Abstract

Metal-on-metal (MoM) hip arthroplasties comprised of cobalt and chromium alloys continue to be successful alternatives to conventional bearings in younger patients with osteoarthritis (OA). A small proportion of patients have unusually high levels of cobalt and chromium ions postoperatively. Given the increasing prevalence of MoM bearings and the potential for cellular toxicity, the purpose of our study was to determine whether patient or surgical factors could account for abnormally elevated ion levels following MoM hip arthroplasty.

Materials and Methods: Cobalt and chromium levels were analyzed from whole blood in 761 patients with MoM hip arthroplasties. Patient outliers were defined as those who had ion levels greater than or equal to three-fold the median value. Thirty-four patients (4.5%) met this criteria. This included 20 patients who underwent standard total hip arthroplasty (THA) and hip resurfacing, respectively. Patients were followed prospectively with the Harris hip scores (HHS) and the University of California Los Angeles (UCLA) activity scores. Serial radiographs and ion levels were analyzed at regular intervals.

Results: At a mean follow-up of 2 years, the median values for outlier cobalt and chromium ions were 13.7 µg/L and 6.0 µg/L, respectively. Postoperative HHS and UCLA activity scores improved significantly when compared to pre-operative values. There was no statistical correlation between outlier ion levels, patient demographics, and HHS and UCLA activity scores. Acetabular inclination correlated with chromium values. Outlier cobalt levels were higher in patients after THA.

Conclusions: We identified that various patient and surgical factors could account for some of the abnormally high metal ion levels in outliers. Further studies are necessary to better understand the effect of abnormal elevations in metal ions, given the recent concerns of adverse local soft tissue reactions following MoM hip implants.
with small femoral head bearing diameters,\textsuperscript{9,10} and in vitro evidence of cellular toxicity.\textsuperscript{11-13} Despite these risks, with proper patient selection, MoM bearing use in THA and hip resurfacing\textsuperscript{8,10} have predictable, good functional outcomes and low failure rates.\textsuperscript{14,15}

Cobalt and chromium metal ion release occur through mechanical wear and galvanic corrosion. The volumetric wear rates of modern MoM articulations are in the range of 0.13 to 5 mm\textsuperscript{3} per 10\textsuperscript{6} cycles, which is significantly lower when compared to conventional metal-on-polyethylene articulations.\textsuperscript{16} Metal debris is small (less than 50 nm per particle), and although volumetric wear rates are decreased, the surface area exposed to various bodily surfaces is substantially higher.\textsuperscript{5,17,18} This large surface area of cobalt and chromium ions are subsequently released into the circulation and have been found in the serum, blood, and urine of patients.\textsuperscript{19-26} Hip simulator, retrieval, and clinical studies have identified technical and prosthetic risk factors for increased systemic metal ion values. For example, the introduction of the Morse taper in the Durom prosthesis (Zimmer, Warsaw, Indiana) led to significantly increased metal ion values forcing the investigators’ recommendation against the use of a modular junction in MoM total hip replacement.\textsuperscript{27} Acetabular abduction angles above 50° in most studies have demonstrated higher metal ion release.\textsuperscript{28-30} Hip simulator studies and tribology suggest that by maintaining all manufacturing parameters constant, increasing femoral head diameter leads to improved lubrication and decreased circulating metal ions;\textsuperscript{16} however, the clinical data have been conflicting.\textsuperscript{10,31-36}

MoM hip implants continue to be successful alternatives to conventional bearings in younger patients with hip arthritis. A subset of patients have unusually high circulating levels of cobalt and chromium ions. Given the lack of consensus regarding the etiology of increased whole blood cobalt and chromium ions following MoM arthroplasty and the increasing the potential for cellular toxicity, the purpose of the current study was to explore the potential patient and surgical factors that could lead to abnormally high concentrations of whole blood metal ion values.

**Materials and Methods**

**General Protocol**

This study represents a cohort of 761 patients who underwent unilateral MoM THA or hip resurfacing from April 2002 to October 2008 at a single institution. Whole blood cobalt and chromium metal ion values, as well as clinical outcomes, were prospectively recorded. We retrospectively reviewed our database to identify patients who had outlier metal ion values, defined as those who had ion levels greater than or equal to three-fold the median values. This resulted in cobalt and chromium concentrations of greater than or equal to 10 µg/L and greater than or equal to 5 µg/L, respectively. The project was approved by our Institutional Review Board (IRB) prior to recruitment of patients. At the 6-week follow-up clinic visit, patients provided informed consent for the study, including analysis of their whole blood metal ion values. The inclusion criteria were patients greater than 18 years of age, no previous metallic implants or chronic medical illness. Patients with limited mobility and abnormal pre-operative screening renal function (serum creatinine range, 55 to 110 µmol/L) were excluded from the study.

**Hip Implants**

Of the 36 outlier patients, two were lost to follow-up. Both were unable to be contacted by telephone and did not present for clinical and radiographic follow-up examinations. Thirty-four patients (4.5%) had complete clinical, radiographic, and blood metal ion values for inclusion in the final analysis. This included 20 patients who underwent THA (20 hips) and 14 patients (14 hips) who had hip resurfacing. All total hip prostheses were implanted without cement. The Articular Surface Replacement\textsuperscript{TM} (ASR\textsuperscript{TM}, DePuy, Warsaw, Indiana) was the implant used for all patients in the resurfacing group. In the MoM THA group, 28 mm femoral heads were used for three patients (Metasul, Zimmer, Warsaw, Indiana), while the remaining femoral head components used were from DePuy (Ultamet\textsuperscript{TM}, DePuy, Warsaw, Indiana). Metasul\textsuperscript{6} and Ultamet\textsuperscript{TM} femoral heads have similar manufacturing properties. They are both forged, wrought, high-carbon cobalt-chrome alloys, with radial clearances of 75 µm and 40 to 80 µm, respectively.

**Patient Demographics**

The study cohort consisted of 17 females and 17 males, whose mean age at the time of arthroplasty was 60 years (range, 48 to 75 years). The mean follow-up was 2 years (range, 6 months to 3 years). The mean femoral head diameters in patients who had outlier metal ions was 37 mm (range, 28 to 44 mm) and 51 mm (range, 46 to 55 mm) for THA and hip resurfacing procedures, respectively. The diagnosis was osteoarthritis (OA) in 32 (94%) patients, osteonecrosis in one (3%) patient, and hip dysplasia in one (3%) patient. One patient, a 54-year-old male, initially underwent hip resurfacing for OA and required conversion to a THA 32 days later, due to a postoperative femoral neck fracture. The patient was included in the THA group. He was converted to a hybrid implant with a 51 mm diameter femoral head and retained his 58 mm acetabular cup.

**Clinical Outcome**

Clinical outcome scores were performed prospectively using the Harris hip score (HHS)\textsuperscript{37} and the University of California Los Angeles (UCLA) activity scores.\textsuperscript{38} Serial radiographs and ion levels were also analyzed at regular intervals. Laboratory personnel involved in data analysis were blinded to the study protocol.

**Blood Collection and Metal Ion Analysis**

Cobalt and chromium ion levels were analyzed from whole blood. Blood sampling was performed using a technique.
aimed at minimizing metal ion contamination, as previously described.\textsuperscript{19,39} At a mean follow-up of 2 years (range, 6 months to 3 years), the median values for cobalt and chromium ions were 13.7 µg/L (range, 4.98 to 105.0 µg/L) and 6.0 µg/L (range, 0.405 to 38.00 µg/L), respectively (Fig. 1). Outlier metal ion levels were calculated from 761 patients (1317 blood samples) and included values of cobalt greater than or equal to 10 µg/L or chromium greater than or equal to 5 µg/L. In 14 samples (41%), both cobalt and chromium ion values were above 10 µg/L and 5 µg/L, respectively and, thus, were considered outliers. In 26 samples (76%), the cobalt but not chromium values were in the outlier range. Finally, in 22 samples (65%), the chromium, and not cobalt metal ion values, were in the outlier range (Table 1).

**Table 1** Results Comparing Patients with Outlier Metal Ion Values and the Different Groups with Non-Outlier metal Ion Levels

<table>
<thead>
<tr>
<th>Functional Outcome†</th>
<th>Outliers</th>
<th>THA, 28 and 36 mm Femoral Heads</th>
<th>THA, 40 and 44 mm Femoral Heads</th>
<th>Hip Resurfacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris hip score (standard deviation)</td>
<td>85.5 (14.0)</td>
<td>86.2 (12.8)</td>
<td>88.3 (11.6)</td>
<td>90.0 (10.0)</td>
</tr>
<tr>
<td>UCLA activity score (standard deviation)</td>
<td>6.6 (1.47)</td>
<td>5.95 (1.64)</td>
<td>6.34 (1.70)</td>
<td>7.6 (2.00)</td>
</tr>
<tr>
<td>Metal Ion‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt (µg/L)</td>
<td>13.7</td>
<td>2.3</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Chromium (µg/L)</td>
<td>6</td>
<td>0.75</td>
<td>0.39</td>
<td>0.56</td>
</tr>
<tr>
<td>Component Position§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetabular inclination (range)</td>
<td>47.5° (32-67)</td>
<td>45.9 (36-58)</td>
<td>42.6 (31-57)</td>
<td>47.8 (37-59)</td>
</tr>
<tr>
<td>Acetabular anteversion (range)</td>
<td>17.8° (4-43)</td>
<td>25.6 (5-47)</td>
<td>18.5 (5-36)</td>
<td>13.0 (1-37)</td>
</tr>
</tbody>
</table>

THA, total hip arthroplasty; †These values are given as the mean at 2 years; ‡these values are given as the median at 2 years; §these values are given as the mean at 2 years; ||p = 0.039 when compared to patients in the outlier metal ion group.

**Table 2** Effect of Patient or Surgical Factors with Outlier metal Ion Values*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (Range)</th>
<th>Cobalt</th>
<th>Chromium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cup Diameter, mm</td>
<td>56 (30-62)</td>
<td>p = 0.45, R² = 0.0198</td>
<td>p = 0.21, R² = 0.00947</td>
</tr>
<tr>
<td>Head Diameter, mm</td>
<td>43 (28-55)</td>
<td>p = 0.23, R² = 0.004</td>
<td>p = 0.73, R² = 0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.5 (48-75)</td>
<td>p = 0.67, R² = 0.083</td>
<td>p = 0.11, R² = -0.276</td>
</tr>
<tr>
<td>Acetabular anteversion, degrees</td>
<td>17.8° (3.5-43)</td>
<td>p = 0.62, R² = 0.086</td>
<td>p = 0.99, R² = -0.002</td>
</tr>
<tr>
<td>Acetabular inclination, degrees</td>
<td>46.4° (8.4-6.7)</td>
<td>p = 0.86, R² = -0.180</td>
<td>p = 0.001, R² = 0.56</td>
</tr>
</tbody>
</table>

*aSpearman’s rank correlation coefficient.

The clinical outcome scores (HHS and UCLA activity scores) in patients with outlier metal ion values were similar to those that were in the 28 to 36 mm and 40 to 44 mm femoral head THA groups and patients with hip resurfacing procedures (Table 1).

We observed similar mean acetabular inclination angles when comparing patients with outlier metal ion values to those in the 28 to 36 mm femoral head (p = 0.44), 40 to 44 mm femoral head (p = 0.06), and hip resurfacing groups (p = 0.87). There was no difference in mean acetabular anteversion between patients in the outlier metal ion group and those that received 28 to 36 mm and 40 to 44 mm femoral head THAs, p = 0.06 and p = 0.75, respectively. However, we observed a higher (p = 0.039) mean acetabular anteversion in the outlier metal ion group, compared to those patients who underwent hip resurfacing procedures (mean 17.8° versus 13.0°) (Table 1).
The femoral head diameter was not correlated with the concentration of whole blood cobalt ($R^2 = 0.004, p = 0.23$) or chromium ($R^2 = 0.001, p = 0.73$). Similarly, there was no correlation with the size of the acetabular cup with cobalt ($R^2 = 0.0198, p = 0.45$) or chromium ($R^2 = 0.00947, p = 0.21$) metal ion values (Table 2). There was also no correlation between the age of the patient and the level of cobalt ($R^2 = 0.083, p = 0.67$) and chromium ($R^2 = -0.276, p = 0.11$). Anteversion did not correlate with cobalt ($R^2 = 0.086, p = 0.62$) and chromium ($R^2 = -0.002, p = 0.99$) ion levels. Inclination also did not correlate with cobalt ion levels ($R^2 = -0.180, p = 0.86$). However, inclination correlated with chromium levels ($R^2 = 0.560, p = 0.001$) in outlier patients (Table 2). Finally, there were no differences between the levels of cobalt (14.2 vs. 13.7 µg/L, $p = 0.99$) and chromium (7.8 vs 4.9 µg/L, $p = 0.14$) in outlier male and female patients. Cobalt ion levels were higher ($p = 0.03$) in patients with THA, compared to those who underwent hip resurfacing procedures (19.4 vs. 10.5 µg/L), while there was no difference ($p = 0.12$) in chromium concentrations (4.53 vs. 6.92 µg/L) (Fig. 2).

**Discussion**

Metal ion release in MoM articulations occurs from corrosion and wear at the bearing surface. Cobalt and chromium are subsequently released into the circulation and have led to concern, because these are biologically active ions that are chronically elevated in blood and tissues of patients. Recent literature has established the trend of metal ion values over time, as well as identifying patient and surgical factors that lead to elevated ion levels. However, there is a paucity of data identifying reasons why patients develop extremely high concentrations of metal ions after hip arthroplasty with MoM bearings. The aim of the present study was to determine if any patient or surgical factors could account for outlier concentrations of cobalt and chromium metal ions from a cohort of 761 patients with MoM hip arthroplasty implants.

There are several limitations to this study. Our project was performed in a retrospective manner, despite the data being prospectively collected. Therefore, our study might not account for all known confounders, even if a multivariate analysis was performed. Another limitation is that we are using cobalt and chromium as markers for poorly functioning implants. Our study, as well as what is published
Similarly, De Haan and associates found no relationship between metal ion levels and found no correlation with chromium ion values. With those acknowledgements, our results should still be considered valid, since all of our patients had no other sources of metal ions in the body, had normal renal function, and were not limited in mobility, all of which could have falsely elevated the results. We were not able to assess for impingement as a potential source of increased concentration of metal ion values, which has proven to be a source of increased levels of cobalt and chromium ions in several studies.

Our study group contained outlier patients with levels of cobalt and chromium between 4.7 to 5.9, and 8- to 15.4-times the levels in non-outlier patients, respectively. Despite this increased metal ion load, we did not demonstrate any difference in the HHS or UCLA activity scores. The data from the literature is contradictory and has included variable sampling and statistical methods. Desy and colleagues demonstrated a negative correlation with cobalt and functional outcome scores and an inverse relationship with chromium and UCLA activity scores. In another 7-year follow-up study, the investigators reported good-to-excellent HHS scores despite higher levels of circulating chromium ions. However, cobalt levels were not reported, and the peak chromium was 1.76 µg/L at a mean of 3-years. Vendittoli and coworkers reported 1-year whole blood mean cobalt (2.2 µg/L) and chromium (1.3 µg/L) ion levels and found no correlation with UCLA activity scores. In our study, we could only account for a difference in acetabular inclination and abduction angles. At a mean 2-year follow-up, we could only account for a difference in acetabular anteversion in patients in the hip resurfacing and outlier group (13.0° vs. 17.8°). However, the anteversion in the resurfacing group may not be clinically relevant, since it was found in the published acceptable range. Similarly, De Haan and associates found no relationship between metal ions and UCLA scores, even in patients with outlier metal ion values. The previous studies did not exclusively evaluate patients with cobalt and chromium ions over 10 µg/L and 5.0 µg/L, respectively, making comparison with the literature difficult.

The surgical variables in our study included analyses of femoral head diameter, as well as acetabular cup size, inclination, and abduction angles. At a mean 2-year follow-up, we could only account for a difference in acetabular anteversion in patients in the hip resurfacing and outlier group (13.0° vs. 17.8°). However, the anteversion in the resurfacing group may not be clinically relevant, since it was found in the published acceptable range. We found a positive correlation with outlier chromium ion levels and acetabular inclination, consistent with previous studies demonstrating that acetabular abduction angles above 50° result in higher metal ion release. It is unclear why cobalt was not correlated, but may be related to our clinically acceptable mean acetabular inclination angle (48°). The acetabular abduction was also comparable to the measurement in the comparative groups. Similarly, hip simulator studies have shown that by increasing femoral head diameters, wear rates are decreased. This occurs because manufacturers can improved diametric bearing clearances only as femoral head diameters increase. The assumption is that in clinical practice MoM bearings are operating with mixed-film lubrication; however, clinical studies regarding wear and femoral head diameters have been inconsistent with in vitro studies. Furthermore, it has been shown that acetabular cup deformation, which depends on patient weight, quality of the underlying bone, and diametric bearing clearance, can lead to poor wear performance.

We only found a correlation with cobalt outlier metal ion values and the type of arthroplasty (THA vs. hip resurfacing). This is similar to other studies published and may, in part, be due to the tribological advantage of larger head use in the resurfacing group. Garbuz and colleagues, in a prospectively randomized trial, compared 73 patients with MoM large-head THA and hip resurfacing at a mean follow-up of 1.1 years. They had serum metal ion values on 30 patients and found a 10-fold and 2.6-fold increase in cobalt and chromium metal ions, respectively, following large-head THA. Comparison to our study is difficult because there is a lack of an outlier metal ion group and an inferior sampling method. Some studies have failed to show any difference in metal ion values comparing 28-mm femoral heads and hip resurfacing procedures, while a similar study design demonstrated a decrease in cobalt and chromium ion values. Study comparison continues to be difficult, due to lack of consensus with regard to sampling methods, manufacturing variables, and statistical analysis.

**Conclusion**

The results of this study suggest that metal ion release after THA and resurfacing procedures is multifactorial and includes patient, surgical, and manufacturing parameters. Prospective studies that can better control for each variable are warranted due to insufficient data to conclude on the optimal bearing couple.

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**Disclosure Statement**

John Antouiu, M.D., is a consultant for DePuy, Johnson & Johnson. None of the other authors have a financial or proprietary interest in the subject matter or materials discussed,
including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

**References**


