Author's response to reviews

Title: Tibolone inhibits bone resorption without secondary positive effects on cartilage degradation

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Author's response to reviews: see over
Dear editor of BMC Musculoskeletal Disorders,

Thank you for the very positive review of our manuscript.

We have corrected all of the comments for the reviewers, which have resulted in a clearer and more nuanced manuscript.

Please find a point-by-point rebuttal below.

We hope that by these changes our manuscript is acceptable for publication in BMC Musculoskeletal Disorders.

Sincerely,

Morten A. Karsdal

Reviewer 2:

All corrections had been accepted.

Reviewer 1:

**Reviewer's report:**
I am of the opinion that the authors have satisfactorily dealt with most comments. There are two exceptions

1. The magnitude of the difference in CTX2 is similar to many other interventions eg risedronate or strontium. It would help to have a comparison of the size of effect from these other treatments to further the discussion on power issues. In
addition, the authors currently state that the difference will become significant with a greater sample size. One cannot be certain that this will happen. The word ‘may’ should be used instead of ‘will’.

Thank you for this important comment. This discussion is important for the understanding and comparison of the results. We have added the following to the discussion.

In the present study the observed effect size of 2.5 mg of Tibolone was an increase of 19% [95% confidence interval -17%;+70%] in CTXII. This is in contrast to other interventions that all have shown a decrease in CTXII, e.g. risedronate a decrease of 30% [1,2], estrogen replacement therapy a decrease of 25% [3], strontium ranelate a decrease of 15-20% [4] and levormeloxifene with a decrease of 50% [5].

In addition, we agree that it is incorrect to state that the difference will become significant with larger sample size and accordingly have changed “will” to “may”.

2. It is foreseeable that the use of the term uncoupling will be controversial. While i would accept that the magnitude of change is different for bone versus cartilage this can imply many things eg sensitivity to change, measurement error, individual variation. I would only accept the use of the term uncoupling if the ratio of the bone to cartilage markers is significantly different between tibolone and placebo. Please provide this data or modify the title even more.

We acknowledge that the use of the term “uncoupling” is controversial, and as suggested by the reviewer we have omitted this term in the title.

3. Lastly, some discussion on where CTX2 is derived from would be useful eg discs, peripheral cartilage and bone.

Thank you for this important comment. It is indeed important with all biomarkers to discuss which are the signal joints. We have added a longer discussion on this subject in the discussion under limitations of the current study.
Biochemical markers of cartilage degradation measured in the systemic fluids, serum and urine, are the net results of the biological activity of all joints and tissues in which collagen type II present. CTX-II is generated by MMP activity [6] have been shown to be produced by catabolically stimulated articular cartilage, and present in damaged articular cartilage [7,8]. However, CTX-II may in addition be generated by the cartilage of non-synovial joints. The main contributors of cartilage degradation biomarkers have been shown to be; knees, hips, hands, vertebral facet joints in addition to spinal disc degeneration (DD) [9,10]. In addition, a smaller contribution of CTX-II may originate from the calcified cartilage in the subchondral bone area [11]. The contribution of each cartilage compartment to the total pool of cartilage degradation measured is important to further understand, for the interpretation of the effect on the total pool of any biochemical marker. Some insights into the relative contribution of the different joints to the total amount of CTX-II have been provided [9]. CTX-II was shown to be related to the number of joint affected, evaluated by radiological OA, in which generalised resulted in an approximately 100% increase in CTX-II [9]. In addition, CTX-II was very recently shown to predict medial knee articular cartilage loss evaluated by quantitative MRI [12]. With respect to the current study, each compartment may have contributed differently to the pool of CTX-II, also in response to therapy. Further research is needed to understand the effects of estrogen and estrogen related compounds on the individual joints.

Reference List


2. Garnero P, Bingham C., Aronstein W., Cohen S., Conaghan P., Cline G. et al.. Treatment with risedronate reduced urinary CTX-II, a specific biochemical marker of cartilage type II collagen degradation in a 24 month study of knee OA. ACR Abstract


12. Dam EB, Byrjalsen I, Karsdal MA, Qvist P, Christiansen C: Increased urinary excretion of C-telopeptides of type II collagen (CTX-II) predicts cartilage loss over 21 months by MRI. *Osteoarthritis Cartilage* 2008.