Author's response to reviews

Title: Implant Based Differences in Adverse Local Tissue Reaction in Failed Total Hip Arthroplasties: A Morphological and Immunohistochemical Study

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Author's response to reviews: see over
Dear Editorial Board,

I have enclosed a revision of the manuscript entitled: "Implant Based Differences in Adverse Local Tissue Reaction in Failed Total Hip Arthroplasties: a Morphological and Immunohistochemical Study" which has been edited based on the reviewers’ suggestions. Changes in the text have been highlighted, responses to the reviewers’ questions have been placed below, and the original reviewer comments were placed in italics. All listed authors and acknowledged contributors have read and approved the final version of this manuscript. There are no conflicts of interest related to this manuscript.

We appreciate the opportunity to provide these revisions, and we believe that all reviewers’ concerns have been thoroughly addressed. We hope that this manuscript will add to the literature on the understanding of the occurrence and natural history of adverse local tissue reactions and generate hypotheses to stimulate further research on the subject. Thank you for your consideration of this revised manuscript. Please address all correspondence concerning this manuscript to me at the Hospital for Special Surgery and feel free to correspond with me by e-mail at perinog@hss.edu.

Sincerely,

Giorgio Perino, MD

Reviewer 1

*line 134 - authors should clarify composition of adapter sleeve*

We agree with this comment. The composition of the adapter sleeve is cobalt-chromium-molybdenum. This has been added to the manuscript on page 6, line 134.

*line 420 - authors should acknowledge possible bias that DMN were possibly revised at an earlier time in part because of the highly publicized recall of this particular stem design*

We appreciate this comment. This has been added to the manuscript on page 19, line 420: A possibility of bias in time to revision might exist because the DMN group had a publicized recall of the implant, however, all patients revised in both cohorts were indicated for revision due to elevated metal ion levels, symptomatic hip pain,
MRI findings of moderate to severe adverse tissue reaction, and/or positive needle biopsies.

*line 77 - clarify the timing introduction of MoM bearings, and also mention decreased wear and osteolysis as reasons for re-emergence*

We appreciate this comment. Page 4, line 78 now reads: One of these modifications included the metal-on-metal (MoM) bearing surface, which was combined with a metallic adapter sleeve for large heads in the early 2000s. Page 4, line 80 now reads: The rationale for the revival of this bearing surface included a reduction in volumetric wear and osteolysis compared to conventional metal-on-polyethylene bearings (MoP), decreased impingement throughout range of motion, and decreased rates of dislocation [1].

*line 115 - authors should comment this is the first study to their knowledge (also on line 406)*

We appreciate this comment. Page 18, line 407 now reads: This is the first study to our knowledge to compare the histologic and immunohistochemical features of ALTR in two different classes of implants.

**Reviewer 2**

*Minor Essential Revisions*

**Introduction**

1. *Is the following sentence correct that no biologic testing was done before marketing? Is there a reference to support this statement?*

We appreciate this comment. These implants were introduced with the requirement of only limited simulated mechanical testing, and biologic testing is not a component of the approval process. Additionally, limited pre-marketing clinical studies were required due to approval of these implants through the 510(k) process. A reference has been added on page 4, line 89.


2. *In the sentence that starts with Retrieved periprosthetic tissue from affected patients... Did the authors mean to say abraded metallic debris rather than abrasion metallic debris?*

We have clarified this statement on page 4, line 94: Retrieved periprosthetic tissue from affected patients showed evidence of corrosion products, metallic debris
generated by abrasion and/or surface fatigue, extensive soft tissue necrosis, combined macrophagic and lymphocytic infiltrate with variable plasmacytic and eosinophilic components, and vascular wall changes [4,12,13,14,15,16,17,18].

Methods
3. In the sentence Between April 2012 and June 2013, all patients with the diagnosis of ALTR... How was the diagnosis made? What were the ALTRs for these patients?

We appreciate this comment. The diagnosis of ALTR was made based on histological analysis. This has been clarified and page 6, line 126 now reads: Between April 2012 and June 2013, all patients with the diagnosis of ALTR based on histological analysis were identified retrospectively from the Osteolysis Tissue Database and Repository at the Hospital for Special Surgery.

4. What was the metal composition for the metallic sleeve in the Smith & Nephew MOM implant? This information should be provided.

This has been clarified on page 6, line 135: MoM THA group had a MoM bearing surface (CoCrMo) with a metallic adapter sleeve (CoCrMo) at the head-neck junction and titanium stem (Smith & Nephew, Birmingham THA) [N=18 hips, 14 patients].

5. Consider revising the following sentence; Exclusion criteria included previous revision... it isn’t clear what is meant by less than 5 blocks with > 75% necrosis.

We appreciate this comment. This has been clarified on page 6, line 137: Exclusion criteria included previous revision arthroplasty, positive intraoperative cultures, and insufficient tissue retrieval for comparative pathologic examination (less than 5 tissue sections and more than 75% tissue necrosis at light microscopy examination on all slides examined).

6. Consider revising the sentence starting with Photographs of each implant... It isn’t clear what you mean by suitable.

We appreciate this comment. Gross pictures were taken when the specimen was significant for unusual features such as bursal involvement, florid synovial hypertrophy, or exuberant necrosis. This has been revised in page 8, line 177 to read: Photographs of each implant and selected gross tissue specimens were taken.

Results
7. Why were numbers only provided for the DMN group?

It is unclear which numbers are being referred to in this comment. The clinical characteristics and histological analysis were presented for both implant types throughout the results section.
Major Compulsory Revisions

8. My only major concern was how the immunopositive cell data was presented. Expressing the data as % positive/total cell number skews the results, as total cell number would include fibroblasts as well as immune cells. It would be more appropriate to present the data as % positive/mm$^3$ tissue area. This will most likely change the final outcome of the immunohistochemical results and conclusions.

We appreciate this comment. The quantitative analysis for lymphocyte distributions were remeasured for all slides using % positive cells/mm$^2$ of tissue in both perivascular and interstitial regions. The updated values have been placed into the new Table 5. The overall conclusions and results from our analysis remained unchanged, although individual numbers did change. The DMN group still had an increased T cell relative to B cell distribution in perivascular regions relative to the MoM THA group. In both groups, a CD4, GATA-3 predominant infiltrate was present in both interstitial and perivascular regions. Subsets of patients in both implant groups had increased CD8 to CD4 ratios, and this was not statistically significant between the two implant groups. The methods have been modified to account for these changes on page 11, line 242:

A quantitative analysis (Bioquant Osteo, Bioquant Image Analysis Corporation, Nashville, TN) was performed on all sections to evaluate lymphocytic distributions in both perivascular and interstitial regions. Two perivascular and two interstitial areas on each slide were randomly selected and evaluated at high power (x400), and lymphocytes with positive stain were counted manually by an investigators blinded to the clinical characteristics (BR, GP). The results were expressed as percentage of positive cells per mm$^2$. The same areas from consecutive sections were chosen for each stain, ensuring consistency in area of evaluation. The ratios between CD20:CD3, CD4:CD8, and GATA3:T-bet on the same sections were then calculated. The CD20:CD3, CD4:CD8, and GATA3:T-bet were described as a > 2:1, 1:1, or > 1:2 ratio.

The results section has been modified to reflect these changes on page 16, line 353: Both implants displayed a mixed perivascular lymphocytic infiltrate, with increased T cell to B cell ratios in the DMN group relative to the MoM THA (Table 5; p=0.032). In the interstitial regions, both implants had T cell predominant lymphocytic infiltrates. The majority of patients had a mixed population of CD4 and CD8 positive T cells, with CD4 cells being more numerous in most cases in perivascular regions (Figures 5A and B; Table 5). In interstitial regions, a subset of patients in both implant types had increased CD8 positive cell density relative to CD4, however, there was no significant difference between the implant types in CD4 to CD8 ratio (p=0.189).
Reviewer 3

Major compulsory revisions

1. The authors present analysis of tissues retrieved from patients in whom the implant failed very early after the surgery especially in case of MoP/CoC (time to revision was 21.3±8.4 and 43.6±13.8 months in Dual-Modular Neck THA and MoM THA, respectively). After exclusion of infection it remains relatively high probability that a technical mistake and/or poor design of the implant could be a plausible explanation for included cases. Under such suspicion the reported data refer rather to the premature mode of failure in a particular implant than to the mechanism of ALTR occurring in implants with much longer survivorship.

We appreciate this comment. The modality of failure of the DMN implant and MoM THA implant analyzed in this study have been attributed in previous publications (Gill et al, 2012; Huber et al, 2009; Cooper et al, 2013) to the formation of corrosion products at the neck-stem junction and not to technical mistakes or poor design resulting in mechanical failure of the implants. Moreover, patients implanted at our hospital with the same implant components with a monoblock neck did not show any ALTR during the same study period, corroborating the fact that the failure is caused by the formation of corrosion products. Gill et al. also found that corrosion at the modular junction correlated with time to revision relative to the same monoblock stem and bearing components [Gill et al, 2012]. Additionally, Cooper et al. have shown a similar time to failure of the DMN implant used in our study, further corroborating our results [Cooper et al, 2013]. This has been clarified on page 19, line 419: The time to revision in the DMN group was significantly shorter than the MoM THA, and this suggests different progression rates of ALTR with different implant designs. Progression of ALTR may depend on length of device implantation, toxicity/immunogenicity of corrosion particles, implant design and alignment, patient co-morbidities, and host immune reactivity. The modality of failure of the DMN and MoM THA implants analyzed in this study have been attributed in previous publications to the formation of corrosion products at the neck-stem junction and not to technical mistakes or poor design resulting in mechanical failure of the implants [4,8,10]. Gill et al. also found that corrosion at the modular neck-stem junction resulted in early revision relative to the same monoblock stem and bearing components [8]. Additionally, Cooper et al. have shown a similar time to failure of the DMN implant used in our study, further corroborating our results were not due to technical error [10].

2. I think that data on controls should be briefly included into the manuscript (for instance into “Clinical demographics”).

We agree with this comment. This data has been added into the methods section under the description of pathologic controls used in the study. Page 11, line 252 now reads:
A comparison control group of periprosthetic tissue was used for immunohistochemistry. For the control group (N=17), average age was 63.5 years (standard deviation 14.0) and 71% were female. These included three cases (N=3) of osteoarthritis with variable amount of lymphoplasmacytic infiltrate without clinical diagnosis of rheumatic disease, three cases of periprosthetic osteolysis from polyethylene/metallic wear debris in standard THA, and three (N=3) cases of MoM implants not examined in our series (1 resurfacing, 2 MoM THA). Average time of implantation was 30 months in these patients. Additionally, we examined all cases of preoperative native synovial tissue (time zero) available for patients in our series with ALTR and identified five cases (N=5) with variable perivascular lymphoplasmacytic infiltrate to provide a baseline comparison.

3. Number of patient-, surgery-, implant-related variables can potentially influence the fate of THA making tremendously difficult interpretation of failure in an individual case. Among them number, size, and origin of the prosthetic particles are the most important in relation to the periprosthetic tissue response. Therefore, at least basic data for the type of polyethylene and its wear rate should be included to enable the reader to understand completely the presented histopathological findings. Currently, almost whole attention is focused on metallic debris while in the group with MoP and CoP the polyethylene particles could also play important role.

We appreciate this comment. All polyethylene used in DMN implant was the same second generation highly cross-linked polyethylene (X3, Stryker Corporation). There have been extensive publications in the literature about wear rates of highly cross-linked polyethylene in vivo, and for the X3 in particular, femoral head penetration rates remain low at two years (head penetration <0.06mm) [Campbell et al, 2010]. Moreover, between years 1 and 5, wear rates in vivo were less than 0.001mm/year in vivo [Callary et al, 2013]. This data suggests that polyethylene wear is unlikely to contribute to the observed reaction to ALTR seen in our study in the DMN group. This is further corroborated by the fact that polyethylene debris was observed in the periprosthetic tissue of only 1 out of 54 patients in our study despite our extensive tissue sampling. The text has been modified on page 6, line 137 to read: All polyethylene used in the DMN implant was second-generation highly cross-linked polyethylene (X3, Stryker).

Additionally, page 22, line 490 has been modified to read: The ALTR reaction seen in the DMN implant is unlikely to be influenced by polyethylene debris. There have been extensive publications in the literature about wear rates of highly cross-linked polyethylene in vivo, and for the X3, femoral head penetration rates remain low at two years (head penetration <0.06mm) [Campbell et al, 2010]. Moreover, between years 1 and 5, wear rates in vivo were less than 0.001mm/year [Callary et al, 2013]. This data suggests that polyethylene wear is unlikely to contribute to the observed reaction to ALTR seen in our study in the DMN group. This is further corroborated by the fact that only 1 of 54 cases examined in our study had polyethylene debris in
their periprosthetic tissue, suggesting that polyethylene debris is unlikely to play a major role in ALTR seen in our study.

The following citations have been added to the manuscript:


4. The immunohistochemistry suffers from problems common to this type of analysis; the authors should demonstrate the functionality of used monoclonal antibodies. I also believe that figures can be improved by inclusion of a “window” with higher magnification for specific cell population (marker) into some figures.

We appreciate this comment. Commercially available monoclonal antibodies were used and each batch was tested by titration for optimal dilution on both internal and external tissue controls. A magnification window has been added to Figure 5 A-E to improve visualization of the individual cell populations.