Prevalence of Adverse Reactions to Metal Debris Following Metal-on-Metal THA

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The purpose of this study was to determine the prevalence of adverse reactions to metal debris (ARMD) following large-diameter metal-on-metal total hip arthroplasty. The authors examined the potential for using magnetic resonance imaging to screen for pseudotumors in 108 hips 2 years postoperatively. Serum cobalt and chromium concentrations were measured in 80 hips that underwent unilateral total hip arthroplasty. The authors considered pseudotumors and aseptic lymphocyte-dominated vasculitis-associated lesions to be ARMD and compared metal ion levels between hips with ARMD (ARMD group) with hips with no ARMD (non-ARMD group).

Magnetic resonance imaging revealed pseudotumors in 9 patients (10 hips, 9%). Five of these 10 hips were symptomatic and underwent revision surgery. Two other patients underwent revision surgery due to symptomatic cup loosening with aseptic lymphocyte-dominated vasculitis-associated lesions. Ten patients (12 hips) had ARMD. Serum cobalt and chromium concentrations were significantly higher in hips with ARMD than hips without ARMD. Other factors, including age, body mass index, sex, clinical score, acetabular cup inclination angle, and femoral head diameter, were not significantly different between the groups.

Elevated metal ion levels suggest that ARMD is associated with increased metal wear. Magnetic resonance imaging provides sensitive screening for pseudotumors following metal-on-metal total hip arthroplasty.
The perceived advantage of metal-on-metal total hip arthroplasty (THA) is that the use of larger femoral heads can minimize the risk of postoperative instability. Another advantage is that metal-on-metal bearing surfaces have demonstrated favorable wear rates compared with more traditional metal-on-polyethylene bearing surfaces, potentially leading to longer survival rates. In England and Wales, the use of stemmed metal-on-metal implants increased rapidly after 2004 to a peak of more than 9000 operations in 2008 but then sharply declined. Recently, material-based concerns have been elucidated. Numerous studies have reported that patients with metal-on-metal bearings exhibit increased serum cobalt and chromium ion levels. Increased wear at the bearing surfaces and corrosion at the head-stem taper interface were the 2 main sources of metal ion debris. Another concern was periprosthetic soft tissue masses (pseudotumors). These pseudotumors have been variously termed cysts, bursae, aseptic lymphocyte-dominated vasculitis-associated lesions, and adverse reactions to metal debris (ARMD). These lesions are the result of tissue reactions to metal debris with lymphocyte infiltration and soft tissue necrosis; however, the pathogenesis remains unclear. The prevalence of pseudotumors following metal-on-metal resurfacing or THA has not been adequately clarified. Due to the identification of these lesions, the Medicines and Healthcare Products Regulatory Agency in the United Kingdom published a safety alert for all metal-on-metal hip resurfacing and THA implants.

Magnetic resonance imaging (MRI), computed tomography, ultrasonography, and metal ion measurements have aided in diagnosing unexplained hip pain following THA with metal-on-metal bearings. Using MRI in the presence of metallic hardware has traditionally been limited by susceptibility artifacts generated by the presence of the metallic components. However, with the development of techniques that reduce susceptibility artifacts, MRI has become a valuable assessment tool after THA.

The aims of the current study were to determine the prevalence of symptomatic and asymptomatic ARMD and to identify the risk factors, including metal ion levels, for their formation in a prospective cohort of patients who underwent THA with a metal-on-metal implant.

**Materials and Methods**

**Demographics**

Between 2008 and 2009, ninety-eight patients (108 hips) underwent THA with a large-diameter bearing metal-on-metal implant at the authors’ institution. Seventeen men and 81 women with a mean age of 65 years (range, 40-84 years) were included. Mean body mass index was 23.7 kg/m² (range, 16.5-37.1 kg/m²). The preoperative diagnoses were osteoarthritis in 102 hips, idiopathic osteonecrosis of the hip in 4, and rheumatoid arthritis in 2.

**Components and Implantation**

All patients underwent cementless THA using a large-diameter head with a Cormet cup and CTi II stem (Corin, Cirencester, United Kingdom) with a metal-on-metal articulation. The numbers of hips that received a femoral head diameter of 40, 44, 48, and 52 mm were 29, 60, 18, and 1, respectively. The Cormet cup and large-diameter head were made of a cast, high-carbon-content cobalt-chromium alloy (0.35% C), which was subject to hot-isostatic pressing and solution annealing (double heat treatment) before the machining process occurred. The Cormet cup was coated with titanium plasma spray for bone ingrowth and implanted using the press-fit technique. This cup can be used with hip resurfacing or THA systems. The large-diameter head had an open design. Between the location of the head and stem, no modular adapter was needed. The CTi II stem, which was made of a titanium alloy, had a proximal plasma spray coating. Articular surface roughness was less than 0.05 µm, articulation surface sphericity deviation was less than 8 µm, and component radial clearance was 100 µm according to the manufacturer. Mean acetabular component diameter was 51 mm (range, 46-58 mm), mean inclination angle was 41° (range, 28°-57°), and mean anteversion angle was 15° (range, 1°-28°). This study was approved by the authors’ institution’s ethics committee, and all patients gave informed consent.

**Clinical Evaluation**

Clinical evaluation was performed using the Merle d’Aubigne and Postel scoring system, assigning a maximum of 6 points each to pain, mobility, and ability to walk; thus, 18 points was the maximum score. The authors assessed the scores pre- and postoperatively. Mean follow-up was 3.8 years (range, 2.9-4.6 years).

**Imaging**

The authors examined the potential of using MRI to screen for pseudotumors following metal-on-metal THA. Magnetic resonance imaging was conducted 2 years postoperatively in all hips. A 1.5-Tesla scanner was used with T1-weighted spin-echo, T2-weighted spin-echo, and short tau inversion recovery sequence (Signa; GE Medical Systems, Buckinghamshire, United Kingdom). The authors defined a pseudotumor of the hip as a semi-solid or cystic periprosthetic soft tissue mass with a diameter of 2 cm or more. Pseudotumors were classified as cystic, solid, and mixed types.

**Metal Ion Concentrations**

The authors measured serum cobalt and chromium ion concentrations preoperatively and at 3 months and 1 and 2 years postoperatively, as they previously reported in 80 hips that underwent unilateral THA. Cobalt levels were assayed using Inductively Coupled Plasma Mass Spectrometry (Perkin-Elmer SCIEX Elan...
tests were used to detect no pseudotumor or aseptic lymphocyte-dominated vasculitis-associated lesions (ARMD) group and hips with pseudotumors or aseptic lymphocyte-dominated vasculitis-associated lesions (non-ARMD group).

**Histology**

The tissue specimens in patients who underwent revision were fixed in 10% neutral buffered formalin prior to processing and embedding in paraffin wax. Sample sections 5 µm thick were stained with hematoxylin-eosin and examined by light microscopy. Sections were also analyzed with immunohistochemistry using antibodies to T lymphocytes (CD3; DAKO, Glostrup, Denmark) and B lymphocytes (CD20; DAKO) to characterize the immunophenotype. Revised components underwent macroscopic and microscopic examinations using scanning electron microscopy. A lymphocyte transformation test was performed in these patients before and 1 month after revision.

**Statistics**

Mann-Whitney U tests were used to compare serum metal levels, age, BMI, Merle d’Aubigné and Postel score at last follow-up, acetabular cup inclination and anteversion angle, and femoral head diameter between the ARMD and non-ARMD groups. Chi-square test was used to compare sex between the groups. Pre- and postoperative Merle d’Aubigne and Postel scores were compared using Wilcoxon signed-rank test. Statistical significance was set at a P value less than .05.

**RESULTS**

Magnetic resonance imaging revealed pseudotumors in 9 patients (10 hips, 9%). Four hips were characterized as having the cystic tumor type, 1 as the solid type, and 5 as the mixed type (Figure 1). Five of 10 hips with pseudotumors were symptomatic (had pain) and underwent revision surgery. Two other patients underwent revision surgery due to symptomatic cup loosening with perivascular lymphocytes and diffusely distributed lymphocytes and extensive necrosis consistent with aseptic lymphocyte-dominated vasculitis-associated lesions. When the authors designated pseudotumors and aseptic lymphocyte-dominated vasculitis-associated lesions as ARMD, 10 patients (12 hips) were categorized as having ARMD (Table 1). The acetabular component was loose in 3 hips but firmly anchored in all other hips. No stem showed loosening. Osteolysis was found in 2 hips with pseudotumors. Preoperative biopsies in all revised hips produced negative microbiological cultures.

Immunohistochemical study revealed that 5 hips with ARMD showed dominant CD20 positive B lymphocyte infiltration (Figure 2), and 2 hips with ARMD showed dominant CD3 positive T lymphocytes. In 6 of 7 hips with ARMD that had been revised, corrosion with black markings and deposits were visible at the taper and modular head interface, possibly contributing to the development of metal debris. Macro- and microscopic examinations revealed stripe wear on the cup and head articular surfaces (Figure 3). Scanning electron microscopy showed a loss of machine mark with fretting at the modular head interface. One patient had a positive lymphocyte transformation test indicating lymphocyte proliferation to cobalt before revision. However, no reactivity to cobalt or chromium was detected in the revised patients following revision (Table 1).

Mean Merle d’Aubigne and Postel score improved significantly from 9.5 points (range, 3-15 points) preoperatively to 14.9 points (range, 10-18 points) postoperatively (P<.001). The ARMD group was associated with significantly higher serum cobalt and chromium levels 3 months postoperatively compared with the non-ARMD group (Figures 4A, B). In addition, serum cobalt levels 2 years postoperatively and chromium levels 1 and 2 years postoperatively were significantly elevated in the ARMD group compared with the non-ARMD group (Figures 4C-F). Other factors, including age, sex, body mass index, clinical score, acetabular cup inclination and anteversion angle, and femoral head diameter, showed no significant differences between the groups (Table 2).

**DISCUSSION**

Pseudotumors are sterile inflammatory masses in the soft tissues surrounding...
Numerous studies have suggested that pseudotumors with metal-on-metal hip prostheses are the result of an adverse local response to metal wear debris and elevated cobalt and chromium levels in patients with a metal-on-metal hip prosthesis. 

In contrast, other studies reported that pseudotumors were not associated with increased wear or metal ion levels.

Adverse local tissue reactions are not limited to metal-on-metal articulations. Fujishiro et al reported many cases of perivascular and diffuse lymphocytic inflammation after non-metal-on-metal THA, with increasing lymphocyte concentrations being correlated with an increased amount of metal particles. Ng et al also reported perivascular lymphocytic infiltration after non-metal-on-metal THA. Both studies showed no evidence of soft tissue necrosis, which was found in aseptic lymphocyte-dominated vasculitis-associated lesions as reported by Willert et al.

Aseptic lymphocyte-dominated vasculitis-associated lesions means histological diagnosis; however, the diagnosis of ARMD was based on a combination of clinical history, examination, and macroscopic and histological appearance of tissues at revision.

Magnetic resonance imaging provides sensitive screening of pseudotumors following metal-on-metal THA. In a Canadian survey, pseudotumors developed after 4 (0.10%) of 3432 metal-on-metal resurfacings at a mean follow-up of 3.4 years. However, the data from the Canadian survey are limited to symptomatic lesions. The pseudotumor prevalence, including asymptomatic cases, has been reported to be from 4% to 61% when patients were screened using MRI, computed tomography, or ultrasonography (Table 3).

The current authors' previous metal ion study showed that cobalt (2.3 µg/L) and chromium (2.1 µg/L) levels had increased significantly 1 year postoperatively, with no additional significant increase over subsequent years.

| Table 1 | Detail of the 12 Hips with ARMD |

<table>
<thead>
<tr>
<th>No./Sex/Age, y</th>
<th>BMI, kg/m²</th>
<th>Years</th>
<th>In Situ, mm</th>
<th>Head, mm</th>
<th>Cup Size</th>
<th>Type of Pseudotumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/58</td>
<td>31.7</td>
<td>1.9</td>
<td>54</td>
<td>48</td>
<td>48</td>
<td>Solid mixed</td>
</tr>
<tr>
<td>2/F/69</td>
<td>24.8</td>
<td>2.5</td>
<td>50</td>
<td>44</td>
<td>44</td>
<td>Swirl</td>
</tr>
<tr>
<td>3/F/59</td>
<td>22.1</td>
<td>2.8</td>
<td>51</td>
<td>44</td>
<td>44</td>
<td>Cystic</td>
</tr>
<tr>
<td>4/F/75</td>
<td>25.8</td>
<td>3.8</td>
<td>52</td>
<td>44</td>
<td>44</td>
<td>Cystic mixed</td>
</tr>
<tr>
<td>5/F/70</td>
<td>22.0</td>
<td>1.1</td>
<td>50</td>
<td>44</td>
<td>44</td>
<td>Solid</td>
</tr>
<tr>
<td>6/F/70</td>
<td>23.8</td>
<td>1.9</td>
<td>51</td>
<td>44</td>
<td>44</td>
<td>Cystic mixed</td>
</tr>
<tr>
<td>7/F/58</td>
<td>23.6</td>
<td>3.2</td>
<td>50</td>
<td>44</td>
<td>44</td>
<td>Cystic</td>
</tr>
<tr>
<td>8/M/79</td>
<td>24.5</td>
<td>3.7</td>
<td>52</td>
<td>44</td>
<td>44</td>
<td>Solid</td>
</tr>
<tr>
<td>9/M/69</td>
<td>24.8</td>
<td>4.1</td>
<td>52</td>
<td>44</td>
<td>44</td>
<td>Cystic mixed</td>
</tr>
<tr>
<td>10/F/59</td>
<td>23.3</td>
<td>2.8</td>
<td>50</td>
<td>44</td>
<td>44</td>
<td>Solid mixed</td>
</tr>
</tbody>
</table>

Abbreviations: ARMD, adverse reactions to metal debris; BMI, body mass index; deg, degree; neg, negative; pos, positive.

- Includes 17 men and 31 women with a mean age of 65 years.
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<table>
<thead>
<tr>
<th>Mean ARMD</th>
<th>Mean total</th>
</tr>
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<tbody>
<tr>
<td>24.6</td>
<td>23.7</td>
</tr>
<tr>
<td>2.7</td>
<td>3.2</td>
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<tr>
<td>51</td>
<td>44</td>
</tr>
<tr>
<td>42</td>
<td>44</td>
</tr>
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<td>12</td>
<td>15</td>
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<td>101/39</td>
<td>101/39</td>
</tr>
<tr>
<td>9/46</td>
<td>9/46</td>
</tr>
<tr>
<td>27/15</td>
<td>27/15</td>
</tr>
<tr>
<td>7/23</td>
<td>7/23</td>
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<tr>
<td>8/27</td>
<td>8/27</td>
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</tbody>
</table>

Metal-on-metal THA: In a Canadian survey, pseudotumors developed after 4 (0.10%) of 3432 metal-on-metal resurfacings at a mean follow-up of 3.4 years. However, the data from the Canadian survey are limited to symptomatic lesions. The pseudotumor prevalence, including asymptomatic cases, has been reported to be from 4% to 61% when patients were screened using MRI, computed tomography, or ultrasonography (Table 3). The pseudotumor prevalence, including asymptomatic cases, has been reported to be from 4% to 61% when patients were screened using MRI, computed tomography, or ultrasonography (Table 3).
increases 2 years postoperatively in patients with the Cormet cup and a large-diameter head.\(^9\) In the current study, serum metal ion levels were significantly higher in hips with ARMD than in hips without ARMD. Metal ion measurement is a valuable tool for diagnosis and patient follow-up.\(^5\) The Medicines and Healthcare Products Regulatory Agency has suggested that patients with cobalt or chromium ion levels above 7 µg/L should be further investigated and ion measurements repeated as a part of a closer follow-up. However, measurements may also need to be repeated in asymptomatic patients with levels between 3 and 7 µg/L, particularly those with a large-diameter metal-on-metal THA.\(^26,27\)

The current findings indicated that wear at the bearing surfaces and the head-stem-taper interface were the 2 main sources of metal ion debris. Fretting corrosion might have contributed to the production of metal debris in the current failed cases. Kwon et al\(^{28}\) reported that lymphocyte reactivity to metal did not significantly differ in patients with pseudotumors compared with patients without pseudotumors. The increased incidence of CD3 positive T lymphocytes over CD20 positive B lymphocytes in the histology of the pseudotumor after metal-on-metal resurfacing
and THA could be considered consistent with a delayed-type hypersensitivity. In contrast, pseudotumors with dominant CD20 positive B lymphocyte infiltration could indicate a cytotoxicity response to metal wear debris. The current study suggested that systemic hypersensitivity might not be the dominant biological reaction involved in the occurrence of pseudotumors but that a cytotoxicity response to metal wear debris could be the major contributor. Patient susceptibility is likely to be more important.

This study had limitations. Magnetic resonance imaging was obtained at a single follow-up time point. A longitudinal study of pseudotumors with MRI would be useful to understand their natural history. A strength of this study is that it determined the prevalence of symptomatic and asymptomatic pseudotumors in patients with THA using the Cormet cup with a large-diameter head, which has not been previously reported.

**CONCLUSION**

Elevated metal ion levels suggest that ARMD (including pseudotumors) is associated with increased metal wear after large-diameter metal-on-metal THA. Magnetic resonance imaging provides a sensitive screening of pseudotumors following metal-on-metal THA.

**REFERENCES**


