Author's response to reviews

Title: Discordance in diagnosis of osteoporosis using spine and hip bone densitometry

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Dear editors,

We are so pleased that your reviewers have found our article well-written and interesting. We have extensively revised our manuscript considering your reviewers' invaluable comments. The main criticism of both reviewers was about the necessity of a multivariate analysis to find the potential risk factors of discordance. Actually, this was our concern too at the beginning of the study, but due to some reasons (that we have explained in our response to reviewers) we did not included such analysis in the first draft. Now, we have inserted the results of multivariate logistic regression analysis to the manuscript (Table 4), but we also think that there is still room to work on the associated factors for evaluation of diagnostic discordance and we should perform additional analyses on our data to suggest a proper approach for confronting with this problem. We cannot incorporate such analyses into this article because of the complexity of the results and the need for statistical consultation. However, we are working on the issue and will soon submit that manuscript hopefully to one of your journals.

We have a request from you now. We have noticed that most of the articles about osteoporosis in your journal series are published in the BMC Musculoskeletal Disorders. Some of our colleagues have advised us to submit our manuscripts to this BMC journal, but we got this advice somehow late. We wanted to see if it is possible for you to publish this manuscript (of course, in the case of acceptance) in that journal. Undoubtedly, all the BMC journals are high-quality and very well edited; but we prefer to publish our manuscript in a journal with more potential readers.

I have highlighted our major modifications in yellow color to make them prominent. Should you think it is unnecessary, I can omit them. We have also answered all the reviewers' comments point-to-point. We hope they will find their answers satisfactory.

Respectfully yours,
Alireza Moayyeri, MD

Dear reviewers,

Many thanks for your thoughtful suggestions. We have revised our manuscript considering your valuable points and addressed any change we have made here.

Referee: Dr. Bo Abrahamson

Major Compulsory Revisions:
1. We have included two separate multivariate logistic regression analyses indicating odds ratios (and 95% confidence intervals) of occurrence of major or minor discordance given a variety of risk factors (Table 4). Actually, some factors such as HRT and smoking had protective nature (indicated by odds ratios less than 1). We have discussed about these findings in the second paragraph of Discussion section.
2. Reasons for referral of patients are added to the first paragraph of the Results section (page 7).
3. All of the BMD measurements were done for the first time for patients (with diagnostic purposes) and
before start of any treatment. So, none of our patients were on the treatment with bone active agents. We have added this point to the Materials and Methods section (page 5, line 15).
4. We have added footnotes for all tables.

Minor Essential Revisions:
1. Sorry for that mistake. We have corrected it on page 3, line 6.

Discretionary revisions:
1. Although none of our participants were using drugs against osteoporosis (bone active agents), hormone replacement therapy was associated to more concordance in the multivariate analysis. We have discussed in this regard at the Discussion section (page 8, paragraph 2).
2. In our center, vertebral bodies with apparent compression fractures during BMD measurement are usually excluded by the operator. Here, with compression fractures, we meant the fractures not visible during absorptiometry but with potential effects on the measurement. We added the word "minor" before compression fractures to indicate this concept.

Referee: Dr. Florent Richy

Major Compulsory Revisions:
1. We did not use data of our population as the reference values. Firstly, there is little knowledge about normal values of BMD in Iranian population. Few studies (references 22 and 23 of the article) in this regard have limited sample sizes and their data is not applicable. Moreover, considering high prevalence of vitamin D deficiency in Iran and lower peak bone mass of Iranian adults, Iranian norms could not be considered really as normal. Secondly, we wanted our findings in this study to be generalizable and comparable to future studies. So we used normative data of the Lunar device as our reference values and mentioned it in page 5, line 20. For BMD measurement in men, we could not use other reference values as the proper reference values are not established yet. We have also added measures of precision (confidence intervals) for estimation of prevalence of discordance to Table 2.
2. We have implemented two multivariate logistic regression analyses predicting the presence of major or minor discordance using various risk factors (Table 4). This analysis points to the factors clinicians and diagnosticians should consider when ordering BMD measurement for a patient. However, it can not help physicians to predict situation of one measurement site on the basis of the data from another site. The main reason for why we did not do this in the first draft of the manuscript was exactly your mentioned facts here. We do not think that the current analysis is so helpful to the physicians. Actually, the multivariate analysis in the present form can only direct physicians to roughly predict presence or absence of discordance. The main question of physicians and policy makers (as you have mentioned here) is that: could the results of BMD measurement in one site predict the situation of osteoporosis in the other site? Especially, with the large impact of hip fractures and considering higher prevalence of lumbar osteoporosis, can the lumbar DXA predict hip condition or vice versa? However, the problem we faced here was the choice of multivariate analysis to find a formula with the best fitting predictive power. The only study we have found in this regard was the one by Larcos G (Mayo Clin Proc. 1998 Sep;73(9):824-8) using discriminant analysis in relatively small sample size and with questionable study design. The main drawback of the discriminant analysis is that it does not give any measure (like odds ratio) for further use of the results of the analysis. So, we decided to use regression analyses. In the next step, we confronted with another problem choosing between multinomial, linear, and binary logistic analysis. While the multinomial analysis is the easiest and most straightforward one, the interpretation of the results and qualification of the assumptions seems so problematic. For prediction of the situation of one site using BMD results of the other site, using binary logistic regression seems rational; but the problem is the number of analyses and the need for larger sample size (for these two sites, we need to perform 4 analysis to predict, for instance, hip situation in patients with osteoporosis in lumbar BMD). There are also other possible statistical approaches to this problem and now we are taking statistical consultation. Hopefully, we will soon publish our findings, mainly focusing in prediction of hip osteoporosis using BMD measurement in other sites. We have discussed about this limitation in page 10, paragraph 3.
3. Please refer to our answer to previous point.

Minor Essential Revisions:
1. We have omitted the sentence and added the results of multivariate analysis.

Discretionary revisions:
1. Taking into account fracture data as target variable is our ideal too. As you have said, the best design for a study searching for the impact of discordance is a fracture study with prospective design. We have included this statement in our discussion section page 10, line 22.
I hope you would find our answers reasonable and be satisfied with the extensive revision we have made on the manuscript.

Respectfully yours,
Alireza Moayyeri, MD