Author's response to reviews

Title: Risk of low bone mineral density in patients with rheumatoid arthritis treated with biologics

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Author's response to reviews: see over
Please find attached our manuscript entitled “**Risk of low bone mineral density in patients with rheumatoid arthritis treated with biologics**” which we would like to submit to *BMC Musculoskeletal Disorders*.

**MS:1804909834177639**

**Risk of low bone mineral density in patients with rheumatoid arthritis treated with biologics**

Please find attached our revised article. We have amended our manuscript in accordance with the reviewers’ comments and hope that it is now suitable for publication in the *BMC Musculoskeletal Disorders*. Please find below our responses to the reviewers’ comments.

**Reviewer #1**

**Comment #1:**

After reading this paper, the purpose of this work is to establish factors in RA associated with low femoral BMD. Conclusion needs to emphasize that factors associated with low BMD at the femoral neck are similar to general population.

As per the suggestion of the reviewer, we discussed in the discussion section as below.

“Although our risk factors were found in patients with RA treated with biologics, these risk factors are compatible with those in the general population [20-22].”

**Reviewer #2**

**Major Compulsory Revisions**

**Comment #1:**

1. Why was univariate analysis performed? I do not think this is necessary. The outcome was categorical variable (binary), and logistic regression was sufficient enough to fit a model that could identify predictors of the outcome.

As per the suggestion of the reviewer, we moved the result of univariate analysis to supplementary Table 1.
Comment #2:
More importantly, I have a concern with regards to exclusion of sex in the logistic regression analysis. In principle, the authors had one outcome and tried to identify a list of independent risk factors for it rather than had one outcome and one exposure, thus needed to adjust for confounding factors. It seems to me that the authors are treating the statistical software as a black box rather than imputing the clinically meaningful predictors into the model. Correlation does not equate to dependency and it is still unclear why sex is excluded – as this variable still satisfies the assumption for a logistic regression analysis.

We put out our data to statistical analysis professional company following previous submission. As per the suggestion of the reviewer, they showed that our previous exclusion rule was wrong. They showed that we can include age, sex, disease duration, history of past vertebral fracture, BMI, MHAQ score, Steinbrocker classification and duration of biologics use as below.

correlation coefficient

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<tr>
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In addition, we change the results as below.

"We performed univariate analysis (supplemental Table 1) and multiple logistic regression analysis of factors associated with a BMD <70% of YAM. Spearman's correlation coefficient revealed no high relationships between a BMD <70% of YAM and age, sex, disease duration, history of vertebral fracture, BMI, MHAQ, Steinbrocker classification, or duration of biologics use. Multiple logistic regression analysis showed that age (odds ratio [OR] 1.065), female (OR 5.019), disease duration (OR 1.077), history of vertebral fracture (OR 7.708), and Steinbrocker classification (OR 2.302) were associated with a greater risk of a BMD <70% of YAM, whereas higher BMI (OR 0.766) reduced the risk for a BMD <70% of YAM (Table 6)."

Comment #3:
In the multivariable analysis, advanced age, history of past thoracic or lumbar vertebral fracture, lower BMI, longer disease duration and higher Steinbrocker classification were significant factors for BMD <70% of YAM. The first 3 are not new findings and in fact, have already been incorporated into FRAX and ORIS tools for fracture prediction. The last 2 may be important however the authors did not emphasise the importance of these factors and certainly higher Steinbrocker classification was not even discussed in the Discussion.

As per the suggestion of the reviewer, we discussed about disease duration and Steinblocker classification as below.

"Disease duration and disease activity are considered the most important risk factors
for generalized osteoporosis [2, 18, 19].”

“We found only one English-language paper in PubMed that showed the relationship between the Steinbrocker classification and bone loss in patients with RA. The article reported that a higher Steinbrocker classification is a risk factor for bone loss of the femoral neck and lumbar spine [25]. Our findings are compatible with this report.”

**Comment #4:**

4·1 Why was femoral neck BMD selected to diagnose osteoporosis but a history of vertebrae fracture was chosen as an independent variable?

It is sometimes difficult to evaluate the bone mineral density by DEXA system when the spinal vertebrae are affected by compression fracture. In this regard, we evaluate the DEXA of femoral neck. Now we are evaluating the change of DEXA of spinal vertebrae for next paper.

4·2 In addition, the confidence interval was very wide (1.9-16.4) and no explanation was given for this.

There were four male patients in the BMD <70% of YAM group. Nine patients in this group had a history of thoracic or lumbar vertebral fracture. When the number of patients associated with a dependent variable is small, the range of odds ratios widens. These findings suggest that patient sex and a history of thoracic or lumbar vertebral fracture were significant factors between the BMD <70% of YAM and BMD ≥70% of YAM groups. However, the reliability of the odds ratios for these factors is not excellent.

**Comment #5:**

In Table 3, what did the p=0.67 represent? There were 4 categories or level of comparisons involved and was the multiple testing corrected?

Mann-Whitney test showed the p=0.67.

**Comment #6:**

It would have been more novel if the logistic regression analysis was carried out after
stratifying the therapy to anti-TNF vs non-anti-TNF groups.

As per the suggestion of the reviewer, this is very important question. Now we are collecting the data for these questions.

**Minor revision**

**Comment #1:**
In Method section line 13, this should be changed to predicting risk factors associated with a BMD #70% rather than #70%.

As per the suggestion, we change it as below.
“Multiple logistic regression was performed to select the best model for predicting risk factors associated with a BMD <70% of YAM using Excel Statistics 2012 and Excel Statistics 2015.

**Comment #2:**
2. The subtitles: “Influence of methylprednisolone therapy on osteoporosis” and “Influence of disease activity on osteoporosis” – Influence should be changed to association. This is a cross-sectional study, hence only association can be deduced but not the “Cause or Effect.”

As per the suggestion of reviewer, we change them as below.
“Association of methylprednisolone therapy on osteoporosis”
“Association of disease activity on osteoporosis”
“Association of disease activity on osteoporosis of duration or type of biologics therapy on osteoporosis”
“Association of disease activity on osteoporosis of duration or type of biologics therapy on osteoporosis of anti-osteoporosis drug therapy on osteoporosis”

**Comment #3:**
3. For a complex statistical analysis, I think other software such as STATA or SPSS should be used.
We put out our data to statistical analysis professional company. They used SPSS.