Reviewer's report

Title: Quantification of Bone Marrow Lesion Volume and Volume Change Using Semi-automated Segmentation: Data from the Osteoarthritis Initiative

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Reviewer: Dawn Doré

Reviewer's report:

This study aimed to validate a new, three-dimensional, semi-automated BML segmentation method. Authors demonstrated that their volumetric BML measurements increased with a well-accepted semi-quantitative BML scoring system (BLOKS). They also showed that change in their BML volume measurements were associated with longitudinal cartilage loss over 24 months. Their method is time-efficient and demonstrated adequate reliability. Time-efficient BML measurements are very important, given the large number of participants in OA cohort studies. This paper would be of great interest to the OA research community.

I have a few minor comments/questions:

1) Can you expand on the rationale for omitting the middle 9 slices? Wouldn’t you get BMLs adjacent to cartilage surface on these slices as well?

2) How does the program distinguish between a BML and a cyst?

3) How does the slice thickness of 3 mm impact on the volume measurements?

4) Why haven’t the authors adjusted for any covariates in their analysis between BMLs and cartilage damage? Age, sex, BMI, radiographic OA status? This may be due to a small sample size, please explain.

5) I assume there were a lot of zero’s for the BML volume measurements, i.e. those who did not have a BML at a specific site. In the analysis with longitudinal cartilage loss, how did the authors deal with this?

6) Both validation studies in this paper were done on participants with denuded cartilage/full thickness cartilage loss. This could have strengthened the association between BML volume change and longitudinal cartilage loss. It is reassuring that this method demonstrated validity in such small numbers (n=48 and n=38); however, it does need further exploration in a larger cohort, with varying degrees of cartilage damage (i.e in those with healthy knees as well).

7) This study does validate a semi-automated method to measure BML volume. BML volume may be a more accurate method to measure BML size; however, this remains to be determined. It would be interesting in future studies to see whether BML volume is more strongly associated with factors such as cartilage loss, pain, joint replacement, compared to a semi-quantitative or quantitative (2D)
measure of BML size. If so, then it would be the optimal BML measure to use.

Overall this is an interesting paper. BMLs are recognised as a key feature in OA and to have a program which can accurately measure their size and size changes in a time-efficient manner is invaluable.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No competing interests.