■ ANNOTATION

Bone grafts and their substitutes

Y. Fillingham, J. Jacobs

From Rush University Medical Center, Illinois, United States

The continual cycle of bone formation and resorption is carried out by osteoblasts, osteocytes, and osteoclasts under the direction of the bone-signaling pathway. In certain situations the host cycle of bone repair is insufficient and requires the assistance of bone grafts and their substitutes. The fundamental properties of a bone graft are osteoconduction, osteoinduction, osteogenesis, and structural support. Options for bone grafting include autogenous and allograft bone and the various isolated or combined substitutes of calcium sulphate, calcium phosphate, tricalcium phosphate, and coralline hydroxyapatite. Not all bone grafts will have the same properties. As a result, understanding the requirements of the clinical situation and specific properties of the various types of bone grafts is necessary to identify the ideal graft. We present a review of the bone repair process and properties of bone grafts and their substitutes to help guide the clinician in the decision making process.

Cite this article: ***Bone Joint J*** **2016;98-B(1 Suppl A):6–9.**

Bone is a dynamic organ with remarkable regenerative properties. However, bone homeostasis requires viable cells (osteoblasts, osteoclasts, and osteocytes), adequate vascularity, stability, the presence of growth factors and a matrix for growth. Unfortunately, there are often situations where one or more of these conditions are inadequate, and as surgeons we have to provide assistance to allow bone to heal. When the process of bone repair requires additional assistance, bone grafting is often used to provide an osteoconductive, osteoinductive, and/or osteogenic environment to promote bone healing and repair.

Key players of osseous homeostasis

The resorption and formation of bone is a delicate balance between osteoblasts, osteocytes, and osteoclasts. The regenerative activity of bone is such that the adult skeleton is replaced in its entirety every ten years. Osteocytes, which are considered to be mature osteoblasts, are derived from mesenchymal stem cells.[1] The primary role of an osteoblast is the deposition of bone osteoid matrix. As the osteoblast matures, it becomes ensheathed within the bone matrix and transforms into an osteocyte.[2] Osteocytes comprise more than 95% of bone cells.[1,2] Osteoclasts are large, multinucleate cells which are created from the fusion of multiple monocytes.[1] The primary role of osteoclasts within the process of bone repair and remodelling is the resorption of bone matrix through the production of proteolytic enzymes.[3]

Osteoblasts and osteocytes play a key role in the signaling pathway of bone through the secretion of two proteins: receptor activator of nuclear factor kappa-β ligand (RANKL) and osteoprotegerin (OPG). RANKL helps to promote the maturation of osteoclasts and upregulates the resorption of bone matrix by osteoclasts. OPG is an antagonist to RANKL; it behaves as a decoy receptor, binding and sequestering RANKL and preventing it from binding to the receptors expressed on the cell membranes of osteoclasts. Sclerostin, a glycoprotein which is also expressed by mature osteocytes, has recently been noted to be important in the regulation of bone mass.[1] Sclerostin is secreted in response to mechanical loading, inflammatory molecules (such as prostaglandin E2), and hormones (parathyroid hormone, gonadotropin-releasing hormone, and estrogen).[4-12] Sclerostin is another member of the bone-signaling pathway, which works as a negative regulator of bone mass by the down-regulation of osteoblasts.[13] Sclerostin has been implicated in osteoporosis-related fractures, failure of the osseointegration of implants, metastatic bone disease, and genetic diseases of bone.[1] Although osteoclasts play a critical role in osseous homeostasis, these cells merely react to stimuli in the bone-signalling pathway and do not actively provide regulation through the secretion of proteins or ligands.[1]

■ Y. Fillingham, MD, Orthopedic Surgery Resident
■ J. Jacobs, MD, Orthopedic Surgery Professor and Department Chair
Rush University Medical Center, 1611 West Harrison Street, Suite 300, 60612, Illinois, USA.

Correspondence should be sent to Dr Y. Fillingham; e-mail: yale.fillingham@gmail.com

doi:10.1302/0301-620X.98B1.36350 $2.00

Bone Joint J 2016;98-B(1 Suppl A):6–9.

Phases of bone repair

The repair of bone has been classified into three distinct phases: inflammatory, proliferative, and remodelling.[14] The inflammatory phase is controlled by a cascade of growth factors, which include transforming growth factor-β (TGF- β), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), interleukins, vascular endothelial growth factor (VEGF), and bone morphogenic proteins (BMPs). These factors, released in response to the osseous insult, aid the inward migration, recruitment, and proliferation of the mesenchymal stem cells which go on to differentiate into osteoblasts, chondrocytes, adipocytes, and endothelial cells.[14,15] The result of the inflammatory phase is the formation of a primitive callus. This callus is organised further during the proliferative, or fibroplasia, phase. During the proliferative phase, a periosteal response occurs, leading to the replacement of the primitive callus by immature woven bone through intramembranous or endochondral ossification.[16] During the final phase of bone repair, this irregular woven bone is converted into lamellar bone.[17] This involves replacement of the mineralised callus with mature mineralised bone and remodelling of the area of bone back to its original shape and size.[14] The final product of bone repair is an area of bone that has returned to its previous biomechanical state.[14]

Role of bone grafting

Bone grafting has been employed for many years by orthopaedic surgeons to assist with the process of bone repair, and is used across all subspecialties within orthopaedics. The complications of traumatic injuries such as delayed union, nonunion, and malunion will often require the use of bone grafts. Aside from trauma, bone grafts are used to fill osseous defects caused by tumours or as a result of periprosthetic osteolysis.

Many forms of bone graft are available, but they are classified into three broad categories: autogenous bone, allograft, and bone graft substitutes. Bone grafts differ in terms of their properties of osteoconduction, osteoinduction, osteogenesis, and structural support. As a result, in order to identify the ideal graft, surgeons should have an understanding of the requirements of the clinical situation and of the specific properties of the different types of bone graft.

Properties of bone grafts

Osteoconduction. The ability to provide an environment capable of hosting the indigenous mesenchymal stem cells, osteoblasts, and osteoclasts is essential for the function of bone graft. Osteoconduction is the process by which a graft acts as a scaffold, passively hosting the necessary cells.[18] Microscopically, the porous osteoconductive lattice of bone graft resembles the structure of cancellous bone.[19] All bone grafts provide some degree of osteoconductive scaffold. The bioceramic bone graft substitutes, such as calcium sulphate and calcium phosphate, behave exclusively as osteoconductive scaffolds.[20]

Osteoinduction. The concept of osteoinduction was first described by Urist in the discovery of BMP.[21] Osteoinduction has been defined as the process of recruitment, proliferation, and differentiation of host mesenchymal stem cells into chondroblasts and osteoblasts. Extensive research has identified BMPs (specifically BMP-2, -4, -6, -7, -9, and -14), FGF, PDGF, and VEGF as common growth factors involved in the osteoinductive process of new bone formation.[18,20]

Osteogenesis. In order for a bone graft to possess the property of osteogenesis, it must contain viable mesenchymal stem cells, osteoblasts, and osteocytes.[18] Osteogenic bone grafts have all the cellular elements, growth factors and scaffolding required to form new bone. The most widely used osteogenic bone graft is autogenous bone, which is commonly harvested from the iliac crest. Additionally, the decortication performed during a spinal fusion is considered to be an osteogenic process as it exposes cancellous bone that is rich in osteogenic cells. Bone marrow aspirate in combination with allograft has also been employed to provide osteogenesis while limiting the morbidity of iliac crest bone graft.[15,18]

Structural support. Under select conditions, bone grafts are required to provide structural support, as well as stimulating bone repair. When structural support is required, bone grafts such as cortical and vascularised bone grafts are effective options.

Autogenous and allograft bone

Autogenous grafts and allografts were among the first types of bone graft used and are still widely used today. Autogenous bone graft is considered the benchmark because it possesses all the properties required while retaining complete histocompatibility. It is osteoconductive, osteoinductive (owing to the presence of growth factors), and contains living osteogenic cells. Some forms of autogenous graft (for instance vascularised fibula grafts) can also provide structural support. However, autogenous grafts are in limited supply and are associated with high rates of donor site morbidity, which may lead to an increased inpatient stay and higher associated costs.[22] The major and minor complication rates of autogenous bone graft harvest have been reported at 8.6% and 20.6%, respectively.[23]

Cadaveric allograft bone is available in either cancellous or cortical forms, or as demineralised bone matrix (DBM). Allografts are primarily osteoconductive, while DBM is processed in such a way as to retain osteoinductive properties.[24] Cortical allografts (such as the strut grafts typically used in reconstruction of the femur in revision hip arthroplasty) can also provide structural support. While they have no osteogenic properties, allografts address several of the disadvantages of autogenous grafts in that they are available in large quantities, are not associated with donor site morbidity or the increased operative time involved in the harvesting of autogenous bone, and are relatively inexpensive.[20,24] However, allografts do not lead to such complete healing as observed with the use of autoge-

nous graft, and they carry the potential for the transmission of viruses and other infective agents.[20,24,25]

Bone graft substitutes

Calcium sulphate has been used as a bone graft material since 1892. Since then, the material properties of calcium sulphate have improved and newer bioceramics have been introduced as bone graft substitutes. Today there are four main types of bioceramic available: calcium sulphate, calcium phosphate, tricalcium phosphate, and coralline hydroxyapatite; composite bioceramics use a combination of these types to provide materials with improved properties.[20,22,26] Bone graft substitutes come in multiple forms ranging from pellets and solid blocks, to injectable and moldable putty. Bioceramics are neither osteogenic nor osteoinductive, but work by creating an osteoconductive scaffold to promote osteosynthesis.[22] However, bioceramics have the potential to eliminate many of the limitations and complications associated with the clinical use of autogenous and allograft bone, and research continues into improved bone graft substitutes.[27]

Properties of substitutes. While all bone graft substitutes work on similar principles, they vary in terms of mechanical properties and the rate at which they are re-absorbed. Calcium phosphate provides the highest degree of compressive strength and is therefore recommended for use in elevating the joint surface of tibial plateau fractures. Calcium sulphate has the fastest resorption, lasting between four and 12 weeks, while coralline hydroxyapatite is very slow with the ceramic form still seen on radiographs more than ten years after implantation.[20] Both calcium phosphate and tricalcium phosphate are considered slow to resorb. For calcium phosphate, resorption takes place over six months to ten years and for tricalcium phosphate, resorption occurs over six to 18 months.[20] Because of the varying degree of compressive strength and rates of resorption, engineers have attempted to optimise the characteristics of a bone graft substitute by creating composites comprised of various forms of the four basic types of bone graft substitutes.[22]

Clinical performance of bone graft substitutes. Whilst there is a great deal of literature relating to the clinical outcomes of bone graft substitutes, it is largely comprised of retrospective studies with few randomised controlled trials. Recently Kurien et al[26] performed a systematic review on the use of bone graft substitutes in orthopaedic practice. They attempted to review 59 bone graft substitutes manufactured by 17 companies, requesting each manufacturer provide all published evidence on their product.[26] After limiting the literature to clinical studies, only 22 bone graft substitutes with 96 articles were available for analysis.[26] The only bone graft substitutes with Level I evidence were Norian SRS (Synthes), Vitoss (Orthovita), Cortoss (Orthovita), and Alpha-BSM (Etex). The authors reviewed the literature regarding the use of bone graft substitutes in the setting of tibial plateau fractures, distal radius fractures, calcaneal fractures, ankle fusions, spinal surgery, nonunion surgery, and revision total hip arthroplasty (THA).[26] Two retrospective studies have been published on the use of coralline hydroxyapatite in the setting of revision THA; in both, it was used in combination with allograft.[28,29] Aulakh et al[28] compared the use of an allograft and Allogran-N mixture with allograft alone in impaction bone grafting and reported similar rates of implant survival at 13 years. McNamara et al[29] published a case series of acetabular reconstructions with a mixture of allograft and Apapore 60, and reported that 18% of patients had radiolucent lines in acetabular zones 1, 2, or 3 by one year following surgery.[29]

BMPs

BMP works to promote osteoinduction by binding to specific transmembrane receptors on mesenchymal stem cells, osteoblasts, and mature chondrocytes.[30] More than 20 BMPs have been described, all of which are members of the TGF-β superfamily of proteins (with the exception of BMP-1 which is a metalloproteinase).[20] Only six of the identified BMPs (BMP-2, -4, -6, -7, -9, -14) have demonstrated any meaningful osteogenic properties. Among those, only BMP-2 and BMP-7 also encourage neovascularisation.[20,31,32] Despite the availability of numerous BMPs, only BMP-2 and BMP-7 are approved by the United States Food and Drug Administration (FDA). The clinical uses of BMP-2 that have FDA approval include its use within a titanium-tapered cage for an anterior lumbar interbody fusion procedures, and in the acute setting of an open tibial fracture.[33] BMP-7 has received approval for long bone nonunion and revision posterior lumbar fusions under the FDA humanitarian device exception, as it has been demonstrated to be equivalent to autogenous bone grafting in the setting of tibial non-unions.[20,33]

Stem cells and tissue engineering

Stem cells have the potential to augment the performance of current bone graft substitutes and are the focus of a great deal of ongoing research. Bone marrow aspirate contains a diluted solution of mesenchymal stem cells and it may be possible to produce a stem cell concentrate from a sample of bone marrow by centrifugation.[34] Alternatively, a robust colony of osteogenic cells could be produced by culturing the cells found in bone marrow to increase the concentration of cells by up to 50 population doublings.[34,35] Tissue engineered bone grafts have been demonstrated to provide all the fundamental properties of an ideal bone graft *in vitro*; however, it has proven difficult to achieve vascularisation in grafts which are large enough for use in clinical applications.[35]

Future developments will focus on improvements of the material composition and vehicles for the delivery of BMPs, and are likely to involve increased use of stem cells. The ideal bone graft will have similar osteoconductive, osteoinductive and osteogenic properties as autogenous bone.

Author contributions:
Y. Fillingham: Literature review, Writing the paper.
J. Jacobs: Writing and editing the paper.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by A. Liddle.

This paper is based on a study which was presented at the 31st Annual Winter 2014 Current Concepts in Joint Replacement® meeting held in Orlando, Florida, 10th-13th December.

References

1. **Compton JT, Lee FY.** A review of osteocyte function and the emerging importance of sclerostin. *J Bone Joint Surg [Am]* 2014;96-A:1659–1668.
2. **Knothe Tate ML, Adamson JR, Tami AE, Bauer TW.** The osteocyte. *Int J Biochem Cell Biol* 2004;36:1–8.
3. **Ulstrup AK.** Biomechanical concepts of fracture healing in weight-bearing long bones. *Acta Orthop Belg* 2008;74:291–302.
4. **Atkins GJ, Rowe PS, Lim HP, et al.** Sclerostin is a locally acting regulator of late-osteoblast/preosteocyte differentiation and regulates mineralization through a MEPE-ASARM-dependent mechanism. *J Bone Miner Res* 2011;26:1425–1436.
5. **Genetos DC, Yellowley CE, Loots GG.** Prostaglandin E2 signals through PTGER2 to regulate sclerostin expression. *PLoS One* 2011;6:17772.
6. **Tian X, Jee WS, Li X, Paszty C, Ke HZ.** Sclerostin antibody increases bone mass by stimulating bone formation and inhibiting bone resorption in a hindlimb-immobilization rat model. *Bone* 2011;48:197–201.
7. **Drake MT, Srinivasan B, Mödder UI, et al.** Effects of parathyroid hormone treatment on circulating sclerostin levels in postmenopausal women. *J Clin Endocrinol Metab* 2010;95:5056–5062.
8. **Mödder UI, Clowes JA, Hoey K, et al.** Regulation of circulating sclerostin levels by sex steroids in women and in men. *J Bone Miner Res* 2011;26:27–34.
9. **Cornish J, Callon K, King A, Edgar S, Reid IR.** The effect of leukemia inhibitory factor on bone in vivo. *Endocrinology* 1993;132:1359–1366.
10. **Vincent C, Findlay DM, Welldon KJ, et al.** Pro-inflammatory cytokines TNF-related weak inducer of apoptosis (TWEAK) and TNFalpha induce the mitogen-activated protein kinase (MAPK)-dependent expression of sclerostin in human osteoblasts. *J Bone Miner Res* 2009;24:1434–1449.
11. **Walker EC, McGregor NE, Poulton IJ, et al.** Cardiotrophin-1 is an osteoclast-derived stimulus of bone formation required for normal bone remodeling. *J Bone Miner Res* 2008;23:2025–2032.
12. **Walker EC, McGregor NE, Poulton IJ, et al.** Oncostatin M promotes bone formation independently of resorption when signaling through leukemia inhibitory factor receptor in mice. *J Clin Invest* 2010;120:582–592.
13. **Lin C, Jiang X, Dai Z, et al.** Sclerostin mediates bone response to mechanical unloading through antagonizing Wnt/beta-catenin signaling. *J Bone Miner Res* 2009;24:1651–1661.
14. **Oryan A, Monazzah S, Bigham-Sadegh A.** Bone injury and fracture healing biology. *Biomed Environ Sci* 2015;28:57–71.
15. **Kwong FN, Harris MB.** Recent developments in the biology of fracture repair. *J Am Acad Orthop Surg* 2008;16:619–625.
16. **Goldhahn J, Féron JM, Kanis J, et al.** Implications for fracture healing of current and new osteoporosis treatments: an ESCEO consensus paper. *Calcif Tissue Int* 2012;90:343–353.
17. **Schindeler A, McDonald MM, Bokko P, Little DG.** Bone remodeling during fracture repair: the cellular picture. *Semin Cell Dev Biol* 2008;19:459–466.
18. **Khan SN, Cammisa FP Jr, Sandhu HS, et al.** The biology of bone grafting. *J Am Acad Orthop Surg* 2005;13:77–86.
19. **McKee MD.** Management of segmental bony defects: the role of osteoconductive orthobiologics. *J Am Acad Orthop Surg* 2006;14 (10 Spec No.):S163–S167.
20. **Roberts TT, Rosenbaum AJ.** Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing. *Organogenesis* 2012;8:114–124.
21. **Urist MR.** Bone: formation by autoinduction. *Science* 1965;150:893–899.
22. **Fillingham YA, Lenart BA, Gitelis S.** Function after injection of benign bone lesions with a bioceramic. *Clin Orthop Relat Res* 2012;470:2014–2020.
23. **Younger EM, Chapman MW.** Morbidity at bone graft donor sites. *J Orthop Trauma* 1989;3:192–195.
24. **Finkemeier CG.** Bone-grafting and bone-graft substitutes. *J Bone Joint Surg [Am]* 2002;84-A:454–464.
25. **De Long WG Jr, Einhorn TA, Koval K, et al.** Bone grafts and bone graft substitutes in orthopaedic trauma surgery. A critical analysis. *J Bone Joint Surg [Am]* 2007;89-A:649–658.
26. **Kurien T, Pearson RG, Scammell BE.** Bone graft substitutes currently available in orthopaedic practice: the evidence for their use. *Bone Joint J* 2013;95-B:583–597.
27. **Healy KE, Guldberg RE.** Bone tissue engineering. *J Musculoskelet Neuronal Interact* 2007;7:328–330.
28. **Aulakh TS, Jayasekera N, Kuiper JH, Richardson JB.** Long-term clinical outcomes following the use of synthetic hydroxyapatite and bone graft in impaction in revision hip arthroplasty. *Biomaterials* 2009;30:1732–1738.
29. **McNamara I, Deshpande S, Porteous M.** Impaction grafting of the acetabulum with a mixture of frozen, ground irradiated bone graft and porous synthetic bone substitute (Apapore 60). *J Bone Joint Surg [Br]* 2010;92-B:617–623.
30. **Kloen P, Di Paola M, Borens O, et al.** BMP signaling components are expressed in human fracture callus. *Bone* 2003;33:362–371.
31. **Even J, Eskander M, Kang J.** Bone morphogenetic protein in spine surgery: current and future uses. *J Am Acad Orthop Surg* 2012;20:547–552.
32. **Khan SN, Fraser JF, Sandhu HS, et al.** Use of osteopromotive growth factors, demineralized bone matrix, and ceramics to enhance spinal fusion. *J Am Acad Orthop Surg* 2005;13:129–137.
33. **Carreira AC, Alves GG, Zambuzzi WF, Sogayar MC, Granjeiro JM.** Bone Morphogenetic Proteins: structure, biological function and therapeutic applications. *Arch Biochem Biophys* 2014;561:64–73.
34. **Rosset P, Deschaseaux F, Layrolle P.** Cell therapy for bone repair. *Orthop Traumatol Surg Res* 2014;100 (suppl):S107–S112.
35. **Fröhlich M, Grayson WL, Wan LQ, et al.** Tissue engineered bone grafts: biological requirements, tissue culture and clinical relevance. *Curr Stem Cell Res Ther* 2008;3:254–264.