Author's response to reviews

**Title:** Time Course of 1,25-(OH)2D (Vitamin D) as well as PTH (Parathyroid Hormone) during Fracture Healing of Healthy and Osteoporotic metaphyseal human Bone

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**Author’s response to reviews:** see over
Dear Ladies and Gentlemen,

Thank you very much for reviewing our manuscript:

„Time Course of 1,25-(OH)2D (Vitamin D) as well as PTH (Parathyroid Hormone) during Fracture Healing of Healthy and Osteoporotic metaphyseal human bone“

With this letter we want to answer the comments of the three reviewers.

First of all we want to point out that we are very thankful for the reviewers comments on our manuscript.

Coming to Reviewer 3 in a first point we are sorry about the fact that we mixed up the 25 (OH) VIT D3 with 1,25-(OH)2D. We did investigate on 25 (OH) VIT D3. To prove this we uploaded our lab investigation plan and sheet.

So we change the title of the manuscript in:

**Time Course of 25(OH)D₃ Vitamin D₃ as well as PTH (Parathyroid Hormone) during Fracture Healing of Healthy and Osteoporotic human Bone**

Reviewer: Richard Stange

1. Thank you very much for providing us with the literature of Meller et al. We are glad about those two papers as they fit perfectly good to discuss our results. We integrated those in our manuscript

2. We are sorry that we cannot provide a control group without fractures, we now that this is a lack in our study. Therefore we are also very thankful for the works of Meller et al. We used these to discuss the different findings with a non-fracture control group and our results. We had to accept it as we hardly see patients without fractures in our trauma and orthopaedic surgery department.

3. A control group of young patients was not in our study design. In our study group we only investigated on patients older than 50 years. So we cannot build a control group out of a younger population to discuss this out of our data. We focused on older patients with and without osteoporosis but we know that it would be interesting to have this control group. In our study group we detected no differences.

4. We worked over table Nr. 1 and added more facts to give better information about our matched pairs concerning BMI, T-Score and lab values

5. All patients who where matched had no history of specific medications and did not receive any afterwards
Reviewer: Britt Wildemann

1. Thank you very much for this comment. We are sorry about the misunderstanding presentation of our results. There are no significant changes in the different groups. We corrected this in the whole manuscript.

2. This is right; we did change this in the text

3. We are sorry about this mistake, we corrected it

4. We appreciate this hint and added two references from Partridge et al and Gagnon et al

5. Our patients did not receive any specific osteoporosis medication in the period the blood samples were taken

6. At the Laboratory Limbach Heidelberg the following kits were used for the PTH and Vit D3 detection: PTH (Draft) cobas®, Roche Diagnostics GmbH, Mannheim Germany and Vitamin D3 (25 OH), cobas®, Roche Diagnostics GmbH, Mannheim Germany. The Datasheets were uploaded in the file manager for your information and we added it in the M&M text

7. We corrected this in the text

8. We did put this into the table 1

9. We put a new table 1 into the manuscript with the missing patient included

10. Thank you very much for his hint, we put in the missing unit ng/ml

11. „kontr“ was corrected in „cont“ in the figure legend

12. We corrected this in the figures

13. This is an important point we missed to discuss. There can be different findings of expression in the human blood samples caused by different fracture localisations, methaphysis versus long bone, tibia head versus distal radius as there are different bone masses that are injured and also depending on the way of fixation with internal devices that do affect the methypseal bone matrix more than a plate for example. That’s why we built matched pairs with same fracture regions and fixation methods to reduce the influence of these points.
Reviewer Koshi Kishimoto:

1. We are sorry about mixing up 25 (OH) VIT D3 with 1,25 (OH) VIT D2. We did investigate on 25 (OH) VIT D3. Prof. Schmidt-Gayk out of our Study Group built up the lab plan (we uploaded a lab sheet to prove this). We corrected this in the whole manuscript

2. We had no patients with decreased renal function in our study groups; this was controlled by preoperative lab samples

3. Osteoporosis was, following the WHO and the DVO (Dachverband Ostologie e.V. Germany) guidelines evaluated by standardized questionnaire and DXA, following this standard we had a group with osteoporosis defined by T-Score and one without. We know that it is discussed, that the fracture alone in older patients after low energy trauma can be enough evidence for osteoporosis

4. To give more information we revised table 1 and put in more data

5. We changed our discussion to point out in a clearer way that we did not find significant changes in our data

6. Thank you very much for his point, we corrected the figures as mentioned