Author’s response to reviews

Title: Improving the prediction of the trabecular bone microarchitectural parameters using dental cone-beam computed tomography

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Author’s response to reviews:

First, we would like to express our sincere appreciation to the reviewers for their detailed examination of our manuscript in addition to their comments and suggested corrections. Many valid points were raised, which have helped us to present our study more clearly. The manuscript has been revised accordingly; all changes are in boldface and underlined in the revised manuscript, and our responses to the reviewers’ comments are given on a point-by-point basis in this document. This revision has been carefully edited by Wallace Academic Editing.

Editor Comments:

Please find the reviewer's comments below and attached. In addition, we have the below editorial requests that we would like you to address:

- Abstract: Please change "Objective" to "Background" (heading)
  Reply: We have modified accordingly.

- Main text: Please change "Materials and Methods" to "Methods" (heading)
  Reply: We have modified accordingly.

- Declaration (ethics approval and consent to participate): What you have written here is irrelevant. Please write "Not applicable".
  Reply: We have modified accordingly.
Reviewer reports:
Ruben Pauwels (Reviewer 1): I strongly suggest that the authors provide a point-by-point response to the reviewers' comments, and clearly highlight the changes made to the manuscript in accordance with these comments.

As such a response was not available at this stage, the following comments are the result of an independent assessment (i.e. not a follow-up of any comments that may have been made previously).

GENERAL COMMENTS
- The topic is of interest, as the processing of images for microstructure analysis is essential (esp. in noisy, unsharp CBCT images) and often overlooked
Reply: Thank you for this comment. We agree with the reviewer’s view point.

- The sample size is relatively large compared with similar studies, resulting in high statistical power
Reply: Thank you for this comment.

- Only a single CBCT unit and exposure setting was used, but this is a common limitation.
Reply: Yes, we agree with the reviewer’s point.

SPECIFIC COMMENTS
- A single ball still allows for multiple degrees of freedom. For marker-based registration, at least 3 balls would be needed. For automatic registration, a marker would not be needed
Reply: This study did not use the automatic registration tool. Instead, we placed a dental composite resin ball on the surface of the bone specimen to enable the subsequent determination of the position of the composite resin ball in the dental CBCT and micro-CT images. We identified the central point of the surface and segmented a 4 × 4 × 10 mm3 cuboid from the central point inward to the bone specimen, and the cuboid served as the ROI (Figure 1). We have added an explanation of this to the manuscript. We appreciate your suggestion.

- Please mention the exposure time that was used
Reply: We have modified accordingly. Thank you for this comment.

- The scan conditions were far from realistic. Not only is the SNR at the detector much higher for such a small bone sample than an actual patient, the scan was quasi scatter-free and without beam hardening or motion. For every factor except the last one, the set-up can be adjusting by placing the sample in a head-equivalent phantom or container. The statement in discussion that "Some studies have indicated no significant differences between dental CBCT imaging settings with water and the settings without water [24]." is not entirely valid, because the study (not studies) in question notices a large difference in SNR between protocols, and rather considerable effects of water on BS and connectivity. Finally, the study does not mention the size of the water container.
Reply: The scan conditions for the use of dental CBCT in the present study were based on that commonly used in clinical dentistry. In addition, we have revised the manuscript. Thank you for the comment.

- The registration of the images should be explained in detail. ImageJ does not have a built-in automatic registration tool. Was a third-party plugin used? Was manual setup or adjustment needed? Which registration metric was used (e.g. mutual information)?
Reply: This study did not use the automatic registration tool. We have added an explanation regarding the registration of the images. Thank you for the suggestion.

Etc
- It is somewhat unclear why a ROI was used rather than the entire sample. The latter option would avoid the need for registration altogether because the measured parameters should be independent from the sample orientation
Reply: We used the 4 × 4 × 10 mm³ cuboid as the ROI mainly because the diameter and length of the artificial tooth root used for evaluating the bone mass and quantity before the dental implantation were 4 and 10 mm, respectively. Therefore, our choice has more clinical significance than analyzing the entire sample. We have added an explanation regarding the reason for using this size of ROI in the revision. Thank you for the comment.

- Sharpening and despecking/denoising are general terms. Please mention exactly the types of convolutions or other processing steps applied in Group 2
Reply: In the experiment, the ImageJ software was used in its default setting for image processing. We browsed the official website of ImageJ, which provides the following information: “sharpen: Increases contrast and accentuates detail in the image or selection, but may also accentuate noise. This filter uses the following weighting factors to replace each pixel with a weighted average of the 3 × 3 neighborhood. Despekable: This is a median filter. It replaces each pixel with the median value in its 3 × 3 neighborhood. This is a time consuming operation because, for each pixel in the selection, the nine pixels in the 3 × 3 neighborhood must be sorted and the center pixel replaced with the median value (the fifth). Median filters are good at removing salt and pepper noise.” Accordingly, we have revised this part of the manuscript to enable readers to replicate our research method. As researchers with backgrounds in dentistry, we believe this information is sufficient for other dentists to understand and reproduce our experiment. If the reviewers think this is still insufficient, please kindly suggest how it should be revised. We appreciate your suggestion.

- Please add more details regarding the radius/area used for local thresholding in Group 3
Reply: Threshold levels were calculated for each individual slice. Similarly, we used the default parameters in ImageJ; please refer to the previous reply.
https://imagej.nih.gov/ij/docs/guide/146-29.html

- There are 15-20 types of automatic thresholding, which was used for each group?
Reply: The automatic thresholding employed in this study was the default method of ImageJ, which is the IsoData method according to the official website of ImageJ. We also used the default parameters, as explained in the previous reply.

The description on the ImageJ webpage is as follows:
Iterative procedure based on the isodata algorithm of: Ridler, TW & Calvard, S (1978), "Picture thresholding using an iterative selection method", IEEE Transactions on Systems, Man and
The procedure divides the image into object and background by taking an initial threshold, then the averages of the pixels at or below the threshold and pixels above are computed. The averages of those two values are computed, the threshold is incremented and the process is repeated until the threshold is larger than the composite average. That is, \( \text{threshold} = (\text{average background} + \text{average objects})/2 \).

Several implementations of this method exist. See the source code for further comments.  
\url{http://imagej.net/Auto_Threshold#Default}

- The rationale and clinical applicability of Group 4 is somewhat questionable. The BMD scale is not intended to differentiate air as being BMD<0. Furthermore, the use of an appropriate thresholding method would imply that the specific removal of air voxels is unnecessary. From the figure, it is clear that this method results in approx. half of the histogram to be cut off, and the threshold to be slightly above this cut-off point. Would a global thresholding with the same cut-off value not yield the exact same result? Would an erosion (or multiple erosion steps) yield the same or a similar result without the need for a BMD phantom (which cannot be routinely used in clinical CBCT due to the small FOV)? Perhaps Group 5 can be added by including a few erosion steps (determined empirically) after binarisation.

Reply: The BMD scale is indeed not intended to differentiate air. However, during the experiment, this method (Group 4) was used to effectively increase the predictive power of dental CBCT for estimating trabecular bone microarchitectural parameters. Because three peak values were observed in the histogram of the overall image density, we expected that removing the peak values that were most unlikely to be cancellous bone images (i.e., images with the lowest density, namely the air) would be helpful for binarization. In the present study, we did not examine whether global thresholding could yield the same or similar result and did not investigate the influence of erosion (or multiple erosion steps) on the results. Thank you for the valuable suggestion. We will consider this suggestion in our future work.

- Only a few structural parameters were used. In literature, others such as BS/TV, fractal dimension, and connectivity density are often reported as well.

Reply: The literature has reported numerous trabecular bone microarchitectural parameters. This study adopted BV/TV (%), TbTh (mm), TbN (1/mm), and TbSp (mm) for assessment indicators, following Bouxsein et al. [1], because they are the most representative parameters for trabecular bone microarchitecture.

Reference

- It is not entirely reasonable to compare microCT and CBCT values directly; due to the large difference in resolution, one can not expect a 1:1 agreement between structural parameter values. I suggest to report the values as such (without t-test) and focus on correlation as your main outcome.

Reply: Micro-CT has been the gold standard for assessing trabecular bone microarchitectural parameters. Many studies have investigated the correlation between using micro-CT and dental CBCT for assessing trabecular bone microarchitectural parameters, especially BV/TV and TbTh. These studies have verified that the two methods may be correlated with each other.
However, because of the poor resolution of dental CBCT images, the trabecular bone microarchitectural parameters cannot be accurately measured. This study aimed to achieve an accurate measurement through the use of CBCT. Specifically, after the images were processed, a higher correlation could be achieved to predict the trabecular bone microarchitectural parameters. This would enable dentists to use dental CBCT images in the future to more accurately determine the bone mass and quantity of jawbones in patients undergoing dental implantation. We have added a detailed explanation in the first paragraph of the discussion section. Please review our description regarding the innovation and contribution of this study, and thank you for your suggestions.

- Table 3 seems to omit several studies; furthermore, the purpose of this table within the scope of this study is somewhat unclear. I suggest removing it or making it a supplementary file
  Reply: We agree with your comment. We have removed Table 3 in the revised manuscript. Thank you for the suggestion.

Reviewer 2 (Reviewer 2): PEER REVIEWER COMMENTS: To view the full report from the academic peer reviewer, please see the attached file.

REVIEWER COMMENTS FROM REPORT: The statement "the estimates of the four trabecular bone microarchitectural parameters obtained through dental CBCT were significantly different from those obtained through micro-CT" seems to contradict the subsequently described results, in which there was significant correlation between some preprocessing CBCT and microCT.
  Reply: According to the results of our experiment, the absolute values of the trabecular bone microarchitectural parameters obtained through CBCT were indeed different from those obtained through micro-CT. However, image preprocessing could improve the predictability of dental CBCT for the trabecular bone microarchitectural parameters. We have modified the description in the abstract. Please refer to the revised content.

It seems that the conclusion does not accurately reflect the results, in which air removal underestimates trabecular bone volume, for example.
  Reply: We have modified some statements in the conclusion. Please refer to the revised content.

There are numerous typos throughout the article. The work should undergo more thorough proofreading for this.
  Reply: This study was proofread by a professional Internet-based English editing service before submission. This revised version has been proofread by an English editing company, focusing on grammar errors and typos. Thank you for the suggestion.

REQUESTED REVISIONS:
Clarify the interpretation of the results and corresponding conclusion.
  Reply: We have revised the interpretation of the results and corresponding conclusion for greater clarity. Please refer to the revised content. Thank you for the suggestion.

ADDITIONAL REQUESTS/SUGGESTIONS:
Better emphasize what is novel about this work, since similar things have been published.
  Reply: Although other studies have demonstrated the ability of CBCT to obtain the trabecular bone microarchitectural parameters and compared CBCT with micro-CT, few studies have undertaken detailed discussions concerning processing CBCT images. The novelty of this study, therefore, was the
discussion of CBCT image processing, which we proposed could improve the ability to predict the trabecular bone microarchitectural parameters. We have revised the first paragraph of the discussion section, adding several new statements to emphasize the novelty of this study. Thank you for the suggestion.