Author’s response to reviews

Title: Clinical characteristics and role of whole body bone scan in multifocal osteonecrosis

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Author’s response to reviews:

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Professor James Mockridge
Editor in chief
BMC Musculoskeletal Disorders

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Dear Dr. James Mockridge

Please find attached our revised manuscript titled “Clinical characteristics and role of whole body bone scan in multifocal osteonecrosis” by Youn-Sil An et al, which we are submitting for consideration for publication as an original article in BMC Musculoskeletal Disorders. This manuscript had been previously submitted to BMC Musculoskeletal Disorders. In your letter of OCT 28, 2018, you advised us to revise our manuscript. We wish to express our gratitude to you
and reviewers for the careful review of our manuscript. We addressed the concerns of the reviewers and made a few corrections and clarification in the manuscript after going over the reviewers’ comments.

Please see the enclosed letter below for our response to reviewers’ comments and additional list specifying changes we made. We hope that the incorporated changes and additions allow the manuscript to be suitable for publication in BMC Musculoskeletal Disorders.

We thank you and reviewers for the time and effort on this matter and look forward to hearing from you.

Sincerely yours,

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07 November 2018

Point-by-point response to the reviewers’ comments

Reviewer 1

We appreciate your review of our manuscript “Clinical characteristics and role of whole body bone scan in multifocal osteonecrosis”. In response to your comments, we have performed the necessary clarifications, as summarized below. The changes are underlined in the revised manuscript.

1. In the introduction section, line 17, the authors can use the term all literature work instead of just works.

Answer: We have changed “all work” to “all studies”.
2. In the variables section, line 25, the authors defined excessive alcohol intake and mentioned it was described previously. I don't think it was described previously earlier in the manuscript. Also, on line 29 the authors can remove per day after 1 bottle of Soju since they already mentioned it is daily intake.

Answer: We have deleted “it was described previously” and “daily intake”.

3. In the results section, line 24, it is better to use the term idiopathic rather than idiopathology.

Answer: We have changed the term “idiopathology” to “idiopathic”.

Thank you for your constructive review. We hope that the revised manuscript now meets the journal’s standards for publication.

Reviewer 2

We appreciate your review of our manuscript “Clinical characteristics and role of whole body bone scan in multifocal osteonecrosis”. In response to your comments, we have added the necessary clarifications, as summarized below. The changes are underlined in the revised manuscript.

ABSTRACT

1. Line 9, MRI and X-rays of the hips or other anatomic districts too?

Answer: Yes. We have added the text “of the hips or other anatomic regions”.

2. Please, report the statistical tests used

Answer: We now describe the statistical tests used.

INTRODUCTION

3. Lines 29-32, I wouldn't say that MRI is used to guide biopsy, since biopsy is not commonly performed to achieve the diagnosis and MRI is not actually used to guide this kind of procedure, although it allows to detect ON when X-ray and CT are still falsely negative.
Answer: We have deleted “and to guide biopsy”.

4. Please rewrite the last sentence of the Introduction section to better convey the purpose of the study.

Answer: As suggested, we changed the last sentence of the Introduction to “We investigated the clinical characteristics and utility of WBBS in patients with multifocal ON.

MATERIALS AND METHODS

Subjects

5. Line 7, X-rays were performed on hips, knees, and ankles, but it is not clear what anatomical district was investigated by MRI, please clarify.

Answer: We have changed “WBBS; MR scans; and X-rays of hips, knees, and ankles” to “WBBS and MRI or X-rays of the hips, knees, and ankles”.

6. Inclusion and exclusion criteria? Were randomly searched in your PACS or in your Orthopedic database?

Answer: We identified 294 patients from the computerized medical records of Ajou University Hospital with the diagnostic code for ON and test code for WBBS; 40 patients were excluded because their MRI findings were negative. We have described this in the revised manuscript.

7. Line 60, 3 T instead of 3.00

Answer: We have changed “3.00” to “3 T”.

8. Please include in MeM how you calculated we calculated the amount of prednisone received by all patients. If they received dexamethasone, please include the prednisone-dexamethasone conversion used.

Answer: Thank you for this valuable comment. The cumulative corticosteroid dose (prednisolone equivalent for all oral, intravenous, subcutaneous, and intramuscular administrations) during the WBBS was calculated. Our patients received methylprednisolone or prednisolone, but not dexamethasone. We have described this in the revised manuscript.
RESULTS

9. Lines 7-9, MRI was performed on more anatomical districts to identify multifocal ON? I guess that 24 cases of multifocal ON were evident only on WBBS because MRI was performed on a single district and not falsely negative. This should be clarified.

Answer: This means that 24 patients had multifocal ON evident on WBBS and MRI or X-rays. Another two patients had multifocal ON confirmed in the evaluation of multiple sites on MRI or X-ray, with negative results on the WBBS. We have clarified this in the revised manuscript.

10. Lines 21-26, how you divided the causes of ON should be included in the MeM section instead of the results.

Answer: As suggested, we have moved this to the Method.

WBBS, MRI and X-ray results

11. How can you compare WBBS, which is a whole body examination, with local MRI? Did all these patients perform MRI of all joints or some joints were not evaluated in some cases (this data should be reported)? Did they undergo a whole body MRI? It's still unclear how these patients were evaluated on MRI, although it's very important when comparing these modalities, especially considering that MRI is the most accurate imaging procedure. As I see from figure 1, there are several cases that you considered positive on WBBS and negative on MRI, it should be clarified if in these cases MRI of the affected segment was not available, alternatively authors should justify how WBBS can see ON not detected by MRI. In the latter case, a figure with images of the patient would be of interest.

Answer: Thank you for valuable comments. In the 294 patients who underwent WBBS with a code of ON, 458 sites were examined by WBBS and local MRI, and 456 sites by WBBS and X-ray. We have clarified this in the revised manuscript. The result occurred because MRI did not confirm all of the positive areas seen on WBBS. In some patients, only X-ray confirmed the positive sites seen on WBBS. Therefore, the data did not show that WBBS is more sensitive than MRI in ON, and instead showed only the results of WBBS and local MRI or X-ray. In the 254 patients with ON, 419 sites were examined with local MRI and 415 sites were examined with X-rays images. A total of 477 sites seen on WBBS were compared with local MRI or X-ray images. We have clarified this in the legend of Figure 1.
12. The authors focused their study on the differentiation of oligofocal ON from multifocal ON, but they did not report if ON lesions were located in metadiaphyseal or epiphyseal regions. However, the location of ON is clinically much more important than the information regarding the number of ON lesions. Indeed, in metadiaphyseal ON, bone collapse does not occur, while in epiphyseal ON the involvement of articular surface gradually leads to osteochondral fragmentation and surface collapse. Epiphyseal osteonecrosis is usually more symptomatic, although in some cases it can be totally asymptomatic. May you please report this crucial data? I suggest to use the following interesting paper to discuss this important point [Osteonecrosis detected by whole body magnetic resonance in patients with Hodgkin Lymphoma treated by BEACOPP. Eur Radiol (2017) 27:2129-2136; DOI 10.1007/s00330-016-4535-8].

Answer: Most of the enrolled patients were suspected of having ON because of their site pain, and were examined using MRI. We found only seven patients with metadiaphyseal ON without epiphyseal ON. Therefore, we did not subdivide the patients according to the location of the ON lesion (metadiaphyseal vs. epiphyseal). Instead, we classified the patients using the ARCO classification of femoral head ON, which is representative of epiphyseal ON. Therefore, as you suggested, we cited a reference relating to this point and have described this in the study limitations [Osteonecrosis detected by whole body magnetic resonance in patients with Hodgkin lymphoma treated by BEACOPP. Eur Radiol (2017) 27:2129-2136; DOI 10.1007/s00330-016-4535-8].

13. Second page of the discussion, lines 13-24. I disagree since other recent papers have already demonstrated the utility of whole body MRI to detect multifocal ON in riskful patients [Eur Radiol (2017) 27:2129-2136; Br J Haematol. 2017 Feb;176(4):637-642; PLoS One. 2017 Jul 17;12(7):e0181069]. MRI, and thereby whole-body MRI, has higher sensitivity and specificity than scintigraphy [Semin Musculoskelet Radiol 15:281-300], besides avoiding radiation exposure, which is crucial in younger patients with longer life expectancy and at higher risk of radiation-induced long-term effects. The conclusion of the paper cannot be that WBBS is useful for evaluating younger patients, especially in the light of the directive 2013/59 by the European Union which states that if a radiation-free imaging technique allows the same diagnostic results to be obtained, it should always be used [Eur Radiol (2018) 28:1187-1193]. Based on this recommendation, WBBS should not be considered the best option. I suggest to better discuss the point of radiation exposure, the potential role of whole body MRI in this setting, and I would rephrase the conclusion.

Answer: We agree entirely. Therefore, we discussed whole-body MRI. We have described the results of the whole-body MRI of 42 patients with Hodgkin lymphoma treated by chemotherapy. We have also changed the last sentence to “Therefore, WBBS may be an additional tool for
diagnosing ON and assessing its progression, particularly in patients with suspected multifocal ON.”

14. I would better underline that WBBS might have missed some locations and that the selection bias might have affected the results, since corticosteroids are well known as the most important cause of ON [Orthopedics 2011;34:39-48]

Answer: Thank you for this valuable comment. We have added a description to the study limitations.

15. There are few outstanding grammatical and syntax errors, but overall English is ok

Answer: We have corrected various grammatical and syntax errors.

16. A figure with a case of the study population, including WBBS, MRI, and x-ray should be added.

Answer: We have added a figure showing a case from the study population, including WBBS, MRI, and X-rays (Figure 2).

Thank you for your constructive review. We hope that the revised manuscript now satisfies the journal’s standards for publication.