Osteobiologics in Foot and Ankle Surgery

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KEYWORDS

- Osteobiologics • Foot and ankle surgery • Bone healing • Clinical application

KEY POINTS

- Osteobiological agents are a welcome addition to the surgeon's armamentarium. These products should always be thought of as a complement to good surgical principles and construct.
- Even if allograft is procured for use, an attempt should be made to combine it with autograft if possible, given the primary index procedure in which it will be used.
- Structural support from corticocancellous autografts is also greater than allografts, which lose mechanical strength during the sterilization and preservation process.

BONE HEALING PRINCIPLES

Bone healing after elective foot and ankle surgery as well as trauma does not always go as expected. Complications such as delayed union, malunion, and nonunion can occur. There are many factors that can contribute to a nonunion/malunion, and so forth, including the presence of systemic diseases such as diabetes mellitus, rheumatoid arthritis, immune compromised patients. In addition, there are pharmaceutical agents that can adversely affect bone healing too. Other causes include infection, inadequate fixation, poor vascularity, bone and soft tissue defects, smoking, and nutritional deficiencies. As the number of foot and ankle fusions being performed is increasing, the outcome for some of these patients is complicated by delayed union or nonunion, and so forth. This situation presents a challenge to the foot and ankle surgeon, who can be faced with an expensive and difficult scenario with patient care. There is no definitive solution to this problem, and therefore, there has been increased effort by industry to attempt to resolve it. Autologous bone graft, which is the gold standard for foot and ankle fusion enhancement, is being challenged by

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industry in attempt to replace autograft with osteobiologics. The goal of osteobiologics is to locally deliver the product into the needed operative site. Orthobiologics fit into 3 main categories: gene therapy, cellular therapy, and protein therapy. In foot and ankle surgery, there has been an increase of new technologies to attempt to enhance bone healing. In addition, superior fixation constructs (internal, external, and locking plates) have been developed and brought to the market, as well as an increase in the number and types of orthobiologics. An abundance of commercially available bone grafts (allografts), bone graft extenders, and osteobiologics have been developed.

In this article, bone healing and how osteobiologics may play a role as a complementary product to advance the bone healing process of high-risk patients is reviewed. Because of the large volume of commercially available products, a broad overview of the products is provided and basic principles are reviewed. Because many osteobiological alternatives are available, this article cannot compare and contrast each product in a fair way, and each surgeon needs to learn the advantages and disadvantages of each product. No product can replace good surgical technique and good academic decision making. Industry has made great strides in orthobiologics, but these products can only be expected to be supportive to good surgical technique and good decision making. The basic science is reviewed, and the clinical application of orthobiologics in foot and ankle surgery is discussed.

Any bony procedure is doomed to fail if the surgeon does not understand the principles of bone healing. The process of bone healing moves through several stages over a 10-week period. The different pathways of bone healing are worth reviewing in the context of this topic. The 2 main delineations of bone healing with which we are concerned are primary and secondary bone healing. Primary bone healing occurs in the absence of motion and interfragmentary strain and is bereft of periosteal reaction, which leads to callus formation. In this process, a rigidly fixated site is infiltrated with cutting cones that bridge the traumatized site, establish new haversian systems, and lay new bone. Primary bone healing can occur by either direct healing, in which 2 cortices are opposed directly, or gap healing of up to 2 mm, in which lamellar bone is primarily laid down perpendicular to the long axis. The axis is then infiltrated by cutting cones, leading to an organized fusion site.[1,2] Secondary healing presents with motion through the arthrodesis site and occurs in the presence of bone callus. This process goes through a combination of endochondral (soft callus) and intramembranous (hard callus) ossification. Intramembranous ossification lays bone primarily; however, endochondral ossification presents first with cartilage, which is not remodeled to bone until a soft, cartilaginous callus is created.[2,3]

Although normal bone healing occurs in most fractures, osteotomies, and arthrodesis procedures performed by surgeons, there are certain patient populations who suffer from greater rates of delayed union and nonunion. These populations include neuropathic and vasculopathic patients, smokers, the elderly, and patients on certain medications such as chemotherapeutics, nonsteroidal antiinflammatory drugs, and corticosteroids.[4] In these cases, bone grafts are used as a complement to surgical intervention. These grafts may be used as scaffolding (osteoconductors), as recruitment for undifferentiated stem cells (osteoinductors), or as a source of bone generation (osteogenesis). Although these products have their place in the surgical arena, they should not be looked on as the sole saving grace of the surgical procedure. No product can overcome poor surgical principles, such as malposition, inadequate removal of intervening cartilage or soft tissue, and inadequate fixation.

Many products tout the ability to aid in bony fusion. These options include osteo-conductive products, which provide a scaffold for osteogenic precursor cells as well as neovasculature to grow in. Osteoinductive products have the ability to promote stem cells into forming mature bone. However, only autograft bone is osteogenic as well as osteoinductive and osteoconductive. For this reason, the gold standard for bone grafting continues to be cancellous autograft. Whichever grafting material is used, the site must be adequately immobilized during the healing process.

OSTEOCONDUCTION

Osteoconduction is a three-dimensional process in which porous material provides a scaffold for bone and fibrovascular tissue to proliferate. It is a passive process in bone healing.[5] Use of porous scaffolds allows the bone ends to fuse together without the need for resorption of the fusion site, as with cortical bone; this decreases the time to solid fusion, when weight can be borne.[6] Examples of osteoconductive materials include cancellous autografts, allografts, demineralized bone matrix, hydroxyapatite, collagen, and calcium phosphate.[5,7] Osteoconductive scaffolds can also bridge bone gaps and relieve shear and strain within an arthrodesis site. Osteoconductive materials may also be used as an adjunct to autograft if the living cells of autograft are desired but there is a limited amount available, based on the need of each case. Autograft and allograft may be mixed together to add bulk to the graft substrate. Osteoconductive products have little value in the treatment of delayed or nonunions, with few exceptions. Toolan[8] found no evidence to support use of calcium/ceramic bone substitute alone in treatment of nonunions and that ceramics offer little structural support, and therefore, should be used only in closed metaphyseal defects. Exceptions include a delayed union caused by significant gapping, interposition of soft tissue, or insufficient fixation during the initial surgical intervention. Bone grafts that are solely osteoconductive should be relied on mainly as fillers and scaffolds in the surgeon's armamentarium.

OSTEOINDUCTION

Grafting materials with osteoinductive properties can recruit pleuripotent stem cells to differentiate into osteocytes in addition to providing an osteoconductive scaffold. Osteoinductive products include bone morphogenic proteins, demineralized bone matrix, and, to a lesser extent, cancellous allograft chips. All autografts, and after the sterilization and preservation processes, some allografts contain these properties.[7,9] Preservation is accomplished by freeze-drying to –70°C, ethylene oxide, or irradiation. Ethylene oxide can cause a local toxic reaction, whereas irradiation may affect the mechanical strength of the graft.[9] These products are best used when primary bone contact has already been achieved at the time of surgery. These products are then integrated into the surgical site. These products may be added to osteoconductive bone grafts to increase volume or may be incorporated with autograft.

OSTEOGENESIS

Human autograft is the only type of bone graft with osteogenic properties. Reasons for the use of autograft include avoidance of an immunologic response or infection, the graft is readily available from multiple sites, there is no additional cost (for the graft), and it provides osteoinductive, osteoconductive, and osteogenic properties. Sites

for harvest of autograft include calcaneus (cancellous/tricortical), distal tibia, proximal tibia, iliac crest, and distal femoral metaphysis. Complications of autograft harvesting include a separate incision; longer operating time; local nerve, artery, and venous cautions; and stress risers. Anatomic sites include the iliac crest, tibia, and calcaneus. Complications specific to harvesting bone graft from the iliac crest include hernia, intrapelvic pulmonary emboli, nerve damage (lateral femoral cutaneous, cluneals),[10,11] and blood vessel damage (superior gluteal). Harvesting graft from the tibia may result in nerve/vessel damage (saphenous), and fracture; however, using a circular window rather than a square results in a decreased incidence of stress fracture.[12] In the calcaneus, stress risers may occur in the body after harvesting tricortical or cancellous autograft (Rowe III). Stress risers are more common in tricortical grafts; because of the disruption in cortical integrity, whereas with windowing cancellous grafts; the cortex can remain intact.

Hemostasis may be achieved via backfilling with sponge, cement, or allograft or applying bone wax.[13]

OSTEOBIOLOGICS

Osteobiologics offers 3 main categories: gene therapy, cellular therapy, and protein therapy. Gene therapy involves delivering osteogenic genes to a specific site. In cellular therapy, on the other hand, scaffolds are loaded with mesenchymal stem cells (MSCs). Protein therapy involves applying proteins to a targeted site or introducing them through systemic administration.

There are few definitive facts related to the use of biologics in foot and ankle conditions. Although some data exist related to the use of bone morphogenetic proteins (BMPs), few of them focus on foot and ankle conditions. Most data on BMPs come from research related to its use in healing long bone fractures and spinal conditions. MSCs hold great promise for fusion augmentation. MSCs are gaining status with regard to fusion in the foot and ankle. Gene transfer is a biological mechanism that holds potential, as do adeno-associated viral vectors, platelet-rich plasma (PRP), and bone marrow aspirate. Most of the available research is based on case studies or series and cannot be compared with other research with a more rigorous outlook. One of the problems for foot and ankle surgeons is a lack level I or II research specific to foot and ankle surgery. Foot and ankle surgeons are then forced to review non–foot and ankle literature, remove specifics from theses studies that pertain to other anatomic regions, and apply it to the foot and ankle. Foot and ankle surgeons need to continue working on obtaining information from high-quality prospective randomized studies that apply specifically to foot and ankle conditions, but these do not exist.

PRP contains growth factors derived from an arterial or venous blood draw. PRP therapy focuses on the local delivery of a highly concentrated volume of platelets at the site of surgery. When activated, these platelets release various critical growth factors involved in the healing cascade. When PRP is injected, it can aid with stimulation of the natural healing process of the body. Intraoperatively, a small amount of a patient's blood is drawn and then spun at high speed, and the platelets are concentrated. This concentrated liquid is then injected around or near the surgical site being treated. Most PRP kits contain 3 to 5 times the concentration of growth factors compared with normal human blood. PRP can be used alone or in conjunction with surgical reconstruction of the foot and ankle in hopes of accomplishing better healing. Our experience has been to either insert the PRP directly in the site of surgery or to mix directly with the bone graft when bone graft is being used. Many surgeons use the

platelet-poor portion of the concentrate with soft tissue closure in hopes of better soft tissue healing.

The initial enthusiasm associated with the use of PRP to positively influence bone healing has been tempered in recent years. PRP is produced by centrifuging or filtering arterial or venous blood to obtain a concentrated slurry of an injectable gel, which has a substantial concentration of autologous key growth factors. The preliminary clinical investigations were flawed by having no case controls, as well as using plain radiographs to determine success or failure of the arthrodesis. More recent thoughts suggest that the active components are variable, depending on the method of production and the equipment being used to harvest (it is different from company to company); therefore, there is no well-known standardization with the use of PRP within the industry (Figs. 1 and 2).

USING OSTEOBIOLOGICS TO AUGMENT WITH FRACTURES, OSTEOTOMIES, AND ARTHRODESIS

Autografts and allografts, the traditional treatment of these problems, have potential drawbacks. Autograft supply is limited, and some of these cases do not occur without complications. The supply of allograft is greater and does not involve donor site morbidity; however, it has a significant cost. There is no better definitive alternative. There is no research that can firmly show that osteobiologics are decisively reliable (Figs. 3–11).

Bone morphogenic protein, a type of BMP that is essential for osteoblast differentiation and is required for bone healing, has been approved by the US Food and Drug Administration for specific indications. Our experience with off-label use of BMP yielded surprising results in high-risk patients with significant comorbidities.[14] In this study, data showed that a statistically significant decrease in the incidence of bone healing was observed if the patient was 50 years of age or older, and all 16 patients younger than 50 years healed their index operation. If 60 years of age was the benchmark, a statistically significant decrease in the rate of healing was observed. Logistic regression showed that a 10-year increase in age almost doubled the risk of not healing. BMPs can be an effective adjunct osteoinductor; healing sometimes cannot be achieved, even with the use of biological augment. BMPs and a combination of
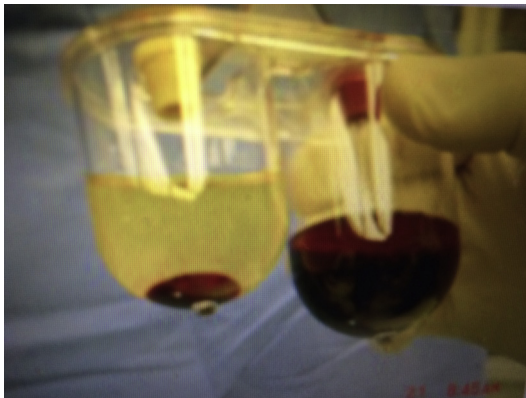

Fig. 1. PRP's (platelet-rich plasma) with divided doses of platelet-poor plasma (*left*) and PRP (platelet-rich plasma) (*right*). The PRP is mixed in with the bone graft to aid with arthrodesis. The platelet-poor plasma is sprayed in the soft tissue on closure to maintain wound healing.

Fig. 2. A patient who is prepared for bone graft and PRP in attempt for arthrodesis.

autograft as well as allograft as its carrier have been used in midfoot, hindfoot, and ankle fusions that did not heal.

DISCUSSION

In bone defects, nonunion, malunion, and so forth, especially in the hindfoot and ankle, the large bony gaps that the surgeon faces are large and taxing. Because of the anatomic location, trying to bridge theses gaps can be difficult and limb threatening. In cases such as these, we use large (to fit the defect) corticocancellous autograft struts from the iliac crest or fibular autograft if available. Some research suggests the use of fresh frozen femoral head allograft. In recent years, this technique has gained popularity as a solution to bridging these often significant gaps. Although the size of this graft is appropriate, the properties of fresh frozen

Fig. 3. Post operative lateral radiograph of a patient who had a tricortical cancellous bone graft harvested from the posterior superior calcaneus. Post operatively, the patient suffered a extra articular calcaneus fracture because the donor site was not packed well with allogenic bone and was not protected well enough in the postoperative period. The treatment of this patient was immobilization, and she went on to have a solid union of the calcaneal fracture.

Fig. 4. Preoperative anteroposterior radiograph of a high-risk patient who underwent an attempted first metatarsophalangeal joint arthrodesis with cannulated screws. The patient experienced a painful nonunion of the first metatarsophalangeal joint.

bulk corticocancellous allografts such as fresh frozen femoral head are not optimal for bony fusion across such potentially cavernous gaps. Reasons for failure of these grafts include resorption of graft, thermal necrosis from fashioning, lengthy storage times, rejection, trabeculation issues over large areas, freeze-dried/frozen nature of

Fig. 5. Intraoperative view of the outline of the tricortical cancellous harvest of the patient's calcaneus.
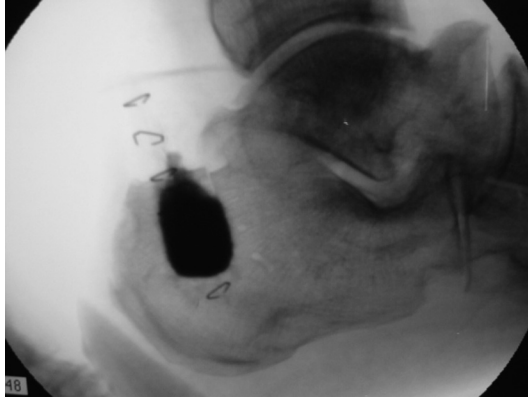
Fig. 6. Intraoperative lateral radiograph showing osteobiologics being used as a bone void filler after harvesting of a tricortical cancellous graft of the calcaneus.

the graft, and cost.[14–20] Bulk corticocancellous allografting is not a technique specific to the foot and ankle. This graft is used routinely for proximal tibial defects in knee arthroplasty, acetabular repair, iliac crest repair, wrist arthrodesis, lumbar fusion, and patellar augmentation. Although widely accepted, bulk corticocancellous allografting is not without complications. In a 10-year study of weight-bearing acetabular repair with femoral head allograft, a 47% failure rate was reported. The investigators also commented[15] that their results at 5 years postoperatively were significantly better than those at 10 years and that long-term studies were needed to determine the true survivability of these grafts. A significant difficulty in incorporation of bulk corticocancellous allograft is that, over large defects, trabeculation is scarce across the central part of the grafted arthrodesis site. Draenert and colleagues[19] in a retrospective study reaffirmed that autograft bone remained the gold standard in cavitary bone defects, because of the difficulty in trabeculation across large sites of bone loss. Techniques used to help incorporate bulk corticocancellous allografts into hindfoot fusions have included multiple drill holes, reaming, burring, augmenting with autograft, and electrical stimulation. Even with these methods of promoting incorporation, there are still consistent issues. In a 7-year retrospective study by Jeng and colleagues,[14] a 50% nonunion rate of fusion in tibiotalocalcaneal arthrodesis using a femoral head was noted. Of diabetic patients in the study, 100% experienced nonunion, and 19% of these

Fig. 7. Long-term postoperative lateral radiograph showing good bony union of the first metatarsal phalangeal joint as well as good incorporation of the autogenous tricortical bone graft harvested from the calcaneus as well as good incorporation of the osteobiologics of the calcaneus.

Fig. 8. Medial oblique radiograph showing complete incorporation of a tricortical cancellous autograft into the first metatarsophalangeal joint of a very high-risk patient. In complex cases, such as this, autogenous bone graft seems to be most predictable.

patients went on to below-knee amputation. Our personal experience is that these grafts may look acceptable postoperatively on radiographs, but obtaining a computed tomography scan to show healing has not been successful, and in most cases, the hardware failed and the construct needed revised.
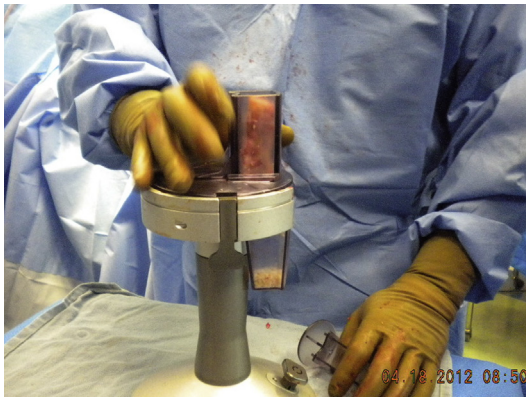
Fig. 9. Intraoperative view of excessive fibular graft, inserting into a bone mill, and using this as backfill for a large bony defect.

Fig. 10. Intraoperative view of excessive fibula being processed through a bone mill. Note the collection of the mulched up version once the fibula has run through the bone mill.

In cases with a large bone void present in the hindfoot and ankle, our experience is that successful bone grafting can be achieved using a mixture of cortical cancellous autograft mixed with remaining milled autograft if present and in combination with allograft bone chips or osteobiologics as a bone void filler as a complementary agent. To be successful, the first principle has to be applied as a significant amount of time must be spent with joint preparation. Without excellent joint preparation and good bony bleeding, no matter which product or construct is applied, the outcome is doomed to failure, because this is a critical step in repairing nonunion, malunion, and so forth. When faced with large defects, our experience has been to soak the graft bone chips once the patient is under anesthesia. This blood soaking of the cancellous chip allows for nature proteins, growth factors, and so forth to integrate in a slurry of the patient's own blood, which we believe promotes osteointegration. Once this surgical site is prepared and good bony bleeding at both ends of the deformity is accomplished, this anatomic location is packed tightly, which can be coupled with osteobiologics or used by itself. This procedure is then combined

Fig. 11. Intraoperative view of the excessive fibula after the bone milling process. The patient's blood was added to the autogenous bone graft to create a bony slurry before implanting the bone graft.
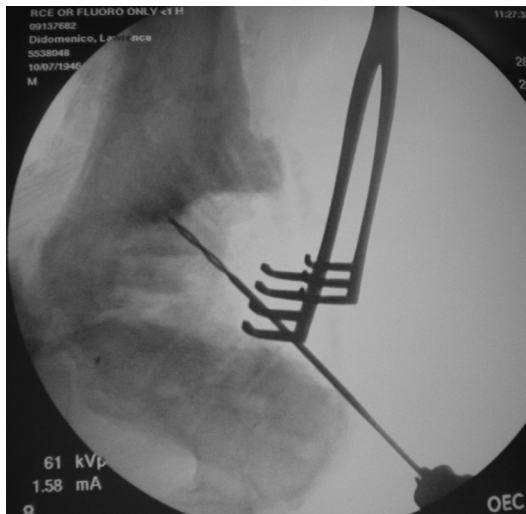
Fig. 12. Intraoperative view of a diabetic patient undergoing a revision Charcot joint reconstruction procedure. Note that all of the necrotic tissue and bone was resected aggressively, leaving a large defect. Significant bone debridement was performed with a ronjeur, osteotome, mallet, curettes, and drills to ensure good bony bleeding.

with an autograft of cortical cancellous struts from either the fibula or the iliac crest, based on the index procedure. We use this as an inlay graft or as only graft based, depending on the given circumstances. Our fixation construct consists of 2 large, fully threaded, axial cancellous positional screws from the inferior calcaneus into the distal tibia, usually around 110 to 120 mm long. The 2 large cannulated screws do obtain a bicortical purchase and act as an intramedullary nail within our construct. This procedure is coupled by a large long locking plate fixation
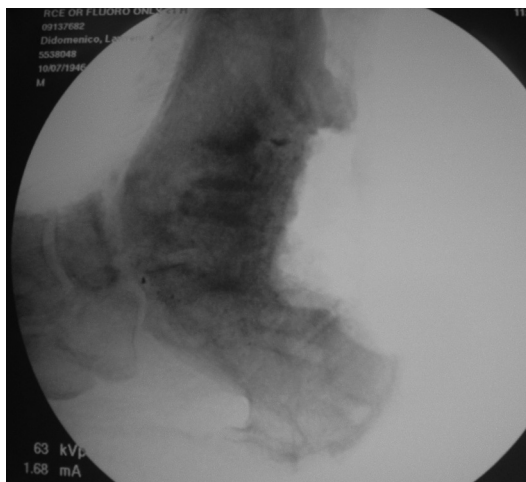

Fig. 13. Intraoperative lateral radiographic projection involving a tightly packed mixture of allogenic and autogenous bone graft.
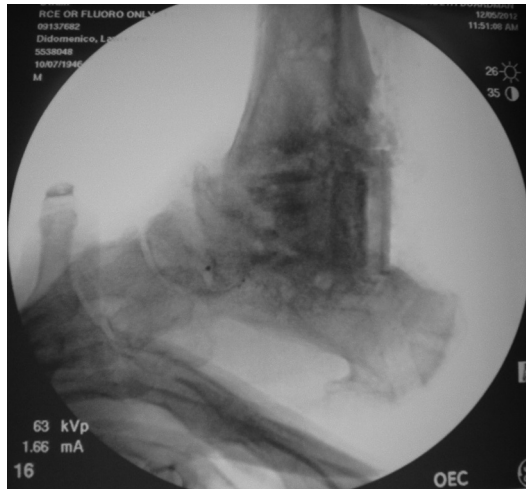
Fig. 14. Intraoperative lateral radiographic projection after aggressive bony debridement and packing of allogenic and autogenous bone graft, as well as fibular struts of inlay autogenous inlay bone graft which includes cortical-cancellous bone.

encompassing the cortical cancellous bone graft strut as well as the bulk graft, which provides stability. The construct should begin more proximal and more distal to the graft targeted site for more stability. Moreover, the plating techniques offer multiple holes of fixation consisting of both locking and nonlocking screws. In theory, this grafting method allows easier incorporation over a larger area because of the primarily cancellous grafting, as well as the autogenous cortical cancellous

Fig. 15. Intraoperative lateral radiographic projection after aggressive bony debridement and tightly packed allogenic and autogenous bone graft, as well as autogenous fibular inlay bone graft struts fixated with two fully threaded 7.3 fully cancellous screws and an anterior ankle arthrodesis locking plate, which was applied to the posterior aspect of the ankle.
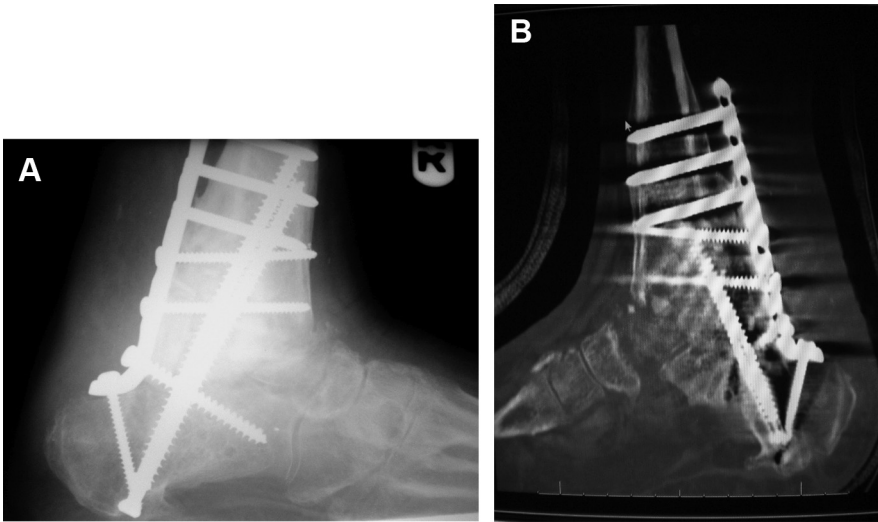
Fig. 16. (*A*, *B*) Postoperative lateral radiographic projection and computed tomography scan showing good bony union of the revision surgery for the diabetic Charcot joint of the hindfoot and ankle.
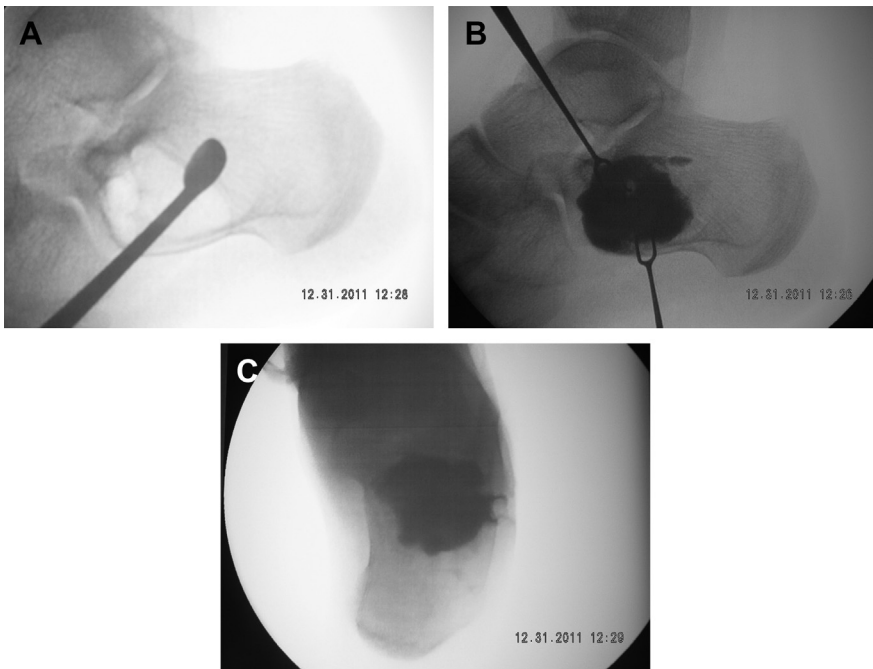

Fig. 17. (*A–C*) Intraoperative view of a large calcaneus bone cyst, which was derided percutaneously with a curette and injected with orthobiologics to fill the cavernous void in the calcaneus percutaneously. Intraoperative lateral and calcaneal projection shows the accuracy of the bone void filler.

Fig. 18. Long-term postoperative view of a patient who had a large calcaneus cyst filled with osteobiologics. One can see how the osteobiologics was incorporated into the calcaneus.

struts and screws along with locked plating, which provide the stability needed for primary bone healing as well as the strength needed for hindfoot and ankle arthrodesis. Furthermore, this technique allows the surgeon to dial in the desired position with optimal biomechanical accuracy and precision. Also, the press-fit autogenous graft inlay/onlay grafts struts can be used for structural support.

With this technique and construct, we achieved cortical apposition with the use of the struts, which allows primary cortical contact. It is essential for this fixation construct to be as stable as possible, because there is an increased potential for motion through the backfilled sites (Figs. 12–24).

COMPARING AUTOGRAFT AND OSTEOBIOLOGICAL AGENTS

There is no paucity of literature dealing with orthobiological agents. Every year, billions of dollars are spent in the operating room on bone grafting, making these devices a

Fig. 19. Intraoperative view of a patient undergoing open reduction and internal fixation of a calcaneal fracture. Because of the significant amount of bone loss, the voided areas were filled in with bone graft substitute.

Fig. 20. Preoperative clinical view of a previously failed Charcot reconstruction. Note that the patient is in extreme valgus, with an unstable hindfoot and ankle.

popular topic for research.[21] However, when compared with autograft, biological agents have been shown to provide a less rapid union. Putzier and colleagues[22] found that allograft had a significantly lower rate of fusion compared with autograft at 12 months. One reason for the variable fusion rates when using biological agents is
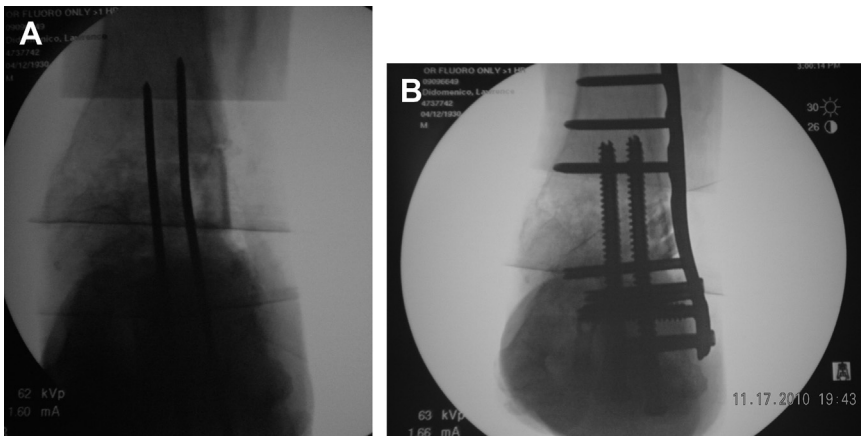

Fig. 21. (*A*, *B*) Intraoperative anteroposterior views of a Charcot joint reconstruction. Preoperatively, the ankle was in significant valgus. Note that the proximal part of the fibula was put through the bone mill and used for autogenous bone grafting at the tibial talar joint. The distal portion of the fibula was split in half, and the cortical cancellous strut was used as an inlay graft along the lateral tibial talar calcaneus. The fixation construct consisted of two fully threaded 7.3 cancellous screws and a lateral based femoral locking plate.

Fig. 22. Intraoperative anteroposterior radiograph after a diabetic Charcot joint midfoot fusion. Note that the fixation is well purchased, and significant bone debridement was performed prior to insertion of the osteobiologics.

Fig. 23. Postoperative anteroposterior radiograph after a diabetic Charcot joint midfoot fusion and application of osteobiologics and rigid internal fixation.
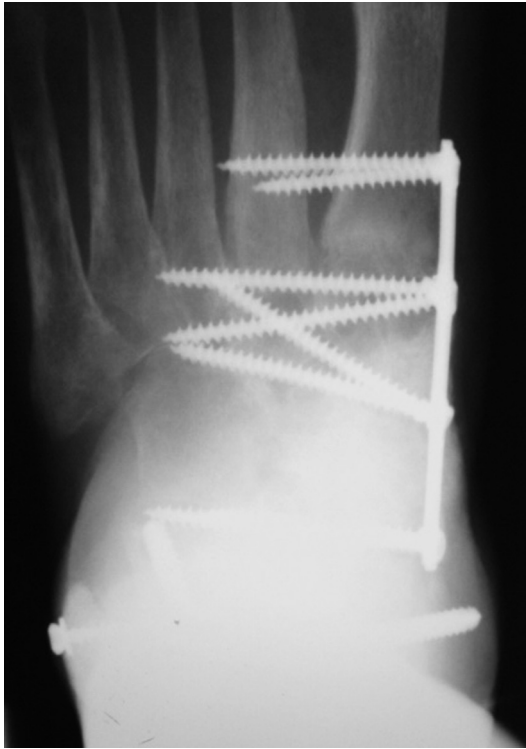
Fig. 24. Long-term postoperative anteroposterior radiograph after a diabetic Charcot joint midfoot fusion with complete incorporation of the osteobiologics along the midfoot.

the variability in manufacturing. Also, there are few public data directly comparing the effect of proprietary processing.[8,23] Other studies have found similar results in comparing allografts and autografts. Cammisa and colleagues in 2004[24] found no significant difference in healing rate of healing using DBM in a 2:1 ratio versus autograft alone.[25] Scranton[26] could not prove difference in outcomes between autograft and injectable BMP for subtalar joint arthrodesis.

SUMMARY

Osteobiological agents are a welcome addition to the surgeon's armamentarium. These products should always be thought of as a complement to good surgical principles and construct. As history has shown, nothing outperforms the osteogenic properties of autograft bone. Even if allograft is procured for use, an attempt should be made to combine it with autograft if possible, given the primary index procedure in which it will be used. Structural support from corticocancellous autografts is also greater than allografts, which lose mechanical strength during the sterilization and preservation process. Bone fillers without structural support should be used only when there are other means of cortical contact. The ability of the human skeletal system to repair itself is amazing. Osseous healing relies on a complicated series of intrinsic and extrinsic factors. Some of these factors include a stable fixation construct, nutritional status, good surgical technique,

and good decision making. Autogenous bone graft remains the gold standard, and the presence of native growth factors and osteogenic cells is mandatory to repair these deformities. When this microenvironment is disruptive, nonunion may result. Understanding the mechanisms of bony healing contributes to the available osteobiologics, which give the foot and ankle surgeon additional tools to enhance the reparative process of bony defects and the ability of the foot to restore itself.

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