Reviewer’s report

Title: Serum and Synovial Fluid Cytokine Profiling in Hip Osteoarthritis: Distinct from Knee Osteoarthritis and Correlated with Pain

Version: 0 Date: 28 Nov 2017

Reviewer: Jeffrey Driban

Reviewer’s report:

The authors present an interesting manuscript describing the differences in cytokine profiles between adults with knee OA versus hip OA and healthy controls. Furthermore, they explore the association between cytokines concentrations and hip pain. While the findings are novel there are several issues that makes interpreting the results challenging. Firstly, it may be ideal to omit the control/normal group. The healthy controls don't address the main question about what is different between adults with knee or hip OA nor the association between cytokines and hip pain. Furthermore, the group is dramatically different from adults with hip OA in age (40yrs vs 59 yrs) and even when analyses are adjusted for age it is likely that there would still be residual confounding. Another concern is that 100% of hip cases had KL=3 or 4 but among knees only 28% had KL=3 and no knee had KL=4. Even when analyses are adjusted for KL grade it is likely that there would still be residual confounding. This limitation makes it challenging to decide if the significant differences between knees and hips are because of differences in joints or simply differences in disease severity. The multivariable linear regression model may not accurately indicate if age, sex, and KL grade are confounders since they are so highly related to the groups.

Major comments:

The manuscript would be strengthened by ensuring that all components of the STROBE Statement for reporting observational studies were included.

Methods, Subjects and clinical evaluation: Please clarify how two readers scored the KL grades for hip or knee. Did they read the same hips or knees and reach a consensus or did each person read different joints?

Methods, Subjects and clinical evaluation: Since two readers read for KL grades it would be ideal to report inter-reader agreement (weighted kappas).

Methods, Subjects and clinical evaluation: It would be helpful to offer more details on how participants were recruited/enrolled. Were these consecutive patients seen during a certain time period or a convenience sample or a group being scheduled for surgery? Were the normal/control participants, who were recruited from a sports medicine program, being seen for any other injuries?

Minor comments:
Abstract, Background: It would be beneficial if the first two sentences highlight why it is important to look at cytokine profiles among people with hip OA (the Introduction of the manuscript does this nicely).

Introduction, Paragraph 4: The sentence about the ACR criteria for OA should be revised to clarify that pain is not the "only necessary condition for clinical diagnosis of OA" but an important component along with other clinical aspects (e.g., radiographic evidence, physical examination findings).

Methods, Subjects and clinical evaluation: Please clarify that KL=1 was considered the criteria for meeting the ACR criteria.

Methods, Subjects and clinical evaluation: Please clarify the statistic used to calculate "intra-reader reliability" for the KL grades. It should ideally be a weighted kappa.

Methods, Subjects and clinical evaluation: Please clarify if medication use was captured among the adults with hip or knee OA. If so, how many people were on anti-inflammatory medication?

Methods, Subjects and clinical evaluation: Please clarify if participants with hip or knee OA were asked if they currently have any symptoms in other joints (to rule out undiagnosed OA in other joints).

Methods, Clinical Assessment of Hip OA Cohort: It would be beneficial to readers if this section was expanded to highlight the constructs measured by each questionnaire and some basic properties of them (e.g., range of possible scores).

Methods, Sample Collection: Please clarify how people were selected that contributed synovial fluid samples.

Methods, Sample Collection: Please expand on who contributed synovial biopsies. Was a sample collected from everyone that had surgery? What surgery was being performed?

Methods, Statistical Methods (second paragraph): Define "two subgroups-impingement and dysplasia".

Methods, Statistical Methods (last paragraph): Please clarify that affected joint was an independent variable or predictor and was not considered a potential confounder in the multivariable linear regression.

Methods, Subjects and clinical evaluation (last paragraph): Please clarify which analyses were performed with scipy versus SPSS.

Results: The text and figure focus on the significant results but it would be beneficial to readers if the nonsignificant comparisons between groups was included in the supplemental file.

Results (first paragraph): Please describe the three components of PCA.
Results: It may be more accurate to change the title "Comparison of cytokines to..." to "Correlations between cytokines and..."

Results (Comparison of Cytokines…, 2nd paragraph): These results suggest that KL grade may be a confounder (if also related to cytokine concentrations). Hence, these associations should be adjusted for KL grade.

Figure 1. It may be ideal to indicate the results reported in section 1.C in 1.A and 1.B.

Figure 1.D may be more appropriate as a separate figure.

Supplement Table 3. It may be more accurate to title this table "Correlations between cytokine concentrations and hip pain"

*Are the methods appropriate and well described?*  
If not, please specify what is required in your comments to the authors.  

No

*Does the work include the necessary controls?*  
If not, please specify which controls are required in your comments to the authors.  

Yes

*Are the conclusions drawn adequately supported by the data shown?*  
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No

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