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COMMENTS TO AUTHORS

**The regulation of periprosthetic tissues due to metallic debris:
Lessons learnt from Metal-on-Metal total hip arthroplasty**

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**Prof. Dr med. Hans-Georg Willert, to whom this work is dedicated, passed away on September 25th, 2006.*

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Abstract

The era of Metal-on-Metal (MoM) total hip arthroplasty (THA) has left the orthopaedic community with valuable insights and lessons on periprosthetic tissue reactions to metallic debris. Various terms have been used to describe the tissue reactions and sometimes the nomenclature can be confusing. We present a review of the concepts introduced by Willert and Semlitsch in 1977, along with further developments made in the understanding of periprosthetic tissue reactions to metallic debris. We propose that periprosthetic tissue reactions be thought of as (i) gross (metallosis, necrosis, cyst formation and pseudotumour), (ii) histological (macrophage-dominated, lymphocyte-dominated or mixed) and (iii) molecular (expression of inflammatory mediators and cytokines such as IL-6 and TNF-alpha). Taper corrosion and modularity are discussed, along with future research directions to elucidate the antigen-presenting pathways and material-specific biomarkers which may allow early detection and intervention in a patient with adverse periprosthetic tissue reactions to metal wear debris.



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Introduction

Retrieval studies on failed Metal-on-Metal (MoM) total hip arthroplasties (THAs) have contributed significantly to the understanding of adverse local tissue reactions to metallic debris. The McKee Farrar and Ring implants used in the 1960s had MoM bearing surfaces (1–3). Weber implanted the first second-generation MoM THA (high carbon cobalt-chrome alloy) in 1988 (4). The success of large-diameter hip surface replacement further popularized MoM hip replacements (5–8). Large-diameter MoM heads (36 mm diameter or larger), started being used in revision hip surgery and were later used in primary THAs. Registry data suggest that MoM devices have been implanted into over 60,000 patients in England and Wales since 2003 and the figure is closer to a million in the United States (9,10).

Metal wear products in periprosthetic tissue may exist as particulate wear debris, metal ions in solution, organic metallo-protein complexes, and byproducts of synergistic corrosion and wear processes (especially when modular interfaces are involved) (11,12). Smaller particles may form complexes with tissue and serum proteins. It has been suggested that these metal-protein complexes may form haptens, to which different individuals may have a different response threshold (13,14). Corrosion and wear at modular interfaces such as the head-neck and neck-stem junction are thought to contribute to failure of MoM hip replacements, among other factors. (15–21). Taper corrosion has also been recognized in metal-on-polyethylene THAs (22). Metal particulate debris tends to be in the nanometre size range and (23) MoM articulations generate approximately 10^{12} – 10^{14} particles per year.



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Difficulties associated in isolating and characterizing these small nanometric particles suggest that the actual number of particles produced in-vivo may be higher. (24,25).

The Willert-Semlitsch concept:

Willert and Semlitsch, in 1977, (26) described the tissue reactions of the articular capsule to wear products of artificial joint prostheses. In their landmark article, they reported the development of a foreign-body reaction (consisting of macrophages and foreign-body giant cells) to wear debris. This foreign-body reaction takes place in the neocapsule and, depending on its magnitude, may lead to the formation of granulation tissue, which may subsequently cause scarring and decrease joint mobility. They went on to discuss the concept of an 'equilibrium state', which is achieved when the periprosthetic lymph vessels are effectively clearing the wear debris at the rate of debris production (Figure 1). If the periprosthetic lymph channels are overwhelmed, excess wear debris then spills over into the implant-bone interface and surrounding tissue. We now know this as the 'effective joint space' as described by Schmalzried and colleagues in 1992 (27). Joint fluid helps to transport wear particles to new sites, resulting in activation of osteoclasts and inhibition of osteoblasts via molecular signaling pathways involving a host of inflammatory mediators. This phenomenon has also been called 'particle disease' (28,29). The 'threshold' of the periprosthetic lymphatics to effectively clear wear debris is subject to interindividual variability, and this phenomenon may partially explain why some people develop adverse tissue reactions and early osteolysis in response to metal debris whilst others seem to have a mild or no reaction, assuming all other factors being equal. Since then, research efforts have focused on the types of tissue reactions, immunological



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and molecular pathways involved. These pathways are still not well-understood, though some light has been shed on the types of tissue reactions to particulate wear debris.

Adverse tissue reactions in MoM THAs

Adverse tissue reactions may be systemic or local. Systemic concerns include elevated metal ion levels in the serum and solid organs as well as potential carcinogenicity and teratogenicity. Various terms have been coined to describe the adverse local tissue reactions seen in MoM THA and the nomenclature is debatable. Essentially, ALTR (adverse local tissue reaction) encompasses all types of adverse local tissue reactions to debris, whereas ARMD (adverse reaction to metallic debris) and ALVAL (Aseptic lymphocyte-dominated vasculitis-associated lesion) represent more specific descriptions. For clarity of thought, it may be useful to think about local periprosthetic tissue reactions at the gross, histological and molecular levels.

Gross tissue reactions

Gross intraoperative findings in revision operations for failed aseptic metal-metal hip replacements range from metallosis, large joint effusions, necrosis and pseudotumours(30-39). A pseudotumour is defined as a granulomatous lesion or a destructive cystic lesion, neither infective nor neoplastic, that is at least 5 cm in size, has developed in the vicinity of the total joint replacement (with or without communication with the joint), and resembles a tumour (40).



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Histology :- Macrophage-dominated and lymphocyte-dominated reactions

Histologically, to avoid confusion associated with the nomenclature, we differentiate the predominant cellular responses into a macrophage-dominated type and a lymphocyte-dominated type. Other features which may be seen are fibrin exudation and necrosis. Essentially, macrophage-dominated responses lack immunological memory and are seen in foreign-body type granulomatous reactions. Lymphocyte-dominated responses represent a T-cell-mediated reaction involving diffuse and perivascular lymphocytic infiltrates and resembles a type IV delayed hypersensitivity reaction. This involves a specific antigen, co-stimulatory molecules, an antigen-presenting cell, and T lymphocytes. The lymphocyte-dominated response is adaptive and has immunological memory. The latter response may contribute to progressive osteolysis and early aseptic loosening of MoM THAs and is also seen in the context of wear and corrosion debris from metal-metal modular interfaces in non-MoM THAs (41-45). The two responses may co-exist and research efforts are being channelled into identifying the factors which are responsible for the predominant type of tissue response.

We analyzed tissue response, serum and periprosthetic tissue metal content among a cohort of 28 small-diameter MoM THAs and found that the total tissue metal content correlates with type of tissue response but not serum metal content (table 1) (46). 27 patients (28 hips) who were revised from second-generation

small-diameter MoM bearing couples (Sikomet®, 0.08% carbon content) to ceramic-on-ultra high molecular weight polyethylene (UHMWPE) (8 hips), metal-on-UHMWPE- (19 hips), or ceramic-on-ceramic (1 hip). The duration of implantation was 54 to 86 months with a mean of 66 months. The metal (Co, Cr, and Ni) content of the periprosthetic tissue ranged from 1.4 to 4604.0 µg/g. Histologically, macrophages containing metal particles as well as diffuse and perivascular lymphocytic infiltration were observed. Fibrin exudation was also visible. Tissues that displayed a predominantly lymphocytic response had a mean metal content of 222.2 ± 52.9 µg/g, whereas those that displayed a macrophage-dominated response had a metal content of 3.0 ± 0.9 µg/g; this difference was significant ($p = 0.001$). The mean serum metal content did not differ significantly between the two subgroups (60.7 ± 13.4 compared with 43.7 ± 3.8 µg/L, $p = 0.105$). The content of Ni in the tissues did not differ significantly between retrievals with macrophage-dominated and lymphocyte-dominated histologies, but the content of Co in the tissues was 150 times greater in the lymphocyte-dominated group and that of Cr was eighty-five times greater. Figure 2 illustrates radiographic, intraoperative, and histological findings of a patient with progressive osteolysis in a small-diameter metal-on-metal THA.

Head size may be another factor which drives the predominant type of tissue response in one direction or another. In general large-diameter MoM THAs have been associated with similar types of gross adverse tissue reactions as seen in small diameter MoM THAs. Bosker et al. (47) reported a higher incidence of pseudotumor formation in patients with large diameter MoM THAs. At a mean follow-up of 3.6 years, 42 out of 108 patients (109 hips) in their series were diagnosed with a pseudotumor by computed tomography (CT) and patients with elevated serum metal levels had a four times increased risk of developing a pseudotumor. Langton and



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colleagues (48) described perivascular cuffs of lymphocytes among metal debris and areas of necrosis in periprosthetic tissue of revised ASR hips, consistent with ALVAL type of tissue reaction. Kawakita et al.(49) reported a case of unilateral leg edema secondary to a pelvic mass after a large diameter MoM THA. The edema was of spontaneous onset and developed 1 year and 2 months after surgery. Histology of the resected mass was consistent with the diagnosis of pseudotumor. Corrosion at the cone-taper (head-neck) junction in these large diameter MoM THAs (17,18) may be a significant contributory factor to their failure and this mode of failure may result in a different profile of wear debris in the periprosthetic tissues. This is presented in more detail in the subsequent section on modularity and taper corrosion.

Molecular pathways

Molecular pathways leading to early aseptic loosening among MoM implants are not well understood either. A variety of inflammatory mediators such as interleukin-6 (IL-6), prostaglandin E2 (PGE2) and tumor necrosis factor-alpha (TNF-alpha) have been shown to be expressed by monocytic cells in periprosthetic tissue of failed joint arthroplasties (50, 51). Caicedo and colleagues suggested that soluble ions more than particulate cobalt-alloy implant debris induce monocyte co-stimulatory molecule expression and release of proinflammatory cytokines which contribute to metal-induced lymphocyte reactivity (52). Tuan et al observed that many pro-osteoclastic inflammatory cytokines not only promote osteoclastogenesis but also interfere with osteogenesis led by osteoprogenitor cells (53). Lin et al. investigated the suppression of chronic inflammation by inhibiting NF- κ B activity as a strategy to combat wear particle induced periprosthetic osteolysis (54). Ren



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and colleagues from the University of Kansas group previously reported that VEGF inhibitor treatment prevented UHMWPE particle-induced inflammatory osteolysis (55). Most of these inflammatory chemokines are upregulated in metal-on-metal implant failures, periprosthetic tissue affected by osteolysis due to polyethylene wear debris as well as other disease states involving chronic inflammation and even malignancy (eg multiple myeloma) and are not specific to the inciting agent or material (56). The common end-point for each of these pathways is osteoclast activation and bone resorption (57,58), leading to implant loosening and revision surgery. Future research efforts should be channeled towards identifying a molecular marker which is material-specific i.e. is upregulated by the presence of metallic wear debris but not affected by polymeric wear debris and infection.

Taper Corrosion and Modularity

Modular interfaces in joint replacement surgery perhaps represent a double-edged sword. Modularity has, beyond doubt, made the technical complexity of surgical operations (particularly revisions) much easier but has also introduced a new set of problems for the revision surgeon – problems associated with the release of corrosion and wear debris from these interfaces. The cone-taper (head-neck) interface and neck-stem interface (when modular necks are used) in THA surgery represent two potential interfaces for a crevice environment and mechanically assisted corrosion leading to instability.

Much of the early work in studying the cone-taper interface has been done by Collier et al. (59,60). In 139



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retrieved THA implants (using mixed metal systems), they found evidence of time-dependent corrosion at the cone-taper interface, compared to no evidence of corrosion among implants which had components made from the same alloy. They observed that the crevice between the head and neck can function as a corrosion site if it is wide enough to allow aqueous intrusion but narrow enough to maintain a stagnant zone. Willert et al.(45)observed that the passivation layer of an alloy safely protects the release of ions and may inhibit electrochemical conduction. However, micromotion may abrade this protective layer and initiate the processes of fretting, crevice, and galvanic corrosion.

Gill et al. (19) identified corrosion at neck-stem tapers as an important source of metal ion release and pseudotumor formation in a cohort of 33 patients with 32 mm heads and 2 with 28 mm heads. Gill's group demonstrated high stresses at the modular stem-neck junction using finite element modeling of dual modular stems. Higgs et al (16) studied 134 heads and 60 stems (41 modular necks) of 8 different bearing designs (5 manufacturers) and concluded that dissimilar alloy pairing, larger head sizes, increased medio-lateral offsets and longer neck moment arms were all associated with increased taper damage at the modular interfaces. Cook et al, (22) have reported pseudotumor formation due to tribocorrosion at the taper interface of large diameter metal on polyethylene modular total hip replacements. Cooper's group reported the occurrence of adverse local tissue reactions (ALTR) similar to those seen in MoM THAs and corrosion at the head-neck junction in ten patients with a metal-on-polyethylene total hip prostheses, from three different manufacturers (21).

We have reported the occurrence of corrosion and instability at the cone-taper interface, tissue metal content



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and element analysis of periprosthetic wear debris and type of tissue response (macrophage-dominated vs lymphocyte dominated) among 2 cohorts of failed Metal-on-Metal (MoM) total hip arthroplasties (THA's) (17,18,46). The first cohort consisted of 27 patients (28 hips) who were revised from second-generation small-diameter MoM bearing couples (Sikomet[®], 0.08% carbon content) to ceramic-on-ultra high molecular weight polyethylene (UHMWPE) (8 hips), metal-on-UHMWPE- (19 hips), or ceramic-on-ceramic (1 hip). The duration of implantation was 54 to 86 months with a mean of 66 months. The second cohort consisted of 110 patients who had 114 revisions of large-diameter head MoM THAs (LDH[®] head (Zimmer Inc, Warsaw, IN, USA) and a DUROM[®] hip cup (Zimmer Inc, Warsaw, IN, USA). The duration of implantation was 26 to 68 months with a mean of 46 months. All implants were revised to ceramic-on-polyethylene articulating couples. Among the first cohort of small diameter MoM THA's, there was no evidence of corrosion or instability at the cone-taper interface of the retrieved implants intraoperatively. All patients, including those revised to a metal-on-polyethylene bearing couple reported complete resolution of symptoms. In contrast, we have reported corrosion at the cone-taper interface as being a significant mode of failure in large-diameter metal-on-metal hip arthroplasties (18). Out of 114 revisions of large-diameter MoM THA's, 107 (94%) retrieved implants had evidence of corrosion as well as gross instability at the cone-taper interface. One hundred six (93%) of the 114 hips had joint effusions and tissues with a grayish necrotic appearance were found around the implants, respectively. Intraoperatively, in 94% (n = 107), the cones and the tapers were unstable and showed a black color resembling corrosion. Interestingly, only 9 cases in this series had a lymphocyte-dominated tissue response and all other cases had a foreign-body type, macrophage-dominated tissue response. Element analysis with Inductive-Coupled Plasma Mass Spectrometry (ICPMS) showed a very different profile of wear debris



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with titanium or iron predominating, suggestive of abrasive wear from the neck taper.

From a practical standpoint, precautions which may lower the risk of taper corrosion include avoidance of blood and debris at the taper prior to impaction of the head, avoiding impaction of the head at an angle and not mixing and matching components from different manufacturers without a thorough knowledge of the materials and alloys which make up the components. The emergence of this phenomenon in non-MoM THAs certainly brings

to light the reality of the problem and we recommend that modularity should be used with a hint of caution.

Summary

Metal-on-metal total hip arthroplasties and their failures have given the orthopedic community valuable insights into periprosthetic adverse tissue reactions. Further research needs to be directed towards the immunological mechanisms, antigen-presenting and molecular pathways responsible for these adverse tissue reactions. Identification of material-specific biomarkers will potentially allow early diagnosis of adverse tissue reactions and facilitate early intervention in these patients.



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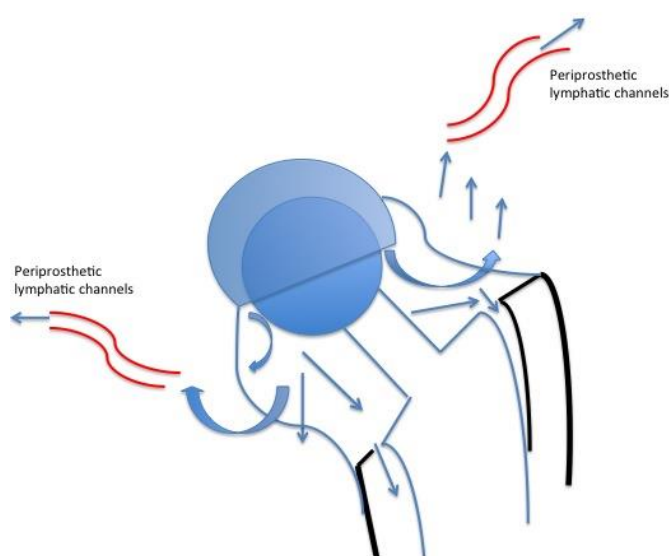


Figure 1 :The Willert-Semlitsch concept of clearance of wear debris by periprosthetic lymph channels. If production of wear debris exceeds the ability of the lymph channels to clear it, the debris then 'spills' over into the effective joint space and initiates osteolytic pathways.



Figure 2 (a): Plain radiograph showing progressive early osteolysis in a patient with small diameter metal-on-metal THA.



Figure 2(b): Intraoperative photograph showing purulent material during revision surgery for a failed MoM THA. There was no evidence of infection in this patient and this purulent material was due to an adverse local tissue reaction.

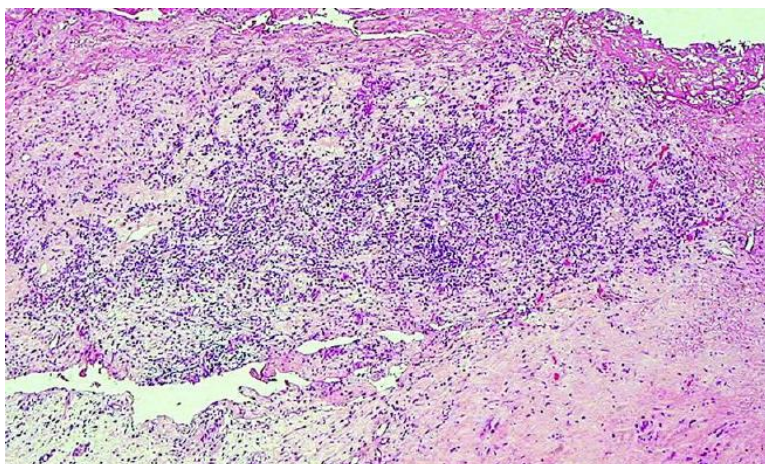


Figure 2(c): Diffuse lymphocytic infiltration seen in periprosthetic tissues. Haematoxylin-Eosin, Magnification x 20

Tables:

Table 1(a)

| | Cobalt | Chrome | Nickel |
|----------------------|--------|--------|--------|
| Macrophage-dominated | 17.25 | 21.0 | 22.5 |
| Lymphocyte-dominated | 13.41 | 21.92 | 8.41 |

Table 1(b)

| | Cobalt | Chrome | Nickel |
|----------------------|--------|--------|--------|
| Macrophage-dominated | 0.3 | 2.0 | 0.6 |
| Lymphocyte-dominated | 45.2 | 163.6 | 1.6 |

Table 1(a) and (b): Tissue metal content, but not serum metal content has a positive correlation with type of periprosthetic tissue response in a series of 28 small diameter MoM THAs. All values are in micrograms/Litre