

Prevalence of Pseudotumor in Asymptomatic Patients After Metal-on-Metal Hip Arthroplasty

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Background: The cause of recently reported pseudotumor formation in patients with metal-on-metal hip replacements is unknown. It has been postulated that there is an association between elevated levels of serum metal ions and pseudotumor formation. The primary purpose of this study was to assess the prevalence of pseudotumor formation in asymptomatic patients with a metal-on-metal total hip replacement after a minimum duration of follow-up of two years. A secondary purpose was to assess whether a correlation exists between elevated serum metal ion levels and pseudotumor formation.

Methods: In the present study, the prevalence of pseudotumor formation, as detected with ultrasound, was evaluated for thirty-one asymptomatic patients with a metal-on-metal total hip arthroplasty, twenty-four asymptomatic patients with a metal-on-polyethylene total hip arthroplasty, and twenty asymptomatic patients with a metal-on-metal hip resurfacing arthroplasty. Serum levels of cobalt and chromium were measured in the metal-on-metal total hip arthroplasty and hip resurfacing arthroplasty groups.

Results: Ten patients (32%) in the metal-on-metal total hip arthroplasty group had a solid or cystic mass, with another three patients (10%) having a substantial fluid collection. Five patients (25%) in the hip resurfacing arthroplasty group had a solid or cystic mass, with another patient (5%) having a fluid collection. Pseudotumor formation was significantly more frequent in the metal-on-metal total hip arthroplasty group compared with the metal-on-polyethylene total hip arthroplasty group ($p = 0.015$). We did not detect a significant correlation between the serum metal ion levels and the size of pseudotumor abnormality. The median serum metal ion level was greater in patients with pseudotumor formation than it was in those without pseudotumor formation, but the difference was not significant.

Conclusions: We recommend high-resolution ultrasound surveillance of all asymptomatic patients with a metal-on-metal implant that is known to result in high serum metal ion levels. Once a metal-on-metal implant is known to be associated with high serum metal ions, the measurement of ion levels does not helpfully contribute to surveillance.

Level of Evidence: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

The rate of failure of total hip replacement in younger, more active patients under the age of forty years has been reported to be 21% to 25%.¹ The tribological properties of the metal-on-metal cobalt-chromium-molybdenum bearing surface²⁻⁹ have contributed to the encouraging five to seven-year clinical results of both metal-on-metal hip resurfacing arthroplasty^{1,10-13} and metal-on-metal total hip arthroplasty^{8,14-21}.

The level of elevated serum metal ions detected in association with metal-on-metal bearing surfaces in general is not

known^{19,22-32}. We are aware of no proven long-term systemic ill effects in patients with metal-on-metal hip replacements^{33,34}. Recently, however, isolated reports of benign but locally destructive masses associated with metal-on-metal hip resurfacing and total hip arthroplasty have appeared in the literature³⁵⁻³⁹. Pandit et al. reported on a series of twenty patients who had a symptomatic "pseudotumor," a soft-tissue mass that is associated with an implant but is neither malignant nor infectious. They estimated the incidence to be 1% at five years in patients

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with hip resurfacing, but they postulated that an appreciable number of unrecognized asymptomatic pseudotumors may exist⁴⁰. All patients were women, raising the possibility of a metal allergy etiology. Patients with steeply inclined acetabular cups developed symptoms within the first year, suggesting that edge loading and the release of metal debris may be important. However, the levels of serum metal ions were not known. Further study revealed higher levels of metal ions in patients with steeply inclined components and a weight-bearing arc of coverage of <10 mm (a function of acetabular component inclination, size, and design)⁴¹.

As part of a recent randomized trial⁴² from our institution, serum cobalt ($p = 0.000$) and chromium ($p = 0.023$) ion levels were significantly higher in patients who had been managed with large-head metal-on-metal total hip arthroplasty as compared with those who had been managed with metal-on-metal hip resurfacing arthroplasty. However, there were no data on the prevalence of pseudotumor formation in the group with elevated ion levels.

The primary purpose of the present study, therefore, was to assess the prevalence of pseudotumor formation in asymptomatic patients with a metal-on-metal total hip replacement after a minimum duration of follow-up of two years. The prevalence of pseudotumor formation in asymptomatic patients with a metal-on-polyethylene total hip replacement and that in asymptomatic patients with a metal-on-metal hip resurfacing implant were evaluated at the same time point for comparison. A secondary purpose was to assess if a correlation existed between elevated serum metal ion levels and pseudotumor formation.

Materials and Methods

Consent to participate in the study was prospectively obtained from a total of seventy-five patients undergoing primary hip arthroplasty. We recruited consecutive groups of local asymptomatic patients to achieve a minimum of twenty patients in each group. Of the seventy-five patients, thirty-one underwent metal-on-metal total hip arthroplasty (M/L Taper/Durom; Zimmer, Warsaw, Indiana), twenty-four underwent metal-on-polyethylene total hip arthroplasty (M/L Taper/Trilogy; Zimmer), and twenty underwent metal-on-metal hip resurfacing arthroplasty (Durom; Zimmer). Institutional review board approval was obtained. The demographic characteristics of the study groups were similar (see Appendix). Procedures were performed by four participating surgeons (B.A.M., N.V.G., C.P.D., D.S.G.) from September 1, 2004, to June 30, 2007, during which time a total of 150 metal-on-metal total hip arthroplasties, 1091 metal-on-polyethylene total hip arthroplasties, and 400 metal-on-metal hip resurfacing arthroplasties were performed at our institution. All patients were evaluated at a minimum of two years after surgery. Patients undergoing multiple joint replacements or revision joint replacement for any reason and patients with a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)⁴³ of <80 (indicating the presence of symptoms) were excluded from the study.

In the metal-on-metal total hip arthroplasty and hip resurfacing arthroplasty groups, the serum levels of metal ions were measured and an ultrasound examination of each hip was simultaneously performed to evaluate for evidence of fluid or pseudotumor formation after a minimum duration of follow-up of two years. In the metal-on-polyethylene total hip arthroplasty group, ultrasound examination of each hip was performed to look for evidence of fluid or a cystic or solid mass after a minimum duration of follow-up of two years. Pseudotumor formation was defined as a solid and/or cystic mass.

All patients completed the WOMAC⁴³, Short Form-12 (SF-12)⁴⁴, and University of California Los Angeles (UCLA)⁴⁵ questionnaires at the time of

admission for surgery and at the two-year follow-up. The WOMAC is a self-administered, multidimensional index containing five dimensions for pain, two dimensions for stiffness, and seventeen dimensions for function. Each item is represented by a Likert scale⁴⁶ ranging from 0 (best health state) to 4 (worst health state). 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 life⁴³. The SF-12 is a subscale of the Short Form-36, with the score ranging from 0 points (worst score) to 100 points (best score)⁴⁴. The UCLA activity rating has ten descriptive activity levels, ranging from wholly inactive and dependent on others (level 1) to moderate activities such as unlimited housework and shopping (level 6), regular participation in cycling (level 7), and participation in impact sports such as jogging or tennis (level 10)⁴⁵.

Blood samples were obtained with use of a BD Vacutainer Safety-Lok Blood Collection Set (BD [Becton, Dickinson]; Franklin Lakes, New Jersey). The first 5 mL of blood was discarded to avoid possible contamination from the needle. A second 5 mL of blood was collected, and serum levels of cobalt and chromium were measured at the Trace Elements Laboratory—London Health Sciences Centre (London, Ontario, Canada) with use of inductively coupled plasma mass spectrometry (Thermo Fisher ELEMENT 2, High Resolution Sector Field Inductively Coupled Plasma Mass Spectrometer [HR-SF-ICP-MS]; Thermo Fisher Scientific, Waltham, Massachusetts). This is considered the gold standard for trace metal ion analysis³².

A separate blood sample was drawn at the same time for analysis of blood urea, creatinine, electrolytes, alkaline phosphatase, aspartate transaminase, and alanine transaminase.

The ultrasound examinations were all performed by two sonographers according to a standardized template with use of the ACUSON Antares Ultrasound System (Siemens Medical Solutions USA; Mountain View, California). The Siemens VFX9-4 linear transducer was used for anterior and lateral views, and the Siemens CH6-2 curvilinear transducer was used for posterior views.

The presence, size, and position of any fluid, cystic mass, or solid mass adjacent to the hip were recorded, along with any involvement of neurovascular structures. A minimum size of 10 mm in any dimension was defined as an abnormality. The volume of any fluid or mass was calculated by multiplying the maximum recorded dimensions in millimeters in each of three planes and dividing by 1000 to convert to volume in cubic centimeters (cm³).

The acetabular cup inclination was measured on a single digitally recorded anteroposterior pelvic radiograph with use of an electronic protractor. This angle and the radius of the articular surface were used to calculate the arc of the cover of the femoral head⁴¹.

Statistical Methods

An ordinal regression model was used to assess the predictors of pseudotumor formation⁴⁷. The dependent variable was the presence of a pseudotumor. This model calculated a single odds ratio (OR) and 95% confidence interval (CI) for each covariate, independent of the rank of the response category. The assumptions of proportionality across thresholds were tested⁴⁸. Summary proportional odds ratios and confidence intervals were then calculated for selected independent variables that included the type of procedure (metal-on-metal total hip arthroplasty, metal-on-polyethylene total hip arthroplasty, or metal-on-metal hip resurfacing arthroplasty), the measured serum chromium and cobalt ion levels, and various demographic parameters, including age, sex, and body mass index (BMI). In the proportional odds model for each covariate, outputs included an estimate of the regression coefficient, its standard error, Wald chi-squared statistic, p value, and the corresponding odds ratio and confidence limits.

Additionally, the Pearson correlation coefficient was calculated to test for a correlation between serum chromium or cobalt ions levels and pseudotumor volume. The Pearson correlation coefficient was also used to test for a correlation between cup inclination or arc of cover⁴¹ and serum chromium or cobalt ions levels (all continuous variables). The Spearman rank correlation coefficient was also calculated to test for a correlation between cup inclination or arc of cover⁴¹ and pseudotumor formation. The Kruskal-Wallis test was used to test for a significant difference between the median serum metal ion levels in

TABLE I Quality-of-Life Scores at a Minimum of Two Years*†

	Metal-on-Metal Total Hip Arthroplasty	Metal-on-Polyethylene Total Hip Arthroplasty	Metal-on-Metal Hip Resurfacing Arthroplasty
WOMAC (points)			
Global	96.4 ± 5.6 (80 to 100)	96.2 ± 5.3 (81 to 100)	95.2 ± 5.7 (83 to 100)
Pain	95.7 ± 6.9 (75 to 100)	96.5 ± 7.4 (65 to 100)	97.5 ± 6.6 (75 to 100)
Function	96.6 ± 5.8 (78 to 100)	96.3 ± 5.7 (78 to 100)	95.4 ± 5.3 (85 to 100)
SF-12 (mental component) (points)	53.8 ± 9.4 (29 to 62)	55.8 ± 4.6 (43 to 63)	54.9 ± 6.1 (37 to 62.8)
UCLA activity level (points)	7.5 ± 1.7 (4 to 10)	6.3 ± 1.5 (4 to 10)	8.4 ± 1.6 (5 to 10)

*The values are given as the mean and the standard deviation, with the range in parentheses. †WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, SF-12 = Short Form-12, and UCLA = University of California Los Angeles.

TABLE II Results of Ultrasound Examination*

	Metal-on-Metal Total Hip Arthroplasty (N = 31)	Metal-on-Polyethylene Total Hip Arthroplasty (N = 24)	Metal-on-Metal Hip Resurfacing Arthroplasty (N = 20)
Solid mass			
No. of patients	7 (23%)	0	3 (15%)
Volume† (cm ³)	96.1 (8 to 437)	—	58.7 (24 to 119)
Cystic mass			
No. of patients	3 (10%)	1 (4%)	2 (10%)
Volume† (cm ³)	73.5 (14 to 176)	9.8	16.0 (6 to 26))
Isolated fluid collection			
No. of patients	3 (10%)	2 (8%)	1 (5%)
Volume† (cm ³)	35.2 (10 to 70)	2.9 (1 to 5)	8.4

*The difference in the prevalence of pseudotumor formation between the metal-on-metal total hip arthroplasty and metal-on-polyethylene total hip arthroplasty groups was significant ($p = 0.015$). There was no significant difference in pseudotumor formation between the metal-on-metal total hip arthroplasty and hip resurfacing arthroplasty groups ($p = 0.755$) or between the metal-on-polyethylene total hip arthroplasty and hip resurfacing arthroplasty groups ($p = 0.077$). †The values are given as the mean, with the range in parentheses.

TABLE III Serum Metal Ion Levels

	Metal-on-Metal Total Hip Arthroplasty (N = 31)	Metal-on-Polyethylene Total Hip Arthroplasty (N = 24)	Metal-on-Metal Hip Resurfacing Arthroplasty (N = 20)
Chromium (µg/L)			
Normal*	0.099 to 0.198	—	—
Median	2.82	—	1.08
Standard deviation	9.12	—	34.28
Range	0.66 to 50.47	—	0.45 to 142.46
Cobalt (µg/L)			
Normal*	0.030 to 0.400	—	—
Median	4.50	—	0.83
Standard deviation	10.46	—	47.21
Range	0.54 to 58.78	—	0.39 to 195.61

*Normal values for anyone undergoing serum metal ion testing, regardless of whether they have a metal implant or not. Normal values are determined by the Trace Elements Laboratory—London Health Sciences Centre.

TABLE IV Results of Radiographic Examination⁴¹

	Metal-on-Metal Total Hip Arthroplasty (N = 31)	Metal-on-Polyethylene Total Hip Arthroplasty (N = 24)	Metal-on-Metal Hip Resurfacing Arthroplasty (N = 20)
Cup inclination* (deg)	41.6 ± 5.0 (35 to 52)	42.5 ± 6.3 (27 to 58)	42.9 ± 5.7 (33 to 58)
Arc of cover* (mm)	16.8 ± 2.0 (13 to 21)	—	17.0 ± 2.6 (11 to 21)

*The values are given as the mean and the standard deviation, with the range in parentheses.

the groups of patients with and without pseudotumor formation. Finally, the rate of pseudotumor formation was compared between the groups (that is, metal-on-metal total hip arthroplasty compared with hip resurfacing arthroplasty, metal-on-metal total hip arthroplasty compared with metal-on-polyethylene total hip arthroplasty, and hip resurfacing arthroplasty compared with metal-on-polyethylene total hip arthroplasty) with use of the Fisher exact test (given the small number of patients in each group), and the p value was multiplied to adjust for three comparisons.

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Results

The demographic details for each group are summarized in the Appendix, and the clinical outcome scores are displayed in Table I. A WOMAC score ≥ 80 (indicating an asymptomatic patient) was one of the main criteria for entry into this study; therefore, the outcome scores in each group were good. In the metal-on-metal total hip arthroplasty group, seven patients (23%) (two men and five women) had a solid mass with mean volume of 96.1 cm³ (range, 8 to 437 cm³) and three patients (10%) (one man and two women) had a cystic mass with a mean volume of 73.5 cm³ (range, 14 to 176 cm³) on ultrasound examination (Figs. 1 and 2). Two of the seven patients who had a

solid mass had an associated fluid collection, and another three patients (10%) had an isolated fluid collection with a mean volume of 35.2 cm³ (range, 10 to 70 cm³) (Table II).

In the metal-on-polyethylene total hip arthroplasty group, no patient had a solid mass and one patient (4%) (a woman) had a cystic mass that measured 9.8 cm³ on ultrasound examination. Additionally, two patients (8%) had an isolated fluid collection with a mean volume of 2.9 cm³ (range, 1 to 5 cm³) (Table II).

In the hip resurfacing arthroplasty group, three patients (15%) (one man and two women) had a solid mass with a mean volume of 58.7 cm³ (range, 24 to 119 cm³) and two patients (10%) (one man and one woman) had a cystic mass with a mean volume of 16.0 cm³ (range, 6 to 26 cm³) on ultrasound examination. One patient (5%) had an isolated fluid collection with a volume of 8.4 cm³ (Table II).

Serum chromium and cobalt ion levels in the metal-on-metal total hip arthroplasty group were a mean of fourteen times (range, five to 255 times) and eleven times (range, two to 147 times) the upper limit of normal (0.198 and 0.400 part per billion [$\mu\text{g/L}$]) for chromium and cobalt, respectively. In the hip resurfacing arthroplasty group, chromium and cobalt ion levels were a mean of five times (range, two to 720 times) and two times (range, one to 489 times) the upper limit of normal (Table III). These data are represented graphically in Figs. 3 and 4, without the two excluded outliers (one patient in the large-



Fig. 1

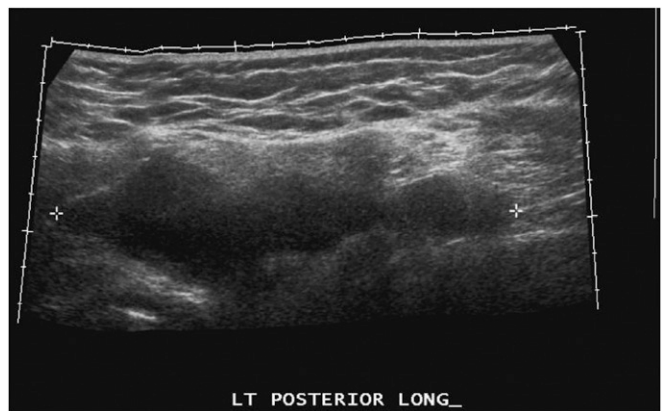


Fig. 2

Fig. 1 Ultrasound image showing a solid mass with a volume of 437 cm³ in an asymptomatic woman with a metal-on-metal total hip replacement. **Fig. 2** Ultrasound image showing a cystic mass with a volume of 176 cm³ in an asymptomatic woman with a metal-on-metal total hip replacement.

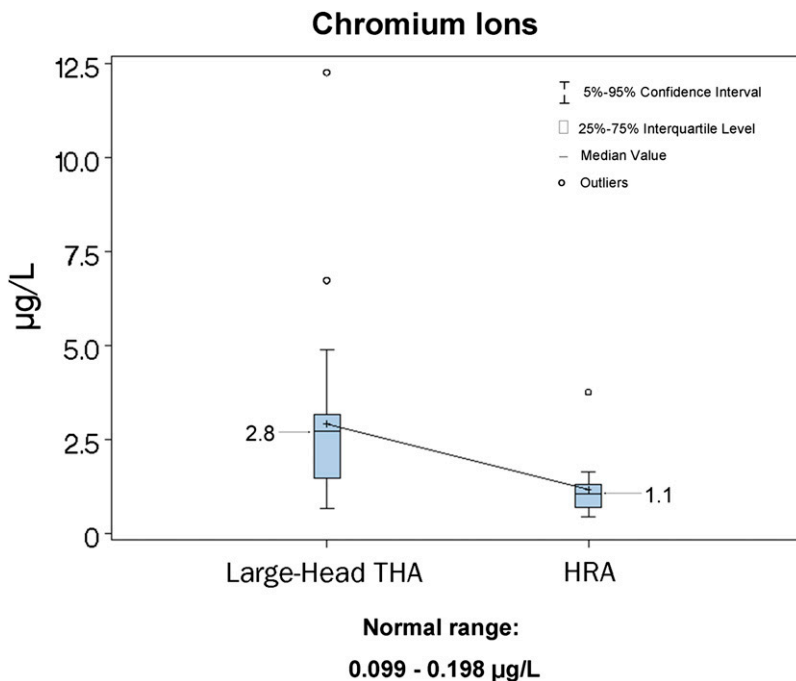


Fig. 3

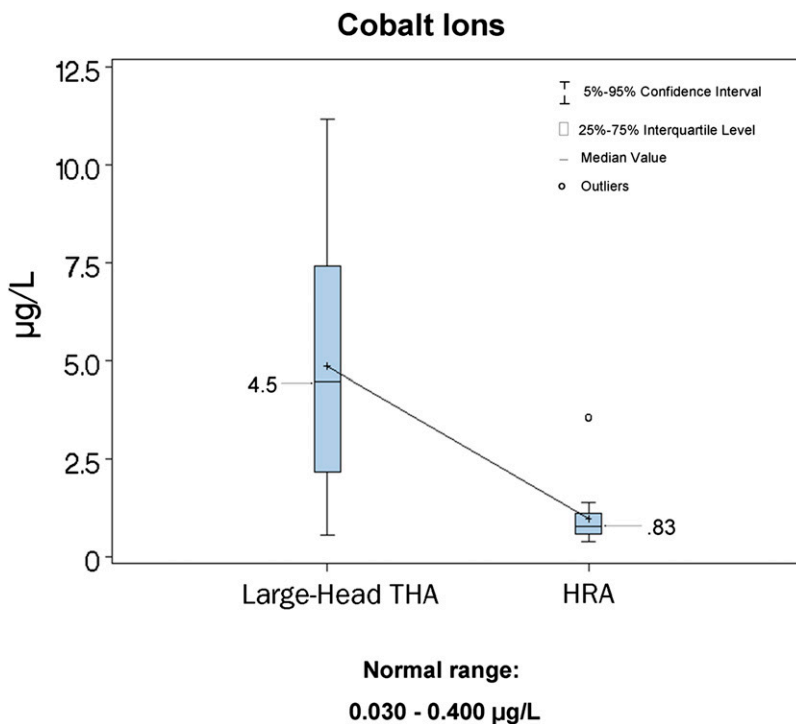


Fig. 4

head metal-on-metal total hip arthroplasty group and one in the resurfacing group). An excluded outlier was defined as a patient with a serum metal ion level that was several times greater than the second-largest value in our results. In our study, excluded outliers had an ion level of >50 µg/L.

Only one cup in the metal-on-metal hip resurfacing arthroplasty group, with an inclination angle of 58° , was con-

Fig. 3 “Trimmed” box plot graph showing serum chromium ion levels (µg/L) after a minimum of two years of follow-up. THA = total hip arthroplasty and HRA = hip resurfacing arthroplasty. **Fig. 4** “Trimmed” box plot graph showing serum cobalt ion levels (µg/L) after a minimum of two years of follow-up. THA = total hip arthroplasty and HRA = hip resurfacing arthroplasty.

sidered to have a steep inclination angle ($>55^\circ$)⁴¹, and it was not associated with an ultrasound abnormality (Fig. 5-A). The resulting arc of cover was calculated as 11 mm on the basis of the radiograph. All other angles of cup inclination in the metal-on-metal total hip arthroplasty and hip resurfacing arthroplasty groups measured $<55^\circ$ (Fig. 5-B), with corresponding arcs of cover >10 mm (Table IV)⁴¹.



Fig. 5-A



Fig. 5-B

Fig. 5-A Anteroposterior pelvic radiograph for a patient in the metal-on-metal hip resurfacing arthroplasty group who did not have a pseudotumor abnormality on ultrasound. The cup inclination measured 58°. **Fig. 5-B** Anteroposterior pelvic radiograph for a patient in the metal-on-metal total hip arthroplasty group who did not have an ultrasound abnormality. The cup inclination measured 35°.

None of the sixteen covariates that were entered into the ordinal regression model (including serum chromium and cobalt ion levels and various demographic parameters and patient characteristics such as age, sex, and BMI) predicted pseudotumor formation.

There was no significant correlation between serum metal (chromium or cobalt) ion level and pseudotumor volume. There was no significant difference between patients with and without pseudotumor formation in terms of the median serum chromium and cobalt ion levels ($p = 0.08$ and 0.07 , respectively). Patients with a detectable abnormality on ultrasound examination had higher median serum metal ion levels than those who did not.

Furthermore, the difference in the prevalence of pseudotumor formation between the metal-on-metal total hip arthroplasty and metal-on-polyethylene total hip arthroplasty groups was significant ($p = 0.015$) and remained so even after adjusting for three comparisons ($p = 0.046$) (that is, metal-on-metal total hip arthroplasty compared with hip resurfacing arthroplasty, metal-on-metal total hip arthroplasty compared with metal-on-polyethylene total hip arthroplasty, and hip resurfacing arthroplasty compared with metal-on-polyethylene total hip arthroplasty). There was no significant difference in pseudotumor formation between the metal-on-metal total hip arthroplasty and hip resurfacing arthroplasty groups ($p = 0.755$) or between the hip resurfacing arthroplasty and metal-on-polyethylene total hip arthroplasty groups ($p = 0.077$) (Table II).

Pseudotumor formation did not correlate with either acetabular cup inclination or arc of cover in either the metal-on-metal total hip arthroplasty group or the hip resurfacing arthroplasty group. The arc of cover in the metal-on-metal total hip arthroplasty group significantly correlated with the serum chromium ion level ($p = 0.01$) but did not significantly correlate with the serum cobalt ion level ($p = 0.078$).

With the numbers available, the acetabular cup inclination in the hip resurfacing arthroplasty group did not significantly correlate with either serum chromium or cobalt ion levels ($p = 0.072$ and $p = 0.076$, respectively).

Discussion

The prevalence of pseudotumor formation in a group of asymptomatic patients with a metal-on-metal implant has not previously been described, to our knowledge³⁵⁻³⁸. A previous study showed that the M/L Taper/Durom (Zimmer) total hip system produced significantly increased serum metal ion levels of chromium ($p = 0.001$ and cobalt ($p = 0.001$)⁴². The present study confirmed very high serum metal ion levels in this group of asymptomatic patients with a metal-on-metal-bearing surface. The serum levels of metal ions in the large-head metal-on-metal total hip arthroplasty group were considerably higher than those in the hip resurfacing arthroplasty group (Figs. 3 and 4).

In the metal-on-metal total hip arthroplasty group, ten patients (32%) had a solid (seven) or cystic (three) mass, with another three patients (10%) having an isolated fluid collection, resulting in an overall abnormality rate of 42% (thirteen of thirty-one). In the hip resurfacing arthroplasty group, five patients (25%) had a solid (three) or cystic (two) mass, with another patient (5%) having an isolated fluid collection, resulting in an overall abnormality rate of 30% (six of twenty). The mean volumes of the solid, cystic, and fluid abnormalities were greater in the metal-on-metal total hip arthroplasty group (Table II). To reiterate, all of the patients in this study were asymptomatic, with a WOMAC score of ≥ 80 at the time of assessment; the higher UCLA scores in the metal-on-metal total hip arthroplasty and hip resurfacing arthroplasty groups were likely secondary to bias in the original selection of the implant (Table I).

Despite the relatively small number of patients assessed, pseudotumor formation was significantly more prevalent in the

metal-on-metal total hip arthroplasty group compared with the metal-on-polyethylene total hip arthroplasty group ($p = 0.015$).


Given the numbers available in the study, we did not find a significant correlation between serum metal ion levels and the size of the pseudotumor abnormality. However, the median serum metal ion level was greater (although not significantly so) in the patients with pseudotumor formation than it was in those without pseudotumor formation. Although there may be other factors involved in the formation of a solid or cystic pseudotumor abnormality, it appeared clinically that metal ions likely played a central role. However, it might be postulated that metal ion levels in the blood serum are only a partial indication of events within the hip joint and are themselves subject to many variable influencing factors⁴⁹⁻⁵².

Similar reasoning might also explain why we did not find a correlation between pseudotumor formation and cup inclination or between pseudotumor formation and arc of cover in either the metal-on-metal total hip arthroplasty group or the hip resurfacing arthroplasty group. However, cup inclination angles in this study were not classified as steep, that is, $>55^\circ$ of inclination⁴¹. Only one patient had a cup angle of $>55^\circ$. The present study demonstrated similar trends to those found in previous studies in terms of the relationship between acetabular cup inclination^{26,41,52} and arc of cover⁴¹ and the serum level of the metal ions measured. However, serum metal ion levels did not correlate with pseudotumor formation. Studying radiographs also did not predict which patients were at risk for pseudotumor abnormality.

The results of the present study indicated that patients with metal-on-metal hip replacements, known to result in high ion levels, had high rates of pseudotumor formation. In this study, the rate ranged from 30% to 40%, depending on the type of hip arthroplasty. The important clinical question not an-

swered in the present study was what treatment recommendations to offer asymptomatic patients with metal-on-metal implants and an associated ultrasound abnormality consistent with pseudotumor formation. The outcome of revision surgery for pseudotumors is poor in symptomatic patients⁵³. Therefore, we recommend high-resolution ultrasound surveillance for all asymptomatic patients with metal-on-metal implants known to result in high serum metal ion levels. Once a metal-on-metal implant is known to be associated with high serum metal ion levels, the measurement of ion levels does not helpfully contribute to continued surveillance. Patients with positive findings, especially those with a large-volume pseudotumor and those who develop symptoms with a pseudotumor, require further investigation and should be considered to be candidates for early revision arthroplasty.

Appendix

 A table showing the demographic data for the study population is available with the online version of this article as a data supplement at jbj.org. ■

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