What Are the Predictors and Prevalence of Pseudotumor and Elevated Metal Ions After Large-diameter Metal-on-metal THA?

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Published online: 2 August 2014
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Abstract

Background Soft tissue masses, or “pseudotumors,” around metal-on-metal total hip arthroplasty (MoM THA) have been reported frequently; however, their prevalence remains unknown. Several risk factors, including elevated metal ion levels, have been associated with the presence of pseudotumor, although this remains controversial.

Questions/purposes The goals of this study were to (1) determine the prevalence of pseudotumors after large-diameter head MoM THA; (2) identify risk factors associated with pseudotumor formation and elevated metal ion

levels; and (3) determine the early failure rate of large-diameter MoM THA.

Methods Between December 2005 and November 2012, 258 hips (215 patients) underwent large-diameter head primary MoM THA at our institution. Clinical followup was obtained in 235 hips (91%). Using an inclusion criteria of a minimum followup of 1 year, a subset of 191 hips (mean followup, 4 years; range, 1–7 years) was recruited for high-resolution ultrasound screening for the presence of pseudotumor. Whole blood cobalt and chromium ion levels, UCLA activity level, WOMAC score, patient demographics as well as surgical, implant, and radiographic data were collected. Bivariate correlations and multivariate log-linear regression models were used to compare the presence of pseudotumor and elevated metal ions with all other factors.

Results Ultrasound detected a solid, cystic, or mixed mass in 20% hips (38 of 191). No correlation was found between the presence of pseudotumor and any risk factor that we examined. After controlling for confounding variables, elevated cobalt ions were correlated ($p < 0.001$, $R = 0.50$, $R^2 = 0.25$) with smaller femoral head size, the presence of bilateral MoM THA, and female sex. Elevated chromium ions were correlated ($p < 0.001$, $R = 0.59$, $R^2 = 0.34$) with smaller femoral head size, presence of bilateral MoM THA, and lower body mass index. The overall survival of MoM THA was 96% at a mean followup of 4.5 years (range, 2–8 years).

Conclusions With the numbers available, we found no associations between the presence of pseudotumor and the potential risk factors we analyzed, including elevated metal ion levels. Further work is needed to explain why larger femoral head sizes resulted in lower metal ion levels despite being associated with higher early failure rates in joint registry data.

This project was funded by Biomet, Inc (Warsaw, IN, USA). All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request. *Clinical Orthopaedics and Related Research*® neither advocates nor endorses the use of any treatment, drug, or device. Readers are encouraged to always seek additional information, including FDA-approval status, of any drug or device prior to clinical use. Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained. This work was performed at Grand River Hospital, Waterloo, Ontario, Canada.

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Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Metal-on-metal (MoM) articulations for THA and hip resurfacing have received much attention recently in the orthopaedic literature as well as the lay press. Previously thought of as a potential solution for the wear-related failures of conventional metal-on-polyethylene bearings, enthusiasm for widespread use of MoM articulations has been tempered by frequent reports of periarticular soft tissue masses, or “pseudotumors” [1, 8, 22, 31, 35, 40, 41, 44, 53], elevated local and systemic metal ion levels [4, 6, 7, 20, 23, 25, 30, 33, 38, 39, 42, 43, 51], and early failure rates in these implants [36, 46]. Pseudotumors are typically defined as solid granulomatous or destructive cystic lesions, neither infectious nor neoplastic, which develop in the vicinity of a THA and resemble a tumor [11]. There is no clear boundary between a variety of terms currently used in the literature including pseudotumor, metallosis, aseptic lymphocyte-dominated vasculitis-associated lesions, and adverse reaction to metal debris [36]. The presence of these lesions may result in pain, pressure effects as well as bone and soft tissue destruction that often requires revision arthroplasty to halt the process [11]. Elevated concentrations of cobalt and chromium ions have raised concerns regarding carcinogenicity [12, 52], neurologic and cardiac dysfunction [48], and local soft tissue destruction.

Several attempts have been made to define the prevalence of pseudotumors after large-diameter MoM THA and MoM hip resurfacing; however, no consensus exists. Depending on the implant used and the patient population, reports have ranged from 4% to 69% [8, 31, 35, 41, 53]. The pathogenesis of pseudotumors also remains unknown. Several risk factors including elevated metal ion levels [8], increased wear debris [22], female sex [36, 43], metal hypersensitivity [55], pain [9], and abnormal acetabular component positioning [29, 33] have been implicated in pseudotumor formation, although little has been substantiated in the literature.

Therefore, the goals of this study were to (1) determine the prevalence of pseudotumors after large-diameter head MoM THA; (2) identify risk factors associated with pseudotumor formation and elevated metal ion levels; and (3) determine the early failure rate of large-diameter MoM THA.

Patients and Methods

Study Design and Setting

Institutional research ethics board approval and informed consent from all participants were obtained before the initiation of the study. Between December 2005 and November 2012, 215 patients (258 hips) underwent large-diameter primary MoM THA at a single, community-based hospital. During this time, a total of 1780 patients underwent primary THA at that same center; the 258 MoM THAs therefore represented 14% of the THAs we performed. The general indications for use of a MoM bearing during that time included younger, more active patients thought to benefit from the theoretically improved wear characteristics offered from a MoM bearing.

Description of Experiment, Treatment, or Surgery

All procedures were performed by one of four experienced arthroplasty surgeons (PG, TH, DS, MS) through a direct lateral (225 hips) or anterolateral (33 hips) surgical approach. All patients received the same press-fit monoblock cup and large metal head design (cobalt-chromium alloy bearing surface and titanium adapter sleeve) with an uncemented, porous-coated femoral stem (M2a-Magnum™ acetabular component and Mallory-Head™ stem; Biomet, Inc, Warsaw, IN, USA). Femoral head diameter ranged from 42 to 60 mm and was a consistent 6 mm smaller than the outer shell diameter. Manufacturing specifications of this implant have been published previously [38].

Variables, Outcome Measures, Data Sources, and Bias

Questionnaires

Patients completed the UCLA activity score [2] and the WOMAC [5] at the time of followup. Both are validated, previously described, self-administered questionnaires. The WOMAC index contains five dimensions for pain, two dimensions for stiffness, and 17 dimensions for function. Each total raw score was normalized into a 0-to-100 scale with 0 representing the worst quality of life and 100 representing the best quality of life [5]. The UCLA activity score has 10 descriptive activity levels, ranging from wholly inactive (level 1) to participation in impact sports such as jogging or tennis (level 10) [2].

Ultrasound Screening

High-resolution ultrasound screening for the presence of pseudotumors was selected based on previous recommendations [19, 34], lower associated costs, and increased availability of testing as compared with metal artifact reduction sequence (MARS) MRI. Ultrasounds were obtained by three sonographers (from Grand River Hospital, Kitchener, Ontario, Canada) using a standardized template. The Philips iU22 xMatrix ultrasound system and C5-1 Curved Array transducer with Purewave technology was used (Philips Healthcare, Andover, MA, USA). The presence, location, and size of any fluid collections, cystic, solid, or mixed masses were recorded in accordance with the protocol used by Williams et al [53]. Pseudotumors were defined [53] as any solid, cystic, or mixed periprosthetic soft tissue mass with a minimum dimension of 1 cm³.

Radiographic Analysis

Digital AP pelvis and AP/lateral hip radiographs were obtained of the affected hip(s). Using the AP pelvis image and an electronic protractor, two investigators (NB, HK) measured the acetabular cup inclination angle and reported the mean value. A third measurement by another investigator (PG) was used if the two measurements differed by > 3°. Osteolysis and implant loosening in the Gruen et al [24] and DeLee and Charnley [14] zones were recorded according to previously described protocols [18, 49].

Ion Levels

Five milliliters of whole blood were collected using a Royal Blue Potassium EDTA Vacutainer #368381 (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and gently inverted eight to 10 times to prevent clotting. Samples were stored in a −20° C freezer and shipped monthly at room temperature. Whole blood cobalt and chromium ion levels were measured at the Trace Elements Laboratory of the London Health Sciences Centre (London, Ontario, Canada) by inductively coupled plasma mass spectrometry (Thermo Fisher ELEMENT 2, High Resolution Sector Field Inductively Coupled Plasma Mass Spectrometer; Thermo Fisher Scientific, Waltham, MA, USA). Whole blood metal ion levels were obtained in 163 patients (198 hips). Median cobalt and chromium values were 0.87 ug/L (range, 0.28–201.82 ug/L) and 1.12 ug/L (range, 0.23–79.36 ug/L), respectively.

Table 1. Bivariate statistical correlations between presence of pseudotumor and potential risk factors

Variable	Presence of solid mass (R value*)	Presence of any mass (R value*)
Ln(cobalt)	0.065	0.072
Ln(chromium)	0.087	0.097
Female sex	0.063	−0.002
Femoral head diameter	−0.069	0.019
Femoral offset	0.051	−0.079
Head-neck taper length	0.085	−0.023
Acetabular inclination angle	0.066	0.118
Age	0.053	−0.11
Body mass index	−0.033	−0.156
WOMAC score	0.034	0.005

* p value > 0.05 for all R values.

Table 2. Cohort demographic and revision surgical data

Variable	Total (N = 213 patients, 258 hips)
Mean age (years)*	55 (18–77)
Males (number, %)	174 (82)
Mean followup (years)*	4 (0.5–8)
Diagnosis (number, %)	
Posttraumatic OA	169 (79)
Idiopathic OA	15 (7)
Avascular necrosis	14 (7)
DDH	5 (2)
Inflammatory arthritides	3 (1)
Other	7 (3)
Surgical approach (number, %)	
Direct lateral	225 (87)
Anterolateral	33 (13)
Median femoral head diameter (mm)*	50 (42–60)
Revisions (number, %)	
Chronic infection	3 (1)
Aseptic loose acetabular component	3 (1)
Failure of femoral ingrowth	1 (0.4)
Fracture at neck-stem taper	1 (0.4)
Unexplained postoperative pain	1 (0.4)
Percent survival (mean followup in years, range)	96 (5 years, 2–8)

* Ranges are shown in parentheses; OA = osteoarthritis; DDH = developmental dysplasia of the hip.

Statistical Analysis and Study Size

Point-biserial correlations and chi-square tests were used to compare presence of pseudotumor with all other factors.

Table 3. Results of ultrasound screening for the presence of pseudotumor

Ultrasound result	Total (N = 191 hips)
Solid mass	
Number of hips (%)	13 (7)
Mean volume (cm ³)*	36 (8–97)
Cystic mass	
Number of hips (%)	12 (6)
Mean volume (cm ³)*	28 (9–102)
Mixed solid/cystic mass	
Number of hips (%)	13 (6.8)
Mean volume (cm ³)*	44 (15–116)
Isolated fluid collection	
Number of hips (%)	76 (40)
Mean volume (cm ³)*	27 (6–45)

* Ranges are shown in parentheses.

Cobalt and chromium ion levels were log-transformed and analyzed as dependent variables, whereas all other factors were taken as independent variables. Bivariate correlation was used to determine factors that were significantly correlated with metal ion levels ($p < 0.05$) (Table 1). These factors were then used to construct multivariate log-linear regression models for both cobalt and chromium ion levels. All statistics were performed using SPSS 21.0 (Chicago, IL, USA).

Demographics and Description of the Study Population

Cohort demographics include a mean age of 55 years (range, 17–77 years), 87% male, and a diagnosis of idiopathic osteoarthritis in 79% of patients (Table 2).

Accounting for All Patients/Study Subjects

Of the 215 patients in our cohort, four died from complications unrelated to their hip, 17 were lost to followup, 23 declined enrollment, and seven with < 1-year followup were excluded. Therefore, a subset of 164 patients (199 hips) with a minimum followup of 1 year (mean, 4 years; range, 1–7 years) were recruited for ultrasound screening, whole blood metal ion level testing, radiographic analysis, and questionnaire completion. All 23 patients who declined participation in the study confirmed by telephone that their implant had not been revised nor was pending revision surgery, yielding a 91% clinical followup rate for our cohort (235 of 258 hips). For determination of overall survival of our cohort, only implants with > 2 years followup were considered. Twenty-three of the total 258

Table 4. Bivariate statistical correlations between elevated metal ions and potential risk factors

Risk factor	Ln cobalt (R value)	Ln chromium (R value)
Ln(cobalt)	–	0.824 [†]
Ln(chromium)	0.824 [†]	–
Acetabular inclination angle	0.171*	0.166*
Femoral head diameter	–0.291 [†]	–0.322 [†]
Bilateral THA	0.316 [†]	0.244 [†]
Age	0.087	–0.079
Female sex	0.244 [†]	0.301 [†]
Body mass index	–0.180	–0.323 [†]
Head-neck taper length	0.089	0.036
UCLA score	–0.093	–0.105
WOMAC global	–0.055	–0.100

Correlation is significant at the * $p < 0.05$ and [†] $p < 0.01$ level (two-tailed).

implants were therefore excluded, resulting in 235 implants as the denominator for purposes of calculating early failure rate.

Results

Thirty-eight (20%) (eight females, 30 males) of the 191 hips that underwent ultrasound screening had a solid (13 [7%]), cystic (12 [6%]), or mixed solid/cystic mass (13 [7%]) (Table 3). Seventy-six hips (40%) had an isolated fluid collection (> 1 cm³) on ultrasound.

None of the potential risk factors we explored were associated with the formation of a pseudotumor (Table 1); however, several factors were associated with elevated metal ion levels. These included smaller femoral head size, the presence of bilateral MoM THA, female sex, and lower body mass index (Table 4). The multivariate regression model for cobalt ions found smaller femoral head size ($p < 0.001$, $R = 0.50$, $R^2 = 0.25$; $\beta = -0.245$), the presence of bilateral MoM THA ($\beta = 0.266$), and female sex ($\beta = 0.228$) to be associated. Elevated chromium ions were correlated ($p < 0.001$, $R = 0.59$, $R^2 = 0.34$) with smaller femoral head size ($\beta = -0.411$), presence of bilateral MoM THA ($\beta = 0.225$), and lower body mass index ($\beta = -0.330$).

The overall survival of MoM THA was 96% at a mean followup of 4.5 years (range, 2–8 years). Nine patients underwent revision surgery (Table 2). Revision surgery occurred for culture-proven, chronic infection ($N = 3$), failure of ingrowth of the femoral component ($N = 1$), aseptic loosening of the acetabular component ($N = 3$), traumatic fracture at the head-neck taper ($N = 1$), and

unexplained postoperative pain ($N = 1$). In the patients with aseptic loosening, there was no evidence of gross metallosis or periprosthetic soft tissue destruction at the time of revision.

Discussion

Several attempts have been made to define the prevalence of pseudotumor after the use of MoM implants; however, many of these studies have been limited by small sample sizes and/or the use of a mixed cohort of THA and hip resurfacing implants, often from several different manufacturers [13, 21, 25, 31, 35, 41]. Williams et al [53] reported a 33% prevalence of pseudotumors as detected by ultrasound surveillance in a small cohort ($N = 31$) of asymptomatic patients after large-diameter MoM THA. Hart et al [31] compared the prevalence of MRI-detected pseudotumors in a group of 30 patients with painful large-diameter MoM THA and a control group of 28 well-functioning patients and found a 57% and 61% prevalence of pseudotumors in the respective groups. Matthies et al [41] reported on a mixed cohort of 105 hip resurfacings and large-diameter MoM THA that underwent aseptic revision and found a 69% prevalence of pseudotumors as detected by MARS MRI. The pathogenesis of pseudotumors also remains unknown. Bosker et al [8] reported that patients with elevated cobalt and chromium ion levels had a four times increased risk of developing a pseudotumor; however, Matthies et al [41] found that patients undergoing revision for pseudotumors had similar ion levels and component wear rates compared with those who were not revised. Other studies have shown no clear association between the presence of a pseudotumor and acetabular component inclination and version [8, 31, 41], pain [9], and sex [8]. Elevated metal ion levels, often thought of as a surrogate for wear debris, have been associated with femoral head size [4, 25, 50], sex [15, 43], component positioning [3, 26–28, 32, 54], and head-neck taper influences [10, 38, 42]. We therefore sought to evaluate a large group of MoM THAs of a single design with cross-sectional imaging and metal ion levels. We specifically wished to determine the prevalence of pseudotumors after MoM THA as well as risk factors both for pseudotumor formation and for elevated metal ion levels.

There are several limitations to this study. Although ultrasonography is a practical and accessible imaging modality in a cost-conscious healthcare system, it is operator-dependent and less sensitive than MARS MRI in the detection of periprosthetic masses or fluid collections, particularly deep ones. The prevalence of pseudotumor in this study therefore is likely underestimated. Additionally, ultrasound image quality begins to deteriorate with

increasing patient body habitus, therefore potentially altering the determination of body mass index as a risk factor for pseudotumor. Furthermore, use of MARS MRI allows for better assessment of the soft tissues surrounding the solid and cystic masses, which may be more a clinically relevant finding than the presence of a mass itself. A second limitation is that our mean followup (4 years) is relatively short, and so we expect more of these patients to develop pseudotumors in the years to come, and as that occurs, we may be able to make more precise estimates of risk factors for the formation of pseudotumors. A third limitation is the M2a-MagnumTM (Biomet, Inc) used in this study has a titanium adapter sleeve. Retrieval analysis studies [37] suggest that laterally engaging taper systems can lead to increased early wear particles from both the cobalt-chromium heads as well as the taper adapter sleeve. Titanium ion levels were not measured, and as such, the contribution of wear debris from the adapter sleeve and stem-neck interface was underrepresented in this study. Additionally, although our sample size was fairly large, only a small number of pseudotumors was detected. There may indeed be risk factors associated with the presence of pseudotumor, but we were underpowered to detect them.

Using high-resolution ultrasound screening, we detected a 20% prevalence of pseudotumor in our cohort. Consistent with other studies [1, 8, 31, 53], our definition of pseudotumor included a spectrum of lesions ranging from small, fluid-filled cysts to large, complex, and potentially destructive lesions with solid components. Of the 38 periprosthetic masses identified, 13 were solid (7%), 12 were cystic (6%), and 13 were of the mixed solid/cystic variety (7%). Almousa et al [1] recently reported on the natural history of pseudotumors in a series of patients, an average of 26 months after initially detected on ultrasound, and concluded that although remission of smaller masses does occur, pseudotumors frequently increase in size in asymptomatic patients. This propensity for pseudotumors to increase in size coupled with our finding of a 20% prevalence after MoM THA reinforces previous recommendations that cross-sectional imaging should be a part of postimplantation surveillance of patients with MoM implants.

The etiology and clinical relevance of these lesions, however, remain unclear. We found no correlation between the presence of pseudotumor and any of the risk factors tested including elevated metal ion levels, femoral head size, femoral offset, head-neck taper length, acetabular component inclination angle, patient sex or age, body mass index, WOMAC score, or UCLA activity score. This was a surprising finding, particularly with respect to the metal ion levels, because Bosker et al [8] previously reported a four times increased risk of developing a pseudotumor in patients with elevated cobalt and chromium ion levels. Our

findings suggest that other factors, perhaps patient-specific such as metal hypersensitivity, may play a more important role in pseudotumor formation than previously thought. That clinical outcome scores (WOMAC, UCLA activity scores) did not correlate with the presence of pseudotumor as defined by ultrasound illustrates the asymptomatic and potentially insidious onset of these lesions as well as their uncertain clinical importance. Despite a high prevalence of pseudotumors, only 10 of 163 patients (6%) had either a cobalt or chromium level > 5 ug/L and only four patients (2%) had an ion level > 7 ug/L, which are previously described cutoff levels for distinguishing between failed and well-functioning MoM implants [30]. An interesting future study would involve imaging-guided hip aspiration to correlate local rather than systemic ions with the presence of pseudotumor.

After controlling for likely confounding variables, the factors correlating with elevated metal ion levels included female sex, the presence of bilateral implants, smaller femoral head size, and decreased body mass index. It is unclear why female sex and decreased body mass index are associated with elevated metal ions; however, previous hypotheses include increased ROM [21] and femoral anteversion [36] in females leading to greater impingement and metal ion release. Decreased body mass index may be a surrogate for increased activity level. More active individuals place more demands on their prosthesis, which may result in increased wear and elevated ions. The effect of femoral head size on metal ion levels in large-diameter MoM THA remains controversial. Data from in vitro and simulator studies reveal that a larger head diameter paradoxically results in lower wear because the lubrication regime changes from less favorable boundary lubrication to more favorable fluid film lubrication as head diameter increases [16, 17, 45, 47]. Several studies have reported substantially lower cobalt and chromium ions in patients with 36-mm MoM THA compared with 28-mm heads [4, 25]; however, others have shown no correlation between head size and ion levels [7, 33, 42]. Vendittoli et al [50] observed the opposite: increased ion levels in patients undergoing MoM THA with head sizes 50 mm or more and concluded [38] that larger femoral heads generate more friction at the articulating surface, which increases the rotational moment between the adapter sleeve and the stem-neck interface, thereby increasing wear. Our study revealed a substantial negative correlation between both cobalt and chromium ion levels and femoral head size. In other words, smaller femoral heads were associated with elevated metal ion levels. This may suggest in large-diameter MoM THA, the effect of larger femoral head size on decreased wear from the articulating surface and the potential negative effect of larger femoral head size on increased wear from the adapter sleeve and the stem-neck

interface. However, the adapter sleeve and femoral neck taper in our study were titanium and therefore we did not measure wear occurring at this interface. Further work is needed to determine if this holds true with other large-diameter MoM THA implants and to explain why despite appearing to be associated with lower metal ion levels, larger femoral head size is associated with higher early failure rates in joint registry data [46].

The overall survival of MoM THA in our cohort was 96% at a mean followup of 4.5 years (range, 2–8 years). Previous studies using large joint registry data have reported a 5-year failure rate of MoM THA at 6.2% (95% confidence interval, 5.8–6.6) [46], slightly higher than we report. Our failure rate, however, may underestimate the true value because patients with ongoing pain and pseudotumor were not included in this calculation. Further long-term, comparative studies of MoM and alternative bearing surfaces remain a priority for future research.

We found that despite a pseudotumor prevalence of 20%, we were unable to identify correlations between the presence of pseudotumor and a variety of potential risk factors including elevated metal ion levels after MoM THA. The observation that elevated ion levels may not correlate with the presence of pseudotumor reemphasizes previous guidelines that a combination of metal ion levels, cross-sectional imaging, and patient symptomatology should all be considered in the postimplantation management and surveillance of patients undergoing MoM THA. Further work is needed to explain why larger femoral head sizes result in lower metal ion levels despite being associated with higher early failure rates in joint registry data.

Acknowledgments We thank the Grand River Hospital (Kitchener, Ontario, Canada) ultrasonographers and radiology department as well as the Kitchener-Waterloo MSK Centre research nurses for their contributions.

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