# Bone transplantation

*DC Rees, FS Haddad*

***Bony deficiency, particularly loss of bone stock associated with failed joint replacements or tumours, is a challenging problem in orthopaedic surgery. Bone transplantation techniques provide solutions that can be tailored to the clinical problem. However, the risks of bone transplantation are well documented and the biology of allograft incorporation remains unpredictable and poorly understood.***

Bone transplantation was one of the earliest methods of skeletal reconstruction and is now common in orthopaedic surgery. Tremendous advances have been made since 1688 when a Dutch surgeon, Job Van Meek'ren, rebuilt the injured skull of a soldier using a canine cranium. By 1908 Lexer had undertaken the first known series of cadaveric bone transplants and over half the grafts were still functional years later (Lexer, 1908).

In the USA over 200 000 surgical procedures involving bone transplantation are performed annually (Friedlaender, 1991). Bone is the second most transplanted tissue after transfused blood.

## BONE GRAFT PROPERTIES

A bone graft is any implanted material that promotes a bone healing response by providing osteogenic, osteoconductive or osteoinductive activity to the local environment.

An osteogenic material is one that contains viable living cells capable of differentiation into bone. The best sources are bone marrow and cancellous bone. An osteoconductive material is one that promotes bone apposition to its surface, functioning in part as a receptive matrix to facilitate enhanced bone formation. An osteoinductive material provides a biological stimulus to induce local or transplanted cells to enter a pathway of differentiation leading to mature osteoblasts. The process is mediated by a host of peptide growth factors including transforming growth factor and bone morphogenetic protein (BMP).

## BONE AUTOGRAFT

Bone autograft from the patient's own donor site is the gold standard method of bone grafting and provides living, bone-producing cells for osteogenesis. Transplanted bone also behaves as an osteoconductive scaffold and results in osteoinductive transformation of cells into osteoblasts. Problems with autograft use include harvest site morbidity such as pain, fracture and deep infection (Banwart et al, 1995). The fact that supplies are limited is also a significant drawback (*Table 1*).

## BONE ALLOGRAFT

Bone allograft is any form of bone transplanted between two genetically different individuals of the same species. Allograft use eliminates harvest site morbidity and potentially offers an almost unlimited source of graft material. Donor bone is obtained from living (primary joint replacement patients) and cadaveric donors.

Bone allograft does not impart osteogenesis but allows for osteoconduction. Limited amounts of growth factors are still present within bone allograft producing a potentially osteoinductive matrix. Bone allograft is available in a vast array of physical states including powder, paste, gels, chips, strips, blocks and massive allografts (e.g. whole femur).

In practical terms, bone allograft can be divided into two main groups: structural and morselized graft. Structural allograft comprises blocks or struts of bone that can be fixed or wired onto defects and can act as bulk supports to prostheses or deficient host bone. Usually cortical in nature they have limited biological activity but do offer mechanical properties similar to the host tissue and provide grafts with appropriate geometry for particular applications.

Morselized allograft consists of small bone pieces that can be sprinkled or impacted into a skeletal defect. Usually cancellous in nature, minimal structural support is conferred by such

**TABLE 1. Differences between allograft and autograft**

| | Autograft | Allograft |
|---|---|---|
| Immunogenicity | – | + |
| Osteogenesis | + | – |
| Osteoconduction | + | + |
| Osteoinduction | ++ | +/– |
| Union | Rapid | Slow |
| Donor site | Morbidity | – |
| Quantity | Limited | No limit |

**Mr DC Rees** is Specialist Registrar in Orthopaedic Surgery, Royal National Orthopaedic Hospital, Stanmore, Middlesex, and **Mr FS Haddad** is Consultant Orthopaedic Surgeon, University College London Hospitals, London W1N 8AA

*Correspondence to: Mr FS Haddad*

allograft. However, when remodelling is achieved grafts do show rapid development of reasonable biomechanical properties.

## BASIC FUNCTIONS OF BONE ALLOGRAFT

The main use of transplanted bone in orthopaedic surgery today is replacement of extensive bone loss associated with failed joint replacement or tumour surgery. From one bone bank over a 10-year period, 83% of all bone graft was used in revision arthroplasties, 12% in fracture treatment, 2% in tumour surgery and 3% in other orthopaedic procedures (unpublished data, Tampere Bone Bank, 1998).

## COMPLICATIONS OF BONE TRANSPLANTATION

Transmission of infection from donor to recipient is the most serious complication of bone transplantation. The incidence of bacterial infection after massive allograft implantation has been reported to be up to 14% (Dick and Strauch, 1994). Wound and soft tissue complications are believed to be major predisposing risk factors but the role of bone allograft as a vector for bacterial organisms remains uncertain.

Viral infections of major concern are hepatitis B and C and the human immunodeficiency virus (HIV). The risk of viral transmission associated with bone allograft screened for hepatitis B is currently estimated at 1 in 63 000 and for hepatitis C is 1 in 100 000, which are both similar to the risks seen with blood transfusion (Friedlaender, 2000). For HIV transmission the estimated risk lies at about 1 in 1.5 million (Buck et al, 1989).

Antigenic incompatibility and its subsequent unwanted immune reaction remain a significant but poorly understood problem. The difference in donors with respect to the biological efficacy of the matrix exposes both patients and surgeons to undesirable variations in performance that could ultimately affect the clinical results of the graft itself. For this reason, the host incorporation of allograft remains somewhat unpredictable.

Fracture is a significant complication post implantation (Mankin et al, 1992). This is seen most often in structural allografts that are effectively alloimplants because they do not incorporate fully. It was often seen when holes were drilled in the allografts, which is no longer common practice. The absence of stable union at the graft–host interface is also a source of failure in many experimental graft procedures (Vander Griend, 1994).

## DONOR SCREENING

Rigorous screening of donors is critical in the use and banking of bone allograft. Consent is required from both the donor and the recipient. The screening process evaluates risk based on donor lifestyle, interviews with the donor's family and physical examination.

Exclusion criteria include HIV, hepatitis, significant past or present infections, steroid use, malignancy, metabolic bone or collagen disorders and any condition of altered immunity (Friedlaender, 2000). Serological investigations include tests for HIV antibodies, hepatitis B surface antigen and hepatitis C antibody. HLA tissue typing is not routinely performed.

Microbiological swabs are also taken from transplanted bone which must be free from significant bacterial disease.

## PROCESSING OF BONE ALLOGRAFT

Bone allografts can be used as fresh, deep frozen or freeze-dried grafts, or in a demineralized form.

Fresh allograft requires no preservation and potentially offers viable articular cartilage for transplantation, which should be undertaken within hours of death of the donor. Fresh allograft is associated with the most intense immune response especially if a significant genetic disparity between host and recipient exists (Stevenson et al, 1991). Rhesus matching is particularly important in young women to avoid rhesus sensitization in those of childbearing age.

Deep freezing is the most common method of preserving transplanted bone. Freezer temperatures are kept at –80°C and bone can be stored for up to 5 years. Freezing decreases the graft's immunogenicity and confers little change to structural integrity (Davy, 1999). Disadvantages include possible retardation of incorporation by the host and a decrease in cartilage viability.

Freeze-dried allografts have their moisture content extracted by using low temperature and pressure treatments. This makes bone more brittle and raises concern over its mechanical strength (Davy, 1999). Freeze-dried allografts demonstrate the lowest immunogenicity but freeze-drying cannot preserve cartilage.

Transplanted bone can be processed with hydrochloric acid which consumes the bone matrix releasing peptide growth factors. Such demineralized bone can be in the form of a putty or paste. It is a potent osteoinducer but has markedly reduced biomechanical strength.

## STERILIZATION OF BONE ALLOGRAFT

Transplanted bone must be clean, sterile and free from infection with preservation of its natural biological and biomechanical properties.

Aseptic processing requires the graft to be handled in a sterile manner in a controlled envi-

ronment. It involves thorough debridement and cleansing of grafts and the use of antibiotics and treatment solutions.

Terminal sterilization relies on chemicals, gamma-irradiation, gas or autoclaving to achieve sterility. Gamma irradiation is widely used and a dose of approximately 40 kGy is necessary to sterilize HIV in bone. However, adverse effects on graft biomechanics have been reported (Godette et al, 1996).

## BIOLOGY OF BONE ALLOGRAFT INCORPORATION

Graft incorporation is defined as the biological interaction between the graft material and the host resulting in bone formation providing adequate mechanical properties. Bone allograft does not contribute viable donor cells to the healing process but provides the potential for immunological reaction (*Table 2*).

There are three potential histological outcomes following bone transplantation (Bos et al, 1983). Most commonly, graft is 'reluctantly' accepted in spite of some genetic incompatibility, which manifests as limited remodelling and modest periosteal new bone formation. Such alloimplants generally proceed to a satisfactory clinical outcome. In the remaining cases, the graft is either 'fully' accepted as in the case of an autograft or it is rejected because of strong genetic disparity with ensuing resorption.

Haematoma formation, rich in growth factors, is the first process observed after bone transplantation. An early inflammatory phase is then seen largely at the periphery of the graft, peaking after about 14 days (Bonfiglio and Jeter, 1972). Lymphocytes continue to proliferate and over the next 8 weeks the allograft is enveloped by a fibrovascular stroma. This permits osteogenic precursor cells to be delivered to the graft. The result is one of resorption around the periphery of the bone graft with a significant decrease in graft mass and an increase in its porosity (Friedlaender, 1987).

Remodelling commences as the graft is revascularized and new bone formation is the end result. On average, union at the host–allograft junction occurs at about 12 months post transplantation (Enneking and Campanacci, 2001).

Structural allografts have very limited biological activity and hence function largely as alloimplants. As with all allografts an inflammatory response ensues after implantation and this provides the influx of pluripotential cells required for new bone formation. Cortical bone processed by modern methods comprises little protein and very few intact cells and the initial trauma-induced inflammatory response usually subsides only days after implantation (Stevenson, 1999). Penetration of large cortical allografts by blood vessels and subsequent substitution with host bone occurs to a very limited degree and only superficially (Enneking and Mindell, 1991).

Morselized allografts are typically characterized by a lattice-like composition permitting potential vascular ingrowth, and so resorption is not a prerequisite for revascularization. Incorporation of morselized allograft is more rapid than that of structural allograft and closely follows the stages of autologous bone graft. Morselized allograft displays poor initial mechanical properties but, as mineralization proceeds, compressive forces can be resisted. It has been successfully used to fill cavitary bony defects where a well-vascularized prepared surface can be regarded as the ideal host environment.

## IMMUNOLOGY OF BONE ALLOGRAFTING

Bone allografts are subject to many of the same principles of transplantation as any other organ. One significant difference remains in the diffi-

**TABLE 2.**
**The properties of bone graft materials**

| Type | Osteogenesis | Osteoconduction | Osteoinduction | Mechanical strength | Vascularity |
|---|---|---|---|---|---|
| Bone marrow | ++ | +/– | + | – | – |
| Cancellous | ++ | ++ | + | + | – |
| Cortical | + | + | + | ++ (early) | – |
| Vascularized | ++ | +++ | + | ++ | ++ |
| Cancellous allograft | – | ++ | + | + | – |
| Cortical allograft | – | ++ | + | ++ | – |
| Demineralized allograft | – | ++ | ++ | – | – |
| Bone morphogenetic proteins | – | – | +++ | – | – |
| Bone graft substitutes | – | ++ | + | +/++ | – |

culty in identifying and quantifying the presence of rejection – no clear clinical or laboratory diagnostic test exists.

Fresh bone allograft will invoke a significant host immune reaction which manifests as graft resorption or at best delayed incorporation. A large bone allograft may provide a slow but continuous release of antigens over a period of several years resulting in a chronic inflammatory response (Stevenson and Horowitz, 1992). The factors determining whether an inflammatory response ceases or insidiously continues remain unclear.

Graft cell surface antigens stimulate a specific response activating macrophages and T-lymphocytes in the host. These cells secrete cytokines, such as interleukin-1 and tumour necrosis factor, controlling both osteoclast and osteoblast recruitment. Host response to allograft implantation is predominantly a cell-mediated one but it has been shown that a humeral response also contributes (Friedlaender et al, 1976).

A fine balance between new bone formation and resorption exists and this must be maintained if revascularization and graft substitution is to follow with no significant loss of mechanical strength.

The effect of histocompatibility matching has been reported (Bos et al, 1983). A strong immune response was elicited with a major histocompatibility mismatch between host and donor and conversely there was an almost undetectable response when recipient and donor were closely related. However, no effect on the biological process of graft incorporation was demonstrated between the two contrasting groups.

The precise nature of the relationship between graft incorporation and antigen presentation and its sequelae is yet to be fully determined.

## EXAMPLES OF BONE TRANSPLANTATION

Bone transplantation mainly occurs in the field of revision joint replacement where the major physiological enemy is osteolysis. This occurs as a result of small debris particles from a prosthesis causing bone to weaken and resorb.

Cortical strut allografts can be effectively used to supplement proximal femoral loss with high rates of host–graft union being reported (Emerson et al, 1992). Grafts are secured with cerclage wires or cables to the host and are replaced completely with host bone in time.

Allograft–implant composites are receiving favourable reports as experience in their use increases. Femoral prostheses have been cemented into proximal femoral allografts and host femora following failed hip replacement with significant functional improvement (Haddad et al, 2000). However, the authors no longer favour cementing the prosthesis into distal host bone as the risk of non-union may be increased and in the absence of cement, the allograft has a greater potential to share load once union has been achieved.

Whole distal femoral and proximal tibial allografts in combination with prosthetic implants have also been shown to offer promising early clinical outcomes in revision knee surgery (Mnaymneh et al, 1990).

Morselized bone allograft is used to reconstruct segmental or cavitary acetabular defects (Haddad et al, 1999). Allograft is impacted into the bony defect and acetabulum to a depth allowing screw fixation of a metallic support ring. A polyethylene acetabular component can then be cemented into the construct. Good bony incorporation with stable acetabular components has been demonstrated at mean follow up of over 5 years.

In cases of a severely deficient acetabulum, bony defects have been reconstructed using a whole acetabular allograft obtained by shaping a hemipelvis allograft to fit the individual defect (Bradford and Paprosky, 1995).

Massive cadaveric bone transplantation is used for treatment of patients with primary bone tumours. Experience of more than 660 massive allograft transplants has been published (Mankin et al, 1992). The overall success rate was reported to be approximately 80%, with wear of articular surfaces noted at about 5 years post surgery.

The potential for bone transplantation is vast. Further examples of bone allograft use include cylindrical buttons in rotator cuff repair, threaded dowels in anterior lumbar interbody fusion, interference screws in anterior cruciate ligament reconstruction and custom-made wedges in high tibial osteotomy procedures.

## BONE MORPHOGENETIC PROTEIN

Use of growth factors as agents to promote bone growth and enhance the incorporation of transplanted bone is a rapidly expanding field of research. BMP is a naturally occurring protein that triggers primitive cells in the bloodstream to differentiate into bone cells.

Through recombinant DNA technology such proteins can be isolated and sequenced. One such protein is recombinant osteogenic protein-1 (OP-1). Implantation of OP-1 has been evaluated in the treatment of segmental defects in canine ulnae (Salkfeld et al, 2001). Results demonstrated improved healing in radiological, mechanical and histological studies. The authors conclude that major bone defects could be treated with allograft bone combined with OP-1.

The reconstruction of femoral fracture non-union using purified BMP implanted in human femora has been evaluated (Johnson and Urist, 2000). Such a composite inductive allograft was reported to be an excellent structural and delivery system inducing host bone formation and implant remodelling allowing salvage of resistant femoral non-union.

Recombinant human BMP has been shown to accelerate and indeed strengthen spinal fusions in rabbits (Virginia Spine Institute, 2001). All rabbits that received BMP demonstrated spinal fusion within 4 weeks compared to only 42% of the rabbits implanted with autogenous bone.

A human clinical trial examining use of a recombinant BMP/collagen sponge composite in anterior lumbar interbody fusion has been completed (Hendricks, 1999). Results indicated significant amounts of new bone formation within the implanted titanium cages. Other peptides such as basic fibroblast growth factor (bFGF) have also been studied. Bone allograft incorporation in rat tibiae was significantly increased in rats receiving allografts pre-treated with bFGF (Wang and Aspenberg, 1994).

## CONCLUSION

With the number of bone transplantation operations increasing every year, further understanding of the host immune reaction and its relationship with bone allograft incorporation and clinical outcome will ensue. Although complications are not infrequent, bone transplantation is generally applied in complex situations and specialist centres are confident that these problems will be overcome as global experience of bone transplantation increases. Allograft implantation combined with recombinant BMP and other growth factors and matrices will undoubtedly continue to expand as a powerful tool in future bony reconstruction. HM

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Banwart JC, Asher MA, Hassanein RS (1995) Iliac crest bone graft harvest donor site morbidity. *Spine* **20**(9): 1055–60

Bonfiglio M, Jeter WS (1972) Immunological responses to bone. *Clin Orthop* **87:** 19–27

Bos GD, Goldberg VM, Zika JM, Heiple KG, Powell AE (1983) Immune responses of rats to frozen bone allografts. *J Bone Joint Surg* **65-A:** 239–46

Bradford MS, Paprosky WG (1995) Total acetabular transplant allograft reconstruction of the severely deficient acetabulum. http://orthomerica.com/reviews/totacet.htm (accessed 2 July 2002)

Buck BE, Malinin TI, Brown MD (1989) Bone transplantation and human immunodeficiency virus: an estimate of the risk of acquired immunodeficiency syndrome (AIDS). *Clin Orthop* **240:** 129–36

Davy DT (1999) Biomechanical issues in bone transplantation. *Orthop Clin North America* **30**(4): 553–63

Dick HM, Strauch RJ (1994) Infection of massive bone allografts. *Clin Orthop* **306:** 46–53

Emerson RH, Malinin TI, Cuellar AD, Head AC, Peters AC (1992) Cortical strut allografts in the reconstruction of the femur in revision total hip arthroplasty. A basic science and clinical study. *Clin Orthop* **285:** 35–44

Enneking WF, Mindell ER (1991) Observations on massive retrieved human allografts. *J Bone Joint Surg* **73-A:** 1123–42

Enneking WF, Campanacci DA (2001) Retrieved human allografts: A clinicopathological study. *J Bone Joint Surg* **83-A:** 971–86

Friedlaender GE, Strong DM, Sell KW (1976) Studies on the antigenicity of bone: 1. Freeze dried and deep-frozen bone allografts in rabbits. *J Bone Joint Surg* **58-A:** 854–8

Friedlaender GE (1987) Bone grafts. *J Bone Joint Surg* **69-A:** 786–90

Friedlaender GE (1991) Bone allografts: the biological consequences of immunological events. *J Bone Joint Surg* **73-A:** 1119–22

Friedlaender GE (2000) Appropriate screening for prevention of infection by musculoskeletal allografts. *AAOS Instructional Course Lectures* **49:** 615–9

Godette GA, Kopta JA, Egle DM (1996) Biomechanical effects of gamma irradiation on fresh frozen allografts in vivo. *Orthopedics* **19:** 649–53

Haddad FS, Shergill N, Muirhead-Allwood SK (1999) Acetabular reconstruction with morcelized allograft and ring support: a medium-term review. *J Arthroplasty* **14**(7): 788–95

Haddad FS, Garbuz DS, Masri BA, Duncan CP (2000) Structural proximal femoral allografts for failed total hip replacements. *J Bone Joint Surg* **82-B:** 830–6

Hendricks RL (1999) Bone morphogenetic protein. http://csosortho.com/safety/hendricksbmp.html (accessed 2 July 2002)

Johnson EE, Urist MR (2000) Human bone morphogenetic protein allografting for reconstruction of femoral nonunion. *Orthop Clin North America* **371:** 61–74

Lexer E (1908) Substitution of whole or half joints from freshly amputated extremities by free plastic operations. *Surg Gynecol Obstet* **6:** 601–7

Mankin HJ, Springfield DS, Gebhardt MC, Tomford WW (1992) Current status of allografting for bone tumours. *Orthopaedics* **15**(10): 1147–54

Mnaymneh W, Emerson RH, Borja F, Head WC, Malinin TI (1990) Massive allografts in salvage revisions of failed total knee arthroplasty. *Clin Orthop* **260:** 144–53

Salkfeld SL, Patron LP, Barrack RL, Cook SD (2001) The effect of osteogenic protein-1 on the healing of segmental bone defects treated with autograft or allograft bone. *J Bone Joint Surg* **83-A:** 803–16

Stevenson S, Li XQ, Martin B (1991) The fate of cancellous and cortical bone after transplantation of fresh and frozen tissue-antigen-matched and mismatched osteochondral allografts in dogs. *J Bone Joint Surg* **73-A:** 1143–56

Stevenson S, Horowitz M (1992) The response to bone allografts. *J Bone Joint Surg* **74-A:** 939–50

Stevenson S (1999) Biology of bone grafts. *Orthop Clin North Am* **30**(4): 543–52

Vander Griend RA (1994) The effect of internal fixation on the healing of large allografts. *J Bone Joint Surg* **76-A:** 657–63

Virginia Spine Institute (2001) Bone morphogenic protein. http://www.spinemd.com/bmp.htm (accessed 13 March 2003)

Wang JS, Aspenberg P (1994) Basic fibroblast growth factor increases allograft incorporation. Bone chamber study in rats. *Acta Orthop Scand* **65**(1): 27–31


## KEY POINTS

- Bone transplantation is widely used in reconstructive orthopaedic surgery especially in the treatment of failed joint replacements.
- Bone transplantation is associated with a number of complications, infection being the most serious.
- The incorporation of bone graft depends on the mechanical and biological interaction between the graft and the host.
- The relationship between bone graft incorporation and histocompatibility mismatching remains poorly understood.
- The use of bone transplantation with recombinant bone morphogenetic protein technology has already proven successful in the treatment of major bone defects.