PERSPECTIVES

Perspectives on the clinical utility of allografts for bone regeneration within osseous defects: a narrative review

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Abstract: A variety of bone grafts and bone graft substitutes is available for treatment of osseous defects although adequate reconstruction of the residual void following fracture, arthroplasty, or tumor/cyst resection remains a therapeutic challenge. This narrative review evaluates the peer-reviewed literature and examines relevant outcomes in patients treated with bone grafts and bone graft substitutes for surgical management of osseous defects. Although autograft, xenograft, and ceramic bone graft substitutes are used for a variety of orthopedic applications, they have distinct limitations in clinical practice. Bone allograft material is a safe and effective adjunct to treatment of osseous defects.

Keywords: allograft, bone graft, osseous defect

Introduction

Bone is the second most commonly transplanted tissue in the human body with 600,000 graft procedures performed each year.[1] A wide variety of bone grafts and bone graft substitutes, each with distinctly different characteristics, is available to the orthopedic surgeon for various reconstructive procedures including arthrodesis, traumatic fracture management, maxilllofacial implants, and cavitary filling following tumor and cyst resection and curettage. Treatment of osseous defects with bone grafting is an underappreciated field that can potentially help patients realize a quicker return to normal activities. Unfortunately, adequate reconstruction of the residual void following fracture, arthroplasty, or tumor/cyst resection remains a therapeutic challenge. Each bone graft option has a unique set of benefits and risks that must be considered in relation to the particular pathology in order to achieve the best possible outcome.

There are 4 desirable characteristics of any bone graft: osteoconduction, osteoinduction, osteointegration, and osteogenesis. Osteoconduction refers to the ability of a bone graft to act as a scaffold to facilitate bone growth over its surface, within its matrix, or both. Osteoinduction is the capacity to recruit mesenchymal cells from surrounding host tissue and to stimulate them to differentiate into osteoblasts. Osteointegration is the ability to chemically bond to the surface of bone in the absence of an intervening layer of fibrous tissue. Osteogenesis describes the ability of a graft to produce new bone de novo, mediated by the transplant of osteogenic precursor cells within the graft material, at the recipient site.[2,3]

Historically, autografts have served as the mainstay bone graft of choice since autologous bone is inherently capable of osteoconduction, osteoinduction, and osteogenesis. Despite the fact that autografts have demonstrated acceptable

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effectiveness, a large body of evidence suggests that the clinical morbidity resulting from harvesting bone from the patient's own hip is substantial and may outweigh the benefits of this procedure.[4–7] Complications such as superficial nerve damage, vascular injury, iliac fracture, infection, and chronic donor site pain occur in 10% to 50% of patients who undergo autograft harvest.[5,6] Furthermore, the quantity of bone available for harvest from the iliac crest is limited and regeneration of the residual defect is slow,[8] which hinders the widespread use of this treatment option, particularly for large osseous defects. Overall, the unacceptably high complication risk and prolonged procedure time associated with autograft harvesting has caused skepticism about this graft material among patients and physicians alike.

Another option, xenografts (or heterologous) bone grafts are derived from nonhuman species (primarily bovine and porcine) and represent an alternative to autologous harvesting. Few human studies with xenografts, aside from spinal and maxillofacial applications, have been conducted.[9] Although there has been a recent concerted effort to improve the biocompatability of xenografts,[10–12] significant risks remain including pathogen transmission, immunogenic rejection, prolonged graft integration, and fracture.[13–15] Despite these risks, xenografts continue to be utilized on a limited basis for the treatment of osseous defects primarily because of their abundant supply and their satisfactory osteoconductive characteristics.

Additionally, ceramic bone graft substitutes such as hydroxyapatite, calcium sulfate, and calcium phosphates have been used with increasing frequency over the last decade in the adjunctive management of osseous defects mainly due to their osteoconductive properties.[16] However, the porosity of these materials has a detrimental impact on mechanical strength, which may increase fracture risk. Furthermore, while biocompatibility of ceramics is generally acceptable, these grafts lack osteoinductive and osteogenic properties unless combined with autologous marrow or other bone growth factors.[17]

Finally, allografts, which are obtained from deceased donors, are used for a wide variety of orthopedic reconstructive applications and have osteoconductive, osteointegrative, and osteoinductive properties, especially when demineralized.[18] Allografts overcome the primary limitations associated with autografts, namely that the risk of donor site morbidity is eliminated and that they are readily available in large quantities. However, processed allograft bone possesses no osteogenic properties since it contains no live cells.

Given that each type of bone graft has distinct characteristics (Table 1), it is important to review the research that has been

Table 1 Characteristics of bone grafts and bone graft substitutes

Variable	Allograft	Autograft	Xenograft	Ceramics
Osteoconduction	+++	+++	+++	++
Osteoinduction	++	+++	+	−
Osteointegration	++	+++	++	+++
Osteogenesis	−	+++	−	−

Notes: +++, excellent; ++, average; +, poor; −, none.

performed on these materials to determine how these physical properties translate into clinical application. This narrative review evaluates the peer-reviewed literature and examines relevant outcomes in patients treated with bone grafts and bone graft substitutes for surgical management of osseous defects.

Clinical outcomes
Autograft

Clinical experience with autografts for osseous defect treatment has yielded mixed results. Radiographic and clinical outcomes at the recipient site are usually, but not always, positive. Rajan and colleagues treated 75 patients with comminuted distal radius fractures with either autograft or allograft.[6] Clinical and radiographic outcomes 1 year following surgery were similar in both groups. Ring and colleagues treated 35 patients with autografts and plate fixation for diaphyseal forearm nonunions and segmental defects. After 6 months, all patients were healed and none required a follow-up procedure.[19] Autografts also yield good-to-excellent results in 90% of cystic talus lesions.[20]

However, several trials have reported mixed outcomes with autologous bone grafting due, in part, to the lack of immediate structural support. Several studies have concluded that union rates following comminuted forearm fracture were similar in patients treated with or without autograft.[21,22] Gershuni and Pinsker[23] treated 40 tibial nonunions with autograft and cast immobilization. Despite a union rate of 85%, significant tibial deformity persisted. Adani et al[24] treated 13 patients with autograft for humeral nonunion. Four (31%) patients required additional bone grafting after only 6 months follow-up.

In addition to these equivocal clinical outcomes, the overwhelming limitation of this bone grafting method is the significant and persistent morbidity related to donor site harvesting, most commonly at the iliac crest.[7] The most common complication is postoperative pain at the donor site, occurring in 50% of patients and persisting through 1 year in up to 29% of patients.[5,6] Additional commonly reported problems include nerve injury, hemorrhage, fracture, and hernia.[25–28] Due to this significant morbidity, autologous bone grafting

has become less desirable in recent years with a concerted effort to identify satisfactory grafting alternatives.

Xenograft

Few human studies of osseous defect treatment with xenografts have been conducted.[9] Schultheiss et al observed delayed incorporation of bovine cancellous blocks for reconstruction of thoracolumbar fractures compared to autologous tricortical iliac crest bone grafts.[29] Liu et al[30] treated 65 patients with xenograft predominantly for long bone fractures and tumor resection. Graft infection was observed in 8% of cases and graft rejection with immunosuppressive treatment was common. Charalambides and coworkers[31] treated 27 patients with xenograft and autograft following hip revision surgery. After a mean 2.5 year follow-up, 3 grafts did not incorporate, 3 patients had graft infection, and 1 patient suffered a deep prosthesis infection. Levai et al[32] used bovine xenograft in 31 patients for treatment of tibial osteotomy defects. At 2.5 years follow-up, 5 (16%) patients experienced local discharge or infection. These authors concluded that xenografts have an unpredictable radiographic and histological outcome, and when also considering the high incidence of local complications, they opined that use of xenografts in humans should be discontinued. Overall, xenografts processed with currently available techniques are not recommended to fill cavitary defects due to the excessive risk of graft rejection and infection.

Ceramic bone graft substitutes

As a whole, ceramic bone graft substitutes result in acceptable, but not excellent, long-term clinical outcomes.[16] Coralline hydroxyapatite has demonstrated clinical outcomes similar to that of autograft in treating tibial plateau fractures.[33] However, the brittleness of this material makes handling difficult and often results in fragmentation while impacting this material into the defect. Several authors have reported excellent results with calcium phosphate for traumatic fractures or cavitary filling after excision of tumors or cysts.[34,35] Anker and colleagues[36] reported that tricalcium phosphate incorporated well into small cavitary defects but incorporation was incomplete after 1 year in large defects (≥43 cm).

Calcium phosphate cement has much greater compressive strength versus other ceramics. A prospective trial of 110 patients with distal radius fractures found that calcium phosphate cement yields a greater frequency of satisfactory results and fewer malunions when used to fill metaphyseal defects versus closed reduction and cast immobilization.[37] A similar study in 52 menopausal, osteoporotic women with

unstable distal radius fractures showed that use of calcium phosphate cement to supplement pin and screw fixation maintained the reduction of unstable distal radius fractures and yielded superior clinical outcomes versus percutaneous pinning.[38] However, a randomized study of 323 patients with distal radius fractures treated with or without calcium phosphate cement for metaphyseal defect filling showed no group differences in grip strength, range of motion, or quality of life at 3 months and 1 year.[39] Furthermore, extravasation into the surrounding soft tissues occurred in 70% of patients treated with calcium phosphate cement. Painful soft tissue reactions have also been reported in up to 20% of patients following calcium phosphate cement injection.[40]

Calcium sulfate use for osseous defects remains controversial. This material undergoes dissolution within 4 to 12 weeks, which is too rapid to provide a long-term framework to support osteoconduction. Calcium sulfate ceramics undergo phagocytosis, which contributes to this accelerated material biodegradation.[41] Consequently, outcomes of tibial defect treatment with calcium sulfate are similar to no treatment at all.[42] Collagraft, which is a composite of bovine collagen and a biphasic ceramic (60% hydroxyapatite and 40% tricalcium phosphate), was shown to perform similarly to autograft in a randomized controlled trial of 325 patients with long bone fractures followed for 2 years, although allergic response to the bovine protein occurs in 1 out of 10 cases.[43]

Allograft

Gajiwala[44] reported his experience with morsellized allografts in patients with tumor defects, primarily of the femur and tibia. Of the patients who were available for follow-up, all patients (21 of 21) had complete incorporation of the graft after 6 to 9 months. Temple and Malinin[45] used small allogeneic cortical graft particles to treat 97 patients with osseous tumors. After an average of 3 years follow-up, both graft incorporation and consolidation rates were over 90%. Lasanianos et al[46] used freeze-dried cancellous allograft following surgical treatment of impacted tibial plateau fractures. After a mean 13 months of follow-up, 21 of 23 (91%) patients had a good or excellent clinical and radiographic outcome with no major complications. Shih and colleagues[47] treated 104 patients with long bone defects with curettage and allografts. Good or excellent functional results were reported in 97% of patients after 4 years with no local recurrence or graft fracture and only a single complication. Treatment of intercalary long bone defects with allograft has consistently shown successful outcomes without the need for adjunctive follow-up procedures in 81% to 85% of cases.[48–50] Overall, allografts yield excellent

clinical outcomes with good versatility in cavitary defects across various anatomic locations.

Discussion

Overall, it is difficult to strictly compare radiographic and clinical success with treatment by different types of bone grafts for osseous defects, primarily due to the varying types and locations of defects encountered in clinical practice and the lack of comparative studies. Regardless, several global conclusions may be drawn from the breadth of literature on this topic.

Autologous bone grafting has long been considered the gold standard for treatment of osseous defects. The iliac crest is the most common site for obtaining autologous bone mainly due to ease of access in obtaining the graft material. The completeness of incorporation, rapid healing rate, and inherent biocompatibility of autografts are ideal. However, the frequency and severity of harvest site morbidity makes autologous bone an arguably unsatisfactory choice for osseous defect treatment, especially considering that all other bone grafting choices are free from this potential complication. Obtaining large amounts of autograft material is exceedingly difficult and is very likely to result in prolonged postoperative pain and ambulation difficulties since the risk of morbidity following autologous bone grafting is in direct proportion to the volume of excised bone.[51]

Despite wide application in animal models and maxillofacial procedures in humans, xenografts are used on a limited basis for osseous defect reconstruction, primarily because more effective and less risky options exist. The porosity of xenografts promotes osteoconduction, although this characteristic also compromises the initial stability of the graft.[52] Furthermore, the required processing of this tissue (eg, autoclaving) reduces infection risk but has the detrimental effect of lowering the graft's resistance to compression by up to 70%.[53] Xenografts also have great potential for rejection and infection transfer to the recipient. In addition, the necessity of immunosuppressive therapy and the associated side effects currently make xenografts an overall poor choice for treatment of osseous defects. Lastly and perhaps most importantly, there is a paucity of clinical study results on xenografts apart from maxillofacial applications and, therefore, little is known about the long-term performance of these tissues in the treatment of osseous defects.[29] Given the fact that delayed xenograft rejection is an ever-present risk,[13] xenograft use represents a treatment option that presents significant known and unknown risks to the patient. In fact, several authors have concluded that xenograft material should not be used

for treatment of osseous defects because of the unacceptably high infection and graft rejection rates.[30,31]

Ceramic bone graft substitutes have somewhat varying biomechanical properties, but as a whole, suffer from common limitations. These synthetic bone analogs have variable biocompatibility, often heal incompletely, and can be expensive.[45] Hydroxyapatite is brittle with little tensile strength and use should be limited to defects that are not subjected to weight bearing and where bending, torsion, and sheer are minimized. Furthermore, the bending strength of incorporated hydroxyapatite in cortical bone is only 10% of cortical bone itself and, therefore, the bone graft may never be able to withstand normal physiological loads in these areas.[54] Finally, residual hydroxyapatite material remains unincorporated for 10 years or more following grafting.[55] Calcium phosphate also suffers from inherent weakness under load and has an extremely slow resorption rate (30% to 60% at 1 year).[39] Tricalcium phosphate is equally slow to resorb and is very brittle. Calcium sulfate absorbs very quickly (4 to 12 weeks) although the resorption occurs faster than bone growth occurs, which results in structural instability and weakness under loading. As a whole, ceramic bone graft substitutes have limited mechanical properties and must generally be used in conjunction with internal or external fixation devices. Furthermore, there is little evidence of their effectiveness, particularly for large cavitary defects.[56] Finally, the cost of ceramic bone graft substitutes can be high, especially for treatment of large defects.

Allografts: the bone graft of choice

Allograft bone has a 50-year history of use for various orthopedic indications.[57] Allografts have become the bone graft of choice for treatment of osseous defects because of their distinct advantages versus other alternatives.[58] The primary advantages are lack of donor site morbidity, simple technique with short operative time, sufficient supply to treat even the largest bone voids, and excellent patient outcomes. Allografts are of particular benefit in the case of large bone defects that require structural support and when inadequate autologous graft volume is available. Furthermore, properly processed allografts have the same structure as native bone and exhibit a uniform ability to withstand stress and intraoperative handling. Allografts are widely available and are quite versatile since the shape, contour, and mineral density can be modified to the particular clinical indication. A comprehensive clinical evaluation of the performance of bone grafts and bone graft substitutes for osseous defect treatment is provided in Table 2.

Table 2 Clinical evaluation of osseous defect treatment with allograft, autograft, xenograft, and ceramics

Variable	Allograft	Autograft	Xenograft	Ceramics
Structural support	+++	+++	++	+
Cost effectiveness	+++	++	+	++
Procedural safety	+++	+	+	++
Long-term safety	+++	+	?	?
Long-term effectiveness	+++	++	?	+

Notes: +++, excellent; ++, average; +, poor; ?, unknown.

Despite the favorable performance of allograft compared with other bone graft materials, allograft suffers from several limitations. Allograft fracture or nonunion has been reported in 15% to 20% of grafts, primarily due to limited revascularization.[59] In large defects, poor anatomical matching between the graft and the host defect can alter joint kinematics and load distribution, which may accelerate bone resorption or joint degeneration. Allograft infection has been reported in 6% to 13% of cases, with the proximal tibia most commonly affected.[59,60] Infection risk can be lowered by employing aseptic processing steps such as soaking the graft in an antibiotic solution at the time of harvest and procurement.

There is a common misperception about the risk for disease transmission from the host to the donor. Although the risk is extremely low, disease transmission is possible from allografts although no cases have ever been documented with irradiation sterilized allografts. Careful selection of an American Association of Tissue Banks (AATB) -accredited bone bank is paramount to attain safe and effective allograft tissue. Such bone allografts undergo strict screening and recovery processes that conform to US Food and Drug Administration and AATB standards.

The process to determine donor eligibility begins with a comprehensive screening program that includes a series of standardized questions, physical examinations, and review of medical records and autopsy reports. The final approval for allograft donation is determined by a licensed physician after a thorough review of these records. Donors are automatically excluded if toxin exposure, bone disease, autoimmune disease, or infectious disease is detected. If a donor meets all eligibility criteria, the tissue is promptly removed from the donor and cultures are performed to further confirm the absence of disease. Donors must also test negative for indications of infective potential, which includes testing for HIV, hepatitis C, hepatitis B surface antigen, and total antibody to hepatitis B core antigen. In addition, bone allografts are typically disinfected through a variety of physical and chemical solution processes.

Conclusion

Based on a narrative review of the peer-reviewed literature, we conclude that bone allograft material is a safe and effective adjunct to treatment of osseous defect. Although autograft, xenograft, and ceramic bone graft substitutes are used for a variety of orthopedic applications, these materials have distinct limitations in clinical practice. The use of allografts obtained from AATB-certified bone banks can improve treatment success for these procedures. Overall, allografts are safe and effective bio-implants and represent the gold standard for treatment of osseous defects.

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Disclosure

The authors declare no conflicts of interest.

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