Autologous Bone Graft: Properties and Techniques

Article *in* Journal of orthopaedic trauma · March 2010

DOI: 10.1097/BOT.0b013e3181cec4a1 · Source: PubMed

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Autologous Bone Graft: Properties and Techniques

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Summary: Bone grafting is involved in virtually every procedure in reconstructive orthopaedic surgery. Although autologous bone grafts have excellent biologic and mechanical properties, considerable donor site morbidity and the limited volume available must be taken into consideration. Currently, there are no heterologous or synthetic bone substitutes available that have superior biologic or mechanical properties. This review article summarizes the biologic and mechanical properties of autologous bone grafts, differentiates various autologous bone graft types, and compares them with other bone substitutes.

Key Words: autologous bone grafting, tricortical graft, properties of bone, cancellous bone graft

(*J Orthop Trauma* 2010;24:S36–S40)

INTRODUCTION

With more than half a million grafting procedures annually, autologous bone is the second most commonly transplanted tissue in the United States.[1–5] The success of autografts in the treatment of nonunions is well established. In the tibia, union rates of more than 90% have been reported using iliac crest bone graft in a mechanically stable environment.[6–8] Similar success rates have been documented in the treatment of diaphyseal nonunions at other sites.[9,10] In posterior cervical fusions, successful fusions in 92% to 100% of patients have been reported when using autologous iliac graft.[11] In addition, iliac crest bone grafting has been successful in treating recalcitrant[12,13] and infected[14,15] nonunions as well as completing the healing at the docking site of nonunions treated with distraction osteogenesis.[16]

In addition to its volume effect, the biologic properties of grafts in terms of new bone formation are essential.[2] Autologous bone graft continues to represent the gold standard for management of bone defects or nonunions. It possesses biologic advantages over heterologous and synthetic bone substitutes as a result of its excellent combination of osteogenic, osteoinductive, and osteoconductive properties.[2] Furthermore, tricortical grafts can be used to improve the immediate strength of constructs ("bioplating"). This combination of biologic and mechanical properties has not yet been achieved by heterologous or synthetic bone substitutes.

Accepted for publication December 9, 2009.
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No funding was received for the preparation of this manuscript.
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Properties of Autologous Bone Grafts

Osteogenetic Properties

In general, osteogenetic properties are induced by osteogenic precursor cells and osteoblasts within a graft. In autologous bone, histoincompatibility with cell degeneration is not an issue. Nevertheless, an interindividual variability of the osteogenic potential does exist. Genetic factors may play a role and age of the donor has been identified as an important variant.[17,18] Furthermore, the osteogenetic properties may be compromised by the techniques of graft preparation with osteonecrosis being a major complication.[11] Careful harvesting and implantation techniques are therefore important along with short harvest-to-implant time and adequate interim storage.[11]

Osteoinductive Properties

The osteoinductive properties of a graft depend on the availability of growth factors. In fresh autologous grafts, several growth factors are detectable.[19] Among these are members of the transforming growth factor-β superfamily (eg, bone morphogenetic protein [BMP]-2, BMP-4), angiogenic factors such as fibroblast growth factor and vascular endothelial growth factor, and platelet-derived growth factor and insulin growth factor I, which have migratory and differentiating effects on cells. In contrast, in demineralized freeze-dried allografts, neither BMP-2 nor BMP-4 are present.[20]

Osteoconductive Properties

Osteoconductive properties depend on the three-dimensional structure of the graft and determine the velocity of osteointegration. This is well illustrated when comparing the osteointegration between dense cortical grafts and highly porous cancellous grafts: the cancellous graft is incorporated much faster.[21,22]

Biomechanical Properties (structural use as biologic plate)

The biomechanical properties of autologous grafts apply for the use of tricortical bone grafts, which commonly are used to improve initial stability. A tricortical graft can be firmly attached to the adjacent bone by using small fragment screws. This applies especially when a unilateral implant is present and support is required on the contralateral side. It is advantageous to use these grafts in young patients in whom the strength of the bone adds to the initial stability.

However, when using large tricortical grafts, the risk of significant donor site morbidity is high. Fractures of the anterior iliac spine can occur and carry a high risk of nonunion and prolonged disability. It is therefore important to harvest the graft as far posterior as possible from the anterior–superior iliac spine to reduce the likelihood of a fracture in this region. A vascularized bone graft such as one derived from the fibula may also be used as an isolated strut for mechanical support. Figure 1 demonstrates a free fibula graft in association with a bioplate for a posttraumatic distal femoral defect. Of note, this technique should be reserved for special indications in which bone loss and instability are substantial, usually with periarticular lesions.

Autologous Bone Graft Types

Different types of autologous bone grafts have variable properties associated with structural anatomy. Cancellous bone has greater cellular diversity and activity than cortical bone, whereas cortical grafts have enhanced mechanical properties (Table 1). Overall, cancellous bone is eight times as metabolically active as cortical bone and cortical bone is four times as dense as cancellous bone.[22]

Cancellous Bone Graft

The trabecular structure of cancellous bone results in a large surface area. This allows for a high number of cellular components (mesenchymal stem cells, immature and mature osteoblasts) to be incorporated and explains its excellent osteogenic and osteoinductive capabilities.[2,19,23] In addition, the trabecular structure allows for easy revascularization and rapid incorporation at the host site.[23] In turn, one of the limitations of cancellous bone is its lack of initial mechanical strength. Also, the formation of new bone on a necrotic cellular structure weakens the construct within the first weeks. As a result of the excellent biologic capacity to induce the production of new bone, increased stability is then achieved within months once the graft is incorporated.[23]

Vascularization of cancellous bone grafts begins within 2 days after implantation and is accompanied by infiltration of the marrow spaces by mesenchymal stem cells.[23] The early stage of osteointegration with revascularization is followed by graft remodeling with active bone formation and resorption of necrotic bone after 4 weeks. Histologically, osteoblasts can be found to line the trabecular scaffolds and deposit a seam of osteoid.[24] Remodeling takes several months.[21]

Cortical Bone Graft

Cortical bone grafts have a more limited biologic profile as compared with cancellous grafts (Table 1). Cortical bone has fewer osteoblasts and osteocytes, fewer growth factors, and less surface area per unit weight, the structure of which constitutes a barrier to vascular ingrowth and remodeling.[21] However, cortical bone does provide good initial mechanical stability and strength to bony fixation constructs as compared with cancellous bone grafts. Osteoclastic activity with resorption of the dense cortices and bone loss begins 2 weeks after the grafting procedure.[25] This results in transient weakness with reduction of mechanical strength of up to 75%.[26]

Differences in graft incorporation between cortical and cancellous grafts become evident during the stage of graft revascularization and remodeling.[25,27] The process takes longer for cortical bone. Revascularization takes approximately 2 months because of the structure of the cortical graft, which does not allow as large a contact area for vascular penetration between the graft and the host.[24,25] In contrast to cancellous grafts in which incorporation is initiated by new bone formation, the osteoclasts must first initiate resorption of the dense cortices in cortical grafts to allow revascularization. In dog studies, it has been shown that cortical grafts have significantly decreased strength at 6 weeks that remains low

FIGURE 1. (A) A bone defect after a distal femur fracture. (B) A filled defect by a vascularized fibula (next to the plate) and a tricortical bone block medially acting as a bioplate.

TABLE 1. Properties of Different Types of Bone Grafts

	Type of graft		Osteogenesis	Osteoinduction	Osteoconduction	Immediate strength	Vascularity
Autologous	Bone marrow aspirate		++	+	–	–	–
	Cancellous bone		+++	+++	+++	–	–
	Cortical	non-vascularized	+	+	+	+++	–
		vascularized	++	++	++	+++	++
Heterologous	cancellous	frozen	–	+	++	–	–
		freeze-dried	–	+	++	–	–
	Cortical	frozen	–	–	+	+++	–
		freeze-dried	–	–	+	+	–
Synthetic	Ceramics (TCP, CPC)		–	–	–	++	–
	DBM		–	–	+	–	–
	TCP+BMA composite		++	++	+++	++	–
	TCP+BMP composite		–	+++	+	++	–

Extent of activity (–, +, ++, +++) from none (–) to maximal (+++).
TCP, tricalcium phosphate; CPC, calcium phosphate cement; DBM, demineralized bone matrix; BMA, bone marrow aspirate; BMP, bone morphogenic protein.

through 24 weeks but returns to normal strength by 48 weeks after transplantation.[25]

Autologous Bone Marrow Aspirates

Bone marrow aspirates can be harvested using minimally invasive techniques. Despite the initial enthusiasm surrounding the injection of bone marrow into fractures sites, two major limitations have been observed. First, the number of stem cells harvested in bone marrow aspirate is not as high as previously suspected; it has been estimated that marrow contains one per 50,000 nucleated stem cells in young adults and as few as one per one million in the elderly.[23] Second, the injected bone marrow tends to move from the insertion site, resulting in higher rates of heterotopic ossification and no observed improvement in fracture healing.[23] Thus, the clinical value of isolated autologous bone marrow aspirate currently appears to be negligible.

Vascularized Cortical Bone Graft

Autologous vascularized cortical bone grafts have favorable biologic attributes as compared with standard autologous nonvascularized cortical grafts. Furthermore, they are mechanically superior during the initial 6 to 12 months postgrafting. Despite their many biologic advantages, their primary limitation is that they are more technically difficult to obtain and implant given that this technique requires orthopaedic and microvascular skill sets.

Vascularized cortical grafts heal quickly at the graft–recipient junction because the remodeling process closely resembles that of normal bone.[23] It has been suggested that if adequate vascular anastomosis and graft stability are achieved, more than 90% of the osteocytes may survive the transplantation.[28] New bone formation by graft and host can lead to rapid graft incorporation and residual weakness of the construct is minimal.[26]

Sites for Bone Graft Harvesting

Although the biologic advantages of autologous bone grafts are numerous, there remain concerns about the availability of autologous grafts resulting from limited volume and considerable donor-site morbidity.[29–34] Furthermore, increased surgical time and hospital length of stay with consequent additional costs are described in the literature.[35]

Although the gold standard for nonvascularized cortical grafts is the iliac crest and for vascularized cortical grafts the fibula, the optimal harvesting site for cancellous grafts is debatable. Cancellous grafts are most commonly harvested from the iliac crest; however, recently, a new method for harvesting cancellous grafts has become available. With the "Reamer Irrigator Aspirator" (RIA) System, large quantities of autologous bone graft can be harvested from the femoral and tibial medullary cavities.

When compared with iliac crest, harvesting cancellous bone with the RIA technique demonstrated several advantages. The volume of bone graft harvested typically exceeds the volume available in the anterior iliac crest.[36–38] Furthermore, bone graft harvested from the femoral canal appears to provide a higher concentration of growth factors[19,39–41] than that derived from iliac crest.[19] Other authors describe that the RIA technique is associated with less postsurgical pain,[36] which may result in a shorter hospital length of stay.

Possible complications of iliac crest harvesting have been extensively discussed in the literature and therefore only possible complications of the RIA technique are further discussed in this review. Critics of reaming suggest that reaming disturbs the endosteal blood flow and thereby increases the risk of infection,[42,43] although this appears not to have been proven.[44,45] Another potential risk of the RIA technique is heterotopic ossification, which is a frequent finding after hip arthroplasty and antegrade femoral nailing.[46] Local risk factors for the induction of heterotopic ossification include surgical soft tissue trauma and spilling of osteogenic substances in the soft tissue during reaming.[47–49] Both risk factors are usually reduced through proper implementation of the RIA technique using an approach that is minimally traumatic to the soft tissues and continuous suction of the marrow contents to prevent the spillage of osteogenic material. Other issues derive from the sharp reamer head that may cause penetration and resultant weakness of the cortex. In addition, the guidewire has to be appropriately positioned within the metaphysis where reaming is directed. Inappropriate guide-wire positioning can add to the risk of cortical compromise and iatrogenic fracture described previously.

Comparison of Biologic Properties of Autologous Bone Grafts With Heterologous or Synthetic Bone Substitutes

One of the major downsides of autologous bone grafting is the limited availability. Therefore, some surgeons favor heterologous grafts. However, heterologous grafts carry the potential for disease transmission and may trigger immunogenic reactions.[50–53] Therefore, irradiation is required for all heterologous transplants, which in turn reduces their osteogenic and osteoinductive capability[54–56] (Table 1).

In comparison, synthetic bone substitutes (eg, tricalcium phosphate, calcium phosphate cement) possess osteoconductive properties and in combination with growth factors (eg, BMPs) may also achieve osteoinductive and osteogenic properties. Such composite grafts are currently being developed and may present an alternative to autologous bone grafts in the future. However, considering that the therapeutic dose of recombinant human BMP-2 for tibia fractures is currently approximately $4000, it is likely that the costs for such implants will be high.[57]

Currently, autologous bone graft remains the only clinically available graft source that is osteogenic, osteoinductive, osteoconductive, and contains viable precursor cells. Although some of the alternatives listed may have some potential in the future, to date, no other graft source appears to be more effective, or more cost-effective, than autologous grafts in stimulating bone formation[19,58] As a result, autologous grafting remains the gold standard for treating nonunions.

CONCLUSION

As a result of its excellent and cost-effective combination of biologic and mechanical properties, autologous bone graft continues to be an important tool in the management of certain bone defects or nonunions. Heterologous grafts lose some of their biologic properties through sterilization and synthetic bone substitutes have only osteoconductive properties if not combined with recombinant human growth factors or autograft. If heterologous or synthetic bone is combined with growth factors, these composite grafts may have equal biologic properties to autologous bone grafts, but further research is required to determine their efficacy and cost–benefit profile.

In clinical practice, the decision as to which type of autologous bone graft should be used must take into account whether the operative site needs metabolic activity (cancellous bone), stability (cortical bone), or both. If the autologous bone graft has to withstand compression and mechanical load, cortical bone may be a way to provide additional support. However, the considerable donor site morbidity has to be considered.

REFERENCES

1. Boyce T, Edwards J, Scarborough N. Allograft bone. The influence of processing on safety and performance. *Orthop Clin North Am*. 1999;30:571–581.
2. Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. *Injury*. 2005;36:S20–S27.
3. Lewandrowski KU, Gresser JD, Wise DL, et al. Bioresorbable bone graft substitutes of different osteoconductivities: a histologic evaluation of osteointegration of poly(propylene glycol-co-fumaric acid)-based cement implants in rats. *Biomaterials*. 2000;21:757–764.
4. Muschler GF, Negami S, Hyodo A, et al. Evaluation of collagen ceramic composite graft materials in a spinal fusion model. *Clin Orthop Relat Res*. 1996;339:250–260.
5. Van Heest A, Swiontkowski M. Bone-graft substitutes. *Lancet*. 1999;353:SI28–SI29.
6. Borrelli J Jr, Prickett WD, Ricci WM. Treatment of nonunions and osseous defects with bone graft and calcium sulfate. *Clin Orthop Relat Res*. 2003;411:245–254.
7. Freeland AE, Mutz SB. Posterior bone-grafting for infected ununited fracture of the tibia. *J Bone Joint Surg Am*. 1976;58:653–657.
8. Phieffer LS, Goulet JA. Delayed unions of the tibia. *J Bone Joint Surg Am*. 2006;88:206–216.
9. Babhulkar S, Pande K, Babhulkar S. Nonunion of the diaphysis of long bones. *Clin Orthop Relat Res*. 2005;431:50–56.
10. Bellabarba C, Ricci WM, Bolhofner BR. Results of indirect reduction and plating of femoral shaft nonunions after intramedullary nailing. *J Orthop Trauma*. 2001;15:254–263.
11. Sandhu HS, Grewal HS, Parvataneni H. Bone grafting for spinal fusion. *Orthop Clin North Am*. 1999;30:685–698.
12. Finkemeier CG, Chapman MW. Treatment of femoral diaphyseal nonunions. *Clin Orthop Relat Res*. 2002;398:223–234.
13. Ring D, Kloen P, Kadzielski J, et al. Locking compression plates for osteoporotic nonunions of the diaphyseal humerus. *Clin Orthop Relat Res*. 2004;425:50–54.
14. Cove JA, Lhowe DW, Jupiter JB, et al. The management of femoral diaphyseal nonunions. *J Orthop Trauma*. 1997;11:513–520.
15. Ueng SW, Wei FC, Shih CH. Management of femoral diaphyseal infected nonunion with antibiotic beads local therapy, external skeletal fixation, and staged bone grafting. *J Trauma*. 1999;46:97–103.
16. Biasibetti A, Aloj D, Di Gregorio G, et al. Mechanical and biological treatment of long bone non-unions. *Injury*. 2005;36:S45–S50.
17. Majors AK, Boehm CA, Nitto H, et al. Characterization of human bone marrow stromal cells with respect to osteoblastic differentiation. *J Orthop Res*. 1997;15:546–557.
18. Strates BS, Stock AJ, Connolly JF. Skeletal repair in the aged: a preliminary study in rabbits. *Am J Med Sci*. 1988;296:266–269.
19. Schmidmaier G, Herrmann S, Green J, et al. Quantitative assessment of growth factors in reaming aspirate, iliac crest, and platelet preparation. *Bone*. 2006;39:1156–1163.
20. Li H, Pujic Z, Xiao Y, et al. Identification of bone morphogenetic proteins 2 and 4 in commercial demineralized freeze-dried bone allograft preparations: pilot study. *Clin Implant Dent Relat Res*. 2000;2:110–117.
21. Burchardt H. Biology of bone transplantation. *Orthop Clin North Am*. 1987;18:187–196.
22. Day S, Ostrum R, Clinton R, et al. Bone injury, regeneration, and repair. In: Buckwalter J, Einhorn T, Simon S, eds. *Biology and Biomechanics of the Musculoskeletal System*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2000:388.
23. Khan SN, Cammisa FP Jr, Sandhu HS, et al. The biology of bone grafting. *J Am Acad Orthop Surg*. 2005;13:77–86.
24. Deleu J, Trueta J. Vascularisation of bone grafts in the anterior chamber of the eye. *J Bone Joint Surg. Br*. 1965;47:319–329.
25. Enneking WF, Burchardt H, Puhl JJ, et al. Physical and biological aspects of repair in dog cortical-bone transplants. *J Bone Joint Surg Am*. 1975;57:237–252.
26. Goldberg VM, Stevenson S, Shaffer JW, et al. Biological and physical properties of autogenous vascularized fibular grafts in dogs. *J Bone Joint Surg Am*. 1990;72:801–810.
27. Puranen J. Reorganization of fresh and preserved bone transplants. An experimental study in rabbits using tetracycline labelling. *Acta Orthop Scand*. 1966;92:Sl–S75.
28. Ashton BA, Allen TD, Howlett CR, et al. Formation of bone and cartilage by marrow stromal cells in diffusion chambers in vivo. *Clin Orthop Relat Res*. 1980;151:294–307.
29. Arrington ED, Smith WJ, Chambers HG, et al. Complications of iliac crest bone graft harvesting. *Clin Orthop Relat Res*. 1996;329:300–309.

30. Banwart JC, Asher MA, Hassanein RS. Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. *Spine*. 1995;20:1055–1060.
31. Kurz LT, Garfin SR, Booth RE Jr. Harvesting autogenous iliac bone grafts. A review of complications and techniques. *Spine*. 1989;14:1324–1331.
32. Ross N, Tacconi L, Miles JB. Heterotopic bone formation causing recurrent donor site pain following iliac crest bone harvesting. *Br J Neurosurg*. 2000;14:476–479.
33. Seiler JG III, Johnson J. Iliac crest autogenous bone grafting: donor site complications. *J South Orthop Assoc*. 2000;9:91–97.
34. Skaggs DL, Samuelson MA, Hale JM, et al. Complications of posterior iliac crest bone grafting in spine surgery in children. *Spine*. 2000;25: 2400–2402.
35. Younger EM, Chapman MW. Morbidity at bone graft donor sites. *J Orthop Trauma*. 1989;3:192–195.
36. Belthur MV, Conway JD, Jindal G, et al. Bone graft harvest using a new intramedullary system. *Clin Orthop Relat Res*. 2008;466:2973–2980.
37. Kobbe P, Tarkin IS, Frink M, et al. Voluminous bone graft harvesting of the femoral marrow cavity for autologous transplantation. An indication for the 'Reamer–Irrigator–Aspirator' (RIA) technique [in German]. *Unfallchirurg*. 2008;111:469–472.
38. Kobbe P, Tarkin IS, Pape HC. Use of the 'reamer irrigator aspirator' system for non-infected tibial non-union after failed iliac crest grafting. *Injury*. 2008;39:796–800.
39. Porter RM, Liu F, Pilapil C, et al. Osteogenic potential of reamer irrigator aspirator (RIA) aspirate collected from patients undergoing hip arthroplasty. *J Orthop Res*. 2008;27:42–49.
40. Tydings JD, Martino LJ, Kircher M, et al. The osteoinductive potential of intramedullary canal bone reamings. *Curr Surg*. 1986;43:121–124.
41. Tydings JD, Martino LJ, Kircher M, et al. Viability of intramedullary canal bone reamings for continued calcification. *Am J Surg*. 1987;153: 306–309.
42. Gregory P, Sanders R. The treatment of closed, unstable tibial shaft fractures with unreamed interlocking nails. *Clin Orthop Relat Res*. 1995; 315:48–55.
43. Krettek C, Schandelmaier P, Tscherne H. Nonreamed interlocking nailing of closed tibial fractures with severe soft tissue injury. *Clin Orthop Relat Res*. 1995;315:34–47.
44. Keating JF, O'Brien PJ, Blachut PA, et al. Locking intramedullary nailing with and without reaming for open fractures of the tibial shaft. A prospective, randomized study. *J Bone Joint Surg Am*. 1997;79: 334–341.
45. Malik MH, Harwood P, Diggle P, et al. Factors affecting rates of infection and nonunion in intramedullary nailing. *J Bone Joint Surg Br*. 2004;86: 556–560.
46. Furlong AJ, Giannoudis PV, Smith RM. Heterotopic ossification: a comparison between reamed and unreamed femoral nailing. *Injury*. 1997;28:9–14.
47. Iorio R, Healy WL. Heterotopic ossification after hip and knee arthroplasty: risk factors, prevention, and treatment. *J Am Acad Orthop Surg*. 2002;10:409–416.
48. Morrey BF, Adams RA, Cabanela ME. Comparison of heterotopic bone after anterolateral, transtrochanteric, and posterior approaches for total hip arthroplasty. *Clin Orthop Relat Res*. 1984;188:160–167.
49. Paley D, Young MC, Wiley AM, et al. Percutaneous bone marrow grafting of fractures and bony defects. An experimental study in rabbits. *Clin Orthop Relat Res*. 1986;208:300–312.
50. Bolano L, Kopta JA. The immunology of bone and cartilage transplantation. *Orthopedics*. 1991;14:987–996.
51. Horowitz MC, Friedlaender GE. Immunologic aspects of bone transplantation. A rationale for future studies. *Orthop Clin North Am*. 1987;18: 227–233.
52. Lane JM, Sandhu HS. Current approaches to experimental bone grafting. *Orthop Clin North Am*. 1987;18:213–225.
53. Reddi AH, Wientroub S, Muthukumaran N. Biologic principles of bone induction. *Orthop Clin North Am*. 1987;18:207–212.
54. Keating JF, McQueen MM. Substitutes for autologous bone graft in orthopaedic trauma. *J Bone Joint Surg Br*. 2001;83:3–8.
55. Palmer SH, Gibbons CL, Athanasou NA. The pathology of bone allograft. *J Bone Joint Surg Br*. 1999;81:333–335.
56. Pelker RR, Friedlaender GE. Biomechanical aspects of bone autografts and allografts. *Orthop Clin North Am*. 1987;18:235–239.
57. Alt V, Eicher A, Bitschnau A, et al. Cost–benefit analysis of the use of rhBMP-2 in open tibial fractures: savings from a health insurer's perspective [in German]. *Unfallchirurg*. 2006;109:463–470.
58. Garrison KR, Donell S, Ryder J, et al. Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess*. 2007;11:1–iv.