

ORIGINAL ARTICLE

G. O. Hofmann · M. H. Kirschner · T. Wangemann
C. Falk · W. Mempel · C. Hammer

Infections and immunological hazards of allogeneic bone transplantation

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Abstract Allogeneic transplantation of human cancellous and cortical bone is a controversially discussed concept in trauma and orthopaedic surgery. Biological and immunological arguments support transplantation of autologous material whenever this is technically possible. On the other hand, synthetic alloplastic materials for bone substitution are available free of immunological and hygienic hazards. In this context the value of allogeneic bone grafts is discussed, especially considering the problem of AIDS. If autologous corticospongiuous bone is to be used its supply is limited. On the other hand, alloplastic synthetic artificial bone does not meet all the requirements demanded for substitution of large osseous defects up to now. The problems of geometric and mechanical stability of these alloplastic materials still remain. Therefore, no alternative to allografting of large, stable, corticospongiuous fragments exists in some cases. Bone transplantation is performed without vital indication in nearly every case. Thus an optimum of hygienic security has to be claimed for recipients of allogeneic bone. The "Munich model" for bone transplantation is presented and discussed.

Introduction

Optimal reconstruction of human skeletal defects is a major topic in orthopaedic surgery. To fulfill these requirements different technical implants and biological transplants are employed.

Autologous and allogeneic transplantations of bone were already being performed in the last century [9, 27, 44]. Today bone grafting is an essential element of treatment of fractures and reconstructive surgery [2, 16, 21, 39]. Some 15% of all operations for reconstructive surgery requires bone transplantations [7]. Yet each individual case demands careful consideration of the indications for autologous or allogeneic transplantation. Autologous spongiosa should be used for transplantation whenever possible, but in certain cases there is no alternative allografting [22]. The importance of spongiuous and cortical bone allografting increases with the size of the defects to be reconstructed [2, 6, 39]. It should be mentioned that allogeneic spongiosa also offers distinct advantages to the patient:

1. There is nearly no limitation to the availability of allogeneic bone, although in practice allogeneic bone procurement may be associated with considerable difficulties, for example, a lack of donors or of consent for bone explantation.
2. If allogeneic spongiosa is used, there is no need for a second operation. Complications like infection, pain or painful scars at the site of autologous bone procurement may be avoided [1, 21]. The additional morbidity of patients in whom autologous bone procurement is performed is about 8% according to our experience.
3. Autologous spongiosa as biologically valuable tissue should be reserved for difficult operative readjustments. This autologous spongiosa is particularly useful for the treatment of large bony defects after posttraumatic osteitis. Therefore, careful consideration should precede the use of autologous spongiosa, especially in multiple trauma patients.

G. O. Hofmann (✉) · M. H. Kirschner
Chirurgische Klinik und Poliklinik
der Ludwig-Maximilians-Universität, Klinikum Großhadern,
Marchioninistrasse 15, D-81366 München, Germany

W. Mempel
Transfusionszentrum, Medizinische Klinik III
der Ludwig-Maximilians-Universität,
Klinikum Großhadern, München, Germany

T. Wangemann · C. Falk · C. Hammer
Institut für Chirurgische Forschung
der Ludwig-Maximilians-Universität,
München, Germany



Fig. 1a-e Allogeneic intercalary bone graft in a posttraumatic defect, Oct. 1985 (femoral stem fracture occasioned during a traffic accident; **a**). Primary osteosynthesis using a large DC-AO plate. Development of a postoperative osteitis. After five revisions with finally removal of all metal and sequester temporary fixation with a fixateur externe one and a half years later (**b**). Consolidation of the fracture with a shortening of the left femur of 9 cm. Femoral lengthening by employing an intercalary allogeneic graft (**c**). Osseous consolidation 2 years later (**d**): three-dimensional CT-scan visualisation of the osseous transplantation site after final osseous remodeling (**e**)

Fig. 2a-c 48-year-old patient with chondrosarcoma (grade 1) of the left femur after biopsy and histological confirmation (**a**). Complete resection of all tumourous parts of the femur, intercalary allogeneic bone graft of 20 cm length, and osteosynthesis using intramedullary nailing and additional plating with the DCS system (**b**). Actual X-ray of the left femur 8 months later at follow-up (**c**)

Fig. 3a, b 61-year-old patient with aseptic loosening of the acetabular cup with material breakdown 10 years following total hip arthroplasty (THA; **a**). Reconstruction with a cementless THA system using huge allogeneic bone blocks for acetabular plastic (**b**)



Indications and contraindications

Indications

According to our experience [18–20], the following three different groups of diagnoses provide good indications for allogeneic bone transplantation:

1. Traumatic or post-traumatic conditions (Fig. 1):
 - Osteosyntheses of closed fractures with large osseous defects
 - non-infected non-unions
 - residual defects following post-traumatic osteitis
2. Tumour surgery of the skeleton (Fig. 2):
 - defects following resection of bone tumours
 - large aneurysmatic bone cysts
3. Revision endoprosthesis and correction osteotomies (Fig. 3):
 - aseptic loosening of acetabular cup or femoral stem following total joint arthroplasty
 - acetabular defects following total hip arthroplasty
 - vertebral fusion procedures
 - corrective osteotomies of diaphyseal bone

Contraindications

On the other hand, there are some clear contraindications for allogeneic bone grafting:

1. Acute surgical treatment of open fractures
2. Closed fractures combined with severe soft-tissue damage must not be performed with allogeneic spongiosa, because of the higher risk of infection following transplantation into infected areas

The use of allogeneic spongiosa in the surgical treatment of atrophic non-unions and reconstruction of osseous defects following burned-out-osteitis is a very controversial issue [20, 22]. Transplantation of allogeneic spongiosa into subchondral bone defects is also a subject of dispute [9]. Whenever possible, autologous material should be employed in those situations.

Biological aspects of bone transplantation

The biological value of an allogeneic bone transplantation depends on donor-specific and recipient-specific parameters. A stable osteosynthesis is of the utmost importance for osseous consolidation of the allogeneic transplanted bone. Immunosuppression can improve the acceptance of the bone transplant. This has been demonstrated in animal experiments [1, 32]. Acceptance and consolidation of the allograft occur optimally between the 12th and 22nd week following transplantation [8]. The incorporation of spongiosa takes less time than the acceptance of corticospongiuous fragments [8]. The metabolic and nutritive situation

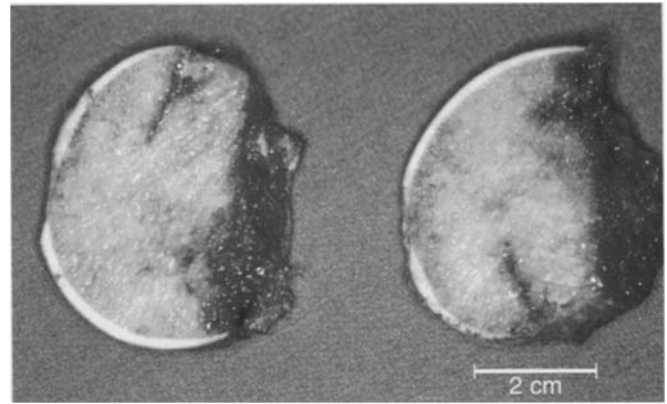


Fig. 4 Resected femoral head following THA. Fatty degeneration of the bone in this 69-year-old patient provides only a poor bone substitute material

of an allograft is superior in a vascularized bone allograft compared with the situation without vascular flap [1, 38]. Up to now all these experiences are derived from different experimental animal systems. With human grafts there is still a lack of experience.

Concerning human bone allografts, different sources for the transplant may be employed.

1. Total hip arthroplasty provides resected femoral heads mostly from older patients. Due to osteoporosis and fatty degeneration, this group of donors may not represent an optimal source of bone from the biological viewpoint (Fig. 4). Although no linear correlation exists between advanced age of the donor and decreased osteoconductive capacity of the allograft [3, 4, 12, 20], femoral heads are not able to fulfill geometric demands in every case of bone transplantation (e.g. tumour surgery of the spine). In the case of an unknown pathological fracture, the transplantation of malignant tumour cells within the femoral head cannot be excluded with absolute certainty in a group of old patients [31].

2. Cadaver bone material from the morgue should be excluded from transplantation due to insufficient serological tests and doubtful hygienic conditions [14, 34–36]. Regarding serological testing, non-heart-beating donors cannot provide organs for transplantation. Therefore, only combined organ and tissue procurement allows for a second serological testing of organ recipients while the tissue is still preservable. Concerning hygienic conditions, it is highly questionable whether bone material of a non-heart-beating donor is still sterile even after just a short conservation time of the cadaver at 4°C [42]. The time interval between cardiac arrest and subsequent bacterial contamination of the different anatomical cavities and topic sites is a highly controversial topic.

3. Amputated limbs provide no biologically valuable bone, because elective amputations are usually the result of severe circulatory problems of the lower limbs. The pre-existing vascular disease may be responsible for essential morphological changes in those tissues.

4. Cortical and cancellous human bone used for transplantation in our trauma centre is explanted from multi-organ donors offered to the transplantation unit of the University of Munich. The bone grafts are taken after the explantation of the heart, lung, liver kidneys and pancreas. The age limitations for the donors are: 15 to 45 years for osteochondral transplants, 15 to 55 years for non-osteochondral transplants. Immediately after the explantation of the parenchymal organs, cortical and cancellous bone is taken within half an hour following cardiac arrest. Explantation is performed under the highly aseptic conditions usually employed in bone and joint surgery [36]. Microbiological swabs are taken from all the explantation sites. Histological examination of a small piece of bone should exclude a plasmocytoma. All surrounding tissues of explanted bones are removed. The cryopreservation of the osseous grafts is performed using a special refrigerator at -80°C .

Hygienic aspects of bone allografting

The recipient of cortical and cancellous bone material is at risk of infectious hazards in the same way as a recipient of parenchymal organs, blood or blood derivatives, or bone marrow [4, 6, 7, 11, 13–15, 17, 23, 26, 28–30, 33–37, 40, 41, 43, 46, 47]. Confronted with the problem of AIDS infections, this is of great importance in connection with bone transplantation [10, 33–36, 40] (Fig. 5). The minimal risk to blood recipient of infection from a HIV-positive blood donor with one single transfusion is estimated at 66% [45]. In the literature there is an increasing number of reports concerning HIV seroconversion, AIDS infection and the occurrence of ARC (AIDS-related complex) following the transplantation of organs, tissue, bone marrow, blood and blood derivatives [4, 11–13, 17, 26, 28–30, 37, 43, 46, 47]. Meanwhile, cases of an AIDS infection following bone transplantation have been reported [12, 40]. Three and a half years following allogeneic bone transplantation from a hospital's bone-bank in the course of surgical correction of a progressive idiopathic scoliosis, the patient developed AIDS. All other infection modes could be excluded.

In 1992 Simonds et al. [40] reported about a case of procurement (four organs, 44 tissues) from a false HIV-negative-tested 22-year-old donor which resulted in the transmission of HIV to the four organ recipients (two kidneys, heart, liver) and to three bone recipients. The long incubation time between HIV acquisition and seroconversion seems to be the central problem for risk limitation [33–36]. The exclusion of all potential donors of organs and tissues with false-negative HIV screening and no symptoms of AIDS or ARC is the diagnostic challenge of the future. On average, an HIV-infected person becomes seropositive 3–4 weeks following contamination (range 2–12 weeks) [6, 33]. During this period the detection of HIV antibodies (ELISA) offers negative results. Using HIV antigen detection a possible infection could already be demonstrated 4 days following contamination [6].

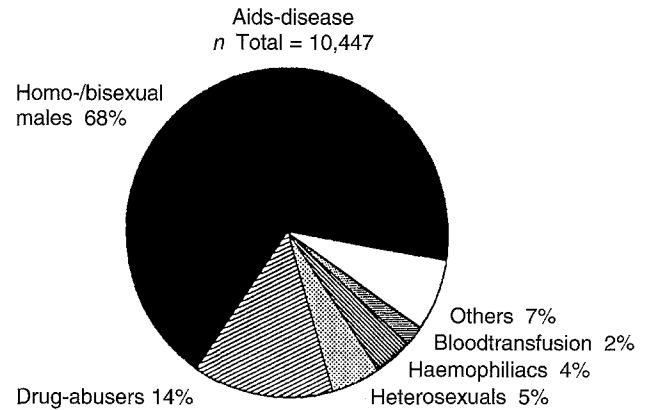


Fig. 5 Risk groups for contamination by HIV-1 infections in Germany in 1993

The preservation technique for bone grafts (-80°C) may be adequate for conservation of its biological value but absolutely unsuitable for the elimination of HIV. The technical aspects of bone banking have already been published and shall not be discussed here [21].

Some bone banks only use resected femoral heads following total hip arthroplasty. Serological follow-up of the “donor” is possible using this donor-group, but does not offer maximal security against HIV infection for the recipients of allogeneic bone grafts. A few cases of HIV transfer by organ allografting following HIV-negative serological screening with various complementary tests have been reported in the literature [4, 11, 28, 29, 33, 40, 43]. The exclusion of a potential HIV-positive donor for organs and tissues is not possible with absolute certainty. Therefore, additional exclusion criteria for tissue donors have been established. A pre-mortal transfusion of blood or blood derivatives excludes the donor from tissue procurement [30, 43].

The “Munich model” of bone transplantation provides an additional aspect of security for the recipient of the tissue graft [19, 20]. Up to now we have exclusively used bone explanted from multi-organ donors. The donor's heart, lung, liver, pancreas and kidneys have generally been transplanted as well. The organ recipients (up to six!) are serologically followed up. They have to take immunosuppressive drugs; some of them require a specific anti-rejection treatment. Meanwhile, the explanted bone of the same donor is stored in the bone bank for at least 6 months. In the very unlikely case of organ transplantation with vital indication after false-negative serological HIV screening, the immunosuppressed recipients of the organs should develop a HIV seroconversion after a short time interval [5, 6, 24, 33]. This has also been powerfully demonstrated by the fatal organ transplantations in the famous case published by Simonds et al. [40].

Our “Munich Model” has been employed since 1986. Up to now only 35 of 1116 multi-organ donors were judged acceptable for bone procurement. Of these 35, 2 were excluded because some of the microbiological swabs were bacteriologically contaminated. Fortunately,

up to now we have had no case of a false-negative serological donor testing leading to an organ procurement. Simonds' publication [40] emphasises the efficiency of our model; the four organ recipients (two kidneys, liver and heart) developed their fatal AIDS infection within 3 months after organ transplantation under immunosuppression. Using our system, the additional infections of three bone recipients could have been avoided.

This logistic of bone transplantation is supported by some American tissue-banks but is also a controversial topic [28]. Immunosuppression with cyclosporin A (CyA) and methylprednisolone possibly suppresses the activation of CD4+ cells, a co-factor of HIV infection. Therefore, HIV replication may be suppressed by CyA [33]. Vice versa, rejection crises activate the cellular immunosystem and enhance HIV infection [24, 43]. Klatzmann et al. [24] found a reduced viral adhesion to CD4+ cells under the influence of CyA. In this way the entry of the circulating virus into the CD4+ cells could possibly be blocked. The consequence is that the helper cells are not deleted, and AIDS cannot develop [24, 33]. On the other hand, an eruption of AIDS in the transplanted and immunosuppressed patient may be enhanced by a reduction of immunosuppression, as the clinical manifestation is accelerated [33, 40]. These mechanisms are highly speculative and require further scientific investigations [24].

Using this method of bone-banking at our trauma centre, bone transplantation was performed in 181 patients between July 1986 and December 1992. In our view it offers an additional dimension of security to recipients of allogeneic bone. Nevertheless, a failsafe protection against HIV infection following bone transplantation still does not exist [6, 23], although the reliability of the ELISA test for antibody detection against HIV used today is very high (sensitivity 99.8%, specificity 99.86%; Behring AG, Marburg). Nevertheless, we cannot detect or exclude an infection with HIV at any stage of the disease with absolute certainty [34, 35].

Criteria for bone tissue donors

It is important to keep in mind that transplantation of cancellous and cortical bone is performed without vital indication in nearly every case [34–36]. This is in contrast to most organ transplantations. Therefore, additional security has to be provided for the recipients of allogeneic bone. The selection of potential tissue donors has to be controlled by very strict exclusion criteria that must not ever be reduced. Those criteria, which are based on the donor's anamnestic data, are listed in Table 1.

There are also contraindications against tissue procurement, derived from the actual status of a potential donor at the moment of his death. The exclusion criteria are presented in Table 2.

Table 1 Donor's anamnestic data: criteria which exclude bone transplantation

HIV+, AIDS, ARDS, hepatitis B, non-A-non-B hepatitis, lues, lepra
Donors of a risk group for AIDS (homosexuals, bisexuals, prostitutes, drug addicts, haemophiliac) (Fig. 5)
Donors from certain geographical areas (i.e. West Africa)
Malignomas of any kind (single exception: primary cerebral tumours)
Active TB, brucellosis, salmonellosis, rickettsiosis, typhoid, paratyphoid and other enteritides
Slow virus diseases (EBV, Jakob-Creutzfeld)
Long-lasting diabetes (type 1)
Autoimmunodiseases (sclerodermia, SLE, LE)
Rheumatoid diseases
Obscure icterus
Neurological, demyelinating diseases (MS, ALS, myasthenia)
Unclear dementia (i.e. Alzheimer)
Exposure to chemicals and heavy metals (Pb, Cr)
Continuous application of drugs, hormones, steroids, etc.
Repetitive i.v. injections
Infectious diseases during the last 4 weeks before death (measles, rubella, mumps, polio, yellow fever, scarlatina, rabies, malaria)

Table 2 Donor' actual status: criteria which exclude tissue procurement

Sepsis, unclear leucocytosis, increased BSR, positive blood cultures, unclear hyperthermia
Active infections: bacteria, viruses, fungi, skin infections, putrid wounds, unclear exanthema
Active urinary tract infections
Respirator treatment longer than 72 h, tracheostoma
Enlarged lymph nodes
Oral or genital sore

Legal aspects of bone transplantation

Bone-banking and bone transplantation are confronted with the problem of potential HIV transfer from tissue donor to recipient. Tissue procurement without HIV screening, as practised some years ago, has to be regarded as obsolete [5, 12, 23, 26, 29, 30, 36, 43]. At the same time intensive education efforts are necessary to convince persons in risk groups for AIDS to exclude themselves from being donors of blood, organs and tissues [46] (Fig. 5). The explicit consent of every potential recipient is necessary for grafting of bone. Therefore, the patient has to be informed about allogeneic bone transplantation, if possible in the course of preoperative planning. The possibility of infectious complications following bone grafting (HIV and AIDS) has to be mentioned. In Germany it is absolutely mandatory to inform the patient about the potential risk of HIV and AIDS in combination with every single blood transfusion [German Supreme Court (BGH) sentence from 26.06.90 in: *Arztrecht* 91, 148–149]. This information is necessary as long as there is a risk of HIV contamination by a false-negative-tested

blood transfusion (estimated as 1:1.2 million, according to our own blood-bank). In the same way, every patient possibly receiving a bone graft has to be informed about this problem. If it was impossible to tell the patient about the hazards prior to the operation, no transplantation of allogeneic bone from the bone bank should be performed. The potential recipient has to realise that it is currently impossible to guarantee 100% certainty against HIV transfer [16, 23, 34–36]. The patient must make the final decision. From a legal point of view, it is highly advisable to perform an additional HIV test with the recipient's blood [36].

Furthermore, it is also necessary to inform a potential bone recipient about the immunological problem of "rejection" of allogeneic grafted bone. The patient has to be aware of an increased risk of infection and the possible necessity of re-operation and removal of the graft [7].

Conclusions

At the moment it seems impossible to treat extensive osseous defects successfully with alloplastic materials and endoprosthetic reconstructions in every single case. Confronted with this status quo, it is impossible to exclude allogeneic bone material from allografting.

With respect to the problem of HIV, a very restrictive indication guide for allogeneic bone transplantation has to be followed. Donor selection has to be performed with a maximum of security criteria as established in the "Munich Model" for bone transplantation. The potential recipient of allogeneic bone grafts has to be informed about the risk of possible infections, especially with HIV, before the operation.

Further efforts are necessary to develop additional test systems for HIV antigen (e.g. p24) to detect the contamination of a potential donor as early on as possible [34–36]. One promising approach is probably provided by the polymerase chain reaction (PCR) technique. At the moment the specificity of this test is insufficient for routine employment.

Some groups are working with different sterilization methods of allogeneic bone [25]. It is questionable whether processing bone for 10 min at 80°C destroys all HIV and also different bacteria everywhere in the bone graft. At the same time all the different proteins in a bone graft – the difference between graft and alloplastic implant – are denatured and destroyed.

For the future, new test systems for HIV antigen detection and new methods of bone processing may provide better security for bone recipients against infection hazards. At present the only way to handle bone transplantation with the necessary care includes: (1) strict donor selection, (2) repeated testing and (3) informing the patient.

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