Reviewer's report

Title: Is Knee Osteoarthritis a Symmetrical Disease? Analysis of a 12 Year Prospective Cohort Study

Version: 3 Date: 3 May 2012

Reviewer: Michael Anthony Hunt

Reviewer's report:

Thank you for the revisions to this manuscript, which I feel have enhanced the readability of the paper. I also appreciate the additions to the manuscript (especially within the Introduction) outlining the anticipated novelty of this research. There are still some issues that I feel would improve the relevance of this paper.

Major compulsory revisions:

1. Thank you for expanding on the novelty of this work. The authors indicate that “we do not know the timescales involved in [bilateral OA involvement]”, that the “timing of progression to bilateral disease has not been clarified”, and that the current approach will “allow researchers, clinicians and patients to understand the disease process and the risk of further disease in the future over a known time period”. However, I am not sure that the current study design is able to address these issues given that only 2 time points were assessed – it would have been nice to have annual radiographs to establish a more definitive time scale of development of bilateral disease. Importantly, it is unclear how knowledge that a given % of participants with knee pain will development unilateral or bilateral disease over a 12 year period will change clinical practice. A clear description of how clinical practice may change (likely in the Discussion) would greatly enhance the applicability of this paper.

2. It is unfortunate that none of the exploratory variables (age, gender, knee pain, or BMI) were different in the bilateral OA group. There does not appear to be a rationale for this in the Introduction as to why any of these variables should be different. Presumably these data came from a larger cohort study with a number of additional variables. Why were none of these chose (alignment for example)? Identification of explanatory variables would certainly be of interest to the clinical community.

3. It would appear that secondary analysis attempting to “understand the effects of these factors on new onset bilateral disease over 12 years)” included all eventual bilateral disease patients with the exception of those with pre-existing bilateral disease at baseline. This suggests that everyone with no OA or just unilateral OA were included in this analysis. What evidence exists to suggest that these 2 groups (no OA vs unilateral OA) should proceed to bilateral OA in the same manner under the same mechanisms. Please elaborate on the
appropriateness of including both of these apparently different phenotypes into a single analysis to determine mechanism of bilateral onset.

Minor essential revisions:

1. Was the same radiologist involved in all assessment of radiographs? While inclusion of kappa values outlining the agreement is important, data pertaining to these actual radiologists would be preferred.

2. As suggested in the previous review, it is unclear what additional information the OARSI-OMERACT criteria add to this study. For example, it would appear that this approach was used as an additional method of classifying OA (see page 10), however no additional analyses were reported on these findings. Further, the breakdown of compartmental involvement in those with bilateral disease does not appear to match the previous numbers (i.e. 73 medial bilateral + 6 medial in one, lateral in the other + 2 lateral bilateral + 25 equal scores = 106 knees, yet page 9 indicates that “At 5 and 12 years the number with bilateral disease had increased to 65 and 100 respectively”).

3. The description of pain is inconsistent throughout. For example, the purpose statement indicates the aim to explore whether “baseline bilateral knee pain” explains development of bilateral OA, while in the Methods it is stated that subjects were asked “if they had pain in any of your knees practically daily for the last three months and were subsequently seen by a rheumatologist” to determine how many knees were painful, and in the Results, it simply describes “those who started the study with knee pain”. Indeed, the inclusion criteria only states that participants had “chronic knee pain”. Thus, it is unclear what relationship between knee pain and eventual OA findings was actually examined. If both unilateral and bilateral pain was allowable, it would be interesting to report the “agreement” between type of pain and eventual OA findings (for example, if pain was only in the right knee but OA developed in the left, or if the pain and OA matched, etc.).

4. Paragraph 2 of the Discussion indicates that with the exception of previous injury cases, early knee osteoarthritis “in most cases is a bilateral disease”. It is unclear what is meant by this statement. Please elaborate with specific examples from the current dataset – the data would actually suggest that early on most (53%) actually had no radiographic changes.

5. As above, the exact novelty of the current data is unclear. This comment is supported by a number of comments throughout the Discussion as currently written. For example, “We are unable to comment on the cause for the pattern of OA progression that we have observed in this paper, although further studies are ongoing” (thus, it may be more prudent to wait on additional data), “the current study did not have sufficient numbers to separate out the effects of these factors properly”, and “further interventions aiming to slow the progression to bilateral disease may well be of benefit to the patient with osteoarthritis” (this is widely accepted and routinely implemented in clinical practice – it would be more beneficial to identify potential strategies or risk factors to target).
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests' below