Biological Response to Common Surface Bearings Used in Orthopaedics

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Wear particles are the most important cause of aseptic loosening of orthopaedic devices. To reduce the amount of particles generated from the conventional metal-on-polyethylene system, alternative bearings have been introduced. However, there are some concerns about so-called ''adverse reactions'' to these bearing surfaces. Despite an apparent longevity, metal particles and metal ions released from the prosthesis can induce a series of adverse reactions. The purpose of this review is to provide the readers an up-to-date overview of the literature on the biological responses to different bearing surfaces with particular reference to metal-on-metal bearings and the local and systemic effect of metal ions. (Journal of Surgical Orthopaedic Advances 17(1):34–39, 2008)

Key words: adverse reactions, bearing surfaces, ceramic-on-ceramic, metal-on-metal

Osteolysis of the bone surrounding total joint replacements remains one of the most undesirable effects of bone prosthesis. On radiographs, it is characterized by areas of radiolucencies in the bone adjacent to the implant mantle. Clinically, periprosthetic osteolysis can lead to aseptic loosening of one or both of the components and sometimes massive bone loss, which may result in periprosthetic fracture. The most common bearing surface used for total hip arthroplasty (THA) is a metal femoral head articulating against an ultra-high-molecular-weight polyethylene (UHMWPE) acetabular cup with or without metal backing (metal-on-polyethylene [MOP]). With passage of time, the bearing surfaces wear and produce relatively large amounts of UHMWPE wear debris. These particles enter the periprosthetic tissues where they are phagocytosed by macrophages. The macrophages then release pro-inflammatory cytokines and other mediators of inflammation, which stimulate osteoclastic bone resorption leading to osteolysis and eventual loosening of the prosthesis. This process of aseptic loosening usually is not a big problem in an older population, and a primary hip replacement with a conventional MOP bearing surface will mostly outlive the patient older than 65 years. However, there are concerns about the implant's longevity in patients who are younger and usually more active. The popular alternatives currently available with the potential for improved longevity are: 1) highly cross-linked polyethylene, 2) ceramic-on-ceramic, and 3) metal-on-metal (MOM) (cobalt–chromium against cobalt–chromium) wear couples. Although these new couples provide the surgeon and the patient with more longevity, they produce some specific biological responses.

Metal-on-metal hip resurfacing or hip replacement in particular is emerging as an attractive option for treating young and active patients with significant hip osteoarthritis (OA). The perceived advantages of MOM bearings include bone conservation (with resurfacing), low wear rate, increased range of movement, and low dislocation rate (due to large head size). Although the wear rates are lower than with MOP bearings, the particles produced are orders of magnitude smaller, and despite a low volumetric wear, the number of particles generated is 100 times higher as compared with MOP bearings. This leads to high ion levels in body fluids and this in theory can have adverse reactions, namely hypersensitivity, risk of carcinogenesis, and toxicity. There is also concern about chromosomal aberrations in the patient as well as passing the chromosomal problems to the next generation. This has led to a more cautious approach to their adoption by surgeons in North America in spite of widespread enthusiasm among European countries. The aim of this review is to provide the reader with a summary of the current literature concerning the local and systemic biological response to the different types of materials on the market, with specific reference to metal-on-metal wear couple.

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Biological Response to UHMWPE

UHMWPE was introduced on the orthopaedic field by Sir John Charnley in the 1960s and has been very widely used with good success. As with any other bearing surface, wear of the UHMWPE acetabular cup articulating against the hard metal or ceramic femoral head leads to the generation of UHMWPE particles, as a result of either wear or corrosion. Despite a relatively good biocompatibility when the material is in bulk, massive inflammation and osteolysis are observed when these particles are in contact with bone marrow cells. In addition, wear of the nonbearing surfaces rubbing together such as back-side wear of an acetabular liner, fretting of the Morse taper in modular stems, and stem/cement or stem/bone fretting wear in cemented and noncemented hip prostheses, respectively, may lead to the generation of metal and polymethyl methacrylate (PMMA) wear particles. Wear particles produced by this type of wear can also lead to an inflammatory reaction and osteolysis (1, 2). This type of wear is not intentional, whereas the wear of UHMWPE is an inevitable consequence of the normal function of the prosthesis.

The volumetric wear rate has shown that degradation of the MOP bearing surface is usually linear and evaluated as 0.2 mm/year, when the femoral head is made in steel alloys (3, 4). The UHMWPE particles isolated from tissues retrieved from failed THA vary greatly in size and morphology, from large platelet-like particles, up to 250 μm in length, to fibrils, shreds, and submicrometer globule-shaped spheroids between 0.1 μm and 0.5 μm in diameter (5–8). However, the smallest particles seem to cause maximum biological response. This is due to the ease with which these particles can migrate from the implantation site as well as the ease with which they can be phagocytosed by inflammatory cells.

In vivo, the osteolysis associated with this type of implant is linked with the formation of a granulomatous periprosthetic membrane rich in macrophages and implant-derived wear particles. It is worth noting that inside this periprosthetic membrane, macrophages are activated by the phagocytosis of UHMWPE particles and can release a variety of pro-inflammatory cytokines and growth factors (TNF-α, IL-1β, IL-6, IL-8, IL-11, TGF-β, PGE_2, M-CSF, GM-CSF, PDGF-α, TGF-α, MCP-1, and MIP-1α) (9–18) known to initiate the differentiation of osteoclast precursors into mature bone-resorbing osteoclasts, leading inevitably to osteolysis of the bone surrounding the implant (19). Although numerous studies have attempted to correlate the levels of various mediators with the degree of osteolysis (11, 20, 21), there is no consistent pattern within the literature. Furthermore, it is worth noting that usually lymphocytes are not observed or are observed at very low concentration in the periprosthetic membrane, indicating that the response to UHMWPE is mainly a macrophagic response.

Biological Responses to Ceramic

The most common alternative bearing combination used in patients in the United States is ceramic (aluminum oxide or zirconium oxide) on polyethylene. This combination has been shown to reduce wear rates, when compared with conventional MOP, by 10% to 50% for periods exceeding 10 years (22). This reduction in wear rate has been accompanied with a significant reduction in the revision rate (23–25).

Ceramic-on-ceramic (COC) bearings made of alumina have the lowest wear rates of any bearing surface combination with an annual head penetration of 0.010 mm/year (26, 27). However, the possibility of component fractures, the sensitivity of component positioning, and the high costs have impeded their widespread application. The data available on the biological consequences of these bearing surfaces in joint replacement are limited. The biological response to ceramic particles has been studied in tissue explant and cell culture studies. Catelas et al. have shown that alumina and zirconia particles induced apoptosis of macrophage in a dose- and size-dependent manner. However, the composition of the particles has no effect on the apoptotic cell death, but the size is a crucial factor because particles bigger than 2 μm induce more cell death than smaller particles (28, 29). Osteolysis has been reported in association with ceramic wear debris (24). Yoon et al. reported on osteolysis of the femur in 23 hips and of the pelvis in 49 hips from a cohort of 103 alumina COC uncemented THAs. Histological and electron microscopic analyses of the periprosthetic membrane revealed abundant ceramic wear particles with a mean particle size of 0.71 μm and a range from 0.13 μm to 7.2 μm. However, it seems that nowadays the improvement of the manufacturing of these prostheses and the use of cementless stems has led to a greater improvement of the biocompatibility of the COC surface bearing, because no evidence of osteolysis was observed after 5 years (30–32). This is encouraging, although longer studies on the follow-up of cementless COC are needed to assess the lower rate of osteolysis of this surface bearing.

Biological Responses to Metals

First-generation MOM articulations were used widely during the late 1960s and early 1970s (McKee-Farrar, Müller, Sivash prostheses), but the early clinical results were disappointing (33, 34). Many of the early MOM implants had a geometry that permitted equatorial contact, leading to high torques that might have caused failure

of the THA. There has been, however, a resurgence of interest in the metal-on-metal articulation because of the observation that some of the early metal-on-metal prostheses have survived for over 20 years, with low wear and no incidence of osteolysis. The degradation rate of MOM bearings is mostly smaller than the rate of MOP bearings. The linear annual wear of retrieved MOM prostheses is only 0.009 mm for the head and 0.006 mm for the acetabular cups compared with 0.08 to 0.25 mm for polyethylene in MOP bearings (35, 36) measured radiologically.

Although their total volume is dramatically smaller than the polyethylene debris, these particles are much smaller and many times more numerous. Particles generated from the articular surfaces of a MOM prosthesis have a size ranging between 30 and 50 nm (37, 38). The biological response is generally associated with lymphocyte infiltration similar to hypersensitivity reaction (39, 40). Wear particles can be generated from the two articular surfaces when the surface roughness is elevated and/or the lubrication is not enough. Wear particles can also be generated at the modular head/neck couplings. The generated metal particles are released in the synovial fluid. Thereafter, particles can be corroded extracellularly by the compounds of the synovial fluid or intracellularly, after phagocytosis or endocytosis by the cells. Because of the near proximity of the bone, wear metal particles and metal ions can exert their effect on bone cells (i.e., osteoblasts and osteoclasts). Moreover, elevated concentrations of cobalt and chromium in serum have been observed in patients with a MOM implant, with a 10-fold increase in Co^{2+} serum levels over controls (1.0 ppb vs. 0.1 ppb) and a 5.7-fold increase in Cr^{3+} (0.80 ppb vs. 0.14 ppb) (41, 42). These elevated concentrations can exert their effect on the white blood cells, containing lymphocytes and osteoclast precursors, as evidenced by a decrease in the number of CD8+ cells (43). Hart et al. studied the relationship between metal ion levels and lymphocyte counts in patients with MOM hip resurfacings (43). Peripheral blood samples were analyzed for lymphocyte subtypes and whole blood Co and Cr ion levels in 68 patients (34 with MOM and 34 with MOP). All components were radiologically well fixed and patients were asymptomatic. The authors found that the Co and Cr levels were significantly higher in the MOM group ($p<.0001$) as expected, and there was a statistically significant decrease in the level of CD8+ cells (T cytotoxic/suppressor) in the MOM group ($p = .005$). At this juncture, the authors did not find any clinical symptoms in this patient group due to decreased CD8 levels.

Cellular Dysfunction Induced by Metal Ions

Reactions with metal ions can lead to the generation of free radicals: reactive oxygen species (ROS) and reactive nitrogen species (RNS). Free radicals can react with DNA (nuclear and mitochondrial) and induce damages to purine and pyrimidine bases as well as to the deoxyribose backbone (44). They can also induce DNA cross-links. Permanent modification of genetic material resulting from these "oxidative damage" incidents represents the first step involved in mutagenesis, carcinogenesis, and ageing.

Local Effects of Metal Wear Debris

It is still unclear whether the metal ions released in synovial fluid can indeed cause clinically significant osteolysis and/or aseptic loosening. The incidence of such cases seems to be quite low and more than one type of clinical presentation is possible. The patients are likely to present with a painful hip with or without presence of a soft tissue mass. Some may have symptoms of nerve irritation, while in some the hip may be quite irritable. Some patients may present with symptoms of instability.

Does Activity Level Matter?

As stated earlier, MOM replacements are predominantly performed in young and active patients. Heisel et al. monitored seven patients with well functioning MOM bearing prostheses and one control patient (with no prosthesis) over a 2-week-long activity protocol (45). All the patients had normal renal function. The lower limb activity was recorded using a computerized 2D accelerometer. During the 1st week, the patients restricted their physical activities, but in the 2nd week, they were encouraged to be physically as active as possible. Serum levels of Co and Cr and urine levels of Cr were assessed at 10 time points during these 2 weeks. Regardless of the activity level, the serum ion levels for a given patient were essentially constant and no correlation was found between patient activity and serum levels of Co and Cr or urine levels of Cr.

Histological Appearance of Periprosthetic Tissues

Davies et al. published their results comparing the histological appearances of the periprosthetic tissues obtained form MOM ($n = 25$) and MOP ($n = 9$) hip replacements (39). They also compared these findings with the appearances of the control tissues retrieved at the time of primary THA ($n = 9$). The tissue samples obtained from MOM hips displayed a pattern of well demarcated tissue layers. A prominent feature seen was that of perivascular infiltration of the lymphocytes. The lymphocytic infiltration was more pronounced in samples obtained at the time of revision for aseptic failure than in samples retrieved at autopsy or at the time of arthrotomy for reasons other

than aseptic failure. In some cases ($n = 10$), they also noted an accumulation of plasma cells in association with macrophages that contained metallic wear debris particles. In addition, the surfaces of tissues obtained from MOM prostheses were more ulcerated than those obtained from hips with other types of implants. Tissue samples obtained from MOP implants showed far less surface ulceration, much less distinction between tissue layers, no pattern of lymphocytic infiltration, and no plasma cells, inflammation predominantly being histiocytic. The authors also noted that their findings were similar to those of Hartman and coworkers (46) and those of Howie and Vernon-Roberts (47). Hartman et al. had described the histological appearance of biopsy specimens of skin obtained from the sites of sensitization and challenge tests following surface application of 2,4-dinitrochlorobenzene. Howie and Vernon-Roberts had shown that intra-articular injection of cobalt–chromium wear particles (less than 3 μm) in rats produced synovial surface ulceration and a dense infiltrate of small lymphocytes in the subsurface tissue layer. Both these findings add weight to the hypothesis that the primary insult is to the surface of the tissues and perivascular lymphocyte infiltration is the secondary phenomenon.

Willert et al. raised the possibility of MOM THA producing a delayed type hypersensitivity reaction to Co/Cr ions (40). The authors noted the presence of macrophages as well as granulomas with metal particles in the tissues, and these macrophages were consistently found in areas in the direct vicinity of the blood vessels. The authors describe these perivascular lymphocytic infiltrates as characteristic of cell-mediated immune response and label it ALVAL.

Chromosomal Aberrations

Ladon et al. investigated changes in metal ion levels and chromosome aberrations in patients within 2 years of receiving MOM hip arthroplasties (48). The authors noted a statistically significant increase in both chromosome translocations and aneuploidy in peripheral blood lymphocytes at 6, 12, and 24 months postsurgery. The authors also noted that generally these changes were progressive with time, the change in aneuploidy being greater than in chromosomal translocations. However, the authors did not find any statistically significant correlations between chromosomal translocation indices and cobalt or chromium concentrations in whole blood. The authors concluded that the clinical consequences of these findings at present are unknown, but future studies should include direct comparisons of patients with implants of different composition.

There continues to be concern about increased risk of carcinogenesis due to elevated metal ion levels. However, to date from current publications there is no evidence that prolonged exposure to elevated metal ions produced from a metal-on-metal hip arthroplasty results in a statistically significant increase in risk of cancer. The SIR (standardized incidence ratio) of observed versus expected cancers in patients with MOM THAs is the same at first 5 years, 1.0 (0.7–1.5); first 10 years, 1.0 (0.8–1.3); and at first 15 years, 1.0 (0.8–1.4), when compared with the general population.

MOM hip bearings are the preferred couplings, particularly in the young and active patient. This preference along with the possible association with chromosomal abnormalities can have implications in the form of ill effects on children born to mothers with MOM hip replacements. Brodner et al. analyzed maternal serum and umbilical cord serum levels of Co and Cr in three women (at the time of delivery) with uncemented MOM THA implanted at an average of 3.8 years postsurgery (49). At the time of delivery, the maternal Cr concentrations were 1.6, 0.5, and 0.9 μg/L with Co concentration being 1 μg in the first woman and below the detection limit in the other two women. Co and Cr concentrations of the umbilical cord sera were below the detection limits. Placenta in addition to production of hormones also controls substance transfer. Four transport mechanisms are described: passive diffusion (oxygen, carbon diaoxide, steroids, fatty acids, etc.), facilitated diffusion (glucose, lactate), active transfer (amino acids, calcium), and receptor mediated endocytosis (lipoproteins, immunoglobulins). Different metals seem to have different abilities to pass through the placenta. Lead easily traverses the placenta, cadmium accumulates in the placenta, and manganese and zinc are actively transported. The authors concluded that possibly the placenta inhibited the passage of Co and Cr.

Conclusions

Use of alternative couplings, namely ceramic-on-ceramic and metal-on-metal, has the advantage of reduced wear rates as compared with metal-on-polyethylene bearing surfaces. However, their introduction (metal-on-metal in particular) has raised concerns because of the occurrence of local or systemic adverse reactions. Currently available data can not draw firm conclusions on these adverse reactions and long-term studies are needed. Any attempts to improve component design or component metallurgy, aimed at reducing systemic metal ion concentration, will help in alleviating these fears. The industry, scientists, and orthopaedic surgeons should continue to work in close liaison to achieve the same.

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