Author's response to reviews

Title: Changes in bone marrow lesions in response to weight loss in obese knee osteoarthritis patients: A prospective cohort study

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Author's response to reviews: see over
Dear Editor,

First of all I would like to thank your editorial team for your work with this paper. With respect to the reviewers comments I have addressed these in the following way referring to the manuscript document containing track changes.

Reviewer 1

Major 1 / Reviewer comment: ABSTRACT/METHODS; Clarify that BMI scores are dichotomized.
Author response: Indeed, this has been stated more clearly in the abstract.
Author action: Please see lines 60-61.

Major 2 / Reviewer comment: ABSTRACTS / RESULTS; Clarify weight loss, < or > 10% of the BW, and mention the measurements of BW.
Author response: This has been clarified.
Author action: Please see lines 66-67.

Major 3 / Reviewer comment: PURPOSE STATEMENT; Clarify study design, not an RCT.
Author response: This should be clear for all readers, and it has been clarified in the introduction.
Author action: Please see lines 56-58.

Major 4 / Reviewer comment: METHOD / INTERVENTION; Clarify that patients were randomized to diet-interventions.
Author response: We fully agree, this should be clear for all readers and it has therefore been clarified in this section.
Author action: Please see lines 131 and 144-146.

Major 5 / Reviewer comment: MRI ANALYSIS; Clarify the selection of the target knee if both were equally symptomatic.
Author response: Indeed a very interesting question, however, we did not encounter this specific problem.
Author action: None

Major 6 / Reviewer comment: MRI ANALYSIS; Did the study crew ensure that all patients were scanned with the same coil at baseline and follow-up?
Author response: We confirm that the study crew ensured that the same patients were scanned using the same image and coil setup over time.
Author action: A phrase has been added to the material and method section stating this; please see lines 155-156.

Major 7/ Reviewer comment: MRI ANALYSIS; Clarify who of the authors did the BLOKS scores and ensure consistency.
Author response: Agree. This has been clarified.
Author action: Please see lines 185-192.

Major 8/ Reviewer comment: MRI ANALYSIS; Please provide inter- and intra-reader agreements, individual scores?
Author response: The kappa values were based on the individual scores.
Author action: Please see the added table 2 plus a section added to the MRI assessment section regarding the selection of individuals for these analyses.

Major 9/ Reviewer comment: RADIOGRAPHIC MEASUREMENTS; Which ICC model was used to evaluate the inter- and intra-reader agreements of the mJSW?
Author action: Please see lines 271-272.

Major 10/ Reviewer comment: RADIOGRAPHIC MEASUREMENTS; What was the intra-reader agreement for the KL gradings?
Author response: We did not perform intra reader analysis of the KL scoring as KL is a well-established method in both clinical studies and in clinical practice at our institution where we use KOA, light, moderate and severe KOA phrases as a surrogate for the grading 0-4 in each chamber. Furthermore, the score was not used as a primary outcome.
Author action: A phrase regarding this matter has been added to the limitation section; please see lines 363-364.

Major 11/ Reviewer comment: ALIGNMENT; What was the reliability for the alignment measures?
Author response: The Intraclass Correlation Coefficient (ICC) of the alignment measures in our gait laboratory at The Parker Institute is 0.81 (95% CI 0.69 to 0.89) indicating good reliability.
Author action: None.

Major 12/ Reviewer comment: IMVC; The order of muscle groups? / The duration of contraction? / The rest interval?
Author response: The protocol was comprised of 6 successive maximal efforts alternating between knee extension and knee flexion. Each contraction lasted 5 seconds with a 10 second pause between contractions.

Author action: Please see lines 230-231.

Major 13/ Reviewer comment: STATISTICS; Did the authors model weight loss as a continuous model? Describe figure 1!
Author response: Yes.
Author action: Please see lines 258-265 and figure 1.

Major 14/ Reviewer comment: STATISTICS; Was weight loss evaluated as percentage BW and/or BMI?
Author response: This has been clarified in the manuscript.
Author action: Please see lines 258-259.

Major 15/ Reviewer comment: STATISTICS; SE for LSC?
Author response: The LSC was calculated on the basis of the ASE derived from the weighted kappa analyses used to assess the inter- and intra-reader relationship of the BLOKS sub scores.
Author action: Please see table 2.

Major 16/ Reviewer comment: STATISTICS; How did you handle patients with no BMLs at baseline?
Author response: These patients were analysed along with the remaining patients and by doing so we ensured a conservative calculation of the potential positive effect of weight loss on BMLs.
Author action: None.

Major 17/ Reviewer comment: RESULTS; Is there a discrepancy in the KL description?
Author response: There is no discrepancy. There was a typo which has now been corrected.
Author action: Please see the radiographic assessments section.

Major 18/ Reviewer comment: RESULTS; How did the authors decide on the most affected compartment? What was the distribution of KL scores?
Author response: The most affected compartment was selected as the one with the worst status on radiographs. 53 patients had unicondylar medial TF KOA (medial KL ≥ 2 and lateral KL ≤ 1) whereas only 12 patients had solely lateral TF KOA.
Author action: Please see lines 250-251 as well as lines 288-289.

Major 19/ Reviewer comment: RESULTS; What was the distribution of weight loss in both groups? Some patients seem to be very close to the cut-off.
Author response: Patients lost on average 12.5% of their body weight (SD 5.6).
Author action: None.

Major 20/ Reviewer comment: RESULTS; No differences in the underlying RCT, no difference between the groups?
Author response: Yes, that is correct. There were no differences in the examined hypotheses between these two groups.
Author action: None.

Major 21/ Reviewer comment: RESULTS; Did you control for alignment?
Author response: No. With this study we aimed to answer the question of whether or not weight loss can improve BMLs and after extensive discussions it was decided not to adjust for alignment as the interpretation of such analyses was judged too complex and to add no further relevant information to this specific manuscript.
Author action: None.

Major 22/ Reviewer comment: RESULTS; Explain the statistics used to explore the association between clinical symptom changes and BML changes.
Author response: Done.
Author action: Please see lines 301-303.

Major 23/ Reviewer comment: LIMITATIONS; Did you measure physical activity?
Author response: Yes, indeed an important aspect, however it did not have any influence.
Author action: Please see below.

Activity measures in relation to BML responses

<table>
<thead>
<tr>
<th>BML exam time response</th>
<th>BML examination sequence</th>
<th>T-test</th>
<th>BML examination sequence</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>T-test</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>tPA</td>
<td>5.7 (3.5)</td>
<td>7.3 (2.1)</td>
<td>T&lt;0.05</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>[3.1, 8.7]</td>
<td>[2.6, 10.2]</td>
<td>5.7 (2.1)</td>
<td>6.7 (2.3)</td>
</tr>
<tr>
<td></td>
<td>[2.6, 8.7]</td>
<td>[2.6, 10.2]</td>
<td>5.7 (2.1)</td>
<td>6.7 (2.3)</td>
</tr>
<tr>
<td>tPA</td>
<td>2.6 (4.1)</td>
<td>12.1 (2.4)</td>
<td>T&lt;0.05</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>[1.4, 3.9]</td>
<td>[1.4, 4.9]</td>
<td>12.1 (2.4)</td>
<td>13.6 (3.6)</td>
</tr>
<tr>
<td></td>
<td>[1.4, 4.9]</td>
<td>[1.4, 4.9]</td>
<td>12.1 (2.4)</td>
<td>13.6 (3.6)</td>
</tr>
</tbody>
</table>

Mean (± SD) Median (parentheses)

<table>
<thead>
<tr>
<th>BML exam time response</th>
<th>BML examination sequence</th>
<th>T-test</th>
<th>BML examination sequence</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>T-test</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PAN</td>
<td>41.1 (15.7)</td>
<td>41.3 (15)</td>
<td>T&lt;0.05</td>
<td>1</td>
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<tr>
<td></td>
<td>[21.4, 61.8]</td>
<td>[20.5, 61.8]</td>
<td>41.1 (15.7)</td>
<td>38.7 (12.4)</td>
</tr>
<tr>
<td></td>
<td>[21.4, 61.8]</td>
<td>[20.5, 61.8]</td>
<td>41.1 (15.7)</td>
<td>38.7 (12.4)</td>
</tr>
<tr>
<td>CMB</td>
<td>428.3 (288.7)</td>
<td>428.3 (288.7)</td>
<td>T&lt;0.05</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>[250.3, 725.7]</td>
<td>[250.3, 725.7]</td>
<td>428.3 (288.7)</td>
<td>428.3 (288.7)</td>
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<tr>
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<td>[250.3, 725.7]</td>
<td>428.3 (288.7)</td>
<td>428.3 (288.7)</td>
</tr>
</tbody>
</table>

Mean (± SD) Median (parentheses)

PAN: Pain Numerical scale
CMB: Total muscle bulk
Minor 1/ Reviewer comment: Define abbreviations.
Author response: Please see lines 375-401.

Minor 2/ Reviewer comment: ABSTRACT; Units after BMI and age.
Author response: Done.
Author action: Please see line 56.

Minor 3/ Reviewer comment: RESULTS; Units after BMI.
Author response: Please see line 285.

Minor / Reviewer comment: FIGURE; Label y-axis with whole units.
Author response: Done.
Author action: Please see the new version of figure 1.

Reviewer 2

Major 1/ Reviewer comment: Number of subjects in the study.
Author response: N = 169.
Author action: Please see table 1, line 283, and lines 295-296.

Major 2/ Reviewer comment: Comment on the paper by Hayashi et al, OAC 2012, 20, 1227-33.
Author response: The data on m alignment is reported to improve the description of the patient cohort. As the interplay between alignment and MRI items in KOA patients in longitudinal studies is not yet fully understood, it was judged inappropriate to include such data in the analyses. Hence the decision of not including this very interesting paper as a reference in the discussion section of this particular paper.
Also, please see the answer to your major compulsory no. 5 which reflects some of our thoughts on including other variables than those already included in the analyses.
Author action: None.

Major 3/ Reviewer comment: Please analyze the relationship between weight loss and BMLs in a compartment specific manner.
Author response: Yes, and so we did. All analyses were performed so that every patients case (n = 169) only participated in the analyses with BLOKS data related to their worst compartment.
Author action: Please see lines 250-252 and 297-298.
Major 4/ Reviewer comment: Please elaborate on the MRI protocol; how can you evaluate BMLs in BLOKS subregions by applying only a coronal BML specific sequence?

Author response: As stated in the article, we fully agree that this is a limitation of the study.

Author action: Please see the discussion of limitations on this subject in lines 256-259.

Major 5/ Reviewer comment: How did the authors integrate BLOKS subscores in the analyses?

Author response: We report other subscores than just the BML scores so that the reader can get the best possible description of the cohort. As there is a very close relationship between most of the subscores in BLOKS we chose to exclude all other subscores from the analyses of the relationship between weight loss and BMLs (1). We believe that including these other subscores will provide data which would be nearly impossible to correctly interpret (unknown causality between subscores).

Author action: None.

Major 6/ Reviewer comment: Cut-off of 10% on weight loss, arbitrary? How about analysing the same using weight on a continuous scale.

Author response: We performed both analyses.

Author action: Please see lines figure 1, lines 258-265 and 301-303.

Minor 1/ Reviewer comment: Please delete the first paragraph.

Author response: This is, in our opinion, a valid comment, and the section has therefore been deleted.

Author action: Please see the background section.

Minor 2/ Reviewer comment: Please revise figure 1.

Author response: Done.

Author action: Please see the new version of figure 1.

Minor 3/ Reviewer comment: Please clarify the selection and use of compartments.

Author response: I appreciate your comment as this is indeed very important.

Author action: Please see lines 250-252.

Reference List