Author's response to reviews

Title: Time-course of Exercise and its Association with 12-Month Bone Changes

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Author's response to reviews: see over
Dear Dr. Graham,

Thank you for your response on our manuscript. Please find enclosed our revision, in which we have considered the comments given by the reviewers. A detailed list of actions taken during the revision is also provided.

We hope that the revised version of the manuscript is found suitable for publication in BMC Musculoskeletal Disorders.

Kind regards,

Riikka Ahola (née Heikkinen)
Corresponding author
Referee 1 (Katherine Brooke-Wavell):

We appreciate the further comments given by the reviewer.

A detailed list of actions taken during the revision:

Major revisions:

1. **Conclusions should be more precisely worded in both the abstract and discussion.** It is the number of high acceleration impacts during 6 months of training that was associated with 12 month bone change.

   We have now reworded the conclusions in the Abstract and Discussion as suggested.

2. **As analyses are cross-sectional it is more precise to refer to correlates rather than predictors of bone changes.**

   As suggested, we have now referred to correlates.

3. **Figure 1 does demonstrate the presence of outliers. Do these have a large influence on the correlation?**

   We fully agree that there is variation in the response variables with the existing sample size. Thus, the results should be confirmed in a larger study. However, the results might suggest that the highest response occurs within those with highest number of high impacts, even if the correlation coefficient remains only an estimate. The Figure helps the reader to consider the possible bias in the results.

4. **The first sentence of the discussion is too strong. This study does not demonstrate the time course or intensity of impact loading needed to stimulate and adaptive response. This sentence should be modified or deleted.**

   This sentence was totally removed and the first paragraph of discussion only gives the main finding.
A detailed list of actions taken during the revision:

Major comments:

In general, I'm happy with the corrections performed by the authors. Most of my previous concerns have been solved. The most critical aspect that remains is that the authors cannot completely account for carry over effects just by statistically adjusting the multiple linear regression models, because as recognized by the authors in the manuscript the osteogenic response to loading is not linear, i.e. the effect observed during the initial months are of greater magnitude than the effects observed between the 6 and 12th month (as reported in other studies where intermediate aBMD measurements were performed). Despite the explanations given by the authors, my concern about vitamin D status remains. This is due to the slow response of bone tissue to changes in calcium and vit D and also because there may interaction between exercise and vit D status. A control group would have help to account for these potentially confounding effects. The authors acknowledge that they have a control group: why not to report the changes in aBMD and geometrical variables observed the control group?

We agree with your concern. We have recently reported vitamin D status of these women, including also the control group (Vainionpää et al. 2009, Osteoporos Int, available Online First). Increases in vitamin D were found in six months followed by decreases in 12 months, which might support the interaction theory. However, there was no significant difference in vitamin D level between the high-impact exercise group and a control group over the trial. We think these changes relate to seasonal variation of vitamin D status that is common in the northern countries. It was also confirmed that the dietary calcium intake was within recommended levels. This is now considered in the Discussion.

The differences in various outcome variables between the exercise and control groups have been thoroughly analyzed and reported previously. Thus, to avoid duplicate reporting, we do not report the results of the control group in this paper.

Following concerns need specific response:

1) By looking at Figure 1 it is clear that 15-16 women (44-47% of the sample studied) did not increase their Trochanter BMD with the training program: why? This deserves some comments in the discussion. Was this pattern similar for the other correlations reported in Table 2? The non-responding women were always the same or this was a "random effect", i.e., a woman may respond in one region but not in another?

We included the women who completed the DXA/QCT scan and whom we had acceleration data, including non-compliants in exercise program. The non-responding women were the ones who had low compliance. It has been suggested that women at this age have around 0.5% (between 0.25-1%) loss in BMD per year (Vondracek SF et al. Pharmacotherapy 2009, Lauretani F et al. JBMR 2008, Kröger H et al. Osteoporos Int 1992), which was also seen in the control group subjects in our previous study (Vainionpää et al. 2005). Considering this, there was only one subject of active exercisers who did not
benefit. A similar pattern was seen in all measured regions. The non-responding women were the same in all measured regions. Additionally, there was some variation in the response variables with the existing sample size. Thus, the results should be confirmed in a larger study. While an overall treatment effect is small, it can have a significant impact on the development of fractures in population level (Wolff et al. 1999). This aspect has been commented in Discussion.

2) (In Fig. 1) Does it make sense to use women that did not increase or even had a reduction in their trochanteric aBMD to defend that daily number of impacts 0-6 months 5.4-9.2g has a positive influence on the enhancement of aBMD?

Please see the previous comment.

I have one suggestion and this is to report the correlation coefficients as a small "r", leaving the capital "R" to report the multiple regression coefficients.

This has been modified as suggested.
We appreciate the comments given by the reviewer.

A detailed list of actions taken during the revision:

Major Compulsory Revisions

In their responses to my initial comments the authors state ‘The cortical attenuation results of premenopausal women are now discussed’. However I was unable to find this new discussion in the revised manuscript. Please specify exactly what new information was included. This is important because the findings indicate that increased loading (0-3 mo) was associated with increased cortical vBMD but had no effect on cortical geometry. Even for the 0-12 month impact data the correlation coefficient appear stronger for cortical attenuation than any of the other bone geometry measures. This is interesting and warrant further discussion. Is it possible that exercise is having a greater effect on bone material properties (increased mineralization or reduced porosity) rather than geometry (or could the threshold level for adaptation differ for material vs structural properties)? However I note that cortical attenuation decreased in both the Ex and Con groups in their previous intervention paper so perhaps the higher number of impacts helped prevent the loss in vBMD (rather than increase it)?

We have now further elaborated the Discussion with this: “In this study we showed that six months of exercise were associated with mid-femur cortical geometric adaptation. Number of high impacts was even more strongly associated with cortical density evaluated as Hounsfield Units. This is contrary to previous studies, in which the exercise-induced improvement in bone strength has been caused by redistribution of bone rather than remineralisation [40, 44]. The relationship found in this study suggests that the higher number of high impacts may help prevent the loss in volumetric BMD”.

The authors report the average number of impacts at different acceleration levels from 0-3 and 0-6 months. Clearly the 0-6 data is going to be influenced by the 0-3 data so why not report the average impacts from 3-6 months and assess whether this was related to the changes in BMD, bone structure and strength?

We agree that this would be one way to analyze this data. Nonetheless, we considered that effects of progressive exercise are cumulative (i.e. 3-6 months exercise is affected by
0-3 months exercise). Thus we decided to use cumulative intervals 0-3, 0-6, and 0-12 months.

What was the rationale for only plotting trochanter BMD changes with the average daily number of impacts from 0-6 months. This figure is really not necessary.

This figure was included on request by another reviewer.

On P11 the authors state on several occasions that many of the results disappeared after adjusting for impacts at later months – but did this analysis also include all the other covariates listed in the statistical analysis section? In other words, was there a significant association between bone changes and impact loads for 0-3 and 0-6 month after adjusting for all covariates (except impacts at later months) that then disappeared after including impacts at later months. This is not clear in the results.

Yes, this is correct. The analysis included all other covariates. First we adjusted for all other covariates using stepwise criteria. Then, keeping the included covariates in the model, we adjusted for impacts at later months. First there was a significant association between bone changes and impact loads for 0-3 or 0-6 month when adjusting for all covariates (except impacts at later months) that then disappeared after including impacts at later months. We have now clarified this in Statistical methods and Results.

P14, line 1-2. Further discussion is needed as to why there were no relationships between the impact loads and the tibial bone changes. It is not enough to simply say that ‘these associations were site-specific.’ when referring to the mid femur. One could argue that the peak forces (loads) on the tibia would be greater than those imparted to the femur and so it seems odd that there was no effect at the tibia. It would be worth a sentence or two in the Discussion to explain these contrasting results.

We agree with the comment and this paragraph in Discussion has been modified. Impact loading was measured at the waist, close to the iliac crest, which may partly explain the lower sensitivity of the method to explain changes at the tibia.
Minor Essential Revisions

P4, last line. ‘Despite of objective..’ should be ‘Despite the objective…’

Modified as suggested.

P13, para 2, line 2-3. This sentence is not clear ‘… to a mechanically appropriate…’

This incomplete sentence has been corrected.

P13, para 2, line 5. Should this read ‘… achieved by reduced endocortical resorption and/or greater periosteal apposition’.

Modified as suggested.

P14, para 2. I would argue that there was very little difference in the DXA and pQCT results in this study. In fact contrary to the authors’ discussion (and the findings that there were no significant correlations with the pQCT tibial measures), it could be argued that perhaps the pQCT (at the tibial site at least) is not sensitive to detect changes in bone in response to loading?

We have now considered this in Discussion: “Additionally, there might be differences in the sensitivity of QCT method to detect changes in bone at different measurement sites”.

P15, line 6. ‘.. not able not…’ should be ‘.. not able to..’

Modified as suggested.