Author's response to reviews

Title: Prediction of fractures using low-frequency ultrasound - comparison with DXA-based BMD

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Author's response to reviews: see over
Dear Editor,

We appreciate the valuable comments raised by the Reviewers. We have carefully revised the manuscript and addressed each of the reviewers´ comments. For clarity, track changes feature of MS Word has been used to emphasize the changes made to manuscript. We wish our revision meet your consideration for publication in BMC Musculoskeletal Disorders.

Sincerely,

Mikko Määttä  
Corresponding author

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Editorial Request:

Requesting name of ethics committee:

Please update your ethics statement to include the name of the ethics committee that approved your study.

The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. This info is now included in the manuscript “Subjects and clinical assessment” section.
Reviewer's report

Title: Prediction of fractures using low-frequency ultrasound - comparison with DXA-based BMD

Version:1 Date:24 December 2013

Reviewer: Albrecht Popp

Reviewer's report:

The authors aimed to evaluate whether and to what extent fractures were associated a low-frequency axial ultrasound velocity measurements at the tibia combined with or without clinical risk factors compared to BMD measured with DXA at the femoral neck and in a cohort of elderly women. The cohort was followed for fractures between 1997 and 2010. The clinical risk factors were collected in 1997, their association with hip fractures has been published by most of the authors in this journal last year (Määttä et al. BMC Musculoskeletal Disorders 2012, 13:173).

The current study design is a mixture of a case-control study (1997-2006) and a prospective study (2006-2010). All incident fractures as well as hip fractures were regarded separately. After the direct comparison between DXA and ultrasound measurements, the predictive value of ultrasound measurements was improved by adding clinical risk factors but their weighting has been specified elsewhere.

Confusing is the focus on the low number of hip fractures: Regardless the model applied, it is hard to believe that any measurement at any skeletal site other than the hip (i.e. tibia) should be more predictive for hip fractures than BMD at the femoral neck. One could argue that there is inconsistent outcome regarding fracture risk association and ultrasound velocity measurements at the tibia.

The article is important in its field. The work is informative but major editing needs to be performed before publication is considered.

Specific comments:

Title

Major Compulsory Revisions:

Since the bone measurements were performed in 2006, the term of 'prediction of fractures' seems to overestimate the results of the study and should be replaced by association.
The title has been modified as suggested. The new title is: *Association between low-frequency ultrasound and hip fractures – comparison with DXA-based BMD*

**Introduction**

**Major Compulsory Revisions:**

The first paragraph is not leading to the meaning of bone measurement on fracture risk evaluation. The context of fracture risk assessment including DXA measurement as diagnostic criterion and clinical risk factors (FRAX® etc.) is missing. Ref 1 is inappropriate (review). Without knowing the authors’ previous article in BMC msd, the rationale for the specified combination of ultrasound measurements and clinical risk factors is missing as well and deserves explanation.

The first paragraph has been changed to focus more on the fracture risk evaluation. It now goes:

> **Osteoporotic fractures possess a significant public health problem that is increasing due to aging population. At the moment, the golden standard used in fracture risk assessment is bone mineral density (BMD) measurements using dual energy x-ray absorbtiometry (DXA). Recently, World Health Organization (WHO) introduced FRAX®, a fracture risk calculator that combines easily obtained clinical information and DXA-based femoral neck BMD, if available, to estimate the 10-year osteoporotic fracture probability [1].**

The previously determined risk factors are now listed in the statistical analysis section and determination of model is explained in more detail.

Please edit/ correct the following sentences:

'The most common osteoporotic fractures occur at wrist, lumbar spine, and hip.’

The sentence was removed from the introduction. See previous comment.

'Quantitative ultrasound (QUS) has raised interest as an alternative method for measuring bone strength.’ Alternative to what?

The sentence has been modified as follows:

> **Quantitative ultrasound (QUS) has raised interest as an alternative method to x-ray-based imaging for measuring bone status.**

**Subjects and methods**

The subtitle ‘Subjects’ should be Subjects and clinical assessment.’
Modified as suggested.

Major Compulsory Revisions: A consort chart would be very helpful.

A chart has been included as recommended.

The reviewer does not understand the reference 10 in this context: 'The standardized coefficient of variation (SCV) [10] of the method was 6.6%. Due to the lack of established reference population data, we used the present study population to define the range in SCV calculation.'

The reference was changed to more suitable (Ogree et al. 1996).

Statistics

What is the exact hypothesis?

Previous studies have shown that decreased $V_{LF}$ is associated with decreased bone strength (Kilappa et al. 2011) and increased fracture risk (Moilanen et al. 2012). We hypothesise that decreased $V_{LF}$ measured on tibia is associated with increased hip fracture risk in elderly females.

Minor Essential Revisions

DXA criterion for osteoporosis (Ref 11) was stated in 1993, not 2003.

Reference changed as requested.

Results

The statement 'Femoral neck BMD did not reach statistical significance when included in the regression analyses.' does not fit 100% into the data from table 5. Please revise.

The text has been revised as follows:

Femoral neck BMD did not reach statistical significance when included in the regression analyses along with lifestyle-related risk factors.

Conclusions

Major Compulsory Revisions:

Essence is not properly supported by the provided data: The statement 'In conclusion, despite the limited measurement precision low-frequency ultrasound velocity was shown to be a promising tool for assessing the risk of hip fracture.'

The conclusion has been modified to better reflect the results observed in the study:
In conclusion, decreased low-frequency ultrasound velocity was associated to increased hip fracture risk despite the limited measurement precision. The results reported here can be used to further improve the measurement precision of the method so as to reliably predict future fractures. To this end carefully planned follow-up studies are needed.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests
Reviewer's report

Title: Prediction of fractures using low-frequency ultrasound - comparison with DXA-based BMD

Version: 1 Date: 18 February 2014

Reviewer: Guoqing Diao

Reviewer's report:

Title: Prediction of fractures using low-frequency ultrasound comparison with DXA-based BMD

General Comments:

In my understanding, the authors intended to evaluate the effects of ultrasound velocity (V_LF) on the risk of fracture and/or hip fracture in community-dwelling women with ages between 78 and 82 years old. However, this objective was not clearly stated in either the abstract or the Introduction section. In addition, this study involves both retrospectively and prospectively collected data. The V_LF data were measured in 2006 whereas data from 1997-2006 were retrospectively collected and the follow-up data from 2006 to 2010 were prospectively collected. It is important to distinguish these two different types of data in both the statistical analysis and the interpretation of the results. In addition, one needs to examine certain model assumptions to ensure the validity of the data analysis. Some interpretation of the results were not accurate. I list my detailed comments below.

1. Page 3, Background: If the objective is to study the ability of the low-frequency (LF) axial transmission ultrasound method to discriminate fracture cases from controls, then one needs to compare the ROC (or AUC) for classifying cases and controls with and without V_LF in the model.

   The study focus has been modified according to other reviewer’s comments. Since the bone measurements were performed in 2006, the term of prediction seemed to overestimate the results. Thus, we focused on showing the associations between US and hip fractures. In this context, we do not see ROC necessary, but rather present the OR/HR values. We have changed the title and adjusted the aims and conclusion accordingly.

2. Page 3, Results: Note that OR is different from relative risk (RR). An OR of 3 doesn't mean that RR is 3.

   The abstract and results sections have been corrected.
3. The analysis of the retrospectively collected data was questionable since the V_LF data were collected in 2006 instead of the beginning of the study. It is not clear whether the difference in V_LF was caused by the difference in the status of fracture or vice versa.

   We acknowledge this limitation of retrospective setup. This has been included into discussion section as follows:

   The other limitation is the retrospective nature of the study. It is possible that the fracture events before the measurements caused the changes in bone properties (e.g. via altered loading conditions) and affected on outcome of the measurement.

4. Page 7, Statistical analysis: In my understanding, patients in group (c) also belong to group (b). Please clarify.

   All the hip fracture subjects were also included in Fx group. This is now clarified in the text. Also, a subject flow chart was included to clarify the patient flow as suggested by the other reviewer.

5. None was done to check the important model and distribution assumptions in the two-sample t-test and Cox proportional model. Violation of the model assumptions can lead to biased results.

   In our previous study (Määttä et al. 2012) we observed a higher hip fracture rate (9.8% vs. 6.3%) and higher mortality (50.8% vs. 25.1%) in those women who did not participate to baseline measurements in 1997 (non-home-dwelling or unwilling to participate) compared with the participants. However, in this study we only included to analysis those women who participated to measurements at 2006 and fracture occurrence was followed up from hospital discharge registers. Thus, we are not worried about the bias in models due to non-informative censoring.

   On the other hand, the increase in osteoporotic fracture risk related to higher age is well documented. The proportional hazards model assumes that the hazard ratio is constant over time. In our previous study on same population (Määttä et al. 2012) we observed an increase in hip fracture risk (HR =1.29; 95% CI 1.04-1.61) per one year increment in age at baseline (1997).

   In this study age was associated with higher hip fracture risk (OR =1.35; 95% CI 1.07-1.71) but not with general fracture risk. As one can see the values are not significantly different. Thus, it could be assumed that the hazard related to age is relatively constant during the follow-up period. In addition, the Cox models were adjusted for age to minimize the possible error.

   All the data were normally distributed. Therefore we used the independent samples t-test. Normal distribution of data is now clarified in text.
6. Page 8, line 11: "using Cox regressions" ----> "using the Cox proportional hazards model".

Corrected as requested.

7. Page 8, line 12: How did you handle those censored subjects due to death or loss of follow-up in the logistic regression analysis?

Thirty five (35) subjects died during the follow-up period (2006-2010). Nine of them had a fracture including one hip fracture. We did additional logistic regression analysis where we excluded these 35 subjects. The observed results were similar to those previously reported.

All fractures 1997-2010:

Neck BMD: OR=2.5 (p<0.001, 95% CI for OR 1.6-3.9)  
VLF: OR=1.3 (p=0.33, 95% CI for OR 0.8-2.0)

Hip fractures 1997-2010:

Femoral neck BMD: OR=4.1 (p=0.003 95% CI for OR 1.6-10.5)  
VLF: OR=3.3 (p=0.012, 95% CI for OR 1.3-8.4)

The result tables 4 and 5 have been updated.

8. Page 9, line 7: Is a difference of 0.4 years in age clinically meaningful?

We removed the text regarding age from text.

9. Page 9, line 8: Were the ages at the time of measurement or at the baseline (i.e., 1997)?

Ages are at the time of bone measurements (2006). This has been included into table header.

10. Page 21, Table 5: The numbers of NF subjects do not add up. NF n=409, 429, and 360 from the periods of 1997-2006, 2006-2010, and 1997-2010, respectively. Why was the number of NF subjects only 360 from 1997 to 2010?

Between 1997 and 2010 there were 360 females who did not suffer any fracture. Corresponding figures for periods 1997-2006 and 2006-2010 were 409 and 429, respectively. E.g. there were women who had a fracture before 2006 but not after 2006-2010. Thus, they were considered as non-fractured. The regression model was adjusted by previous fracture. A study flow chart also clarifies this.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.