Do Ion Levels in Metal-on-metal Hip Resurfacing Differ From Those in Metal-on-metal THA at Long-term Followup?

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Abstract

Background Metal-on-metal hip resurfacing arthroplasty (MOM HR) has become an established alternative to traditional metal-on-metal total hip arthroplasty (MOM THA) for younger, more active patients. Nevertheless, concerns remain regarding wear and corrosion of the bearing surfaces and the resulting systemic metal ion distribution.

Questions/purposes We therefore asked whether (1) serum ion concentrations in patients with MOM HR at the time of long-term followup were higher than concentrations in a control population with no hip implants; (2) the

ion concentrations in patients with MOM HR were different from those in patients with MOM THA; and (3) sex would influence ion levels with regard to implant type.

Methods The MOM HR and MOM THA groups consisted of 25 patients (evaluated at a minimum of 96 months) and 16 patients (evaluated at a minimum of 106 months), respectively. Forty-eight healthy donors were recruited for reference values. Cobalt, chromium, nickel, and molybdenum were measured by furnace graphite atomic absorption spectrophotometry.

Results Ion concentrations of cobalt, chromium, and molybdenum in MOM HR were higher than in controls. Chromium and cobalt release were higher in MOM HR than in MOM THA. The sex-based analysis showed the difference was because women had higher concentrations in the MOM HR group than in the MOM THA group, whereas there was no difference between the men in the two groups.

Conclusions In MOM HR, high metal ion release persists for the long term. Consequently, it is important to implement strict biomonitoring for patients who have received these implants. The sustained high levels of chromium in females within the MOM HR group are concerning and merits strong consideration when choosing implants in this patient group.

Level of Evidence Level III, therapeutic study. See the Instructions for Authors online for a complete description of level of evidence.

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Introduction

During the last decade, the use of metal-on-metal (MOM) bearings has increased because they exhibit reduced wear and osteolysis compared with standard metal-on-polyethylene

bearings [3, 13, 28, 42]. In particular, MOM hip resurfacing (MOM HR) may be appealing for some young and active patients because it allows femoral bone stock preservation, lack of stress shielding [4], better functional outcomes, lower rates of dislocation [1, 21, 31], and resumption of sporting activity [14]. Nevertheless, concerns regarding wear and corrosion of the bearing surfaces and the resulting increase in metal ion levels remain [26]. Potential effects of a chronic exposure to raised ion metal levels include local tissue toxicity, inflammation, soft tissue reactions [5, 36], bone loss, renal function alteration, immune modulation, hypersensitivity, chromosomal damage, teratologic effects, and malignancy [24, 29, 30]. Although we have not identified any published evidence of adverse events, these concerns remain.

To establish acceptable levels of safety and determine the implication of elevated ion levels, data must be gathered and analyzed over extended periods of time [27]. In previous studies, assessment of chromium (Cr), cobalt (Co), and molybdenum (Mo) levels in patients treated with either MOM HR or MOM THA showed higher Cr and Co serum levels in both groups when compared with controls but no differences within implant groups at 2- and 5-year followup [33, 34]. However, some clinical studies contradict these findings and show an increasing trend in metal ion levels in blood or its fractions over time [12, 40].

We therefore asked whether (1) serum ion concentrations in patients with MOM HR at the time of long-term followup were higher than concentrations in a control population with no implants; (2) the ion concentrations in patients with MOM HR were different from those in patients with MOM THA; and (3) sex would influence ion levels with regard to implant type.

Patients and Methods

We performed an observational cross-sectional study and retrospectively created two groups of patients. The Institutional Ethics Committee on Human Research approved the study and the participants signed informed consent forms. To determine the sample size, a pretest power analysis was performed. For the effect size, we considered previous data [34] concerning the MOM HR group at 5-year followup in comparison with controls, taking into account the fact that a significant difference had been found between the two groups. We used the means and one SD of both groups and found a sample size of 12 in each group gave a power of 95% for the Cr test and a power of 80% for the Co test. Consequently, the study was not underpowered.

The MOM HR group consisted of 25 patients implanted with Birmingham HipTM Resurfacing (Smith & Nephew, Inc, Memphis, TN, USA). Twenty-three patients had

unilateral MOM HR, whereas two had bilateral implants. This group was compared with a MOM THA group, previously described [38], consisting of 16 patients who had Metasul[®] 28-mm MOM THA (Zimmer, Inc, Warsaw, IN, USA). Eleven patients received unilateral MOM THA, whereas five had bilateral implants. The MOM HR was manufactured from a cast, high-carbon Co-Cr alloy (ISO 5832-4, alloy composition: Cr 26.5%–30%, Ni 0%–1%, Mo 4.5%–7%, Mn 0%–1%, C 0%–0.35%, Si 0%–1%, Fe 0%–1%, Co balance). The mean (SD) head diameter was 48.9 ± 4.9 mm (51.12 ± 3.99 mm and 44.5 ± 3.66 mm in men and women, respectively, $p = 0.002$). The average acetabular component diameter was 55.7 ± 4.22 mm. In the MOM HR group the acetabular component was uncemented, whereas the femoral component was cemented. The MOM THA acetabular component consisted of a titanium alloy shell with a polyethylene insert reinforced with a Co-Cr alloy liner (Protasul-21[®] WF, ISO 5832-12, alloy composition: Cr 30%, Ni 2.5%, Mo 7%, Mn 1%, C 0.32%, Si 1%, Fe 1%, Co balance) and a 28-mm-diameter Co-Cr alloy femoral head (Protasul-21[®] WF, see previously). The head was assembled on a titanium alloy femoral stem. Both acetabular and femoral components were uncemented. All implants remained in situ throughout the course of the study (Table 1). Minimum followup was 96 months (mean $\pm$ SD, 104.8 ± 9.5 months) for the MOM HR group and 106 months (mean $\pm$ SD, 120.9 ± 8.8 months) for the MOM THA group.

Further information about the patients' lifestyles and activity level was collected, and the patients were classified using the UCLA activity scale [2]. The Harris hip score (HHS) [19] was assessed at the followup visit and plain radiographs of the treated hip were taken. Implant size, inclination angle of the acetabular cup, and body mass index (BMI) were evaluated. The MOM HR and MOM THA groups were matched for age (mean, range, 53.9, 26–73 years, and 54.4, 46–63 years, respectively; $p = 0.98$), sex (16 males, nine females in MOM HR; seven males, nine females in MOM THA; $p = 0.17$), HHS (mean, range, 94.1, 68.7–100 in MOM HR, and 97.5, 80–100 in MOM THA; $p = 0.06$), cup inclination angle (mean, range, 45, 35–55 in MOM HR, and 43.6, 31–55 in MOM THA; $p = 0.41$), and BMI (mean, range, 25, 17–45 kg/m² in MOM HR, and 25, 22–30 kg/m² in MOM THA; $p = 0.73$). UCLA activity level was significantly different between the two patients groups (mean, range, 7.1, 3–10 in MOM HR, and 5.0, 3–7 in MOM THA; $p = 0.001$). Baseline demographic data for the HR, THA, and control groups are reported (Table 1). Among each group, no difference was found between males and females regarding all variables considered. Patients were questioned regarding prescription drugs, alcohol intake, smoking history, and chronic occupational exposure to hazardous substances. Intake of

Table 1. Profile in patients with MOM HR, patients with MOM THA, and healthy subjects (controls)

Variable	MOM HR	MOM THA	Controls
Sex (number of patients)			
Male	16	7	38
Female	9	9	10
Age (years)*	53.9 (26–73)	54.4 (46–63)	42.6 (20–71)
Diagnosis (number of patients)			
Osteoarthritis	18	3	
Congenital hip dysplasia	4	6	
Rheumatoid arthritis	1	0	
Fracture	0	2	
Trauma	0	3	
Necrosis	1	2	
Tuberculosis	1	0	
Followup (months)*	104.8 (96–132)	120.9 (106–136)	
Body mass index (kg/m ²)*	25 (17–45)	25 (22–30)	
UCLA scale [2]	7.1 (3–10)	5.0 (3–7)	
Cup inclination angle (°)*	45 (35–55)	43.6 (31–55)	
Harris hip score (points) [18]*	94.1 (68.7–100)	97.5 (80–100)	

* Values are expressed as mean and range (in parentheses); MOM HR = metal-on-metal hip resurfacing; MOM THA = metal-on-metal THA.

prescription or nonprescription drugs containing metal ions was considered exclusion factors as was renal impairment. The criteria used for the interview were reported previously [37]. Primary pathology was not considered a potentially confounding variable. Before enrollment, we excluded patients with infection, malignancy, and radiographic signs of loosening, osteolysis, an acetabular component inclination angle of greater than 55° [47], and environmental or occupational chemical exposure. Two female patients, one with radiographic signs of implant loosening and another with an acetabular component inclination angle of 60°, did not match the inclusion criteria and were therefore excluded from the statistical analysis. Forty-eight healthy blood donors (37 men and 11 women; age: mean, range, 42.64, 20–71 years) who were not receiving medication and who did not have metal implants were used for reference ranges.

Cr, Co, nickel (Ni), and Mo ions were measured in the serum. Blood samples were obtained from the antecubital veins of fasting subjects using a disposable intravenous cannula. The blood was collected in metal-free Vacutainer® tubes (Becton Dickinson and Co, Meylan, France). To avoid contamination from the needle, the first 5 mL of blood withdrawn was discarded. Serum was separated by centrifugation at 400 g for 10 minutes at 4° C. Ion content was measured using a graphite furnace atomic absorption spectrometer equipped with double background correction Deuterium/Zeman (ThermoFisher ICE4000; Thermo Fisher, Cambridge, UK). Environmental and sampling contamination was avoided by using a dedicated room with efficient fume extraction and a temperature monitoring

system. A clean bench area was reserved for solution preparation. Every tool used from the time of sampling until data analysis was regarded as a potential source of contamination and was used only after soaking it in 2% HNO₃ in twice-distilled and deionized water followed by thorough rinsing in twice-distilled and deionized water. Each instrument was then checked using a nitric acid leach test to ensure it did not contain detectable amounts of the relevant trace elements. Calibration was performed by applying the standard addition method and by using certified standard solutions at three concentrations for each element (National Institute of Standards and Technology [NIST], Gaithersburg, MD, USA). The accuracy and precision of the methods were validated using SRM 1598 NIST human serum as well as UTAK® normal and high-range trace elements (UTAK Laboratories, Inc, Valencia, CA, USA). Rejecting ion levels with a relative SD greater than 10% ensured test repeatability. All results were expressed as nanograms per milliliter (ng/mL, equivalent to micrograms per liter and parts per billion). The sensitivity of the method was established by using detection limits for sample matrix, ie, 0.06 ng/mL for Cr, 0.08 ng/mL for Co, 1.1 ng/mL for Ni, and 0.83 ng/mL for Mo. All ion levels below the detection levels were adjusted to the detection limit.

We used the Mann-Whitney U test to test differences in age, UCLA activity score, and HHS and the Fisher's exact test to test differences in sex between the MOM HR and MOM THA groups. The ion values are reported as mean and range. The Mann-Whitney U test, calculated according

to the exact test for small numbers, was applied to detect the association of ion release with the presence of unilateral versus bilateral implant within the MOM HR and MOM THA groups. Differences among the three groups in relation to ion release were tested using the Kruskal-Wallis test and the Mann-Whitney U test, depending on the number of variables tested. Furthermore, we stratified the implant groups by sex and compared the subgroups of men and women using the Mann-Whitney U test calculated according to the exact test for small samples. StatView[®] software (Version 5.01.0; SAS Institute Inc, Cary, NC, USA) was used to analyze the results and the level of significance was set at $p < 0.05$. MedCalc[®] Version 11.5.1 software (MedCalc Inc, Mariakerke, Belgium) was used to perform the Mann-Whitney U test, calculated according to the exact test for small numbers.

Implant type and presence of unilateral versus bilateral implants did not influence ion levels ($p = 0.42$ and $p = 0.82$ for Co and $p = 0.32$ and $p = 0.19$ for Cr in MOM HR and MOM THA, respectively). Consequently, patients were not further divided.

Results

At the time of long-term followup, the serum concentrations of Cr and Co in patients with MOM HR were still seven to 10 times higher ($p < 0.001$) than concentrations found in a control population with no implants (Cr, mean, range, 1.94, 0.56–6.19 ng/mL and 0.24, 0.06–0.67 ng/mL in MOM HR and controls, respectively; Co, mean, range, 0.98, 0.29–2.45 ng/mL and 0.26, 0.08–0.53 ng/mL in MOM HR and controls, respectively), whereas Ni levels were similar (mean Ni values, range, as ng/mL, 0.40, 0.1–1.50 in MOM HR and 0.49, 0.1–0.81 in controls; $p = 0.07$) (Table 2). Mo concentrations were below detection limits in the controls.

Serum Cr levels (ng/mL) in patients with MOM HR were two- to threefold higher ($p = 0.002$) than in patients with MOM THA (mean, range, 1.94, 0.56–6.19, and 0.86, 0.26–2.22, respectively) (Table 2). With the numbers available, Co concentrations (ng/mL) were not higher ($p = 0.06$) in MOM

HR than in MOM THA (mean, range, 0.98, 0.29–2.45, and 0.69, 0.32–1.58, respectively). Mo concentrations (ng/mL) were not different ($p = 0.24$) between the MOM HR and MOM THA groups (mean, range, 1.03, 0.83–2.19, and 0.85, 0.83–0.97, respectively). Furthermore, these levels were always within the reference normal ranges reported by the Italian Istituto Superiore di Sanità (Mo range, 0.20–2.75 ng/mL) [6] and were not further analyzed.

Eventually, we asked whether sex would influence ion levels with regard to implant type: when each group was analyzed according to sex, women showed a higher Cr and Co release in the MOM HR group than in the MOM THA group ($p = 0.004$ and $p = 0.03$, respectively). In contrast, men in the MOM HR group did not show any differences from men in the MOM THA group (Table 3). Among the MOM HR population, females showed higher Co and Cr levels ($p = 0.05$ and $p = 0.08$, respectively) compared with males.

Discussion

The increasing use of MOM HR implants has led to concerns about the biologic consequences of a chronic metal ion release, making it essential to continue biomonitoring of patients receiving these implants. Longer-term followup seems especially important, and few studies have evaluated this [12, 20]. We therefore asked whether (1) serum ion concentrations in patients with MOM HR would still be more than in a control population with no hip implants at long-term followup (minimum 8 years); (2) ion concentrations in patients with MOM HR were different from those in patients with MOM THA; and (3) sex would influence ion levels with regard to implant type.

We acknowledge some limitations of our study. First, the sample size was calculated to find possible differences between MOM HR patients and healthy subjects; therefore, to address the smaller subpopulations obtained splitting patients by sex, we used the Mann-Whitney U test, calculated according to the exact test for small numbers. Second, metal ion content was only measured in serum; therefore, our findings might reflect different transport modes for specific

Table 2. Ion values in patients with MOM HR, patients with MOM THA, and healthy subjects (controls)

Ion	Ion value (ng/mL)			p value*	p value [†]
	MOM HR	MOM THA	Controls		
Chromium	1.94 (0.56–6.19)	0.86 (0.26–2.22)	0.24 (0.06–0.67)	< 0.001	0.002
Cobalt	0.98 (0.29–2.45)	0.69 (0.32–1.58)	0.26 (0.08–0.53)	< 0.001	0.06
Nickel	0.40 (0.1–1.50)	‡	0.49 (0.10–0.81)	0.07	
Molybdenum	0.85 (0.83–0.97)	1.03 (0.83–2.19)	Less than detection limit	0.001	0.24

Values are expressed as mean and range in parentheses; * MOM HR versus controls; [†]MOM HR versus MOM THA; [‡]insufficient serum was available for nickel testing; MOM HR = metal-on-metal hip resurfacing; MOM THA = metal-on-metal THA.

Table 3. Ion values in patients with MOM HR and MOM THA divided by sex

Ion	Ion value (ng/mL)		p value*	Ion value (ng/mL)		p value†
	Men			Women		
	MOM HR	MOM THA		MOM HR	MOM THA	
Chromium	1.65 (0.56–6.19)	0.90 (0.26–1.60)	0.20	2.45 (0.93–6.01)	0.87 (0.46–2.22)	0.004
Cobalt	0.82 (0.29–2.39)	0.73 (0.32–1.58)	0.62	1.26 (0.32–2.45)	0.65 (0.41–1.34)	0.03
Molybdenum	0.85 (0.83–0.97)	1.21 (0.83–2.19)	0.84	0.86 (0.83–0.95)	0.85 (0.83–0.96)	0.14

Values are expressed as mean and range in parentheses; * MOM HR versus MOM THA men; †MOM HR versus MOM THA women; MOM HR = metal-on-metal hip resurfacing; MOM THA = metal-on-metal THA.

elements, ie, what goes in serum, urine, or is maybe stored in the local tissue or accumulated in organs [32, 35], or is the result of selective dissolution of some of the alloying elements [23, 35]. Another possible limitation is that MOM HR patients had a significantly higher UCLA activity score at the time of withdrawal; nevertheless, one major indication for hip resurfacing is the willingness of the patient to resume sporting activity. We believe that selecting MOM HR patients with a lower UCLA activity score would not have reflected the real characteristics of this patient population. It was therefore not possible to match the two study groups for this parameter.

We found serum concentrations of Cr and Co were higher in patients with MOM HR than in control subjects. It is clear that the ratios of alloy elements released into the serum do not correspond to the alloy composition. In vivo transport and excretion of corrosion products are different for the different elements: the excretion of Ni and Mo is rapid and complete, most of the Co is excreted, with elevation of Co levels in the liver, kidney, and lung, and Cr excretion is much lower as a result of significant red cell binding and in vivo storage, especially in the kidney and spleen [8]. Nevertheless, concerns remain as a result of the fact that, in some patients, after 8 to 10 years, Cr and Co concentrations are still seven to 10 times higher than those found in healthy subjects. Clinical understanding of high ion levels is challenging; there are no well-defined safety parameters or safety levels for serum metal ions in patients who have received an MOM bearing. Studies reporting local or systemic damage caused by metal ion increase are scarce and there is no clear evidence of a correlation between ion concentrations and exposure [16–18, 22, 39, 46]. It is difficult to apply occupational safety standards to the clinical situation of patients with a bearing in situ, and from any of such applications, no specific conclusions can be drawn [30]. To demonstrate a cause-and-effect association between resurfacing implant application and any potential risk will require a significant number of patients and ultimately require information from, and correlation between, total joint registries and other illness or mortality registries. It should however be noted that all patients in

this study had Co and Cr levels within the occupational range. Moreover, as reported by De Smet et al. [11], serum Cr levels of more than 17 µg/L (ng/mL) and serum Co ion levels of more than 19 µg/L (ng/mL) are strongly associated with metallosis and should be considered as an index of implant loosening or malfunctioning, and therefore revision surgery should be considered.

Our study showed that serum concentrations of Cr and Co in patients with MOM HR continue to be higher than those in patients with MOM THA. Several authors [9, 10, 28, 44] have evaluated ion levels at medium-term followup (Table 4); nevertheless, these were not comparative studies of MOM HR versus MOM THA. To our knowledge, only deSouza et al. [12] and Hartmann et al. [20] have reported serum Cr and Co levels in patients with HR over a 10-year period. However, deSouza et al. [12] reported on only a few patients for the long-term analysis and no comparison with MOM THA implants was shown. Similarly, Hartmann et al. [20] reported long-term results in 75 patients, but they included patients with high ion levels, high cup inclination, and suspected loosening in the statistical calculation. Moreover, they did not perform a comparison with patients with MOM THA either as a whole population or subanalyzed by sex. In contrast, we judged it very important to compare the two types of prostheses over a longer period of time and considered only patients with well-fixed prostheses and cup inclination angle of less than 55°. In this series at a minimum followup of 8 years, the level of Cr still remained significantly higher in MOM HR patients than in MOM THA patients, whereas other ions did not differ between groups regardless of the component size. This may be explained according to the better lubrication regimen of larger articulations and to the possible metal ion release from the stem taper junction. Moreover, several other factors may influence ion release such as differences in design and geometry of the component, orientation of the acetabular component and metallurgy as well as metal corrosion and wear mechanisms [41].

We observed a relationship between sex and serum ion levels with regard to implant type. This result confirms our previous findings, which showed that, at medium term,

Table 4. Literature comparison of metal ion levels in patients with metal-on-metal hip implants at medium- or long-term followup

Study	Analysis	Implant	Type of study	Time	Matrix and ion values
Clarke et al. [9]	ICP-MS	BHR TM Cormet 2000 TM Ultima [®]	Retrospective	7–56 months (median, 16 months)	Serum median values (nmol/L): Co: 38; Cr: 53 Ultima [®] : Co: 22; Cr: 19
Daniel et al. [10]	ICP-MS	BHR TM	Prospective	Preoperatively, 1, 2, 4, and 6 years	Whole blood mean values (ng/mL): 1 year: Co: 1.26; Cr: 2.41 4 years: Co: 1.21; Cr: 1.12 6 years: Co: 1.17; Cr: 1.11
Moroni et al. [34]	GFAAS	BHR TM Metasul [®] (28 mm)	Retrospective	2 and 5 years	Serum mean values (ng/mL): 2 years: Metasul [®] : Co: 1.3; Cr: 1.8 BHR TM : Co: 1.2; Cr: 2.2 5 years: Metasul [®] : Co: 1.4; Cr: 1.9 BHR TM : Co: 1.1; Cr: 2.3
deSouza et al. [12]	GFAAS	Corin	Prospective	Preoperatively; 6, 12, and 18 months; 2, 3, 4, 5, 6, 7, 8, 9, and 10 years	Serum mean values (nmol/L): 8 years: Co: 102.9; Cr: 102.4 9 years: Co: 81.8; Cr: 99.3 10 years: Co: 86.5; Cr: 116.4
Hartmann et al. [20]	GFAAS	BHR TM	Retrospective	Mean, 10 years	Plasma mean values (μg/L): Cr: 1.9; Co: 1.3
Current study	GFAAS	BHR TM Metasul [®] (28 mm)	Retrospective	Median, 9 years	Serum mean values (ng/mL): Metasul [®] : Co: 0.69; Cr: 0.89 Women: Co: 0.65; Cr: 0.87 Men: Co: 0.73; Cr: 0.90 BHR TM : Co: 0.98; Cr: 1.94 Women: Co: 1.26; Cr: 2.45 Men: Co: 0.82; Cr: 1.65

Conversion factors: Co: ng/mL = μg/L = nmol/mL*0.059; Cr: ng/mL = μg/L = nmol/mL*0.052; ICP-MS = inductively coupled plasma mass spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; BHRTM = Birmingham HipTM Resurfacing; Co = cobalt; Cr = chromium.

women with MOM HR had higher Cr levels than women with MOM THA (mean ± SD, 3.17 ± 2.89 and 1.28 ± 1.07, respectively) [34]. Higher Cr and Co levels observed in MOM HR females compared with those with MOM THA may have been influenced by physical activity, as assessed by the UCLA scale, which was significantly higher in MOM HR group ($p = 0.001$). We agree with Bowsher et al. [7] who showed that serum ion levels were acutely affected by physical effort. In the MOM HR group, higher Cr and Co values were found in women compared with men, even if the difference was not significant. In agreement with Vendittoli et al. [47], high ion levels in MOM HR females may be secondary to differences in metal ion metabolism such as different body mass, cellular or extracellular storage, or renal excretion. Another possible explanation for the observed result could be the different hip anatomy [45] as well as different head/neck ratios between sexes [15]. Other hypotheses have been

reported in the literature: Jack et al. [25] demonstrated that small-diameter MOM HR performs poorly when compared with large-diameter MOM HR. In our study, average head diameter was 51.12 mm and 44.5 mm in men and women, respectively ($p = 0.002$). However, this finding cannot simply be explained by the use of smaller head sizes, because women fared less well than did men even with the same head size [43].

In conclusion, in patients with MOM HR, high metal ion release persists for at least 8 years after surgery. Clinical decision points for test interpretation are not clearly defined. Consequently, it is important to implement strict biomonitoring for patients receiving these implants. Furthermore, we believe that the increased distribution of Cr ions in women with MOM HR suggests that these implants are performing worse in women and that this deserves consideration during implant selection, especially when counseling women of childbearing age.

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