Author's response to reviews

Title: 1,25-Dihydroxyvitamin D3 prevents bone loss of the secondary spongiosa in arthritic rats by an increase of bone formation and mineralization and inhibition of bone resorption

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Version: 4 Date: 26 August 2014

Author's response to reviews:

Dear Prof Ali Mobasheri, dear Dr. Reynaldo R. Aldea Jr.,

Herewith we send you the revised version of our manuscript entitled

1,25-Dihydroxyvitamin D3 prevents bone loss of the secondary spongiosa in arthritic rats by an increase of bone formation and mineralization and inhibition of bone resorption

with the hope that is now suitable for publication in BMC Musculoskeletal Disorders.

The changes made in the manuscript were marked in red colour and explained in the cover letter.

Sincerely

Peter Oelzner

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Reviewer's report
Title: 1,25-Dihydroxyvitamin D3 prevents bone loss of the secondary spongiosa in arthritic rats by an increase of bone formation and mineralization and inhibition of bone resorption

M&M

1. You mentioned that the ethical guidelines for experimental investigation in animals were used and all procedures complied with the regulations of the Thuringian Commission for Animal Protection. Please add a sentence representing the approval of your local ethics committee.

We have included the sentence:
“The approval of our local ethics committee was obtained for our study.”
at the end of the part “Arthritis induction” of the Methods section.

2. Why did you start with a diet containing vitamin D before arthritis induction?

The rationale for starting with a diet containing vitamin D before arthritis induction was presented after sentence 1 of the part “Arthritis induction” of the Methods section.

“Because of the complex regulation of vitamin D metabolism including both a strongly regulated renal synthesis of 1,25(OH)2D3 and a substrate dependent 1,25(OH)2D3 synthesis in osteoblasts and immune cells [13-15, 19], 1,25(OH)2D3 effects could also be influenced by vitamin D intake. To keep the influence of vitamin D intake on the results of our experiment constant, a diet containing a physiological and standardized concentration of vitamin D was started in arthritic animals before arthritis induction and also in healthy animals.”

3. Why did you inject Group 1 and 2 before AIA induction?

The rationale for starting injection of 1,25-Dihydroxyvitamin D3 before AIA induction was presented after sentence 3 of the part “Drug administration” of the Methods section:
“The time point to start 1,25(OH)2D3 application in our experiment three days before AIA induction was determined by both using more a therapeutic than a prophylactic regimen of 1,25(OH)2D3 administration and to achieve a complete treatment effect in the early acute phase of AIA. At this time point the immunologic changes characteristic for AIA were established [36, 37]. On the other hand, regarding the time course of AIA with an early acute phase with high disease activity and a longer chronic phase with lower disease activity we targeted a complete treatment effect in the early acute phase of the arthritis.”

4. Did the healthy animals also receive this diet?

Both healthy and arthritic animals received a diet containing vitamin D. The answer was presented after sentence 1 of the part “Arthritis induction” of the Methods section (see above).

5. Did you check the vitamin D serum levels throughout the experiment?

The serum levels of vitamin D were not measured throughout the experiment. This sentence was inserted at the end of the part “Drug administration” of the Methods section:

6. "Preparation of bones" should precede "Histopathologic assessment of inflammation and joint destruction"

The sequence of the parts “Preparation of bones” and “Histopathologic assessment of inflammation and joint destruction” was changed in the Methods section as the reviewer indicates.

7. The figures should appear in an ascending sequence in the text. Figure 5 should not be mentioned before figure 4.

The sequence of the description of the results in the part “Influence of AIA on periarticular and axial bone (secondary spongiosa)” was changed so that the figures appear in an ascending sequence in the text as indicated by the reviewer.

8. Please describe the score used in figure 2B (0-10) more detailed.

The histopathologic score in the figure was described more detailed in the legend with hyperlink to the detailed description in the methods section. An additional description was included in the part “Influence of 1,25(OH)2D3 therapy on arthritis severity” of the results section.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer’s report
Title: 1,25-Dihydroxyvitamin D3 prevents bone loss of the secondary spongiosa in arthritic rats by an increase of bone formation and mineralization and inhibition of bone resorption
Version: 3 Date: 24 July 2014
Reviewer: Thomas Pufe

Reviewer's report:
Minor essential Revisions:
in general well prepared study the manuscript would benefit from mentioning the role of ROS in AIA in the introduction chapter - please cite Wruck et al. ARD 2011;70:844-50

As the reviewer indicates, regarding the importance of reactive oxygen species in AIA, the following sentence were inserted after sentence 2 of the introduction chapter:

“Furthermore, the finding that the knockout of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that maintains the cellular defence against oxidative stress, in mice with antibody-induced arthritis was associated not only with an increase in cartilage destruction but also with a high number of spontaneous fractures underlines the importance of reactive oxygen species for bone damage in arthritis models [12].”

The paper of Wruck et al. ARD 2011;70:844-850 was included as reference number 12 and all references from reference number 12 got new numbers as well in the text as in the reference section.

Level of interest: An exceptional article
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests