High Frequency of Adverse Local Tissue Reactions in Asymptomatic Patients With Metal-on-Metal THA

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Abstract

Background The key to successful management of patients with metal-on-metal (MOM) THAs is to diagnose adverse local tissue reactions (ALTRs) early. ALTRs have been described in asymptomatic patients with resurfacing arthroplasties. Whether this concerning finding applies to modular MOM THAs is unknown.

Questions/purposes We (1) determined the prevalence of ALTRs in asymptomatic patients with modular MOM THAs, (2) described any differences in the appearance of these lesions between symptomatic and asymptomatic patients, and (3) analyzed potential predictive factors for any associations with ALTR prevalence.

Methods We evaluated 114 patients with modular MOM THAs who had MRI with metal artifact reduction sequence software and metal ion laboratory results at a mean of

57 months postoperatively. There were 83 asymptomatic and 31 symptomatic patients. We defined ALTRs as abnormal fluid collections, solid or semisolid pseudotumors, or muscle or bone damage. Ion levels, lesion size, and cup abduction angles were analyzed.

Results Twenty-six (31%) asymptomatic patients had ALTR lesions, all of which were in the greater trochanteric area. Most lesions in symptomatic patients also were in that location, but there was more diversity of location in this group. The cup position among patients with ALTRs was generally good; the average abduction angle for the asymptomatic patients with ALTRs was 40°. In 24 (92%) and 22 (85%) of 26 asymptomatic patients with ALTRs, respectively, chromium and cobalt levels were below the 7-ppb threshold.

Conclusions A 31% incidence of periarticular fluid collections in asymptomatic patients with modular MOM THAs is alarming and calls into question any algorithmic approach dependent on symptomatology. The presence of pain was insufficient to identify patients at risk for ALTRs. To determine whether routine cross-sectional imaging of all asymptomatic patients with MOM implants is necessary will require a larger study cohort, longer followup, and clearer understanding of the natural history of periarticular lesions in these patients.

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

One of the authors certifies that he (TKF) has received or may receive payments or benefits, during the study period, an amount of USD 100,001 to USD 1,000,000 from DePuy Orthopaedics Inc (Warsaw, IN, USA).

Each author certifies that his or her institution approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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. Data were collected at each institution. Data analysis was conducted at OrthoCarolina Research Institute, Charlotte, NC, USA.

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Introduction

Large-head metal-on-metal (MOM) bearing surfaces were introduced as an approach that might decrease the

likelihood of dislocation after THA and avoid polyethylene-induced osteolysis. However, the identification of adverse local tissue reactions (ALTRs), defined as abnormal fluid collections, solid or semisolid pseudotumors, or muscle or bone damage, to these bearing surfaces has discouraged their use. Whether such reactions will occur occasionally and inconsistently or become an inevitable complication of this bearing surface is not known. At one time, MOM articulations accounted for more than 1/3 of the hip arthroplasty market in the United States [1]. Therefore, the proper diagnosis, management, and treatment of patients with MOM bearings are critical.

The key to successful management of patients with MOM implants is to diagnose ALTRs before irreparable damage occurs. Management of a patient with a painful MOM bearing includes a careful physical examination, serum ion levels, and cross-sectional imaging. Diagnostic clues for a malfunctioning bearing include pain, mechanical symptoms, and muscle weakness. Recognition of a recalled implant or of a poorly aligned implant also should alert the clinician to a potential problem related to the metal bearing.

Initially, the use of serum cobalt and chromium ion levels was promoted as a means to identify a malfunctioning bearing. However, controversy exists concerning whether serum ion levels correlate with ion concentrations in synovial fluid [2, 3]. Additionally, recent studies have questioned the diagnostic accuracy of ion levels at a threshold level of 7 ppb established by the 2010 British Medicines and Healthcare products Regulatory Agency [9]. The sensitivity of metal ion levels as a predictive diagnostic test has also been shown to be low in studies from two different centers. These studies were unable to find a direct correlation between ion levels and the tissue damage observed at the time of revision surgery [5, 7]. Therefore, it appears that, not unlike patients with metal-on-plastic bearings, patients may have variable responses to metal debris and variable thresholds for when cobalt and chromium ion levels lead to ALTRs.

An algorithmic approach incorporating a variety of clinical and diagnostic parameters has been recommended by the British Medicines and Healthcare products Regulatory Agency [9] and the American Hip Society [8]. While each of these algorithms has a unique approach to the treatment and management of patients with MOM implants, the presence or absence of symptoms determines the decision tree path taken.

While the presence of pain has been used as a harbinger of bearing-related problems, the sensitivity of pain as diagnostic of a bearing-related problem has recently been challenged. ALTRs have recently been described in asymptomatic patients with resurfacing arthroplasty in four different studies with a prevalence of 5%, 30%, 61%, and

68%, respectively [4, 6, 10, 11]. Another MRI study of 59 large monoblock THAs and 16 resurfacings noted that 26 of these patients had “perfect” Oxford Hip Scores yet six had MRI evidence of ALTRs [12]. Such information may lead clinicians to surmise that all MOM resurfacings require cross-sectional imaging to determine the presence or absence of ALTRs. Whether these findings apply to patients with modular MOM THAs is unknown. The addition of modular interfaces at the head-neck junction or within the acetabular component could potentiate ALTRs due to corrosion at the modular junctions. The cost of routine cross-sectional imaging of all patients with modular MOM implants for asymptomatic ALTRs would be significant and should not be recommended without supporting data.

In light of the unanswered questions about the prevalence of ALTRs in asymptomatic patients with modular MOM THAs, we (1) determined the prevalence of ALTRs in asymptomatic patients with modular MOM THAs, (2) described any differences in the appearance of these lesions between symptomatic and asymptomatic patients, and (3) analyzed potential predictive factors such as ion levels and cup abduction angles to see whether any were associated with the prevalence of ALTRs.

Patients and Methods

In 2012, our institution mandated that MRI be included in the standard of care diagnostic workup for MOM THAs. To that end, we evaluated the first 114 patients with modular MOM THAs who had complete metal ion reports and MRI with metal artifact reduction sequence software (MARS MRI). The presence of ALTRs was compared between 83 asymptomatic patients with modular MOM THAs and 31 symptomatic patients with modular MOM THAs.

These patients had the THAs implanted a mean of 57 months (range, 26–240 months) before the MRI scans were taken. One asymptomatic patient had an MRI at 5 months due to suspicion of adductor avulsion. Of the 114 implants, 110 (97%) were the Pinnacle® Hip System (DePuy Orthopaedics, Inc, Warsaw, IN, USA). Of the 114 patients in this series, 113 had THAs performed at our center and one was referred for management from an outside center.

We evaluated the MARS MR images for the presence or absence of an ALTR lesion. We defined an ALTR lesion as abnormal fluid collections, solid or semisolid pseudotumors, or muscle or bone damage. The location of each lesion was identified while the size and volume of each lesion were calculated as cubic centimeters. The type of lesion was classified according to the MRI Classification System of Hart et al. [4]. In this system, a Type 1 lesion is thin walled

and cystic, a Type 2 lesion is thick walled and cystic, and a Type 3 lesion is solid.

Additional variables that were analyzed included the time in situ, type of implant, and serum cobalt and chromium levels. Ion levels were compared between asymptomatic and symptomatic patients with modular MOM THAs. The abduction angle and anteversion angle of each acetabular component were measured using TraumaCad[®] software (Voyant Health, Ltd, Petach-Tikva, Israel).

Statistical Analysis

All statistical analyses were performed using SAS[®] Version 9.2 (SAS Institute Inc, Cary, NC, USA). Standard descriptive statistics including frequency, percentage, mean, and variation were calculated. Bivariate analysis was conducted using two-tailed chi-square tests for categorical variables, two-tailed independent T-tests for continuous variables, and Pearson correlation coefficients. An alpha level of 0.05 was used to determine statistical significance for all tests.

Results

Twenty-six of 83 (31%) asymptomatic patients with modular MOM THAs had ALTRs, and 16 of 32 (50%) symptomatic patients with modular MOM THAs had ALTRs ($p = 0.08$). The mean time in situ for each group was similar, 54 months (range, 30–111 months) for the asymptomatic patients with ALTR lesions and 58 months (range, 26–240 months) for the symptomatic patients with ALTR lesions.

All asymptomatic patients had lesions in the greater trochanteric area. Eleven of 16 (69%) symptomatic patients had lesions in the greater trochanteric area. Eighteen of 26 (69%) asymptomatic patients had Type 1 lesions, 10 of 26 (39%) had Type 2 lesions, and none had solid Type 3 lesions. Eight of 16 (50%) symptomatic patients had Type 1 lesions, seven of 16 (44%) had Type 2 lesions, and one had a Type 3 lesion. With the numbers available, the average lesion size was no greater ($p = 0.39$) in the asymptomatic group than in the symptomatic group: 45 cm³ versus 29 cm³, respectively. The size and volume of the lesions in both of these groups were variable. In the asymptomatic group, 39% had lesions 10 cm³ or smaller, 21% had lesions larger than 10 cm³ but smaller than 20 cm³, and 39.3% had lesions larger than 20 cm³. In the symptomatic group, 44% had lesions 10 cm³ or smaller, 12% had lesions larger than 10 cm³ but smaller than 20 cm³, and 44% had lesions larger than 20 cm³. There was no correlation between lesion size and time in situ

($R^2 = 0.13$). Small osteolysis lesions limited to the greater trochanter were noted in six of the 26 asymptomatic patients. The average size of these lesions was 4.25 × 2.3 cm, with a range of 7 × 2 to 3 × 1 cm (Table 1).

There were no significant differences in abduction angle between groups ($p = 0.08$) (Table 2). The average abduction angles were 40° (range, 31°–45°) for the asymptomatic patients with ALTRs and 42° (range, 34°–55°) for the symptomatic patients with ALTRs. The average anteversion of the asymptomatic patients with ALTRs was 26° (range, 19°–33°). Ion levels also were poorly predictive of ALTRs in this series. Twenty-four of 26 (92%) asymptomatic patients with ALTRs had chromium levels below the 7-ppb threshold while 22 (85%) had cobalt levels below the 7-ppb threshold. The average cobalt ion levels were 4.2 ppb (range, 0–16 ppb) for asymptomatic patients with ALTRs and 12.2 ppb (range, 0–110 ppb) for symptomatic patients with ALTRs ($p = 0.32$). The average chromium ion levels were 2.2 ppb (range, 0–10 ppb) for asymptomatic patients with ALTRs and 4.4 ppb (range, 0–30 ppb) for symptomatic patients with ALTRs ($p = 0.33$).

Discussion

MOM implants were commonly used in the last decade, at one time occupying 1/3 of the US market. Perceived advantages included a lower dislocation rate due to large head technology and the promise of diminished wear-related problems in young, active patients. Unfortunately, the advent of ALTRs resulting occasionally in periarticular tissue necrosis has dampened the enthusiasm for this bearing couple. A variety of diagnostic and treatment algorithms for patients with MOM implants have been brought forth with decision trees based primarily on the presence or absence of pain. However, ALTRs have been seen in asymptomatic patients with resurfacing implants [4, 6, 11]. Our findings here suggest that ALTRs are also seen in patients with well-positioned modular MOM THA implants: 31% prevalence with average ion levels below the 7-ppb threshold.

This study had a number of limitations. First, it was a retrospective review. Volunteers for this study were recruited from patients returning for routine followups. Second, the majority of these implants (97%) were from one manufacturer and may not reflect the findings seen in other modular MOM implants on the market. Additionally, due to the small number of Type 2 and 3 lesions, we were unable to evaluate the relationship between MRI classification and ion levels. Finally, the MR images were read by five different musculoskeletal radiologists.

While the approach to symptomatic patients with MOM THAs continues to be clarified through a variety of algorithmic approaches, the proper way to manage asymptomatic

Table 1. Frequency of osteolysis and implant characteristics in asymptomatic patients

Patient	Osteolysis (lesion size [cm])	Modular	Prosthesis*	Head size (mm)
1	Yes (2.7 × 1.1)	Cup	Summit [®] , Pinnacle [®]	36
2	No	Cup/stem	S-ROM [®] , Pinnacle [®]	36
3	No	Cup	Summit [®] , Pinnacle [®]	36
4	No	Cup	Summit [®] , Pinnacle [®]	40
5	No	Cup	Summit [®] , Pinnacle [®]	36
6	Yes (1.9 × 6.7)	Cup	Summit [®] , Pinnacle [®]	40
7	No	Cup	Summit [®] , Pinnacle [®]	36
8	No	Cup	Summit [®] , Pinnacle [®]	36
9	No	Cup	Summit [®] , Pinnacle [®]	36
10	No	Cup	Summit [®] , Pinnacle [®]	36
11	No	Cup	Summit [®] , Pinnacle [®]	36
12	No	Cup	Summit [®] , Pinnacle [®]	36
13	No	Cup	Summit [®] , Pinnacle [®]	44
14	No	Cup/stem	S-ROM [®] , Pinnacle [®]	40
15	Yes (2.4 × 5.9)	Cup	Summit [®] , Pinnacle [®]	36
16	Yes (1.1 × 5.1)	Cup/stem	S-ROM [®] , Pinnacle [®]	36
17	No	Cup	Summit [®] , Pinnacle [®]	36
18	No	Cup	Summit [®] , Pinnacle [®]	36
19	No	Cup	Summit [®] , Pinnacle [®]	40
20	Yes (4.0 × 1.5)	Cup	Summit [®] , Pinnacle [®]	40
21	No	Cup/stem	S-ROM [®] , Pinnacle [®]	36
22	No	Cup	Summit [®] , Pinnacle [®]	36
23	Yes (1.9 × 5.1)	Cup	Anthology [™] , R3 [™]	40
24	No	Cup	Summit [®] , Pinnacle [®]	36
25	No	Cup	Summit [®] , Pinnacle [®]	36
26	Yes (4.25 × 2.3)	Cup	Summit [®] , Pinnacle [®]	36

* Summit[®], Pinnacle[®], and S-ROM[®] manufactured by DePuy Orthopaedics, Inc (Warsaw, IN, USA); Anthology[™] and R3[™] manufactured by Smith & Nephew, Inc (Memphis, TN, USA).

Table 2. Comparison of results between the asymptomatic and symptomatic patients with modular metal-on-metal THAs

Variable	Asymptomatic	Symptomatic	p value
Abduction angle (°)	38 (5.5)	41.3 (5.4)	0.08
Lesion volume (cm ³)	45.5	28.7	0.39
Time in situ (months)	53.6 (23)	58.3 (51.9)	0.73
Cobalt (ppb)	4.2 (4.7)	12.2 (29)	0.32
Chromium (ppb)	2.2 (2.6)	4.5 (8.0)	0.2

Values are expressed as mean, with SD in parentheses.

patients with MOM THAs remains unanswered. We therefore determined the prevalence of ALTRs in asymptomatic patients with modular MOM THAs. While we were not surprised to find that 50% (16 of 32) of our symptomatic patients had ALTRs, we were concerned that 31% (26 of 83) of our asymptomatic patients had demonstrable ALTR lesions on MARS MR images. Such findings are comparable to the findings of Hart et al. [4] and Williams et al. [11], who noted ALTRs in asymptomatic patients with resurfacing.

These findings stand in contrast to Kwon et al. [6] who noted only a 5% prevalence of ALTRs in patients with resurfacing.

We also determined whether there were differences in the appearance of ALTR lesions between symptomatic and asymptomatic patients. There were no differences in the type of lesions between the two groups, both having a majority of cystic Type 1 lesions. While all asymptomatic patients had greater trochanteric lesions, approximately 1/3 of the symptomatic group had lesions noted in other

Fig. 1A–B (A) The smallest and (B) largest lesions (arrows) in an asymptomatic patient are shown.

periarticular areas. The lesion sizes in each group were variable; however, the average lesion sizes between groups were similar (Fig. 1). While the prevalence of ALTRs in this study is concerning, it should be noted that all lesions in this study were cystic and 39% were categorized as small, that is, less than 10 cm³. Additionally, the prevalence of cystic collections in other bearing couples (such as metal-on-polyethylene or ceramic-on-ceramic) is unknown and is a source of further investigation at our center. Whether such MRI abnormalities occur in metal-on-polyethylene, ceramic-on-polyethylene, or ceramic-on-ceramic bearings remains to be determined.

Finally, we analyzed potential predictive factors for any association with the prevalence of ALTRs. The average abduction angle in the asymptomatic group was 40°, with no cup abduction angle greater than 45°. Therefore, despite very well-positioned cups, 1/3 of patients had ALTR lesions. Additionally, ion levels were poorly predictive of ALTRs in this series. Twenty-four of 26 (92%) of asymptomatic patients with ALTR lesions had cobalt levels below the 7-ppb threshold.

Current algorithms concerning the management and treatment of patients with MOM implants rely on the type of implant, ion levels, cross-sectional imaging, and symptoms to determine progress along a specific decision tree. The British Medicines and Healthcare products Regulatory Agency medical device alert published in February 2012 divide this diagnostic algorithm into symptomatic and asymptomatic patients with different recommendations based on their symptoms [9]. Likewise, the American Hip Society algorithm presented at the American Academy of Orthopaedic Surgeons' meeting in 2012 has a similar algorithmic division based on symptoms [8]. Our study calls into question an algorithmic approach heavily dependent on symptoms to dictate management. At this time, relying on the presence of pain appears insufficient to

reliably identify patients at risk for ALTRs in MOM THAs. It remains to be determined whether routine cross-sectional imaging of all asymptomatic patients with MOM implants is required. Once the natural history of these lesions in asymptomatic patients is established, the algorithmic management of these patients should be simplified.

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