Author's response to reviews

Title: Osteoporosis Imaging: Effects of bone preservation on MDCT-based trabecular bone microstructure parameters and finite element models

Authors:

Thomas Baum (thbaum@gmx.de)
Eduardo Grande Garcia (grande@tum.de)
Rainer Burgkart (burgkart@tum.de)
Olga Gordijenko (o.gordijenko@campus.lmu.de)
Hans Liebl (lieblhans@googlemail.com)
Pia M Jungmann (pia.jungmann@tum.de)
Michael Gruber (michael.gruber@meduniwien.ac.at)
Ernst J Rummeny (ernst.rummeny@tum.de)
Simone Waldt (simone.waldt@tum.de)
Jan S Bauer (jsb@tum.de)

Version: 3
Date: 20 March 2015

Author's response to reviews: see over
München, 20.03.2015

Resubmission of the research article

“Osteoporosis Imaging: Effects of bone preservation on MDCT-based trabecular bone microstructure parameters and finite element models”

Dear Editor,

Please find attached our revised manuscript entitled “Osteoporosis Imaging: Effects of bone preservation on MDCT-based trabecular bone microstructure parameters and finite element models” for publication as Research Article in BMC Medical Imaging.

We would sincerely like to thank you and your reviewers for your excellent work on our manuscript, which has substantially improved the quality of the manuscript. We have addressed the comments in the accompanying letter, and we have also submitted an annotated manuscript clearly indicating the changes performed. In addition a clean version of the manuscript is enclosed.

I confirm that each person listed as an author has participated in the study to a significant extent. All authors state no conflict of interest. This work was supported by grants of the Deutsche Forschungsgemeinschaft (DFG BA 4085/2-1 and BA 4906/1-1).

Thank you for considering the revised manuscript.

Sincerely,

Thomas Baum, MD
Accompanying letter answering the editor’s and reviewers’ comments point-by-point

Editor’s and reviewers’ comments in regular font and author response in italics:

**Editor’s comments to Author:**
Requesting name of ethics committee **Full name of IRB - Please update your ethics statement to include the name of the ethics committee that approved your study.**  
*E1: The full name of IRB – Ethikkommission der Fakultaet fuer Medizin der Technischen Universitaet Muenchen - was added to the Methods section.*

**Referee(s)’ Comments to Author:**

**Reviewer: 1**
The authors investigated the potential effect of bone preservation of up to 6 months by freezing samples or fixation in formalin on bone microarchitecture. Using MDCT, FEM, and mechanical testing the authors could not find a significant difference in bone microarchitecture, FEM results, and mechanically tested failure load within each preservation method or between the two. Thus, the authors conclude that both methods are suitable preservation methods for bone. This paper will be beneficial to readers considering the large number of studies performed of preserved bones. Overall, it is generally well written. However, the Results and Discussion section are combined, which is unusual. It is recommended to separate those sections formally. Furthermore, there is specific information missing from the Results section, such as a table for failure load. Please add these details. Finally, the Discussion repeats introductory material and is unnecessarily long. Please write it more concisely.  
*R1.1 Results and Discussion were presented as separate sections in the revised manuscript as suggested by the reviewer. Failure load values were added as Table in the revised manuscript. The Discussion section was shortened as suggested by the reviewer.*

**SPECIFIC COMMENTS**
The title could be more specific: e.g. “bone preservation” instead of “tissue preservation”.  
*R1.2 Revised as suggested by the reviewer.*
Please add figure captions.

*R1.3 Figure captions were added as suggested by the reviewer.*

Considering the already low number of samples/donors why were the vertebrae harvested not the same for each cadaver? It is states that 4 vertebrae where harvested between the 5 and 12 thoracic vertebra. Why not always harvest the same one: e.g. 5-8?

*R1.4 It was not possible to receive the same vertebral levels from all donors from the pathologists, since vertebrae of each donor were rather randomly distributed to different research groups.*

Did all donors have osteoporosis? It is only stated that all bone diseases but osteoporosis were an exclusion criterion but not whether or not the donor actually had OP. Please indicate whether bones were from donors with OP.

*R1.5 The female donor aged 74 years had osteoporosis, the two men aged 46 and 62 years had no osteoporosis. We thought the inclusion of normal and osteoporotic donors to be more representative for this study. A corresponding statement was added to the Methods section.*

I assume that uniaxial compression tests were performed. Please clarify.

*R1.6. This point was clarified as suggested by the reviewer.*

There is a difference between spatial resolution and voxel size. I assume the 250x250x600µm³ is voxel size, not spatial resolution. Please clarify.

*R1.7 The interpolated voxel size was of 146 x 146 x 300 µm³, while the real spatial resolution, as determined at ρ50 of the modulation-transfer-function, was 250 x 250 x 600 µm³. A corresponding statement was added to the Methods section.*

Please justify the ROI placement, and why the entire vertebral body not used? The reference to the study using this protocol is not sufficiently informative. Please give a brief reasoning for this decision. This is particularly important as the FEM was applied to the entire vertebral body while the other parameters were extracted from only that 15 slice ROI.

*R1.8 ROI placement was performed similar to clinical QCT-based BMD measurements (e.g. the QCT review article by Adams (reference 5)). By definition, only BMD measurements in the trabecular compartment (central, ventral part) are used for QCT-based osteoporosis diagnostics (e.g. see manufacturer Mindways QCT). A corresponding statement was added to the Methods section.*

What is meant by “ROI were drawn in the phases of the calibration phantom”? Please clarify.
**R1.9** ROIs were drawn in the phases of the calibration phantom in the MDCT images to convert BMD-values in HU into mg/cm³ calcium hydroxyapatite. A corresponding statement was added to the Methods section.

The German word “Probe” translates into “sample” and not “probe”.

**R1.10** The wording was corrected.

There are several grammatical mistakes in this paper. For example, in the Methods, page 5, line 17-20 is unclear. Thorough editing of grammar would be beneficial.

Several times context was not explained very efficiently or even confusing. E.g. page 4, line 9 “…BMD values of patients with and without OP fracture overlap…” could be restated more elegantly.

**R1.11** The wording was changed accordingly.

Page 4, line 8: DXA measures 2D areal BMD (aBMD) while CT measures 3D volumetric BMD (vBMD). This is not distinguished in this paper, but should be.

**R1.12** A corresponding statement was added to the Introduction section.

Osteoporosis is characterized by a reduction in bone mass, which in turn reduces bone strength. This is not clearly defined on page 4, line 2 (as well as other locations such as the Abstract). Please clarify.

**R1.13** The wording was changed accordingly.

At several occasions the following reference is used: “These computational methods” which is clearly refereeing to more than one previously introduced method. However, the only method introduced prior to this statement is FEM. Please correct.

**R1.14** We added the trabecular bone microstructure analysis so that computational methods are applicable to trabecular bone microstructure analysis as well as FEM.

Preference is to use “mechanical testing” instead of “biomechanical testing”.

**R1.15** The wording was revised accordingly.

“Destructive biomechanical testing” could be rephrased as “mechanical testing to failure”.

**R1.16** Rephrased as suggested by the reviewer.

Vertebral body vs. vertebra: It would be more accurate to state the ROI placement and Figure 2 (FEM) are in the vertebral body.

**R1.17** The wording “vertebral body” was used in the Methods section accordingly.
Reviewer: 2

Discretionary Revisions:

Please, add the reconstructed slice thickness value ranges in the Methods.

R2.1 The slice thickness was 600 µm.

In order to facilitate the interpretation of the results presented in the 2 Tables, the authors should consider to add -as a table footnote-, the spelling of the abbreviations used.

R2.2 Footnotes were added to Table 2 and 3 as suggested by the reviewer.