Author's response to reviews

Title: Empirical evaluation of the inter-relationship of articular elements in the pathogenesis of knee osteoarthritis using Magnetic Resonance Imaging

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The BMC Musculoskeletal Editorial Team

To Whom It May Concern:

Thank you for your recent review of our manuscript (4454333122625116) “Empirical evaluation of the inter-relationship of articular elements in the pathogenesis of knee osteoarthritis using Magnetic Resonance Imaging.” The attached pages detail the changes that my colleagues and I have made in response to the reviewers’ comments. We found the comments to be insightful and reasonable, and believe they have helped us to strengthen and clarify the manuscript. We appreciate your review and look forward to hearing from you soon.

Thank you.

Sincerely,

Dennis Meredith, MD
Reviewer 1

The authors have articulated their question as being that cartilage damage would be associated with the number of articular features that are damaged as well as with the severity of damage of those features. However, until reading final sentence on page 3, it is unclear why the authors are interested in this question. There should be more of a set up for this question in the introduction. Why is it expected that damage occurs in parallel in OA as opposed to sequentially?

Response: The sentence: “This hypothesis reflects a view of OA pathogenesis that posits that each of these features progress essentially in parallel,” was deleted. The final paragraph was modified to better set up the rest of the study as suggested by the reviewer:

Page 2: We first hypothesized that the severity of cartilage damage in a given knee will be associated with both the number of articular elements involved and the severity of the changes for each articular element. We selected cartilage damage as our initial common measure of OA severity since cartilage degeneration has been a central element of previous traditional imaging studies and chondrocyte dysfunction has been shown to be a key element in the cellular/biochemical study of OA pathogenesis (38-43). We then hypothesized that multiple articular elements will have correlations with one another independent of their relationship to cartilage damage.

Also, the scoring system used in this study is very confusing. Figure 1 in particular, is intended to address this point, but this figure is also very confusing. If the focus of this paper is on looking how the scales of knee OA abnormalities are associated with one another, then the greater detail of the description of those features should be included in this paper. Also, while many of the features included in this study are commonly read on MRIs, it would make sense to clarify the definition of each of the features – in particular, subchondral sclerosis needs to be defined. This feature has not frequently been read off MRIs – it is usually read using X-rays.

Response: By “Figure 1” we believe the reviewer is referring to Table 1, the table in which we present the details of the scoring system. The reviewer suggests that the table would benefit from a more explicit definition of each feature. We agree and have expanded the description of elements which are not routine standard of care in both Table 1 and in the text.

Page 5: Of note, fraying was defined as increased signal with superficial linear pattern on fast spin echo proton density weighted or fat saturated fast spin echo proton density weighted sequences. Fissuring was defined as full thickness cartilage defect measuring < 1mm in size on its largest dimension. Lesion size was graded on a five level scale from 0 = normal to 4 = >3 cm. In cases were multiple lesions, were present, the most severe lesion was scored.

Page 5: Subchondral sclerosis was defined as an increase the area of low signal intensity on both T1 and T2-weighted images within the subchondral bone.
Page 6: Joint effusion was assessed based on the greatest width of the fluid accumulation perpendicular to the long-axis of the leg.

Page 6: Synovitis was assessed based on the number of thickened villi visible on T2-weighted scans.

Table 1: The definitions of cartilage signal heterogeneity, fraying and fissuring were expanded as well as joint effusion, synovitis and bone marrow lesions.

Furthermore, many of the scores have been performed using absolute scales (e.g. cut offs using cm measurements). This seems to be potentially problematic if the individuals included in the study vary in size. For instance, a BML of 3mm in a 6 foot tall male is probably different from a BML of 3mm in a 5 foot tall female. Is there some mechanism for normalization of these measures?

Response: The reviewer makes a good point. There is a trade-off between the precision afforded by exact measurement and the issue of proportionality and body size that the reviewer raises. We acknowledge this as a potential limitation of the scoring system and have noted this limitation in the discussion. Because we do not make specific comparisons across gender or height, this issue is unlikely to distort the findings of our analyses. The following statements were added to the Discussion on page 22 to address this issue:

Another potential limitation of this study is the use of exact measurements to assess the size of specific articular elements such as cartilage defects, BMLs or osteophytes rather than proportional measurements normalized to patient size. However, this issue is unlikely to distort the findings of our analyses because we do not make specific comparisons across gender or height.

Also, the cut-offs for many of the features seems arbitrary—especially for articular cartilage. It almost seems that these cut-offs could have been chosen to maximize the differences seen in this study. It would help if there were a validation study population available to confirm these findings using these definitions.

Response: We made specific cut-offs based upon distributional considerations, independent of our hypotheses. We agree with the Reviewer that the findings of this study merit validation in an independent population and have so indicated in the final paragraph of the Discussion.

These findings highlight the need for future studies of OA pathogenesis in humans using MRI. Specifically, future studies will need to investigate the correlation of the scale linearity of semi-quantitative scoring methods used in this study with clinical symptoms and radiographic progression of OA in a prospective cohort.

The authors conclude that these study results support that OA pathogenesis involves all articular elements of the knee. It is unclear how the findings of this
study support this conclusion. This study shows that individuals with greater cartilage damage are more likely to have multiple other features that are damaged in a cross-sectional assessment. It is unclear how this finding can be extrapolated into these authors conclusion.

Response: This point was made by both reviewers. As OA is traditionally viewed as a cartilage-centric disorder, our figures and were designed to demonstrate that along with cartilage changes one observes changes in a range of other tissues. We acknowledge that the next step in supporting this argument would be a set of analyses that are not anchored by cartilage per se. Thus, in response to the reviewer comments we have added a new table, pasted below, which shows non-parametric (Spearman) correlations among the various joint features. We do not include subchondral sclerosis since it is binary. As the table demonstrates, several other associations emerge aside from those involving cartilage. For example, bone marrow edema has a modest correlation with effusion and osteophytes and synovitis and effusion have a modest correlation. We comment on these findings in the Results and Discussion.

Table 3: Correlations among joint features (Spearman correlation coefficients)

<table>
<thead>
<tr>
<th></th>
<th>Cartilage</th>
<th>BME</th>
<th>Synovitis</th>
<th>Effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BME</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovitis</td>
<td>0.04</td>
<td>-0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effusion</td>
<td>0.05</td>
<td>0.36</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Osteophytes</td>
<td>0.69</td>
<td>0.27</td>
<td>0.10</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Page 8: Methods - For the correlation table in Figure 3 we utilized a Spearman test for non-parametric correlations between worsening levels of pathology for each articular element.

Page 10: Spearman correlation coefficients between individual elements. Finally, we investigated the relationship between individual articular elements using the Spearman non-parametric correlation coefficient. The test assessed the correlation between increasing severity of pathology in each articular element. The results of this analysis are shown in Table 3. Of note, cartilage damage had a moderately strong correlation with BMLs and osteophytes. There was a moderate correlation between joint effusion and synovitis. However, joint effusion and synovitis had only a weak correlation with osteophytes or cartilage damage.

Page 11: We also examined the correlation between increasing severity of pathology in each articular element. This showed a moderate correlation between cartilage damage, osteophytes and BMLs as well as a moderate correlation between joint effusion and synovitis. However, cartilage damage and osteophytes were only weakly associated with synovitis or joint effusion.

While the discussion section of this study describes some of the existing literature regarding MRI findings, this section seems particular disjointed – the
paragraphs do not seem to flow together.

Response: The following sentence was added to the discussion of existing literature regarding MRI findings to provide better context and the discussion was condensed into a single paragraph to better demonstrate its coherence:

In the following paragraph, we briefly review the inter-relationships of the various articular elements that have been previously reported.

WORMS and BLOKS were never intended to be used as an aggregate score as suggested by these authors on page 3, paragraph 1.

Response: The previous statement has been modified to read “…presented semi-quantitative forms that attempt to include all of the articular structures visible on MRI in a comprehensive assessment of knee OA.”

Portions of the methods are included in the results section – particularly bottom of page 8-top of page 9.

Response: The elements of the results section which the reviewer identifies as belonging to the methods are necessary to allow the reader to understand the subgroups being compared. We do not feel that they can be moved to the methods section without creating confusion.

Figure 2 is very confusing. It is unclear how to interpret this table. Please clarify.

Reviewer 2

Much of the classification and categorization is arbitrary and relies upon flawed assumptions of scale linearity and equal weighting of different regions. Alternate categorizations including analysis of count approaches may avert these concerns.

Response: We acknowledge that the data are not inherently linear and that any summation carries implicit assumptions about relative weights. As a result we performed analyses that do not rely upon strong normality assumptions. The alternative, not to aggregate these data at all, would make it very difficult to see meaningful patterns.

The methods rely upon an historical presumption that cartilage is the central pathology in OA whereas modern definitions assess the whole joint. Introduction 2nd paragraph creates a sense that cartilage loss is the critical central feature of OA whereas this is just part of the picture. Apparent density may be increased but true bone density is reduced irrespective it is unclear how this sentence contributes to the rationale for the study.
Response: We appreciate the reviewers comment. The introduction attempts to acknowledge that earlier work on OA pathogenesis has been focused on cartilage damage and bony changes such as osteophytes. We sought in figure 1 and figure 2 to demonstrate that cartilage was in fact associated with pathology in other elements of the joint. To further address this comment we have added Table 3 (detailed previously), which analyzes the correlation between articular elements in a way not centered on cartilage damage. With respect to the reviewer’s comments about bone density we have modified the text as follows:

Page 2: Cartilage loss is associated with subchondral sclerosis, a process of subchondral bony remodeling that alters relative bone density.

Page 3 first paragraph BLOKS was never designed to be summed into one score-Whilst both WORMS and BLOKS are comprehensive scoring systems most would not advocate given the non-linearity of the scales and the multiple constructs measured that they should not be summed.

Response: The previous statement has been modified to read “…presented semi-quantitative forms that attempt to include all of the articular structures visible on MRI in a comprehensive assessment of knee OA.”

The methods don’t speak to a population with OA. Was any OA definition met in recruiting the target population. If not please amend the title.

Response: We enrolled a population of patients who had undergone arthroscopic partial meniscectomy and who met an age criterion (>45 years-old). We did not select for OA per se (e.g. based upon the ACR classification). As the Reviewer suggests, we have amended the title accordingly.

Title: Empirical evaluation of the inter-relationship of articular elements involved in the pathogenesis of knee osteoarthritis using Magnetic Resonance Imaging

Please detail in this paper the reliability of assessments to save referencing the other paper. Who was the reader for this study and what is their level of expertise.

Response: The reader was a medical student trained by two attending musculoskeletal radiologists. The intra-rater reliability for this student was assessed with weighted kappa’s for cartilage lesion grade and cartilage lesion size. Each of these features was judged over 12 regions, giving 12 weighted kappa’s. The median of these 12 weighted kappa values for cartilage grade was 0.62 and for cartilage lesion size was 0.56.

Page 5: The reader was a medical student trained by two attending musculoskeletal radiologists. The intra-rater reliability for this student was assessed in 28 patients with weighted kappas for cartilage lesion grade and cartilage lesion size. Each of these
features was judged over 12 regions, giving 12 weighted kappas. The median of these 12 weighted kappa values for cartilage grade was 0.62 and for cartilage lesion size was 0.56.

**If all osteophytes were summed how then were they categorized on a 0-3 scale.**

**Response:** As described in Table 1, each osteophyte in the knee was assigned an individual score based on its size. The scores for each individual osteophyte were then summed across the entire knee to generate a final score which was categorized on a 0-3 scale.

*What evidence is there that the scales are linear- for example is there any validity to summing 3 grade 1 BM lesions and assuming that is equal to one grade 3 lesion? Likewise for the cartilage involvement. Once summed how were the 0-3 categories created?*

**Response:** The creation of the categories is detailed in Table 1. We do not make assumptions of linearity in our analyses.

**Is there any demographic difference between the 140 selected and the 216 they were selected from?**

**Response:** The 140 patients included in the analysis had MRIs available for review. These patients were an average to two years older than those not included. 61% of those included were female as compared with 50% of those not included. Neither of these differences were statistically significant.

*Please provide the BMI for the cohort and the prevalence of radiographic OA.*

**Response:** This information is not available, unfortunately.

*How specifically should this “serve as the basis for future studies of OA pathogenesis”?*

**Response:** The statement in question has been changed to read: “These findings highlight the need for future studies of OA pathogenesis in humans using MRI. Specifically, future studies will need to investigate the correlation of the scale linearity of semi-quantitative scoring methods used in this study with clinical symptoms and radiographic progression of OA in a prospective cohort.”