Polyethylene Wear Particle Induced Osteolysis in Total Hip Replacement

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INTRODUCTION

Total hip replacement has consistently been shown to be one of the most reliable and successful surgical procedures in orthopaedic surgery [1,2]. However time, the longevity of total hip replacement implants may be limited by osteolysis and aseptic loosening regardless of the method of fixation [3-5]. Osteolysis manifests itself by causing progressive periprosthetic bone resorption secondary to the biological response to particulate wear debris that is generated by the implant. Historically, osteolysis, also referred to as "cement disease", was considered to be the result of bone resorption secondary to the fragmented cement [6]. Previously published studies, on the other hand, have demonstrated that the periprosthetic osteolytic process stems from a combination of foreign body cellular responses to particulate wear debris. The debris may be generated from the articulating surfaces, fixation surfaces, modular component junctions, or acetabular screws [7]. Particulate wear debris from total hip replacements is predominantly generated by adhesive, abrasive or fatigue mechanisms.

In its early stages, osteolysis does not cause pain. As the process continues, bone loss occurs, and there may be local pain, abnormal function, subluxation or dislocation, and pathologic fracture due to the osteolytic lesions. Radiologically, osteolysis appears as a ballooning radiolucency with varying extent and patterns. Currently, osteolysis with subsequent loss of implant fixation is considered to be the leading cause for revision hip replacement surgery. This review will provide a brief overview of the basic scientific and clinical aspects as well as future trends in clinical and basic science research of periprosthetic osteolysis.

Cellular cascade and mediators of osteolysis

There has been extensive research into the cellular events that lead to periprosthetic osteolysis. Although it is hoped that the incidence and severity of particulate wear mediated osteolysis will reduce with the increasing use of alternative bearing surfaces in total hip replacement, the role of cellular mechanisms in the osteolytic process will likely remain the same.

Retrieval studies of periprosthetic tissue around implants both with and without osteolysis have provided vital information for elucidation of the basic cellular mechanisms of periprosthetic bone loss [8-18]. It is currently thought that proinflammatory factors released by macrophages, fibroblasts and other cells in response to particulate debris less than 10 microns in size are the principle mediators of periprosthetic osteolysis [18-22]. Osteoblasts and fibroblasts have also been recently shown to play an intermediatory role in the osteolytic process. Phagocytosis of wear particles (< 5 microns in size) by the cells of osteogenic lineage has been shown to induce a dose dependent down regulation of factors involved in bone formation [22-27]. Among the many known cellular mediators, cytokines such as interleukin 1, interleukin 6, tumour necrosis factor alpha, and prostanoids (such as prostaglandin E2, nitric oxide and other super oxide factors) are considered to be the most important inducers of osteoclastic proliferation and stimulators of osteoclastic bone resorption [12,18]. Osteoblasts, stimulated by tumour necrosis factor alpha to produce granulocyte-macrophage colony stimulating factor [GM- CSF], in turn causes up regulation of transformation of immature macrophages into osteoclasts and multinucleated giant cells [28]. Ultimately, RANKL (receptor activator of nuclear kappa B ligand) and osteoprotegerin [OPG], the final effectors of bone metabolism, are affected by a cascade of events initiated by all of these factors. Periprosthetic osteolysis then occurs as a consequence of increased RANKL and decreased OPG [29-32]. In addition, degradative enzymes, metalloproteinases, collagenases and stromelysin released by activated macrophages are involved in the sequence of events leading to osteolysis [33-42].

Morphology and Bioreactivity of wear debris

Loosened total hip arthroplasties are surrounded by an interpositional membrane composed of fibrovascular stroma, fibroblasts , macrophages, foreign body giant cells, polymethylmethacrylate, polyethylene and metallic debris wear debris, depending on the materials used in the implant. Polyethylene debris less than 1-2 microns in size are phagocytosed by macrophages, while larger particles of 10 microns or greater are surrounded by multinucleated giant cells in a fibrous stroma. Smaller polyethylene wear particles are more bioreactive, and thus stimulate a greater release of proinflammatory cytokines [8,43-46].

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Interestingly, Haynes *et al* demonstrated that stainless steel and cobalt chrome molybdenum particles were toxic to human monocytes, while titanium particles did not affect cell viability [47]. Goodman et al found that titanium and polymethylmethacrylate particles not only inhibited bone cell viability and proliferation, but also down regulated markers of bone formation in a dose and time dependent manner. Polymethylmethacrylate particles, initially thought to be relatively less toxic due to their larger size, can also contribute to periprosthetic bone loss by inhibiting early phases of osteoprogenitor cell differentiation [27,48]. Ceramic bearing surfaces generate far less wear particles than polyethylene surfaces, and the ceramic particles are much smaller in size than polyethylene particles. These particles appear to be more benign compared to polyethylene debris.

Shanbag et al demonstrated that macrophage response to particulate debris is dependent upon on particle size, composition and dose as measured by surface area ratio. Some studies have suggested that the higher particles' phagocytosable size stimulate increased response up to the saturation level [22,49]. In contrast, Yamamoto et al found that the shape of ceramic particles and not their size influenced the level of cytotoxicity, with dendritically shaped particles having higher cell toxicity than spindle and spherically shaped particles [50]. In conclusion, it is evident that the bioreactivity of wear debris particles is determined by its size, shape, composition and concentration, but at this time it is not possible to determine which particle type [polyethylene, metal, ceramic] is the least detrimental to periprosthetic bone.

Periprosthetic Osteolysis in Total Hip Replacement

It is the effective joint space, defined as the periprosthetic region that is accessible to joint fluid, that determines both the extent and pattern of osteolysis [51]. As the concentration of biologically active wear particles circulating in effective joint space increases with implant lifespan, periprosthetic bone resorption becomes a self-perpetuating process, which increases with time. Large spaces form secondary to bone resorption, resulting in further ingress of joint fluid and wear particles, causing further bone resorption [52]. Long- term clinical studies involving more than 10 years of follow- up have documented clinically significant periprosthetic bone resorption revealing the actual scope of the problem [53].

Periprosthetic osteolysis often remains asymptomatic, even with substantial bone loss. Patients may not present to the orthopaedic surgeon until bone loss is so great that it leads to implant failure, loosening or periprosthetic fracture [54]. Pain associated with osteolysis with or without loosening manifests as groin and/or buttock pain when involving the acetabular component, or thigh pain when involving the femoral component. On physical examination, there may be pain with range of motion, shortening or other deformity of the involved extremity [55]. With gross loosening, it may be possible to piston the implant in femoral canal [56].

Since the osteolytic process is largely asymptomatic, early detection and monitoring of osteolysis is recommended to prevent serious complications secondary to end stage osteolysis such as periprosthetic fracture and loosening. Osteolysis may be an incidental finding on long term follow-up radiographs of a well functioning implant, or manifest in the form of radiographic loosening in advanced cases. Advanced osteolysis of the proximal femur often presents as loss of cancellous bone in regions of the lesser and greater trochanters [53]. Plain radiographs may lead to underestimation of the extent of osteolytic lesions and are therefore usually a poor measure of the extent of osteolysis, especially on the acetabular side. Special radiographic views, such as Judet oblique views of the acetabulum, better estimate the extent of pelvic osteolysis. Three-dimensional computed tomography [3D CT] is the most sensitive tool for detection of osteolysis in its earliest phases and is the most accurate in quantifying the size and extent of the process, and in evaluation progression over time [57]. Although 3D CT is considered to be much superior to conventional radiographs in assessing osteolytic lesions, its use may be limited due to concerns about cost and radiation exposure of, thus making it impractical for routine monitoring of total hip replacements[58,59].

Polyethylene wear debris in Total Hip Replacement

The most common bearing combination currently used in total hip replacement is a metal cobalt chromium femoral head articulating with an ultra-high molecular weight polyethylene socket. Polyethylene wear is influenced by many factors that can be broadly divided into endogenous and exogenous [60-63]. Endogenous factors are those determined by biomaterial properties, such as method of fabrication, the thickness and toughness of polyethylene, sterilization conditions, storage environment and shelf age. Exogenous factors are design features of the implant and articulation, including modularity, roughness of the femoral head surface roughness, component alignment, third body particulates, etc. In total hip replacements, polyethylene wear occurs primarily as a result of micro-adhesion and micro-abrasion wear mechanisms [64].

Various clinical and experimental studies have described polyethylene wear patterns based on location, surface alteration, fusion defects or spots, and subsurface white bands [60,65]. Radiostereometric analysis or computer-assisted edge-detection techniques are the most accurate methods of assessing the magnitude of linear polyethylene wear [66-68], while volumetric wear is determined by mathematical calculations using linear wear and head size values.

Numerous approaches have been adopted to minimize polyethylene wear such as the introduction of highly cross-linked polyethylene, improvements in the manufacturing and sterilization processes, and optimizing design characteristics like reducing micro-motion between the acetabular shell and polyethylene insert [69-71]. In order to reduce oxidative degradation of polyethylene, highly cross-linked

polyethylene can be treated with antioxidants like alpha tocopherol. Studies have shown that reduction of oxidation can significantly improve the service life of polyethylene [72,73]. Other advances include improvements in the fabrication process of highly cross-linked polyethylene. The so-called second generation highly cross-linked polyethylene known as X3 HXPE, uses a sequential irradiation and annealing process [74]. This method better preserves the mechanical properties of polyethylene, yielding very low free radical content, and demonstrates the highest survivorship in functional fatigue testing.

Future Trends

There are two basic strategies to combat polyethylene wear and subsequent osteolysis – i) preventing the generation of wear particulates through improvements in implant design and fabrication, ii) surgically treating existing osteolysis, or pharmacologically modulating the inflammatory reaction and subsequent bone destruction. Alternative bearing surfaces such as ceramic-on-metal, ceramic-on-ceramic, or metal-on-metal have much lower wear rates than polyethylene articulations and hold great promise as components in future joint replacements [75,76]. If indeed wear debris mediated osteolysis is the primary cause of implant loosening, substantial improvement in longevity and performance of total hip replacements can be anticipated with the use of alternative bearing surfaces. Younger patients with end stage destruction of the hip joint could then be treated with hip replacement surgery and the need for revision surgery would be minimized for patients of all age groups. Additionally, improved manufacturing accuracy in geometrical form, surface finish and further refinement of highly cross-linked polyethylene also appears promising.

Pharmacological measures to combat osteolysis are an attractive option so that patients potentially need not face additional surgery to treat the condition. The pharmacological modulation of osteolysis can be achieved by influencing osteoclast function and signalling, inhibition of the inflammatory cascade, or by local infusion of growth factors [77,78].

For example, biphosphonates inhibit osteoclastic function, influence the differentiation of osteoclast precursors, and induce macrophage apoptosis. Early studies with biphosphonates provide encouraging results in inhibiting wear particle-induced osteolysis [79,80]. Nonsteriodal anti-inflammatory drugs may also potentially be of benefit due to their inhibition of cylcooxygenase [COX2], an important isoenzyme involved in the inflammatory cascade at sites of local tissue injury [81,82]. Etanercept, a soluble inhibitor of TNF (tumour necrosis factor) alpha, has been shown to experimentally inhibit osteoclastic bone resorption and may potentially reduce osteolysis [83,84]. Local infusion or direct application of growth factors like Transforming Growth Factor beta [TGFß] and basic Fibroblast Growth Factor-2 [FGF-2] also appear to be possible treatment alternatives due to their stimulatory action on osteoblast-like cells [85,86]. Although there are many potential and theoretical pharmacological options, at this time, there is no clinical data in humans demonstrating that these agents can inhibit or reverse wear particle-induced osteolysis in vivo.

Currently, other than the use of alternative bearing surfaces, the use of highly cross-linked polyethylene with either a cobalt chrome or ceramic femoral head gives the best performance in terms of wear debris reduction, and thus has the potential to substantially decrease the resulting osteolysis historically associated with total hip replacements. Further clinical and basic science research is warranted to determine the best materials for total hip prosthesis that possess optimal wear characteristics as well as superior longevity and performance.

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