REVIEW

Femoral osteolysis following total hip replacement

R Dattani

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Total hip replacement represents the most significant advance in orthopaedic surgery in the 20th century. Periprosthetic osteolysis remains the most significant long-term complication with total hip replacement. It has been reported with all materials and prosthetic devices in use or that have been used to date. This paper reviews the current thinking on the aetiology, pathogenesis, management and future treatment options for osteolysis.

Over the last two decades, complications associated with total hip replacement (THR) have declined significantly.[1] Prophylactic antibiotic treatment has reduced infection rates and anticoagulants have lowered the incidence of deep venous thrombosis. However, bone loss following a total joint arthroplasty (periprosthetic osteolysis or aseptic loosening) still remains a significant concern.[2] It was identified as the most significant long-term adverse effect associated with THR at the National Institutes of Health consensus conference on total hip joint replacements.[3] The incidence of periprosthetic osteolysis in many studies is greater than the sum of all the rest of the complications.[2] In the Swedish Total Hip Replacement Register, osteolysis accounted for over 75% of the patients undergoing revision hip surgery.[4]

Both the acetabular and femoral components may be affected. Prevalence of aseptic loosening, in most series beyond 10-years, is reported to be between 32–62%, depending on the type of prosthesis used.[5–8]

HISTOLOGY

The formation of a ''synovial-like membrane'' between implant and bone is fundamental to most theories of aseptic loosening.[9] Histological analysis of tissue surrounding loosened components after joint replacement reveals the presence of three distinct zones: (1) a thin synovial layer of lining cells supported by fibrovascular tissue at both the cemented and bone surface; (2) a middle layer containing histiocytes (tissue macrophages), giant cells, mononuclear cells (lymphocytes and mast cells) and periprosthetic particles; and (3) a fibrous layer that blends into the marrow spaces between bone.

PATHOGENESIS OF BONE LOSS FOLLOWING TOTAL HIP REPLACEMENT

Normal bone maintenance depends on the balance of bone formation and bone resorption that mainly involves the coordinated function of osteoblasts and osteoclasts. There are several mechanisms by which bone loss after a joint replacement may occur.

Ageing

Bone loss may occur as a result of natural ageing. Women can lose up to one third of their cortical bone and half of their trabecular bone throughout their lifetime, while men lose about 60% of that amount.[10] However, bone loss secondary to the ageing process has not proved to represent a major threat to the mechanical stability of prosthetic components.[11]

Adaptive bone remodelling or stress shielding

Adaptive bone remodelling or stress shielding can occur in response to an altered mechanical environment following a hip replacement. This occurs because there is a redistribution of load and therefore stress, when the femoral head is replaced by the femoral component of a total hip replacement. Consequently, stress on the proximal femoral cortex is lessened, as most of the load bypasses this area and is transmitted in the metal stem to the distal femur. Cemented stems are associated with less stress shielding than uncemented stems.[11] Studies have shown that hydroxyapatite fully coated stems are associated with an increased cortical bone stress shielding compared with proximally coated porous stems.[12 13] The amount of coating on most prosthetic stems available today is still greater than that necessary to lower the stress-shielding effect on the proximal femur.[3] However, reducing porous coating to lower stress shielding must be balanced against providing adequate coating to ensure fixation. Long-term effects of stress shielding on stability of components and further revision surgery are not known.[10]

Mechanical factors

Migration of prosthesis is defined as a change in position of prosthesis, cement mantle or both and is thought to indicate implant failure and represent loosening.[14] Once migration has begun, stability is lost and periprosthetic particles may modulate latter stages of loosening.[14] Mechanisms by which migration occurs are not fully understood. It could be due to fatigue failure of cancellous bone surrounding the prosthesis[15] leading to loss of osteo-integration of a stable prosthesis, or it could be attributed to surgical

Correspondence to:
Mr R Dattani, St Helier Hospital, Wrythe Lane, Carshalton, Survey SM5 1AA, UK; rdattani@.doctors.org.uk

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Abbreviations: BMPs, bone morphogenic proteins; HA, hydroxyapatite; MSCs, mesenchymal stem cells; THR, total hip replacement; UHMWPE, ultra-high-molecular-weight polyethylene

techniques—for example, reaming which disturbs capillary circulation of periprosthetic bone, leading to necrosis. The initial use of cement with first generation cementing technique allowed defects and stresses to occur within the cement which resulted in a weaker bone–cement interface and permitted the ingress of polyethylene particles. thus resulting in loosening.[16] With improved cementing techniques which include the use of a medullary plug, a cement gun, lavage of the canal, pressurisation, centralisation of the stem, and reduction in porosity in the cement, the incidence of femoral lysis has been reduced.[16]

Fluid pressure

Once a synovial-like membrane has formed, synovial fluid pressure within the joint may cause osteolysis.[17 18] With loading on the prosthesis, pressure on fluid within the membrane may rise significantly. Sustained elevated pressure can ultimately disturb normal perfusion and oxygenation of bone and, when transmitted to the membrane–bone interface, results in osteocyte destruction and bone necrosis.

Particulate debris

Bone loss can occur secondary to a biological reaction to particulate debris from implants. It is now widely accepted that this is the principal mechanism responsible for periprosthetic osteolysis.[10] Particulate polyethylene is considered to be the substance causing the most tissue reaction, forming up to 90% of the debris volume.[19–21] Other particles that have been implicated in development of osteolysis include submicron-sized ultra-high-molecular-weight polyethylene (UHMWPE), polymethylmethacrylate (cement), and metallic debris such as cobalt and titanium alloys, silicates and stainless steel.[19 22] These particles probably exert their effects by either promoting third body wear of polyethylene, with UHMWPE triggering the cellular response; or they instigate the release of inflammatory mediators which results in chronic inflammation and tissue damage that erodes the supporting bone with subsequent implant loosening.

Migration of particles

Particulate matter and cement are dispersed in joint fluid. The concept of ''effective joint space'', which includes all periprosthetic regions that are accessible to joint fluid and thus particulate debris, has been proposed as a mechanism for migration of particles.[23] Presence of particulate matter in joint fluid will initiate a localised macrophage-induced phagocytosis and result in bone resorption. As bone is resorbed, a pool is formed, promoting more flow (preferential flow) into that region and thus delivering more particles and causing more localised bone resorption.[23] This cycle continues and eventually a significant quantity of bone is resorbed which becomes evident as an osteolytic area on a radiograph. As fluid pressure propels joint fluid and thus particulate debris through the effective joint space, it will result in progressive bone loss.[23]

Small particles (0.5–10 μm) are the most active and when generated will follow a route of least resistance and become interposed between the bone–cement interface or between the bone–implant interface in uncemented prostheses.[22] In cemented femoral components, the path of least resistance is along the cement–metal or cement–bone interface. For example, particles may be driven along the interface through defects between stem and cement and provide a route through which joint cavity contents may reach the endosteal surface of the femur, leading to localised bone lysis.[24]

The coating of implants with ceramics such as hydroxyapatite has been shown to reduce wear particle migration along the implant interface by creating a seal between the bone–implant interface.[11–12 25] In extensively coated stems, osteolytic lesions are more likely to occur proximally and do not always result in loosening of the implant.[4 11 12 25] This is in contrast to patch-coated stems, which allow the joint fluid to reach the diaphysis, thus resulting in osteolysis more distally.[4 11 12 25]

Cellular response to particles

The cellular response to particles is complex and not fully understood.[22] The presence of particulate debris initiates phagocytosis by macrophages and macrophage-derived foreign body giant cells. As a consequence, macrophages and possibly other cells including fibroblasts release cytokines such as tumour necrosis factor-α, interleukins (IL-1, IL-6, IL-10), proteolytic enzymes and prostaglandins (PGE2).[10] Osteoblasts may also cause secretion of specific cytokines by activated macrophages. [10] These intracellular mediators induce a complex cellular response, which initiates a focal bone resorptive process mediated primarily by osteoclasts and to a lesser degree by monocytes.[10] This in turn results in loosening of components.

Biological response to wear debris

Presence of wear debris does not always result in osteolysis. For osteolysis to occur, rate of production of wear particles must exceed an individual's capacity to remove the debris such that a threshold is reached above which development of osteolysis is more likely.[26] Furthermore, normal repair mechanisms that are responsible for preventing formation of osteolytic lesions must become unable to halt the disease progression.[26] Therefore, an individual's biological response to presence of wear debris must play an important role in development of osteolysis. This explains why in some cases of osteolysis the entity is self-limiting while in others the biological process is progressive.[2] The rate of progression seems to be higher in patients with prosthetic loosening.[2]

Wear and osteolysis

Wear is defined as the loss of material from a surface due to motion. It is thought that the main types of wear in a metal on polyethylene bearing surfaces are adhesive wear (when two bearing surfaces bond together on loading and the weaker of the bearing surfaces is transferred onto the harder one on relative motion) and abrasive wear (due to asperities on the harder of the bearing surfaces producing grooves onto the surface of the softer material, resulting in removal of material). Third body wear refers to motion between two primary bearing surfaces with third body particles (cement, bone, metal or polyethylene) trapped between them. Linear wear rate is defined as penetration of the metallic head into the plastic cup. The incidence of osteolysis rises significantly as linear wear rate rises above 0.1 mm/year, while osteolysis is rare at a wear rate of less than this.[26]

Clinical and radiographic manifestations of osteolysis

Radiolucent lines are seen around loose prosthesis on radiographs, most commonly in lateral and anterior aspects of the femur. Radioisotope scans may reveal areas of increased activity in areas of loosening. In the majority of cases, radiographic evidence of the disease process only manifests five years or more after insertion of the prosthesis.[2] Clinically, most patients are asymptomatic and diagnosed only following an incidental finding on late postoperative radiographs.[2] In a minority of cases, patients are symptomatic and present with thigh pain (usually indicates femoral component loosening), groin pain (usually indicates acetabular loosening) or fractures of the femur or acetabulum.

OSTEOLYSIS AND REVISION JOINT SURGERY

Various methods have been attempted to reduce the incidence of osteolysis and thus extend the life of artificial joints. For

example, changes have been made in device designs, implants, materials and fixation methods. Despite this, revision rates remain at around 10% after 10 years, with cemented prostheses having a lower revision rate than cementless prostheses.[27]

Most patients with aseptic loosening will, therefore, need to undergo revision surgery. Furthermore, at a time when average life expectancy is continuing to rise, joint replacements are being performed on ever younger patients. It can therefore be expected that the need for revision hip arthroplasty will continue to rise for the foreseeable future. Currently, revision hip replacements account for around 15% of all total hip arthroplasties performed in the UK.[28]

Considerations in revision hip surgery

The two main aims of a revision procedure are to achieve immediate fixation and long- term stability. However, the reduction of bone stock available for subsequent implant fixation probably accounts for inferior results attained in revision surgery compared with the primary procedure.[29] This is partly due to an inadequate amount of bone being available into which new prosthetic components can be fixed, and partly due to the fact that the existing bone is often not strong enough to support loads that are placed on the prosthetic components.[30–32] Furthermore, bone loss that accompanies aseptic loosening is often extensive and involves many areas in combination.[30] For this reason bone grafts and bone graft substitutes are increasingly been used to replenish bone loss that occurs with loosening.

Bone grafts

Bone has three unique properties that is essential for successful healing and incorporation of bone grafts.[33] These include osteogenesis (ability of bone to self-generate new bone formation), osteoinduction (ability to recruit mesenchymal stem cells, from the surrounding host, which then differentiates into new bone), and osteoconduction (process of ingrowth of capillaries, perivascular tissue and osteoprogenitor cells from host bed into graft structure; the graft functions as a scaffold for ingrowth of new bone).

Autografts

Autografts are considered the gold standard of bone transplantation because they posses all three unique properties described above.[33 34] They are usually obtained from the iliac crests, femoral heads or fibula of the patient. There are, however, several limitations in use of autografts: (1) only a restricted amount of bone can be acquired by this technique and this is usually insufficient to fill large defects that are associated with loosening; (2) harvesting the graft from patient's own skeleton can compromise normal skeletal architecture and mechanical integrity of donor sites; (3) donor site complications and morbidity can result in increased patient recovery time, disability and chronic pain[35]; (4) acquisition of bone graft increases operative time and blood loss; (5) viable cells harvested from the donor site may not survive when they are detached from their vascular supply.[35]

Allografts

Due to the previously mentioned limitations of the use of autografts, allografts have become an attractive alternative. These are most often obtained from femoral heads of other patients undergoing THRs, or from femurs or tibias harvested from fresh cadavers. Although use of allografts in the form of morselised chips to fill cavitary defects have had good clinical success,[36 37] their use in revision surgery has shown inconsistent results.[38] Unlike autografts, they only possess osteoconductive and limited osteoinductive properties but lack osteogenesis and remodel at a much slower rate.[35]

There are also several other disadvantages of using allografts. For example, up to a fifth of all donated femoral heads have shown to be contaminated with bacteria.[39] Furthermore, grafts have been known to transmit pathogens such as hepatitis B, hepatitis C and HIV to patients, and they may contain prions.[40 41] For this reason, allografts are intensively treated before preservation for storage. However, the preservation process can affect mechanical and biological properties of the graft[42] and may not inactivate prions.[41]

In contrast to autografts, allografts in general have a higher incidence of delayed incorporation, non-unions, delayed unions and failure rates.[43 44] Finally, due to increased use of allografts, demands for cancellous allografts may outstrip supply in the future.[45]

Bone graft substitutes

A variety of bone graft substitutes including titanium fibremetals, collagen, bioactive glasses and ceramics composed of hydroxyapatite (HA), tricalcium phosphate or both have also been used to overcome problems that have arisen with bone grafts.[46] HA and calcium phosphates have been shown to evoke a biological response similar to bone and show great potential as bone graft substitutes, particularly in contained bone defects.[47] Furthermore, they can be readily moulded into desired sizes and shapes and the porous nature of these materials facilitates bony ingrowth. In addition, these materials are osteoconductive, biocompatible, easily sterilised, not immunogenic and can be used when large amounts of bone grafts are not available. However, their disadvantages include a lack of osteogenic and osteoinductive properties and their limited ability to offer immediate structural support.[47]

Clinical practice

Several considerations must be taken into account when managing the patient with osteolysis. In the asymptomatic patient, factors such as patient age, past medical history, degree and type of bone loss, rate of progression of osteolysis, properties of the implant to be revised, and patient's activity level must be borne in mind. Surgery is usually indicated if bone loss is extensive or progressive.[32] Curettage and grafting of the defects, stem retention with exchange of the femoral head is a viable option in the asymptomatic patient with a well-fixed stem. In the medically unfit patient or in the elderly, a conservative approach with regular follow-up is a reasonable approach.

In the symptomatic patient, surgery is usually warranted and is guided by host factors mentioned above and the extent of femoral bone loss. The main principles in the management of osteolysis are to identify and remove the source of the wear particles, remove the loose components and fill in any cavitary defects. In cases where osteolysis is minimal, any primary cemented or non-cemented prosthesis can be used. In patients with moderate and moderate to severe osteolysis, the treatment options include a cemented prosthesis and a proximal or extensively porous coated un-cemented implant. In cases of severe osteolysis or in the multiply revised patient, a long stem prosthesis cemented into a proximal or distal femoral allograft is often used.

Impaction grafting

Another method that has been employed to treat cavitary defects, in the proximal femur, has been the use of impaction allografting, whereby a morsellised cancellous allograft is impacted into the proximal femur to provide immediate mechanical function. While in structural grafts bone ingrowth does not usually exceed 2–3 mm, in impacted morsellised allografts the bone growth distance has been shown to be greater than this distance, suggesting that the impacted graft

may be superior with bone growth distance.[48] Furthermore, to date, this is the only technique that has been shown to reverse the loss of bone stock caused by osteolysis.[48] However, early subsidence of the femoral component, prosthetic dislocations and a high incidence of intra- and postoperative femoral fractures have been reported with this technique.[48]

Excision arthroplasty (Girdlestone's procedure)

This procedure involves removal of the femoral head and allowing a fibrous union to occur between the proximal femur and acetabulum. It converts a painful but stable joint into one that is unstable but less painful. Most patients require walking-aids and mobilise only for short distances postoperatively. In modern times, this procedure is only undertaken as a salvage procedure and is not suitable for young patients.

Acetabular revision options

The goals of acetabular revision surgery are to restore the biomechanics of the hip and to restore structural integrity and continuity. The results of cemented acetabular revisions have been disappointing.[30] Cemented reconstructions using allograft has also produced discouraging results.[11] Uncemented porous-coated sockets can be used successfully to reconstruct most acetabular defects encountered during revision surgery.[49] Screws or cages may need to be used to secure the acetabular component into the pelvis. Where major segmental defects are present and prosthetic stability is not possible in host bone, structural allografts are often used.

Cost

For routine revision cases, involving revision of the acetabular and/or femoral components, the average hospital cost is over US$34 000 (£17 500, €26 000) but this increases to over US$50 000 (£26 000, €38 000) for complex cases which require major structural grafting or impaction allografting.[50] Furthermore, the number and complexity of revision surgery is increasing presumably due to a rise in the number of revision surgeries being performed.[50] In patients older than 65, revision surgery is associated with an increased complication rate and therefore higher costs.[51]

THE FUTURE

Medical treatment

In animal studies, bisphosphonates have shown promising results in the prevention and treatment of aseptic loosening.[52 53] However, clinical trials of the drug are awaited to determine its efficacy in the treatment of osteolysis in patients.

Mesenchymal stem cells

Bone marrow contains a population of cells capable of differentiating into bone, cartilage, muscle, tendon, and other connective tissues. These mesenchymal stem cells (MSCs) have been isolated from the periosteum or bone marrow derived from humans and animals.[54 55] Furthermore, techniques for directing commitment of MSCs into bone cell lineage and differentiation into osteoblasts, thus resulting in new bone formation, have now been developed.[55 56] MSCs are present in only small quantities in marrow, but ex-vivo expansion over one billion fold is possible and produces cells without a loss in their osteogenic potential.[57]

One possible approach to solve the problem of reduced bone stock in revision arthroplasty is to form a composite graft from the osteoconductive matrix of an allograft and/or HA combined with MSCs, which provides osteoinductive and osteogenic properties.

MSCs combined with HA/tricalcium phosphate have been shown to regenerate bone in a large segmental femoral defect in rats.[58] Similar results reproduced in dogs has proved that this method is transferable to larger animals and application of this technique to humans is feasible.[59]

Bone morphogenic proteins

Bone morphogenic proteins (BMPs) are a family of osteoinductive growth factors that can initiate endochondral bone formation, presumably by stimulating osteoblast progenitor cells, and by enhancing bone collagen synthesis. Recombinant human bone morphogenic protein-2 (rhBMP-2) has shown good results in the treatment of fracture non-unions and spinal fusion surgery.[60 61] Use of BMPs in the treatment of osteolysis holds great potential.

Gene therapy

Recent advances in gene therapy techniques have suggested that viral vectors may be capable of delivering anti-inflammatory cytokine genes to the periprosthetic tissues, thus controlling the local inflammatory reaction associated with wear debris and extending the life of the prosthesis.[62] The delivery of IL-1Ra and vIL-10 genes using a retroviral vector has been shown to inhibit the inflammation associated with periprosthetic osteolysis in a murine model.[63] Furthermore, gene therapy also has the potential to reduce osteoclastic bone resorption that follows the inflammatory phase, by neutralising crucial osteoclast differentiating factors.[63 64] However, large animal studies evaluating these vectors with quantitative outcome measures are warranted.

CONCLUSION

The need for revision hip arthroplasty will continue to increase for the foreseeable future. The principal aims of revision hip surgery are to achieve immediate fixation and long- term stability and to reconstitute bone loss. Despite the remarkable intrinsic capacity for bone to regenerate and repair defects using bone grafts or currently available bone graft substitutes, there are several shortcomings in achieving optimal therapy. These limitations—combined with the fact that demands for cancellous allografts may outstrip the supply in the future—have prompted a search for alternative bone graft substitutes. As advances in molecular biology are made there will be a move from a tissue approach to a more cellular approach to provide more efficient means of reconstituting bone stock in the future. If successful, these methods could have a substantial public health impact and would improve functional results of thousands of patients undergoing revision joint arthroplasty.

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