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Tahsin M. Rahman

Nicholas B. Frisch

Brian Darrith

Ishan Patel

Craig D. Silverton

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Tahsin M. Rahman, MD 
 Nicholas B. Frisch, MD, MBA
 Brian Darrith, MD
 Ishan Patel, MD 
 Craig D. Silverton, DO 

From the Wayne State University School of Medicine, Detroit, MI (Dr. Rahman and Dr. Patel), the Ascension Providence Rochester Hospital, Rochester, MI (Dr. Frisch), and the Department of Orthopaedic Surgery, Henry Ford Health System, Detroit, MI (Dr. Darrith and Dr. Silverton).

Correspondence to Dr. Rahman: trahman@med.wayne.edu

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Abstract

Background: The purpose of this study was to compare the incidence of pseudotumors in metal-on-metal (MoM) titanium modular neck hip arthroplasties to non-MoM modular neck hip arthroplasties. A secondary goal was to determine whether a correlation exists between elevated metal concentrations and pseudotumor incidence.

Methods: The data were collected and evaluated from 49 MoM joints and 26 non-MoM joints between the years 2012 and 2017. Hip ultrasonography was done after a minimum of 5 years postimplantation. Whole serum metal (titanium, cobalt, and chromium) concentrations were measured at the hip ultrasonography study.

Results: The average time elapsed between surgery and ultrasonography visit was 7.6 years. In the 49 patients with MoM joints, 22.4% (n = 11) had a pseudotumor. In the 26 patients with non-MoM joints, 9.1% of metal-on-polyethylene hips (n = 1) and 0% of ceramic-on-ceramic/polyethylene hips developed a pseudotumor. No significant statistical correlation was observed between serum metal concentrations and pseudotumor formation ($P > 0.05$). A significant correlation was observed of serum titanium concentration to pseudotumor size ($P = 0.024$).

Conclusion: The incidence of pseudotumor formation in MoM total hip arthroplasties was more than five times the incidence associated with non-MoM bearings. The correlation between serum titanium concentration and pseudotumor size suggests that titanium levels may be a useful indicator for pseudotumor formation in patients with this particular titanium modular neck femoral implant. No notable correlation was observed between serum cobalt and chromium concentration and pseudotumor formation or size.

Metal-on-metal (MoM) implants for total hip arthroplasties (THA) were originally designed to be an attractive alternative to the more traditional metal-on-polyethylene (MoP) implants. However, MoM implants have been criticized for having a variety of unexpected consequences, such as higher revision rates, systemic metal toxicity, and adverse local tissue

reaction (ALTR).¹ Pseudotumors are non-neoplastic, noninfectious masses that can be solid or fluid filled and may or may not communicate with the joint space (see Figure, Supplemental Digital Content 1, <http://links.lww.com/JAAOS/A503>).^{1,2} Pseudotumors may initially present as asymptomatic; however, if left untreated they can progress to cause pain,

tissue destruction, swelling, pressure effects, and subluxation that can eventually require revision arthroplasty.³ Kleeman et al⁴ demonstrated that 22% of patients with MoM implants required a revision procedure. Of the patients who required revision, 82% had demonstrated the presence of a pseudotumor via magnetic resonance imaging (MRI).⁴ Bosker et al² demonstrated a 32.2% incidence of both symptomatic and asymptomatic pseudotumors in 723 MoM THAs, with the most important predictive factor for the presence of a pseudotumor being pain. In addition, serum levels of cobalt ≥ 4 $\mu\text{g/L}$ and the presence of swelling are notable risk factors for pseudotumor development. Previous studies have also shown a correlation with increased serum cobalt ion level and the presence of ALTRs.^{5,6}

Although these previous studies report the incidence of pseudotumor formation in MoM cohorts, the current study prospectively compares the incidence of pseudotumors in MoM versus non-MoM THA implants, with both groups having a dual modular titanium neck of the same design. The purpose of this study was to (1) demonstrate the prevalence of pseudotumors in MoM versus non-MoM implants and (2) demonstrate the relationship between pseudotumors and serum metal levels with this particular design.

Methods

After institutional review board approval, 75 of 137 contacted patients who previously underwent implantation of modular neck THAs between 2004 and 2010 (Profemur Z; Wright Medical Group Inc) were consented for

participation in this study. Sixty-two contacted patients refused participation. Patients were included if they had undergone a primary THA procedure with a posterior approach done by the same board-certified orthopaedic surgeon. Of the 75 patients enrolled, 49 patients had undergone implantation of a MoM hip joint, whereas 26 patients had undergone implantation of a non-MoM hip joint. The 49 MoM THAs had cobalt-chromium acetabular cup and femoral head components, whereas non-MoM THAs included one of the following bearing combinations: MoP (11), ceramic-on-polyethylene (3), and ceramic-on-ceramic (12). All the patients in both groups had the same titanium stem and titanium modular neck. At the time of enrollment, no patients were known to have a pseudotumor. No patients were actively excluded because of the length of follow-up; however, because of the chronology of study onset, all patients within the study were at least 6 years post-THA. At this visit, serum cobalt, chromium, and titanium concentrations were measured, and hip ultrasonography was completed. All metal concentrations were analyzed at the Mayo Clinic Laboratory (Rochester, MN). Hip ultrasonography studies were done by the same trained ultrasonographer with a GE Logiq ultrasonography machine (General Electric). The ultrasonographer assessed for the presence of pseudotumor and determined the dimensions of the pseudotumor if applicable.

All statistical analyses were conducted using SPSS 25.0 (IBM, 2017). Student *t*-tests were conducted to compare serum metal concentrations between MoM and non-MoM groups. The Chi square analysis was used to

compare the incidence of pseudotumors in MoM and non-MoM joints. Similar chi square analyses were conducted to compare incidence of pseudotumors between patient groups stratified by MoM versus MoP versus ceramic-on-ceramic/polyethylene (CoC/CoP). Binary and multivariate logistic regressions were then used to assess for correlation between serum metal concentrations and pseudotumor incidence. Finally, joints were stratified into groups with and without pseudotumor, after which these groups were analyzed by Student *t*-tests for a difference in the mean serum metal concentrations.

Results

The mean time elapsed between surgery and follow-up visit was 7.62 ± 1.90 years. Eleven of the 49 MoM hips (22.4%) and one of the 26 non-MoM hips (3.8%) developed a pseudotumor ($P = 0.033$). When patient groups were further stratified, 1 of 11 MoP hips developed a pseudotumor (9.09%) and 0 of 15 CoC/CoP hips developed a pseudotumor (0%). Chi-square analyses showed a significant difference in pseudotumor formation between MoM versus CoC/CoP ($P = 0.001$), but no significant difference between MoM versus MoP ($P = 0.235$). Revision surgery data showed revision surgeries were done on two of the 11 MoM patients with a pseudotumor secondary to pain. Both these patients had abnormal cobalt and chromium serum concentrations. There were no reported revisions in the non-MoM patient groups.

The results of the bivariate logistic regression analysis suggested no correlation between serum metal

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concentrations and pseudotumor incidence ($P > 0.05$). The results of the bivariate linear regression analyses comparing pseudotumor size with serum metal concentrations showed no significant correlations ($P > 0.05$). However, multivariate regression suggested a significant correlation of pseudotumor size to serum titanium concentration ($P = 0.024$) and patient age (0.039).

When comparing patients with and without a pseudotumor, the mean serum cobalt, chromium, and titanium concentrations metal levels were greater in the pseudotumor group (See Figure, Supplemental Digital Content 2, <http://links.lww.com/JAAOS/A504>), but this difference was not statistically notable ($P > 0.05$) (see Table, Supplemental Digital Content 3, <http://links.lww.com/JAAOS/A505>).

Discussion

MoM and modular neck THAs have been scrutinized for various local and systemic complications.^{1-4,7} Pseudotumors are a manifestation of an ALTRs and implant corrosion. In modular neck systems, corrosion can occur at the head-neck and neck-stem junctions.⁸ In MoM modular neck THAs, the MoM head-cup articulation is an additional location that can be at a higher risk for implant corrosion. This is the first study to our knowledge to directly compare whether those patients with modular neck MoM THAs have a greater incidence of pseudotumor formation compared with non-MoM modular neck implants. Our study suggested that the incidence of pseudotumor formation is greater in MoM (22.4%) compared with non-MoM articulations (3.8%), with MoM joints accounting for most cases with elevated metal concentrations. When the non-MoM groups were further stratified, our study confirmed that pseu-

dotumors were only prevalent in patients with at least one cobalt-chromium component.

Our study was unique in that it focused on pseudotumor formation in patients with a particular titanium modular neck system, the Profemur Z. Pour et al⁹ critiqued this same implant system for the risk of failure in a cohort of 102 patients with various bearing surfaces. The authors cited fracture of the modular neck ($n = 6$) as the most common cause of aseptic revision with only 3 cases of revision for ALTR. The rate of fracture incidence was low, similar to the current study and other cited literature.^{10,11} However, unlike the current study, they only did advanced imaging on symptomatic patients with negative radiographs, and therefore, they were unable to report the incidence of pseudotumor formation. Moreover, they did not stratify their findings by bearing type. In the current study, however, all patients received an ultrasonography to assess for pseudotumor formation, and we report the incidence of this complication for the different bearing combinations.

The current literature suggests that pseudotumors may be a result of either bearing (head-cup) or trunnion (stem-head) corrosion.^{7,12-14} Goldberg and Gilbert¹² described specifically the process of corrosion initiated by mechanical mechanisms in modular hips in which the protective oxide layer coating of metal is disrupted, and trunnion geometry may play a role in promoting trunnionosis and fretting.¹³ MoM corrosion promotes a macrophage exocytotic response and subsequent tissue necrosis.^{7,15}

Our study was aimed to better understand pseudotumor prevalence in MoM versus non-MoM THA. Large cohort studies have described pseudotumors regarding their appearance as a solid or cystic lesion of varying sizes.¹⁶ Histologic evidence of extensive lymphocytic infiltration in

periarticular tissue suggested metal hypersensitivity as the underlying mechanism for pathogenesis,¹⁷⁻¹⁹ and retrieval studies have since reported the presence of pseudotumors to be greater in those joints with greater bearing wear and metal ion leeching.²⁰⁻²² Previous reports have shown that pseudotumors form in well-positioned MoM hips with minimal evidence of corrosion.²³ Given the variability in presentation and clinical course of pseudotumors, it is unclear why cobalt-chromium wear may cause no clinically relevant response in some patients but pseudotumors in others. Genetic predisposition is being investigated to provide some insight.²⁴

When comparing serum metal ion concentrations in patients with and without pseudotumors, no statistically notable difference was observed in mean serum cobalt and chromium. Interestingly, our analysis correlating serum metal concentrations and pseudotumor size showed that serum titanium concentrations were notably correlated to increased pseudotumor size. Because all THAs in our study consisted of a modular titanium neck and titanium stem, the correlation between pseudotumor size and titanium levels could be explained by corrosion of the trunnion at the head-neck junction or corrosion at the modular neck-stem junction. However, we cannot postulate whether titanium corrosion is a cause of pseudotumor formation or simply a sign of the local inflammatory process.

An association between pseudotumor formation and corrosion of a titanium femoral implant has been reported in the literature, although these reports have been limited to case-studies. Sakamoto et al²⁵ reported on a 77-year-old woman with a cobalt-chromium head, polyethylene liner, and titanium stem who went on to develop hip pain in the context of a pseudotumor. The primary arthroplasty

was complicated by an intraoperative fracture of the greater trochanter which was prophylactically secured with a cerclage cable during the index surgery. The patient developed hip pain and swelling secondary to progressive osteolysis in addition to pseudotumor formation 6 years after the index surgery, at which time serum cobalt and chromium concentrations were within normal limits but serum titanium was 30 ng/mL. The patient had the cable removed, with visible fretting of the titanium stem underlying the cable, and the pseudotumor was débrided with further study by plasma atomic emission spectrometry showing high density titanium deposition and relative absence of cobalt or chromium in the pseudotumor.²⁵ Another instance of titanium associated osteolysis and pseudotumor formation is reported by McPherson et al²⁶ in a 59-year-old woman with a porous titanium stem, ceramic head, and a polyethylene liner in a titanium cup who presented with hip pain 10.5 years after implantation. They found titanium particles throughout the pseudotumor with local histiocytosis. The source of the titanium particles was attributed to leaching from the porous coating on the femoral stem.²⁶ Given our study findings and these past reports, it can be postulated that titanium modular necks are still at risk of pseudotumor formation secondary to the head-neck trunnion with Co-Cr heads. Further investigations are necessary to determine the role of titanium in destructive and inflammatory processes in patients with these particular titanium modular neck THA systems.

Our study shows that patients without a cobalt-chromium head were not at risk of developing a pseudotumor, regardless of bearing components used. Some studies have indicated increased serum cobalt concentrations are associated with pseudotumor inci-

dence^{1-4,27,28}; however, our data do not support a correlation between increased serum cobalt or chromium concentrations and pseudotumor formation. A few possible explanations exist for this. Patient factors exist that may impact the accumulation of metal levels that are unaccounted for.²⁴ Although the development of corrosion and subsequent elevation of metal levels was detected in previous studies, the etiology is likely multifactorial.^{2-4,24} In addition, diagnostic limitations in ultrasonography and operator skill may have led to the lesser detection of pseudotumors in the current study, although a recent study suggests that ultrasonography sensitivity may be comparable with MRI when conducted by a skilled technician.²⁹

In the reviewed literature, the incidence of pseudotumors is reported at variable rates.³⁰⁻³² Wiley et al³⁰ reported an incidence of 0.6% in near 14,000 MoM patients, but Reito et al³¹ subsequently suggested that the nature of clinical investigations, such as serum ion screening and cross-sectional imaging with ultrasonography or MRI, increases the finding of pseudotumors with rates up to 9.5%. Another report conducted by Goldstein et al³² examined 82 patients with modular MoM hip joints with 26 of 82 patients (31.7%) having cystic lesions on Metal Artifact Reduction Software MRI. Such variability in incidence in MoM patients points to elements of pseudotumor pathogenesis that still need to be elucidated. In addition, different rates of diagnosis between ultrasonography and MRI studies brings up the question as to what imaging modality is best suited for pseudotumor diagnosis. Kwon et al²⁹ investigated the validity of ultrasonography as a tool for diagnosing ALTRs in patients with MoM THA, concluding that there is comparable sensitivity and specificity of ultrasonography to Metal Artifact Reduction Software-MRI. Considering the various pro-

posed mechanisms that point to metal hypersensitivity as the driving force for pseudotumor genesis,¹⁷⁻²² further study is indicated at this time to determine why pseudotumors form asymptotically. Although corrosion plays a role, it is unclear at this time what degree of corrosion is necessary to generate an inflammatory reaction. More research is warranted to determine which THA components, trunnion or bearing, are most involved in a wear and pseudotumor formation.

Our study did have multiple limitations. First, our prospective patient cohort was limited in sample size. Because this study maximizes internal validity by including only primary THA patients with one type of modular neck femoral implant, the generalizability to other MoM systems is limited. In addition, our ultrasonography analysis was conducted at a minimum of 5 years postoperatively, and further follow-up may reveal a higher incidence of pseudotumor formation. Loss of patients to follow up may have consequently impacted study outcomes. Further study is warranted to have better insight into the natural history of pseudotumor development. Finally, the experience of the ultrasonography technician can be a limiting factor in the sensitivity of pseudotumor detection. Our radiology department has extensive experience and training using ultrasonography for this purpose which may not be available at all institutions, and therefore, the generalizability is again limited based on the resources available at individual institutions.

Conclusion

ALTR and pseudotumor formation is a complication of corrosion in MoM articulations and modular neck implants. Our study demonstrated that the incidence of pseudotumor formation in MoM THAs was more than five

times the incidence associated with non-MoM bearings. The correlation between serum titanium concentration and pseudotumor size suggests that titanium levels may be a useful indicator in patients with this particular modular neck femoral implant. For patients with a MoM THA of this particular design, we recommend routine serum metal levels to screen for pseudotumor formation secondary to ALTR.

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