Review Article

Local and systemic consequences of metal-on-metal hip resurfacing implants

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Abstract: Hip resurfacing arthroplasty (HRA) has a long clinical history and has utilized a variety of bearing material combinations with mixed clinical success. This paper reviews the local and systemic consequences of metal-on-metal hip resurfacing implants. Local tissue reactions cover a spectrum from no clinically adverse effects to adverse complications leading to revision associated with pain, osteolysis, or pseudotumor formation. Factors affecting the local tissue response to any implant include surgical, implant and patient factors. Metal particle size, shape and volume are important to the response around metal-on-metal implants. Surgical placement, particularly of the acetabular component, is important to the generation of wear debris. The number of patients with a sensitivity to the cobalt or chromium constituents of metal-on-metal implants is thought to be low and the cause and effect between patient sensitivity and implant failure is considered to be uncertain. Systemic toxicity from chronic exposure to the ions from metal-on-metal implants is still extremely rare although studies into potential cardiac or neurologic effects have suggested that subtle changes may be present that warrant continued and larger follow-up studies of longer-term cohorts.

Keywords: Hip resurfacing arthroplasty (HRA); metal-on-metal; tissue; ions; toxicity

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Introduction

Hip resurfacing arthroplasty (HRA) is a potentially bone-conserving operation that has a long history and mixed clinical success (1). Contemporary metal-on-metal HRA can be attributed to the early procedures by Wagner (2) which inspired later designs by McMinn (3) and also by Amstutz (4). The clinical use of metal-on-metal HRA expanded from the early 2000's and, during the peak period, 13 different designs were available worldwide (5). Metal-on-metal articulations typically produce significantly less volumetric wear compared with early generation metal-on-polyethylene bearings that were associated with osteolysis. The observation that the local tissue response to well-functioning, early generation, metal-on-metal bearings was markedly less inflammatory than the typically macrophage-dominated tissues around metal-on-polyethylene bearings encouraged the reintroduction of metal-on-metal bearings in the late 1990's. However, the metal particles are predominantly nanometer-sized and these can potentially corrode into metal ions. When present in excessive amounts, both the particles and the ions have the potential to cause adverse local and systemic biological responses.

The aim of this review is to examine the local and systemic consequences of metal-on-metal hip resurfacing implants. With the exception of femoral neck fracture and revisions for complications of modular taper corrosion, the modes of failure experienced by metal-on-metal hip resurfacings and standard, stemmed metal-on-metal total

hips are similar, i.e., aseptic loosening, infection and metal hypersensitivity. The degree of component wear has been found to be similar (6). The opportunity to evaluate HRA components revised for early failure due to femoral neck fracture or mid-term loosening provided a contrasting set of data with which to compare with cases that failed for reasons related to implant wear. This has resulted in a large body of literature based on multifaceted retrieval analysis and histopathology. This review will survey some of the key findings from those studies in terms of the local and systemic consequences of hip resurfacing.

The local reaction of cells to wear particles

The size, concentration and shape of particles, regardless of material (7,8) appear to affect the type of response elicited by the cells in the tissues surrounding arthroplasty components. In well-functioning metal-on-metal hips with low wear rates, only small volumes of particles are produced and these generally consist of oxidized chromium nanoparticles with minimal to no cobalt content (9). This is in contrast to malpositioned hips which produced larger particles with higher concentrations of cobalt (10). Caicedo *et al.* consider the inflammasome to be a key element in the intracellular response to metals and they examined the effect of cobalt-chromium particle size and surface irregularity in the stimulation of this response in human primary monocytes (11). They reported that larger, irregular particles induced a greater inflammatory response via IL-1beta production through the Nalp3 inflammasome pathway, probably secondary to greater degree of lysosomal damage. Brown *et al.* (12) compared the effects of nanometer and micrometer sized cobalt-chromium particles in mice knees and found that the larger particles persisted longer in the joint. The larger particles also induced more chromosomal aberrations in the short term, but these changes were not persistent and were not observed at 40 weeks. Although several studies have reported chromosomal damage after exposure of cells to cobalt or chromium particles (13,14), to date, there is no clear evidence that this leads to an increased risk of cancer in joint replacement patients (15,16).

The wear particles that are released into the joint fluid may come into contact with synovial lining cells of the capsule. The debris can then become internalized by phagocytosis or pinocytosis, depending on their size. Some particle-laden cells may be distributed away from the joint via the vascular and lymphatic systems (7,17), Studies conducted using post-mortem donated total hips have demonstrated that, while migration of biomaterial, or iatrogenic particles through the vascular or lymphatic system has been reported, distant organ pathogenesis is typically not seen unless there is an abundance of debris (18,19). Particles that remain in the local tissues can be found within synovial phagocytic cells and histiocytes in the tissues lining the joint. Particles can also be stored freely in the synovial fluid, interstitial fluids and in fluids that can accumulate within tissue bursae or masses.

When ingested by phagocytes, metallic particles are exposed to the aggressive intracellular environment of lysosomes and endosomes. The particles undergo a complex series of molecular events that result in the formation of various corrosion products, complexed proteins and metal ions (20). Kwon *et al.* (21) showed that cobalt nanoparticles and ions demonstrated a dose-dependent cytotoxicity in a macrophage cell line while titanium and chromium nanoparticles did not show this effect. In a series of experiments, Scharf *et al.* (22) concluded that several different mechanisms potentially exist which could cause cellular damage following particle phagocytosis and subsequent corrosion, particularly oxidative damage and the release of reactive oxygen species. They found a strong positive correlation between the amount of Cr and Co ions and tissue oxidative damage but noted that cells are equipped with a variety of enzymes that help to dispose of reactive oxygen species and lessen the damage. In contrast, one experimental study demonstrated that the cytotoxicity of cobalt-chromium particles was reduced after phagocytosis by macrophages, and the authors postulated that an intracellular detoxification process might account for the variable degrees of cellular necrosis observed histologically (23). Indeed, the histological appearance of viable dusty or black, particle-filled phagocytic cells in some tissues around metal-on-metal joints shows that intracellular particles do not necessarily induce extensive tissue necrosis (19,24).

Following the production and deposition of metal particles into periprosthetic soft tissues the resulting biological responses can range from no detectable cell or tissue abnormalities to a variety of clinical complications that have been combined under the umbrella terms of adverse local tissue reactions (ALTRs) or adverse reactions to metal debris (ARMD). These can include extensive necrosis and/or the formation of tumor-like masses (pseudotumors) (25) bone resorption (26) or painful inflammation possibly related to excessive particle deposition (27) or metal hypersensitivity (28). None of these

complications, however, is unique to metal-on-metal hips.

Metal hypersensitivity (allergy)

Another concern with metal-on-metal bearings when they were considered for reintroduction in the 1990's was that some patients would have an allergic reaction to the constituents of the alloy (29). This was thought most likely to be to the nickel content (typically trace to 2% of the alloy constituents) but cobalt sensitivity was also questioned because this typically makes up 60% of the CoCr alloy and has a tendency to elicit a comparable response to nickel in some individuals. This concern was based on occasional reports of apparent metal sensitivity reactions in a small number of patients with first-generation metal-on-metal total hips and included periprosthetic effusions, local necrosis, or, rarely, skin urticaria (30,31). At the time, however, it was the consensus view that the more widespread benefits of reduced osteolysis and long-term durability would far outweigh this potential adverse event (29). It was suggested that fewer than 1% of patients would require revision for metal allergy, a figure largely supported over time (32,33) although the variability in defining the criteria for hypersensitivity reactions results in controversy over the clinical incidence of this complication.

While cutaneous patch testing is considered the gold standard for detecting type IV hypersensitivity reactions by dermatologists, methods to accurately and efficiently identify patients at risk for implant-induced metal hypersensitivity have been elusive. Although still used in some centers (34), the utility of cutaneous patch testing in orthopaedic implants has been equivocal and currently there are no well-defined guidelines for preoperative metal sensitivity screening.

Caicedo *et al.* (35) using a lymphocyte transformation test (LTT), found that females with total hip and total knee replacements exhibited a higher rate and greater severity of metal sensitization and unexplained pain. When data from the Danish knee arthroplasty registry was cross-referenced that with a contact allergy patch test database from the greater Copenhagen area, Munch *et al.* identified 327 patients who were patch-tested prior to TKA; their study found that revision surgery was not associated with higher prevalence of contact metal allergy (36). However, in patients who had 2 or more revision surgeries, the prevalence of cobalt and chromium allergy was "markedly" higher. As recently as 2018, despite a large body of orthopaedic literature on the topic, the cause and effect relationship between metal hypersensitivity and implant failure was noted to be "uncertain" (37).

Osteolysis in patients with metal-on-polyethylene implants was the impetus for the reintroduction of metal-on-metal implants. The rapid, destructively expansile type of osteolysis that occurred with polyethylene has been greatly reduced but there are still documented cases in metal-on-metal hip recipients, possibly secondary to metal hypersensitivity. For example, Park *et al.* (38) reported that patients with rapidly progressive osteolysis also had significantly higher rate of sensitivity to cobalt, determined by cutaneous patch testing and supported by histological findings. They suggested that, following second generation metal-on-metal hip replacement, antigen-specific activation of T cells may be a pathway involved in osteolysis.

Aseptic lymphocytic vasculitis-associated lesions (ALVAL)

As the number of patients with second-generation metal-on-metal hip replacements increased, concerns over metal allergy or hypersensitivity re-emerged. Early reports of well-fixed Metasul (Sulzer/Zimmer, Winterthur Switzerland) implants revised for pain and, in some cases osteolysis, noted that pain was not relieved when the patient received a second metal-on-metal hip (39). Tissues from those suspected metal hypersensitivity cases showed histologic features consistent with metal allergy (prominent, perivascular and/or diffuse lymphocyte and plasma cell infiltrates, fibrin deposition, and extensive necrosis). Predominant T lymphocytes, coupled with a clinical presentation of pain in the absence of loosening, infection, or high wear of the bearings, were interpreted to represent a form of type IV delayed-type hypersensitivity (DTH) response to metal (39). Other features of this reaction included a distinct tissue layering, for example, perivascular lymphocytes were located behind surface fibrin or necrosis (40). The presence of B lymphocytes, fibrin and macrophages with drop-like inclusions made this phenomenon different enough from classical delayed type IV hypersensitivity that it warranted a new name. The term ALVAL was introduced (39) and has been widely adopted both to describe histological rankings (41,42) as well as to describe painful soft tissue reactions around metal-on-metal hips.

Pseudotumors

In 2008, when HRA was in wide clinical use, reports from a large-volume teaching hospital in England described

revisions for painful masses near the components of female HRA patients (43). These were termed pseudotumors and they were initially attributed to metal hypersensitivity (25). Similar masses were observed in association with revisions for elevated serum cobalt and chromium ions in patients with steep acetabular components (44,45). Retrieval analysis documented a strong correlation between acetabular implant position, metal levels and component wear (46-49). In severe cases, those malpositioned joints were characterized by extensive tissue metallosis, the formation of large, fluid-filled or semi-solid masses with histology that included abundant debris-filled macrophages, lymphocyte infiltrations and varying degrees of necrosis (44,50-52). Further support for the role that cup malposition, elevated wear and metal ion levels played in the failure of HRA was provided by a low incidence of such complications in cohorts with fewer cases of steep cups. For example, within a group of 52 unilateral HRA patients, metal ion levels ≥7 microg/L were found in 9 cases. These patients had more likelihood of having malpositioned cups as determined by the contact patch to rim measurement, i.e., the distance between the point of intersection of the hip reaction force with the cup and the closest point on the inner side of the cup rim (53). A low incidence of pseudotumors was also found in a large series of hip resurfacing arthroplasties (54) but the authors used stricter criteria for complications and proposed a cobalt level of 4 microg/L as a cut-off for predicting problematical cases. Similarly, a review of a single surgeon series of nearly 2,600 metal-on-metal hip resurfacings found that failures associated with high wear accounted for 0.27% (55). The patients found to be at risk for these failures included females and those with components smaller than 48 mm.

These reports imply a cause and effect between wear, metal ion levels and clinical consequences but such a relationship is controversial at best (42,56-58). A large degree of variability has been reported between metal levels, pseudotumor rates and revisions. In a review of the literature, Campbell *et al.* (59) reported that metal ion levels were generally elevated in patients with complications including pseudotumors, but retrieval analysis of component wear typically showed a range of linear wear, thus reducing the degree of correlation between clinical outcome and wear. Pseudotumors have been noted in well-positioned, low wearing metal-on-metal hips (60,61), possibly as they may be the result of metal sensitivity (41). Taken together, these observations suggest that factors other than wear are important to the clinical outcome of HRA (58). Individual patient susceptibility or genetic predisposition to potentially adverse reactions to wear debris or metal ions is likely to be one explanation.

One recent study found genetic differences among patients with a primary metal-on-metal total hip with pseudotumors and those who did not form pseudotumors (62). They concluded that an allelic variation within the HLA Class II loci may be a strong, independent risk factor associated with pseudotumor formation, but cautioned that confirmatory prospective clinical studies are required to further elucidate this correlation. Interestingly, differences in the synovial fluid protein content between patients with metal-on-metal hips with and without pseudotumors have recently been reported (63). Further studies to characterize differences between patients with adverse reactions and those who seem to tolerate wear debris may help to devise a method to predict a patient-specific response to implanted devices.

Systemic effects

Cobalt toxicity from excessive wear of joint arthroplasty devices is an exceedingly rare event, but the term "cobaltism" has been introduced to describe it (64). In an extensive review of the orthopaedic literature up to February 2014, Bradberry *et al.* reported that there were 18 individual cases of systemic toxicity related to total hip prostheses (65). Using a slightly broader search strategy, Gessner *et al.* in 2015 reported finding 25 cases (66). In both reviews, rare cases of neuro-ocular toxicity, cardiotoxicity, and thyroid toxicity were attributed to cobalt rather than chromium toxicity, based on known clinical effects of cobalt. Although metal-on-metal hip patients were among the reported cases, the most severe instances involved massive wear of metallic femoral heads that were inserted in revisions for fractured ceramic bearings. Extremely high blood cobalt levels (for example 300 to 600 microg/L) were documented and clinical symptoms included blindness, deafness, neuropathy, cardiopathy, fatigue, and headaches. Lower cobalt levels (20 microg/L) have been associated with symptoms of cobaltism in one report (64). In nearly all reported cases, cobalt levels were documented to fall following revision of the worn implants and usually, but not always, with an accompanying decrease or resolution in symptom severity (65).

A survey of the data within the Australian Government Department of Veterans' Affairs health claims database was conducted to compare the risk for hospitalization for heart problems for metal-on-metal total hip recipients and metal-

on-polyethylene total hip recipients (67). Of the 4,019 patients with no prior history of heart failure, men with one type of metal-on-metal total hip were found to have a higher rate of hospitalization, but no such association was found for the other types of metal-on-metal total hips or for women with that particular implant. No statistically significant difference in mortality was observed for any of the metal-on-metal bearings compared to metal-on-polyethylene total hips. The authors of the study pointed out that causality between the metal-on-metal implant and heart failure could not be established but suggested that their observations warranted further monitoring of metal-on-metal patients for long-term cardiac complications.

While the majority of patients included in the above study had stemmed total hips, one group selected to examine patients with well-functioning metal-on-metal hip resurfacings (68). MRI imaging was used to compare liver and heart tissue features and cardiac structure and function, and the findings were correlated with metal ion levels in a group of 10 unilateral and 10 bilateral metal-on-metal resurfacing patients and a group of 10 patients with non-metal-on-metal total hips. The metal-on-metal HRA patients had slightly larger indexed right and left end diastolic volumes and a small decrease in T2 time that were associated with higher metal ion levels.

Both cobalt and chromium can cross the blood-brain barrier and studies specifically on the potential neurological effects of metal ion exposure have attempted to address this concern. An MRI study of the brains of 29 asymptomatic hip resurfacing patients found that the occipital cortex grey matter attenuation and optic chiasm area tended to be lower compared with patients with non-metal-on-metal total hips matched for age at surgery, gender and time since surgery (69). Other measures such as total brain volume, total grey and white matter area, were similar in the two groups. Blood levels of Co and Cr were higher in the metal-on-metal patients. The authors point out that the subtle differences they detected in brain morphometry between the groups did not remain after multiple-comparison correction procedures and, as such, further research with larger groups is warranted.

Several case reports have described sensory effects of excessive metal levels including hearing loss (66). A recent study used an extensive battery of auditory and vestibular tests to examine the ototoxic effects of metal-on-metal hips in a group of 20 metal-on-metal hip patients and a group of non-implanted controls matched for age, gender and noise-exposure (70). Small changes were found in the high frequency hearing function in the metal-on-metal group but no differences in the vestibular outcomes were found. Although there was no association with the circulating cobalt levels, the authors suggested that the hearing changes may reflect cobalt-induced damage, citing previous findings on drug-induced ototoxicity and recent animal experiments.

Metal-on-metal implants have typically been contraindicated for patients with chronic kidney disease because of the concern that the metal ions would not be cleared efficiently and would therefore accumulate in vivo. The question of whether chronic exposure to Co and Cr ions leads to kidney problems was addressed in a retrospective study of serum creatinine levels are urine renal markers in 31 patients who had received metal-on-metal hip resurfacing arthroplasties 10 years or more prior (71). A group of age- and gender-matched subjects without known kidney problems or metal exposure acted as controls. No elevation in renal markers was detected in the HRA patients.

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Footnote

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