Author's response to reviews

Title: Tibolone inhibits bone resorption without secondary positive effects on cartilage degradation - suggestion of uncoupling of bone and cartilage effects

Authors:

Morten A Karsdal (mk@nordicbioscience.com)
Diana J Leeming (djl@nordicbioscience.com)
Inger Byrjalsen (ib@nordicbioscience.com)
Claus Christiansen (cc@nordicbioscience.com)

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Author's response to reviews:

Dear Editor of BMD Musculoskeletal Disorders

Thank you for the positive reply on our manuscript.

We have complied with all of the reviewers comments. This have resulted in a more clear and concise paper.

The changes are described point-by-point below.

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

Sincerely,

Morten A. Karsdal, PhD, corresponding author

Reviewer 1:

1) Tibolone is described as having estrogenic, androgenic and progestogenic properties.

However in the conclusion, it is described as a SERM.

We regret this mistake. We have corrected this mistake throughout the manuscript.

2) The differences between tibolone and SERMs on bone and cartilage markers can however not be interpreted on assumption of a SERM effect. Indeed, tibolone is not selective for the estrogen nor for testosterone or progesteron
receptors

We regret this confusion. We have now described in the discussion that the effects observed by Tibolone is a combination of effects on this range of receptors.

3)
Specific remarks
Introduction
Par 2: a cause-effect relation between OA after menopause and increased bone resorption has not yet been demonstrated. The authors should put this statement in a more careful context with some discussion of the literature.

Thank you for this comments. We have corrected this wording into a more suggestive nature. We have in addition added some references suggesting these potential cause-effects.

4)
Par: “cartilage health”: please specify

Thank you for this clarifying comment.

We have clarified the terminology cartilage health, as the combination of normal bone and cartilage turnover.

5)
Please add reference of effect of tibolone on BMD (e.g. Geusens et al)
Give references about tight coupling of bone and cartilage turnover. Cite also references that indicate an inverse relation between osteoporosis and osteoarthritis

We have added the suggested reference, and further references and discussed the tight coupling between bone and cartilage turnover.

Major points:
- I am unhappy with the broader view in the discussion and particularly in the title: the title must focus on the results of tibolone on bone and cartilage degradation, and not "some but not all estrogen like molecules have both bone and cartilage protective effects: suggestion of uncoupling of bone and cartilage effects: this title can only be used when several estrogen-like molecules are tested!

We regret this lack of clarity.
We have corrected the title accordingly to, “Tibolone inhibits bone resorption without secondary positive effects on cartilage degradation - suggestion of
uncoupling of bone and cartilage effects

"and have in more details discussed that the effect of tibolone is the combination of the effect on estrogen, testosterone and progesterone receptors. This is in the text compared to the previous described positive effect of some SERMS and HRT.

- in the paper, the authors give the impression that the use of estrogen like molecules are associated with low bone and cartilage breakdown: however, the data on cartilage breakdown are not overwhelming, depending on a small number of intervention studies and further on case-control studies. this should probably be mentioned in the discussion.

We agree. We have modified the discussion accordingly, and induced the important recent WHI study describing significant less joint replacement in women taken estrogen. We have highlighted that currently there are no randomized clinical trials focused on documenting this effect, which is needed to substantiate the current research and following speculations.

Minor points:
- first sentence abstract: postmenopausal osteoporosis is associated with increased bone resorption and increased cartilage degradation: increased cartilage degradation is characteristic for osteoporosis?????

We have corrected this sentence which lacked clarity.

- no effect on cartilage degradation: when looking at figure 2, I have the impression that CTX2 is elevated (not significant): suppose a larger group of patients was tested, can it be imagined that the changes in CTX2 were significant? the authors should probably mention the trend to increase in their results section, and discuss it in their discussion.

We completely agree but at first did not want to overstate this. We have altered this discussion accordingly.

- introduction: sentence 2: OA is a progressive degeneration of articular cartilage and joint space narrowing: but also by osteophytes, an omission!

We have included osteophytes. Than you for pointing out this embarrassing mistake.

EDITORIAL COMMENTS

Please move your "Conflict of Interest" statement to the end of the manuscript, just before the reference list and re-name it "Competing Interests", and add an Authors’ contributions and Acknowledgements sections, which should comply
with the following guidelines:

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This has been carefully stated in the materials and methods sections.

As described in the original publication, [21], after being introduced thoroughly
about the trial, participants gave their informed consent to participate (Helsinki
Declaration II). The study was approved by the ethical committee of Copenhagen
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evaluation of quality/degradation of sample over time. We would invite you to
discuss how sample degradation might affect your results in the discussion of the
submission.
We have in more details in the discussion stated the potential problems with sample analysis.

The reason for the re-analysis is the increased attention drawn to the tight coupling between bone resorption and cartilage degradation. Several publication have shown effect of SERM end estrogen like compounds on both CTX-I and CTX-II. We though this was an excellent opportunity to reanalysis of the trial to further investigate and understand the coupling between bone and cartilage degradation.