolding.

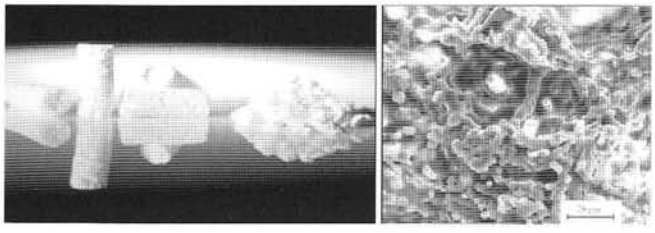

Figure 15. Orthovita's Vitoss TCP, pellets and granules (A) and micrograph (B), 1000x, showing blood cells adhering to the scaffolding.

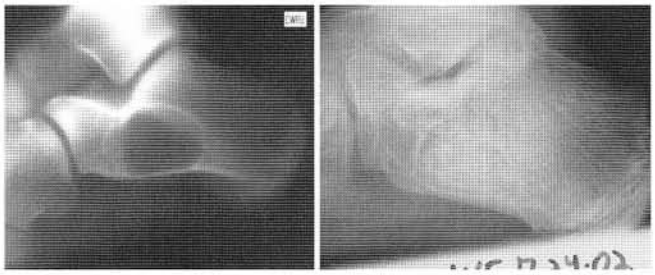

Figure 16. Solitary calcaneal cyst before (A) and after (B) TCP back-fill.

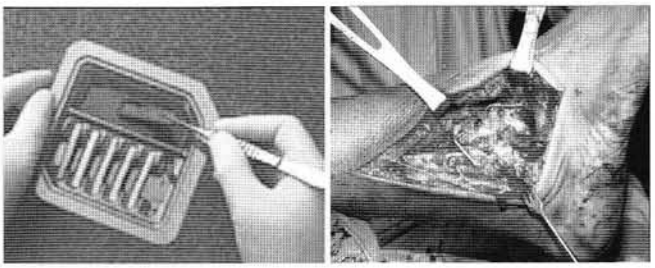

Figure 17 A & B. Collagraft 6-strip kit provides bioceramic-bovine collagen osteoconductive expander which, when combined with autogenous blood or marrow aspirate, also provides osteoinduction.

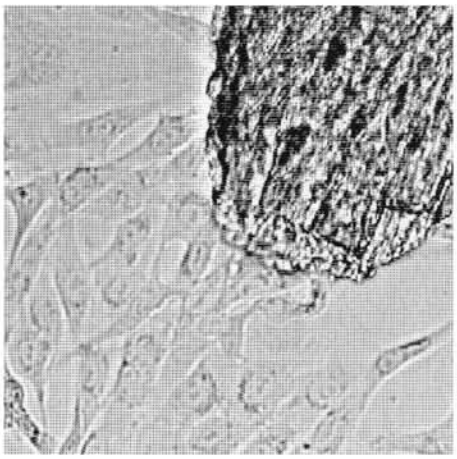

Figure 18. Coral–osteocyte interface.

Figure 19 A & B. Coralline hydroxyapatite

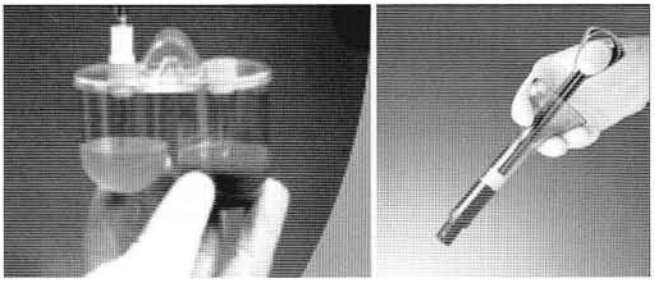

Figure 20. Symphony platelet rich plasma separated (A) and releaseate ready for implantation (B).

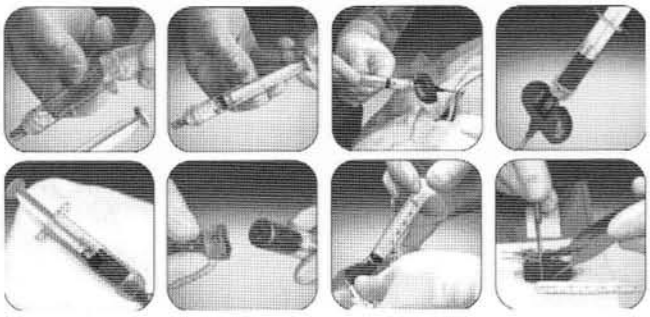

Figure 21. Orthovita Imbibe Bone Marrow Aspiration Syringe.

SUMMARY

Biosynthetic bone graft substitutes can be used to provide osteogenic, osteoinductive, and osteoconductive properties while decreasing the necessity of autogenous bone grafts and associated donor site morbidity. Bone graft substitutes include demineralized bone matrix, bioceramics, polymers and combinations of these materials. Adjunctive therapies used with BGS include stable bone fixation, vascular reconstruction, electrical bone growth stimulation, nutritional supplementation and anemia treatment, immobilization and non-weight bearing.

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