Title: Quantitative ultrasound does not identify patients with an inflammatory disease at risk of vertebral deformities

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Author’s response to reviews: see over
Veghel, January 17th 2008

Dear dr. Norton,

First of all we would like to thank you to give us the opportunity to resubmit a revised version of our manuscript entitled: “Quantitative ultrasound does not identify patients with an inflammatory disease at risk of vertebral deformities”. (Manuscript ID: 1235782149150958). We thank the reviewer for his valuable comments that have been very helpful in improving the quality of this manuscript. We have addressed his comments point by point and we sincerely hope that we have adequately answered all the points that have been raised. All changes made to the manuscript are highlighted in red.

We hope it meets your requirements now and you will consider the revised version for publication in BMC Musculoskeletal Disorders.

Awaiting your reply,

Yours sincerely,

Caroline Heijckmann.
Major Compulsory Revisions:

1. It would be more informative if the authors could provide details of the study design, study subjects. How were they recruited or identified? We did leave out more detailed information for reasons of space. However, we agree that these data can be helpful so therefore we have inserted in the methods session (page 3): Between January 2002 and July 2003, all patients with inflammatory bowel disease or sarcoidosis who had a disease duration of at least one year, and attended the outpatient clinic of the University Hospital Maastricht, were asked to participate in this cross-sectional study. Sixteen patients with known causes of bone mass abnormalities, such as renal failure, thyroid dysfunction, alcoholism, long-term anticoagulant use and ankylosing spondylitis were excluded. Thirty-six patients were excluded because of the use of bisphosphonates or hormone replacement therapy.

2. Presumably the study was approved by an ethics committee. If that is the case, please state so. This was already stated in original manuscript in the last sentence of the paragraph on “Patients” (page 4, section Subjects and Methods).

3. More details of statistical analysis should be provided. For example, did the authors check for assumptions of their model of analysis? We have adapted the paragraph on statistics (please see page 5). To be clear (see also question 5 and 8) the purpose of the logistic regression analysis was to evaluate the strength of the association between the different measures (BMD–femoral neck or BMD trochanter or QUI) and the presence of a vertebral deformity and not to establish a predictive model.

4. What was the correlation between QUS and FNBMD. Is this correlation comparable to previous estimates from other studies? The correlation between quantitative ultrasound index (QUI) of QUS and BMD of the femoral neck in our study was 0.33 (p<0.001). This is comparable to other studies in post-menopausal osteoporosis (Nayak et al, Ann Intern Med 2006;144:832–84, CC ranged between 0.27 and 0.7) as well as to studies in IBD patients (Schwartz et al, Inflamm Bowel Dis 2005;11:749–754, CC 0.4 at either hip or spine); No studies with QUS have been performed in patients with sarcoidosis.

5. It is not clear what “three separate analyses” mean. Do the authors mean univariate analyses? We apologize that this part of the paragraph was unclear, and we have changed the text in order to clarify this section (please see page 5, statistics). As mentioned above we have used logistic regression analysis to evaluate the strength of the association between the three variables (BMD femoral neck or BMD trochanter or QUI) with correction for age and gender which were entered in the model as covariates. The analysis showed that, in contrast to BMD (FN or trochanter), QUI values were not significantly associated with having a vertebral deformity.
6. The expression of “per 1 SD T-score” (page 6) is rather odd, because the T-score is expressed per SD change from “young normal”. Therefore, SD of SD is difficult to understand. Please clarify! We apologize that this sentence is not clear to the reviewer. We would like to clarify in this sentence that the unit to which the OR relates is 1 unit change in T-score (= 1 SD change from “young normal”). We have changed this sentence in the text.

7. Patients with IBD may have greater risk of vertebral deformity. Moreover, men tend to have greater risk of vertebral fracture than women (32 % vs 14%), so sex could be an important confounder as well. It is strongly recommended that both sex and IBD should be taken into account in the analysis. In the logistic regression analysis, values were corrected for both age and gender. In our study population we did not find a significant difference in the prevalence of vertebral deformities between patients with IBD and patients with sarcoidosis (Sarcoidosis 21%, Crohn’s Disease 22% and Ulcerative Colitis 23%) so therefore we did not correct for this variable in the analysis. Our data on prevalence of vertebral deformities in sarcoidosis have been published recently (Heijckmann et al, sarcoidosis Vasculitis and diffuse lung diseases 2007;24:51-58); we have attached a PDF – file of this manuscript.

8. It seems clear from the authors’ data (Table 3) that hand QUS was not predictive of vertebral fracture. However, what happen if the authors consider both QUS and FNBMID in the same model, does QUS increase the fit of the multivariable logistic regression model? As discussed above the logistic regression analysis was not used to build a predictive model, but to evaluate the strength of the association between the different measures and having a vertebral deformity in order to study which measure can be used to identify patients likely to have a vertebral deformity. However, when both BMD – femoral neck and QUI are entered simultaneously in the regression analysis the respective OR’s are 1.81 (1.18 – 2.75, p = 0.006) for BMD-FN and 1.09 (0.77 – 1.56, p = 0.623) for QUI. However these analyses may be complicated by the fact that these variables are probably co-linear.

Minor Essential Revisions:

9. The word “risk”(vertebral deformity risk) in the Abstract is strictly incorrect, because the unit is odd (not probability of vertebral deformity). We agree with the reviewer that this phrase is strictly incorrect and we have changed the text of the abstract accordingly.