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Citation
Hussey, Daniel K, Rami Madanat, Gabrielle S Donahue, Ola Rolfson, Orhun K Muratoglu, and Henrik Malchau. 2016. “Worse health-related quality of life and hip function in female patients with elevated chromium levels: A prospective study of 659 patients with a recalled THR metal-on-metal implant.” Acta Orthopaedica 87 (5): 485-491. doi:10.1080/17453674.2016.1213596. http://dx.doi.org/10.1080/17453674.2016.1213596.

Published Version
doi:10.1080/17453674.2016.1213596

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Worse health-related quality of life and hip function in female patients with elevated chromium levels

A prospective study of 659 patients with a recalled THR metal-on-metal implant

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Submitted 2015-05-19. Accepted 2016-05-30.

Background and purpose — Blood metal ion levels can be an indicator for detecting implant failure in metal-on-metal (MoM) hip arthroplasties. Little is known about the effect of bilateral MoM implants on metal ion levels and patient-reported outcomes. We compared unilateral patients and bilateral patients with either an ASR hip resurfacing (HR) or an ASR XL total hip replacement (THR) and investigated whether cobalt or chromium was associated with a broad spectrum of patient outcomes.

Patients and methods — From a registry of 1,328 patients enrolled in a multicenter prospective follow-up of the ASR Hip System, which was recalled in 2010, we analyzed data from 659 patients (311 HR, 348 THR) who met our inclusion criteria. Cobalt and chromium blood metal ion levels were measured and a 21-item patient-reported outcome measures (PROMs) questionnaire was used mean 6 years after index surgery.

Results — Using a minimal threshold of ≥ 7 ppb, elevated chromium ion levels were found to be associated with worse health-related quality of life (HRQoL) (p < 0.05) and hip function (p < 0.05) in women. These associations were not observed in men. Patients with a unilateral ASR HR had lower levels of cobalt ions than bilateral ASR HR patients (p < 0.001) but similar levels of chromium ions (p = 0.09). Unilateral ASR XL THR patients had lower chromium and cobalt ion levels (p < 0.005) than bilateral ASR XL THR patients.

Interpretation — Chromium ion levels of ≥ 7 ppb were associated with reduced functional outcomes in female MoM patients.

Since the late 1990s, the popularity of metal-on-metal (MoM) hip implants has risen due to the potential for low volumetric wear and high performance in young and active patients (Bozic et al. 2009). By 2010, however, the use of MoM declined over concerns of adverse local tissue reactions (ALTRs) (Porter et al. 2010). The Articular Surface Replacement (ASR) Hip System, comprised of the ASR hip resurfacing (HR) and the ASR XL total hip replacement (THR), was a MoM system implanted in over 90,000 patients worldwide prior to its recall in 2010 due to higher than expected 5-year revision rates (DePuy Orthopaedics, Warsaw, IN) (Cohen 2011, Bernthal et al. 2012). Recommended protocol for patients with MoM implants includes regular clinical follow-up with physician assessment, blood metal ion testing, plain radiographs, and soft-tissue imaging when necessary (MHRA 2012, Kwon et al. 2014). Metal ion levels may be useful as a method for detection of increased wear and poor hip function in MoM patients (Haddad et al. 2011, Van Der Straeten et al. 2013). Currently, guidelines for metal ion levels only apply to unilateral MoM implants due to the confounding nature of interpreting blood metal ion levels in patients with bilateral MoM hip arthroplasty (Kwon et al. 2014).

The connection between chromium or cobalt and ALTRs is not fully understood. There is neither an established metal ion “safe zone” nor a maximum threshold that can reliably predict implant failure (Langton et al. 2011, Hart et al. 2014). Little has been published on how cobalt and chromium metal ion levels differ between patients with unilateral and bilateral ASR hip systems. Although many studies have investigated the blood metal ion levels in MoM arthroplasty patients, they have been limited by several factors: use of a mixed cohort of different THR and/or HR systems, focusing solely on unilateral implants, or grouping unilateral and bilateral patients...
Consenting patients with a unilateral or bilateral ASR HR or ASR XL THR n = 1,328

Excluded (n = 669):
- missing required data, 504
- missing metal ion data, 8
- non-ASR contralateral side, 165

Study population n = 659

ASR HR n = 311
Unilateral n = 271
Bilateral n = 40

ASR XL THR n = 348
Unilateral n = 301
Bilateral n = 47

Figure 1. Flow chart of patients included in the study population.

Patients and methods

The study population consisted of 1,328 arthroplasty patients enrolled in a multicenter follow-up study of the ASR Hip System (DePuy Orthopaedics, Warsaw, IN). Enrollment of unrevised, primary ASR patients willing to participate in a 6-year follow-up study took place from May 2012 through December 2014. Data abstractors reported anonymized medical record data and PROMs to Massachusetts General Hospital in Boston from 15 centers in 5 countries through a secure, web-based data entry and monitoring system. All the patients enrolled signed the informed consent document and met the following inclusion criteria: any patient (1) who received the ASR XL THR implant as a result of a hip resurfacing conversion or a revision THR; or (2) who had difficulty in comprehending the informed consent form for any reason.

For our analysis, we included all patients with complete data at enrollment using the following criteria: (1) available femoral and acetabular component catalog numbers; (2) valid AP pelvis X-ray to measure cup inclination angle; (3) completed PROMs including the Harris hip score (HHS) (Harris 1969), EQ-5D (EuroQolGroup 1990), UCLA activity score (Amstutz et al. 1984), and VAS pain score (0–10) (Hawker et al. 2011); and VAS pain score (0–10) (Hawker et al. 2011); (4) whole blood cobalt and chromium ion levels. We excluded patients from our analysis if they had: (1) a non-ASR contralateral implant system; or (2) an ASR HR on 1 side and a contralateral ASR XL THR.

The metal ion concentrations and PROMs were obtained at a mean of 6 (2–11) years from index surgery. Whole blood samples were assessed by certified laboratories using standardized collection methods. The study cohort was divided into 2 groups, ASR HR and ASR XL THR. Each of these groups was further divided into 2 subgroups: patients with unilateral implants and those with bilateral implants (Figure 1). We used 7 ppb and 10 ppb as the metal ion threshold levels described for high-risk patients based on recent MoM follow-up algorithms (MHRA 2012, Kwon et al. 2014).

Demographics of the patient population

The inclusion criteria gave 659 patients (311 ASR HR, 348 ASR XL THR). The mean age at index surgery was 59 (18–95) years and 246 patients (37%) were female (Table 1).

Statistics

The study questions were analyzed as follows. Differences in blood metal ion levels and PROMs between unilateral and bilateral ASR HR or ASR XL THR patients were assessed using the Mann-Whitney U-test for variables that did not follow a normal distribution and Student’s t-test for normally distributed data. The Shapiro-Wilk test was used to determine the normality of each variable and Levene’s test was used to ensure that the assumption of equal variances was met. The
HHS was recorded for each hip. For bilateral patients, we randomly selected a score from 1 hip for statistical analysis. We stratified our cohort into 2 groups (ASR patients and ASR XL patients) and then conducted a series of linear regression analyses. First, we performed analyses to identify which covariates were associated with blood metal ion levels. For this purpose, 2 models were built that assessed cobalt and chromium separately as outcome variables with all available covariates that had previously been associated with metal ion levels: age, gender, time from surgery, bilateral status, femoral head size, and cup inclination angle (≤ 55° or ≥ 55°) as exposure variables (Brodner et al. 2004, De Haan et al. 2008). Then, in an effort to determine which covariates were associated with various PROMs, we separately assessed EQ-5D index, HHS, VAS pain score, and UCLA activity score as outcome variables. The same set of exposure variables was used for all of these analyses and included age, sex, bilateral status, and chromium and cobalt with ≥ 7 ppb and ≥ 10 ppb binary thresholds.

In order to assess possible non-linearity of age, we set up 4 competing models: a linear model, a model with 1 knot spline, one with 2 knots, and one with 3 knots. The fit of the models was then compared with the help of information criteria. Our data did not indicate a non-linear relationship between age and PROMs, so age was used as a linear term in our analyses.

The p-values, standardized coefficient (expected change in outcome that accompanies 1 unit change in exposure), and 95% confidence intervals (CIs) were calculated for all linear regression analyses. Any p-value < 0.05 was considered significant. Statistical analyses were performed using SPSS version 19 and R version 3.0.2 (Team 2015).

Ethics and registration

Informed consent was obtained from all patients and the study was approved by the Institutional Review Board or Ethics Committee at all participating centers and Massachusetts General Hospital. The study is registered at ClinicalTrials.gov (registration number: NCT01611233).

Results

Patient-reported outcome measures (PROMs)

Patients with a unilateral ASR XL THR reported lower HHS, EQ-5D index, and UCLA scores than unilateral ASR HR patients (p < 0.05) (Table 2). Patients with bilateral ASR XL THR reported lower UCLA activity scores than patients with unilateral ASR HR (p < 0.01) (Table 2). Patients with bilateral ASR XL THR had lower HHS and UCLA activity scores than patients with unilateral ASR XL THR (p < 0.05) (Table 2).

Linear regression analyses of PROMs using thresholds of 7 ppb for chromium and cobalt

In ASR XL patients, elevated chromium levels of ≥ 7 ppb in women were associated with lower hip function as measured by the HHS (p < 0.05). Bilateral hip replacements and chromium levels ≥ 7 ppb in female patients were associated with worse health-related quality of life (HRQoL) as measured by the EQ-5D index (p < 0.05) (Figure 2). Female sex, increasing age, and chromium levels ≥ 7 ppb in women were associated with lower activity as measured by the UCLA activity score (p < 0.05) (Table 5, see Supplementary data). In ASR patients, no significant associations were observed between cobalt or chromium levels ≥ 7 ppb and the HHS, UCLA, EQ5D, or VAS pain scores (Tables 7–14, see Supplementary data).

Linear regression analyses of PROMs using thresholds of 10 ppb for chromium and cobalt

In ASR XL patients, female patients with chromium levels ≥ 10 ppb had lower hip function as measured by the HHS (p < 0.05) (Figure 2). Female sex, increasing age, bilateral hip replacement, and chromium levels ≥ 10 ppb were associated with lower activity as measured by the UCLA activity score (p < 0.05) (Table 6, see Supplementary data). Bilateral hip replacements and chromium levels ≥ 10 ppb in female patients were associated with worse HRQoL as measured by the EQ-5D index (p < 0.05) (Figure 2). In ASR patients, no statistically significant associations were found between cobalt or chromium levels ≥ 10 ppb and the HHS, UCLA, EQ5D, or VAS pain scores (Tables 7–14, see Supplementary data).

Differences in metal ion levels between ASR HR and ASR XL THR

Non-parametric univariate analysis showed that the blood metal ion levels of cobalt were higher in patients with unilateral ASR XL THR than in patients with unilateral ASR (p < 0.001), although blood metal ion levels of chromium were similar (p = 0.1) (Table 2). The cobalt to chromium (Co/Cr) ratio was also higher in patients with unilateral ASR XL THR than in patients with unilateral ASR HR (p < 0.001).

Table 2. Median (interquartile range) patient-reported outcome measures and blood metal ion levels in patients with an ASR HR or an ASR XL THR prosthesis

|                     | ASR HR                 | ASR XL THR              |
|---------------------|------------------------|-------------------------|
|                     | Unilateral Bilateral   | Unilateral Bilateral    |
| No. of patients     | 272                    | 40                      |
| Cobalt ions, ppb    | (1.1–3.0) 2.5           | (1.2–3.7) 5.3           |
| Chromium ions, ppb  | (1.75–2.15) 1.4         | (1.9–2.4) 2.4           |
| Ratio Co/Cr         | (0.7–1.3) 1.1           | (0.9–1.4) 1.7           |
| Harris hip score    | (94–97) 92             | (74–97) 91             |
| EQ-5D               | (1.0–1.0) 0.95          | (0.7–1.0) 0.8           |
| UCLA                | (7–6) 6                | (6–6) 6                |
| VAS pain            | (0.5–0.1) 0.5           | (0.0–3.0) 0.5           |

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The cobalt ion levels were higher in patients with bilateral ASR XL THR than in patients with bilateral ASR HR (p < 0.001), although chromium ion levels were similar (p = 0.1) (Table 2). The Co/Cr ratio was higher for patients with bilateral ASR XL THR than for those with bilateral ASR HR (p < 0.001).

**Effect of bilateral ASR HR or ASR XL THR on blood metal ion levels**

The cobalt ion levels in blood were higher in patients with bilateral ASR HR implants than in those with a unilateral ASR HR implant (p < 0.05), but chromium ion levels were similar between the groups (p = 0.09) (Table 2). The Co/Cr ratio was higher in patients with bilateral implants than in those with a unilateral implant (p < 0.05).

Cobalt and chromium ion levels in patients with bilateral ASR XL THR implants were higher than in those with a unilateral ASR XL THR implant (p < 0.005), although the groups had similar Co/Cr ratios (p = 0.2) (Table 2).

**Linear regression analysis of metal ions**

In ASR XL patients, female sex and having bilateral hip replacements were associated with higher chromium ion levels (p < 0.01). Both female sex and bilateral hip replacements were also associated with higher cobalt levels (p < 0.01) (Figure 3).

In patients with the ASR hip resurfacing prosthesis, having 1 or 2 (a potential case for patients with bilateral ASR) acetabular cup inclination angle ≥ 55° was associated with higher chromium metal ion levels (p < 0.01). No variables assessed were found to be associated with higher cobalt metal ion levels (Figure 4).

**Discussion**

In this multicenter study, we found an association between chromium ion levels and a reduction in both hip function and HRQoL in female patients with unilateral or bilateral ASR XL THR. Interestingly, this association was not observed in male patients. Cobalt ion levels, using both 7 and 10 ppb thresholds, were not associated with hip function or HRQoL. In addition, we found similar chromium ion levels in ASR HR and ASR XL THR patients when comparing unilateral or bilateral groups. Furthermore, we found that patients with unilateral ASR HR had chromium ion levels that were comparable to those in patients with bilateral ASR HR. However, bilateral ASR XL THR implants were associated with higher chromium ion levels than unilateral ASR XL THR implants. Although blood cobalt ion levels were statistically significantly higher in patients with ASR XL THR than in those with ASR HR, and also higher in bilateral groups than in unilateral groups, cobalt ion levels ≥ 7 ppb or ≥ 10 ppb were not found to be associated with any negative patient symptoms that were assessed. The lack of association between time from index surgery and blood metal ion levels may in part be explained by a previous study, which demonstrated a lack of temporal variation in blood metal ion levels for patients with ASR HR (Langton et al. 2013). Finally, our study highlights the importance of optimal acetabular cup orientation in order to minimize edge loading and blood metal ion levels.

Cobalt ion levels appeared to deviate more strongly between patients, whereas chromium ion levels showed greater consistency in our study cohort. This observation may have been due...
to smaller fluctuations in chromium ion levels in whole blood caused by its higher affinity for proteins such as albumin and transferrin, to which it can bind (Newton et al. 2012). Thus, chromium has lower renal excretion than cobalt, which has a high renal clearance (Daniel et al. 2010). High chromium ion levels in blood may be a more consistent indicator of a poorly functioning MoM prosthesis, which would explain its strong association with poor hip function and health-related QoL in our study. Although we found no association between health outcomes and blood cobalt ion levels, cobalt levels > 4.5 ppb have been identified as being highly sensitive and specific for abnormal wear in MoM hip arthroplasty, and cobalt blood ion levels as low as 2 ppb may be considered abnormal (Sidagnimale et al. 2013).

In 2014, the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, and the US Hip Society published a consensus statement that outlined criteria for stratifying MoM patients into groups with low, medium, and high risk of failure (Kwon et al. 2014). As a multicenter registry study, we could not evaluate whether patients had additional sources of Cr or Co such as occupational exposure, spinal hardware, or metal dental implants. We acknowledge that the present study had some limitations.
associations that were observed. Height and weight were not collected on all patients, so we were unable to assess associations between BMI and metal ion levels and PROMs. It is possible that an overweight patient would have worse HRQoL and higher chromium levels due to implant load. Lastly, we tried to analyze the relationship between current established metal ion thresholds and functional outcomes. Future efforts should be directed at establishing new thresholds.

The study had a number of strengths. First, we focused on a single hip replacement system and compared the HR and THR variants. The multicenter and multinational nature of the study prevented bias that might be introduced from any individual surgeon’s experience. Strict inclusion criteria enabled robust statistical analysis on a broad set of data. The study made use of several PROMs to assess a diverse set of patient symptoms. Finally, this was the first multicenter study to analyze a large cohort of ASR patients that differentiated HR from THR and unilateral from bilateral.

In summary, we found that time from index surgery and patient age were not associated with high blood metal ion levels, which highlights the necessity to have continuous annual follow-up of MoM patients. Blood metal ion testing should be evaluated as part of frequent and comprehensive follow-up that includes a physical examination, plain radiographs, and soft-tissue imaging, if available. Regarding assessment of blood metal ion levels in female patients with MoM hip replacement, chromium ion levels ≥ 7 ppb appear to be associated with reduced functional outcomes in both unilateral and bilateral patients.

Supplementary data

Tables 4–14 and Appendix are available on the website of Acta Orthopaedica (www.actaorthop.org), identification number 8884.

DKH, RM, GSD, OR, OKM, and HM devised the study and were all responsible for data collection. DKH, RM, GSD, and OR interpreted the data. DKH drafted the paper. DKH, GSD, and OR performed statistical analysis. RM, GSD, OR, OKM, and HM critically revised the manuscript for important intellectual content. OKM and HM supervised the study. DKH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

We thank Szilard Nemes for his critical input as a biostatistical consultant during revision of this manuscript. We also thank clinical research project manager Slav Lerner for his help with the study and Marc Bragdon for technical assistance.

This study was supported by DePuy Orthopaedics, Warsaw, Indiana. The publication of these results was not contingent on the sponsor’s approval. RM received research support from the Orion-Farmos Research Foundation. The authors have no relevant competing interests to disclose.

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