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PERIPROSTHETIC OSTEOLYSIS AFTER TOTAL HIP REPLACEMENT: MOLECULAR PATHOLOGY AND CLINICAL MANAGEMENT

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Abstract

Periprosthetic osteolysis is a serious complication of total hip replacement in the medium to long-term. Although often asymptomatic, osteolysis can lead to prosthesis loosening and periprosthetic fracture. These complications cause significant morbidity and require complex revision surgery. Here, we review advances in our understanding of the cell and tissue response to particles produced by wear of the articular and non-articular surfaces of prostheses. We discuss the molecular and cellular regulators of osteoclast formation and bone resorptive activity, a better understanding of which may lead to pharmacological treatments for periprosthetic osteolysis. We describe the development of imaging techniques for the detection and measurement of osteolysis around total hip replacement prostheses, which enable improved clinical management of patients, provide a means of evaluating outcomes of non-surgical treatments for periprosthetic osteolysis, and assist in pre-operative planning for revision surgery. Finally, there have been advances in the materials used for bearing surfaces to minimise wear, and we review the literature regarding the performance of these new materials to date.

The problem of periprosthetic osteolysis

Loosening of hip replacement prostheses due to loss of adjacent bone, known as peri-prosthetic osteolysis, is the most common reason for revision of total hip replacements in the medium to long-term[1-3]. Non-linear periprosthetic osteolysis is characterised by localised and often ballooning lesions in bone adjacent to prostheses and is often first noted around stable prostheses before the bone loss leads to loosening[4]. Even when this type of osteolysis is progressive and results in major bone loss, patients may remain asymptomatic until the bone fails to support the prosthetic implant, at which time major revision surgery is required.

Fluid pressure and wear particles at the bone prosthesis interface cause osteolysis

The mechanism of periprosthetic osteolysis is likely to be multifactorial. While factors such as prosthesis design, surgical technique and quality of fixation are known to be important for early loosening of prostheses, loosening of prostheses due to osteolysis in the medium to long term is related more to prosthesis materials and the type and volume of wear particles generated, and the resultant tissue reaction. Osteolysis around long-term implanted prostheses has been attributed to both the tissue response to wear particles derived from both the articular and non-articular interfaces of prostheses and to fluid movement and pressure at the prosthesis-bone interface.

Histological examination of tissue retrieved from the joint capsule and from the prosthesis-bone interface around hip replacements revised for loosening and osteolysis revealed large numbers of prosthesis-derived particles and an inflammatory response. This was characterised by the presence of macrophages, multinucleated foreign body giant cells containing engulfed particles, lymphocytes, fibroblasts and osteoclasts on bone surfaces.[5,6] We reported a direct association between wear particles

and osteoclastic bone resorption in 1988[7]. In an *in vivo* rat model of joint replacement, which allowed movement of fluid and wear particles to the periprosthetic bone, the presence of wear particles led to the formation of a connective tissue layer of variable thickness at the prosthesis-bone interface and osteolytic lesions.

Animal studies and studies examining retrieved interface tissue have determined that a number of particle-associated factors influence the extent and type of chronic inflammatory tissue response and the extent of osteolysis[8-14]. These include the chemical composition of the prosthesis, the size, shape and surface area of the particles generated, as well as the rate of production and thus concentration of particles present. While wear resulting in excessive numbers of particles being shed from any of the components of a hip replacement will initiate an inflammatory response leading to osteolysis, irrespective of the material used, the large numbers of wear particles generated by wear of the polyethylene liner are the most common cause[15-17]. Wear of metal components resulting in the generation of metal particles and metal ions is usually related to poor prosthesis design or occurs as a result of wear through of the polyethylene liner leading to metal on metal wear.

Identification of bone resorbing mediators

Phagocytosis of these wear particles by macrophages is now known to initiate a cascade of events that leads to osteolysis and prosthesis loosening. The particle-stimulated macrophages express a number of inflammatory mediators, including cytokines (IL-1β, TNFα, IL-6, IL-8 and IL-11), colony stimulating factors (M-CSF and GM-CSF), prostaglandins (PGE_2), matrix metalloproteinases and chemokines[18-23]. The release of these mediators stimulates the recruitment and activity of more macrophages and other cells such as fibroblasts to the prosthesis-bone interface. Mononuclear precursors of osteoclasts are known to be present within the macrophage infiltrate, which are capable of differentiating into functional bone resorbing osteoclasts in the presence of inflammatory mediators[24-26].

In addition to these inflammatory mediators, we have shown that an accumulation of wear particles is also frequently associated with a marked increase in expression of receptor activator NF-κB ligand (RANKL) and its receptor, RANK[27,28]. It is well established that the activated RANKL/RANK ligand-receptor complex is central to the differentiation and activity of osteoclasts, and therefore bone resorption[29-31]. The expression and activity of RANKL is known to be induced by a number of pro-inflammatory cytokines and we and others have shown that TNFα can greatly enhance RANKL activity[28,32-34].

Immunohistochemical and *in situ* hybridisation studies of periprosthetic tissue from sites adjacent to osteolytic lesions have revealed that macrophages, multinucleated giant cells and, to a lesser extent, fibroblasts express high levels of RANK, RANKL and TNFα[26,28,35]. Our studies have found strong correlations between osteolytic lesion size, the concentration of polyethylene particles, and RANK, RANKL and TNFα expression[28]. We have investigated the direct effect of prosthesis-derived polyethylene particles on differentiating human osteoblasts, using a 3D collagen gel culture system[36]. This system provides the necessary architecture and microenvironment to allow normal human osteoblastic cells to undergo differentiation into a mature osteocyte-like phenotype over a 21 to 28 day culture period, indicated by increased mRNA expression of osteocyte markers such as E11, DMP1 and SOST, and adoption of a stellate morphology[36]. In the presence of polyethylene particles, the osteocyte-like cells increase their expression of mRNA species that are associated with the promotion of osteoclast formation and activity (RANKL, IL-8 and M-CSF) and a concomitantly decreased expression of the osteoclast antagonist, osteoprotegerin. Qualitatively similar results were found after exposure of the mouse MLO-Y4 osteocyte-like cell line to polyethylene particles. We have also shown that inflammatory mediators can upregulate the expression, by human osteocyte-like cells, of the

negative regulator of bone formation, sclerostin[37]. These results suggested that polyethylene particles might directly or indirectly influence the behaviour in bone of osteocytes, now increasingly recognised as directing both bone formation and bone resorption[38]. In support of this, we have shown expansion of the osteocyte lacunae adjacent to polyethylene particles in the mouse calvarial osteolysis model (Atkins et al., unpublished). Direct effects were also found on osteoclast differentiation and activity after exposure to polyethylene particles in the collagen gel model. Osteoclasts generated by treatment with RANKL had increased resorptive activity if they were concurrently exposed to polyethylene particles, as well as increased expression of the immunoreceptor tyrosine-based activation motif (ITAM)-related molecules OSCAR, FcRγ, TREM2 and DAP12, which are important for osteoclast formation[39].

These findings from *in vitro* and *in vivo* studies and studies examining interface tissue directly link polyethylene particles to key mediators of osteoclast formation and bone resorption activity in periprosthetic osteolysis and suggest that treatment with inhibitors of these mediators may be useful in preventing or delaying periprosthetic osteolysis.

Non-surgical treatment of osteolysis

A better understanding of the biology of periprosthetic osteolysis may lead to pharmacological approaches to its treatment when prostheses remain well fixed *in situ*. Studies with anti-resorptive agents in animal models have shown promise[40,41] and a small number of studies have been carried out in patients with periprosthetic osteolysis using anti-resorptive drugs, including bisphosphonates and the anti-TNFα inhibitor, Etanercept[42,43]. Gene therapy has also been proposed for the treatment of periprosthetic osteolysis[44-46]. However, although agents such as bisphosphonates and a human monoclonal antibody to RANKL, denosumab, have shown efficacy in reducing the systemic bone loss of osteoporosis[47], an evidence base for using these agents clinically in established periprosthetic osteolysis is so far lacking. To evaluate the role of these and other potential treatments for

periprosthetic osteolysis, treatment protocols will need to be based on the severity of the osteolysis and its rate of progression and, importantly, accurate measurement of osteolysis will be required for such treatments to be properly evaluated.

Detection, assessment, measurement and monitoring of osteolysis

It is now generally accepted that plain radiography is not sufficiently sensitive for the reliable detection of the presence or extent of periprosthetic osteolysis[48-50]. High resolution multi-slice or helical CT with metal artifact reduction protocols have been developed to provide a sensitive and accurate measure of the volume of osteolytic lesions close to metal prostheses[49-54]. We and others have evaluated the accuracy of CT to detect osteolytic lesions[49,50,54], and have used it to identify patient and prosthesis-related factors that may influence development of osteolysis[52,53,55-58].

Our clinical CT studies to date have focussed on periacetabular osteolysis around cementless acetabular components in the medium to long term post-implantation[56-58]. Periacetabular osteolysis is the major long-term complication of these prostheses, and is often seen in the presence of well-fixed components. The aim of our studies has been to understand the natural history of these lesions and the factors that promote their formation and progression. Specifically, we have sought to obtain accurate data on the size and progression of periprosthetic lesions in patients suspected of having osteolysis, so as to improve patient management and to assist in planning for revision surgery.

The progression of periacetabular osteolysis over prolonged periods of up to nine years was monitored using CT, in a cohort of patients with cementless acetabular components who were suspected of having periacetabular osteolysis. We found that patients either developed low volumes of osteolytic lesions that were relatively quiescent, even after long periods of implantation, or patients had extensive, progressive periacetabular osteolytic lesions after a similar post-operative period[56,58]. The latter group

is therefore likely to be at higher risk of acetabular component loosening, component migration and acute periprosthetic bone fracture. Several factors were found to be good predictors of progression of osteolysis, particularly the volume of the osteolytic lesions at initial CT and patient activity[58]. The strongest predictor of progression was obtained by combining these two risk factors. Thus, patients with a high volume of osteolysis at the initial CT and those who were most active had the largest increases in osteolytic lesion size over the monitoring period. These data have significant implications for monitoring patients over time and will potentially identify which patients might best be targeted for novel treatments or early surgical intervention.

Surgical treatment of osteolysis

The decision to revise patients with asymptomatic periacetabular osteolysis adjacent to radiographically stable acetabular components is complex. Important factors to consider include impending wear-through of the polyethylene liner or large, rapidly progressing osteolytic lesions, particularly if fixation of the cup is threatened[59,60], as well as life expectancy and co-morbidities of the patient, and prosthesis type[2,3,60]. The loss of bone due to periprosthetic osteolysis can compromise the outcome of revision joint replacement and multiple revisions on the same joint are not uncommon, with a reduction in average prosthesis survival for each subsequent revision procedure[61]. When revision surgery is indicated in the presence of significant periprosthetic osteolysis, the planning of that surgery is facilitated by the use of CT to identify the location and extent of osteolysis[62].

With the introduction of modular hip components, liner exchange surgery, without removal of the metal shell, has emerged as a surgical treatment option in certain circumstances in the presence of well-fixed acetabular components. During this surgery, if osteolytic lesions can be accessed through empty screw holes in the metal shell or by cortical ‘windows’, debridement and bone grafting of the lesions

can be undertaken to replace bone lost in the osteolytic process. The alternative surgical treatment option is revision of the entire acetabular component. However, removal of a well-fixed acetabular component could potentially result in significant loss of acetabular bone stock, thereby increasing the risk of insufficient bone ingrowth and hence subsequent loosening of the new acetabular component.

Using serial CT scans, it is now possible to monitor and subsequently compare the progression of individual osteolytic lesions prior to and after liner exchange surgery, thereby enabling assessment of the effect on osteolytic lesion progression of removing the source of polyethylene particles as well as being able to monitor the integration of the bone graft[63]. An example of longitudinal monitoring of periacetabular osteolytic lesions pre- and post-liner exchange surgery/grafting using serial CT scans is shown in Figure 1. Despite this patient maintaining his activity levels following liner exchange, this surgery appeared to halt the progression in size of the osteolytic lesions.

Advances in orthopaedic materials

The orthopaedic device industry continues to develop materials with purportedly improved wear properties. Polyethylene, the polymer most commonly used in articulations, has undergone evolution over the five decades of its use. Most recently, the ongoing problem of wear of the conventional ultra high molecular weight polyethylene in bearing surfaces prompted the development of highly cross-linked polyethylenes. Increasing the cross-linking of the polymer has been shown *in vitro* to result in significantly lower polyethylene wear rates in hip simulator studies[64-66]. Over the last decade, highly cross-linked polyethylenes have largely replaced conventional polyethylene as the polyethylene of choice in acetabular liners, and their lower wear has been confirmed clinically using sensitive radiographic *in vivo* measures of wear[67-69]. Polyethylene cross-linking is achieved with the use of 5 to 10 Mrad of gamma or electron-beam irradiation. Early cross-linked polyethylenes were manufactured

using 5 Mrad irradiation and were known as moderately cross-linked polyethylenes. Currently, most polyethylenes are highly cross-linked, achieved through the use of 9.5-10 Mrad irradiation.

The decreased wear rate has, however, been identified as a trade-off against reduced mechanical properties of the highly cross-linked polyethylenes, compared to the previous conventional polyethylenes[70,71]. A small number of cases of rim cracking and rim fractures have been reported[72,73]. Most of these appear related to excess loading on unsupported thinner polyethylene in malpositioned acetabular components. This has led to the development of a new generation of polyethylenes, namely highly cross-linked polyethylenes stabilised with vitamin E to reduce oxidation which appear to provide improved mechanical properties *in vitro*[74,75]. Long term results of these materials are not yet available.

Laboratory studies have suggested that wear particles generated from highly cross-linked polyethylene may cause an increased biological response, which may in turn lead to osteolysis despite a low wear rate[76-78]. Specifically, highly cross-linked polyethylene particles were found to be significantly more inflammatory than conventional polyethylene particles, based on the relative cytokine release from macrophages *in vitro*[77,78]. Furthermore, although laboratory wear of highly cross-linked polyethylene particles produces fewer particles overall, the relative percentage of small wear particles, namely those in the 0.1-1.0µm size range, is higher, compared to that found with conventional polyethylene particles[76].

Importantly, there is little clinical evidence to date that the reduction in wear of highly cross-linked polyethylene translates to a decrease in periprosthetic osteolysis. A number of studies of highly cross-linked polyethylenes have reported a low incidence of osteolysis on plain radiographs[67-69], but the

sensitivity of plain radiographs in detecting osteolytic lesions is poor. In two small studies using CT, the reported incidence of osteolysis at 5-6 years ranged from 2% to 8% in patients with cross-linked polyethylene liners[79,80]. Using CT, we have also identified a number of cases of osteolytic lesions exceeding $1cm^3$ at seven years following total hip replacement with highly cross-linked polyethylene liners (Howie et al. unpublished). The concern arising from these studies is that osteolysis was detected in the absence of significant wear of the polyethylene liner. Reduced wear of cross-linked polyethylene may therefore not correspond to a similar level of reduction in the incidence of osteolysis.

Concluding remarks

An integrated approach to understanding periprosthetic osteolysis has identified particles resulting from wear of the prosthetic materials, especially polyethylene, as essential drivers of this process. Knowledge of the cellular and molecular mechanisms for periprosthetic osteolysis may lead to non-surgical approaches to inhibiting bone loss and thereby prolonging the useful life of prostheses. Improved imaging of osteolytic lesions through the use of CT is providing new insights into the natural history of periprosthetic osteolysis and more informative ways to monitor osteolytic lesions in patients. Imaging will also assist not only in identifying patients who may benefit from drug therapy, but also in determining clinically relevant outcomes. Finally, although it is now recognised that cross-linking reduces polyethylene wear, more clinical studies are needed to determine if cross-linking will also reduce the incidence of periprosthetic osteolysis and hence significantly improve the long-term outcomes of total hip repacement.

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Figure Legends

Fig 1A-D. A. Longitudinal monitoring of periacetabular osteolytic lesions pre- and post-liner exchange surgery using serial CT scans. Total osteolytic lesion volumes are shown for one patient prior to () and following () liner exchange surgery. **B-C.** Selected sagittal images from the CT scans of this patient, which show an osteolytic lesion adjacent to the acetabular component (arrows) increasing in size from 20.1 cm^3 (**B**) to 29.7 cm^3 (**C**) three years later. **D.** Sagittal CT image of the same osteolytic lesion three years after liner exchange surgery showing fill of the lesion with bone graft (arrow) with good graft incorporation and no evidence of ongoing bone loss.

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