Effect of low-dose CT and iterative reconstruction on trabecular bone microstructure assessment

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ABSTRACT

The trabecular bone microstructure is an important factor in the development of osteoporosis. It is well known that its deterioration is one effect when osteoporosis occurs. Previous research showed that the analysis of trabecular bone microstructure enables more precise diagnoses of osteoporosis compared to a sole measurement of the mineral density. Microstructure parameters are assessed on volumetric images of the bone acquired either with high-resolution magnetic resonance imaging, high-resolution peripheral quantitative computed tomography or high-resolution computed tomography (CT), with only CT being applicable to the spine, which is one of clinically most relevant fracture sites. However, due to the high radiation exposure for imaging the whole spine these measurements are not applicable in current clinical routine. In this work, twelve vertebrae from three different donors were scanned with standard and low radiation dose. Trabecular bone microstructure parameters were assessed for CT images reconstructed with statistical iterative reconstruction (SIR) and analytical filtered backprojection (FBP). The resulting structure parameters were correlated to the biomechanically determined fracture load of each vertebra. Microstructure parameters assessed for low-dose data reconstructed with SIR significantly correlated with fracture loads as well as parameters assessed for standard-dose data reconstructed with FBP. Ideal results were achieved with low to zero regularization strength yielding microstructure parameters not significantly different from those assessed for standard-dose FBP data. Moreover, in comparison to other approaches, superior noise-resolution trade-offs can be found with the proposed methods.

Keywords: Computed tomography, iterative reconstruction, osteoporosis, trabecular bone microstructure, fracture risk, low-dose CT

1. INTRODUCTION

Osteoporosis is a disease that compromises bone strength and causes an increased fracture risk of the bone.\textsuperscript{1} Because osteoporotic fractures are a major cause of morbidity and disability in older people, such fractures impose a considerable economic burden on health services worldwide.\textsuperscript{2}

Traditionally, osteoporosis diagnoses relied on dual-energy X-ray absorptiometry (DXA) for the measurement of bone mineral density (BMD). However, BMD values of patients with and without osteoporotic fractures statistically overlap. Therefore, considerable research has been undertaken to develop non-invasive imaging techniques focusing on the assessment of cortical and trabecular bone microstructure to improve fracture risk predictions. It has been demonstrated that CT-based bone microstructure parameters and finite element models (FEM) improved the prediction of bone strength beyond BMD.\textsuperscript{3} However, the high radiation dose needed for imaging

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the whole spine prevents these measurements from the use in clinical routine and limits them to research trials. Therefore, it is necessary to reduce the radiation dose for those examinations. However, a reduced radiation dose will result in increased image noise and reduced diagnostic image quality. On the contrary, statistical iterative reconstructions (SIR) are known to reduce noise and to improve the diagnostic image quality.

In our study we investigate the effects of low-dose CT and SIR algorithms on trabecular bone microstructure parameters. We hypothesized that trabecular bone microstructure parameters assessed by low-dose CT and SIR algorithms adequately predict vertebral bone strength as compared to established standard-dose CT protocols.

2. METHODS

2.1 Specimens

Twelve vertebrae between thoracic vertebra 5 and 12 were harvested from three fresh human cadavers (one woman aged 74 years and two men aged 46 and 62 years, respectively). The donors had no history of pathological bone changes other than osteoporosis, i.e. bone metastases, hematological, or metabolic bone disorders. Each vertebra was embedded in resin (Rencast Isocyanat and Polyol, Huntsman Group, Bad Säckingen, Germany) up to 2 mm above respectively below their vertebral endplates for the purpose of biomechanical testing. All vertebrae were in sodium chloride solution at least 3 hours before imaging to prevent air artifacts. The vertebrae were sealed in vacuum plastic boxes filled with sodium chloride solution during imaging. The study was reviewed and approved by the local institutional review boards (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Munich, Germany).

2.2 CT imaging

CT imaging was performed with a 64-row CT scanner (Somatom Definition AS, Siemens Medical Solutions, Erlangen, Germany). For calibration purposes, a reference phantom with a bone-like and a water-like phase (Osteo Phantom, Siemens Medical Solutions Erlangen, Germany) was placed in the scanner bed beneath the plastic container. A standard-dose (SD) and a low-dose (LD) protocol were applied to each vertebra. The SD and LD protocol had a pitch of 0.8, tube voltage of 120 kV, and tube current of 220 mA and 70 mA, respectively. Voxel size and slice thickness amounted to 300 x 300 $\mu m^2$ and 600 $\mu m$ in both protocols. That amounts to an effective dose of 2.5 mSv for SD and 0.79 mSv for LD for one vertebra.

2.3 Image reconstruction

CT images were reconstructed with FBP and SIR based on separable paraboloidal surrogates (SPS) with ordered subsets. The noise of the measurement is modeled with Poisson distribution. Paraboloidal surrogates are used to find the maximum of the log-likelihood:

$$L(\mu) = \sum_i y_i \log(b_i e^{-|A\mu|}) - b_i e^{-|A\mu|},$$

where the sum runs over all measured rays $i$, $y$ is the measurement, $A$ is the system matrix, $\mu$ is the image and $b$ is the intensity that would be recorded if the object was absent. Ideally, this maximization is performed iteratively until the result converges. A penalty function (regularization) is used during the update step to control image noise. We employ

$$\Delta(\mu) = L(\mu) - \beta R(\mu),$$

where $R$ is a roughness penalty and the parameter $\beta$ controls the strength of the penalty. The roughness penalty can be expressed by:

$$R(\mu) = \sum_j \sum_{k \in N_j} v_k \psi(\mu_j - \mu_k),$$

where $N_j$ is the set of neighbors of pixel $j$, $v_k$ is a weight depending on the order of the neighboring pixel $k$ and $\psi$ is the potential function. We used Lange’s potential function:

$$\psi(x) = \delta[|t/\delta| - \log(1 + |t/\delta|)].$$
This potential function belongs to the group of edge-preserving regularization. $\delta$ is a threshold defining what intensity differences are smoothed. The number of iterations was selected by comparing the intermediate results after each iteration. In our case, ideal image quality was reached after 15 iterations.

SIR was performed without regularization (SIR w/o reg.) and with different regularization parameters. Results in this work were reconstructed with $\beta = 0.1$ for stronger regularization and $\beta = 0.001$ for a low regularization. Ideal image quality was reached with $\delta = 0.0001$.

2.4 Image Analysis

According to QCT-based BMD measurements, the most central third of all slices displaying the vertebra equidistant to its endplates were identified. Then, circular regions of interest (ROIs) were manually placed in the ventral half of the vertebra in the selected slices of the CT images. The circular ROI had a diameter of 10 mm. Furthermore, ROIs were drawn in the phases of the calibration phantom in the CT images.

BMD in the ROIs was calculated by converting the pixel attenuations in Hounsfield Units [HU] into BMD values by using the calibration phantom. Four morphometric parameters were calculated in the ROIs: bone volume divided by total volume (BV/TV), trabecular number (TbN; [m$m^{-1}$]), trabecular separation (TbSp; [m$m$]), and trabecular thickness (TbTh; [m$m$]). Parameters were labeled as apparent (app.) values, since they cannot depict the true trabecular structure due to the limited spatial resolution. In addition, fractal dimension (FD) as texture measurement of the trabecular bone structure was determined in the CT images using a box counting algorithm.

2.5 Biomechanical Testing

The resin embedded vertebrae were fixed in a mechanical testing system (Wolpert Werkstoffprüfmaschinen AG, Schaffhausen, Switzerland). Ten pre-conditioning cycles with uniaxial tension-compression up to a load between 10 N and 400 N with a rate of 5 m$m/min$ were applied. Then, a monotonic, uniaxial compression was performed at the same rate. The load-displacement curve was recorded and vertebral fracture load (FL) was defined as the first peak of the load-displacement curve with a subsequent drop of $> 10\%$.

2.6 Statistical Analysis

Statistical analyses were performed with SPSS (SPSS, Chicago, IL, USA). All tests were done using a two-sided 0.05 level of significance. Mean and standard deviation of the trabecular bone microstructure parameters were calculated. The Kolmogorov-Smirnov test showed for most parameters a significant difference from a normal distribution ($p<0.05$). Therefore, correlations between trabecular bone microstructure parameters and FL were evaluated with the Spearman’s rank correlation coefficient $r$. The parameters assessed from each reconstruction were compared to the parameters as assessed with SD-FBP using the Wilcoxon rank sum test.

3. RESULTS

Trabecular bone microstructure parameters showed significant correlations with FL in the range of $r = 0.88 - 0.91$ (SD-FBP), $r = 0.62 - 0.85$ (LD-FBP), $r = 0.69 - 0.93$ (LD-SIR w/o reg.), $r = 0.58 - 0.81$ (LD-SIR $\beta = 0.1$, $\delta = 0.0001$) and $r = 0.84 - 0.91$ (LD-SIR $\beta = 0.001$, $\delta = 0.0001$) ($p<0.05$; Table 1). Comparing all parameters to the values assessed with SD-FBP using the Wilcoxon rank sum test showed significant differences ($p<0.05$; Table 2) for microstructure parameters assessed for LD-FBP and LD-SIR with $\beta = 0.1$, $\delta = 0.0001$. There was no significant difference between SD-FBP and LD-SIR without regularization and between SD-FBP and LD-SIR with $\beta = 0.001$, $\delta = 0.0001$.

Comparing the CT images visually (see Figure 1) shows that LD-SIR with $\beta = 0.001$, $\delta = 0.0001$ is very similar to images from SD-FBP. Further it illustrates that a stronger regularization removes the ultra-small structures.
Table 1. Spearman’s rank correlation coefficient $r$ between FL and trabecular bone microstructure parameters as assessed with SD and LD protocols and reconstructed with FBP and SIR. All parameters correlated significantly ($p < 0.05$) with FL.

|               | SD-FBP | LD-FBP | w/o reg. | $\beta$: 0.1, $\delta$: 0.0001 | $\beta$: 0.001, $\delta$: 0.0001 |
|---------------|--------|--------|----------|-------------------------------|----------------------------------|
| app.BV/TV     | 0.90   | 0.85   | 0.93     | 0.81                          | 0.90                             |
|               | ($p<0.001$) | ($p<0.001$) | ($p<0.001$) | ($p=0.002$)                  | ($p<0.001$)                      |
| app.TbN       | 0.88   | 0.77   | 0.87     | 0.67                          | 0.91                             |
|               | ($p<0.001$) | ($p=0.003$) | ($p<0.001$) | ($p=0.020$)                  | ($p<0.001$)                      |
| app.TbSp      | -0.90  | -0.85  | -0.90    | -0.67                         | -0.91                            |
|               | ($p<0.001$) | ($p<0.001$) | ($p<0.001$) | ($p=0.020$)                  | ($p<0.001$)                      |
| app.TbTh      | 0.91   | 0.85   | 0.92     | 0.58                          | 0.84                             |
|               | ($p<0.001$) | ($p<0.001$) | ($p<0.001$) | ($p=0.046$)                  | ($p<0.001$)                      |
| FD            | 0.89   | 0.62   | 0.69     | 0.66                          | 0.89                             |
|               | ($p<0.001$) | ($p=0.031$) | ($p<0.014$) | ($p=0.024$)                  | ($p<0.001$)                      |

Table 2. Wilcoxon rank sum test of trabecular bone microstructure parameters as assessed with different reconstructions versus SD-FBP. $p < 0.05$ indicates significant differences.

|               | LD-FBP | w/o reg. | $\beta$: 0.1, $\delta$: 0.0001 | $\beta$: 0.001, $\delta$: 0.0001 |
|---------------|--------|----------|-------------------------------|----------------------------------|
| app.BV/TV     | p=0.603 | p=0.564  | p=0.057                       | p=0.403                          |
| app.TbN       | $p<0.001$ | p=0.863  | p=0.001                       | p=0.436                          |
| app.TbSp      | p=0.194 | p=0.544  | p=0.001                       | p=0.341                          |
| app.TbTh      | p=0.729 | p=0.544  | p=0.017                       | p=0.470                          |
| FD            | p=0.046 | p=0.285  | p=0.014                       | p=0.236                          |

4. DISCUSSION

Recent research showed that CT-based trabecular bone microstructure assessment can improve therapy monitoring and diagnostics in the context of osteoporosis. However, the X-ray radiation exposure, when using a standard clinical CT protocol, is too high for the clinical routine of osteoporosis diagnostics and therapy monitoring. Therefore, the purpose of this study was to investigate the diagnostic quality, at reduced radiation dose, for the calculation of trabecular bone microstructure parameters.

The Wilcoxon rank sum test reveals that structure parameters for LD-SIR with low ($\beta = 0.001$) and without regularization are not significantly different from parameters for SD-FBP. However, the results show a strong dependency on the regularization strength. The similar visual appearance of image noise and the small trabecular microstructure might cause the regularization to remove not only image noise but also trabecular structure (see Figure 1). As a consequence, the introduction of SIR for trabecular bone microstructure analyses requires a specific optimization of the regularization parameters. In addition, it could be thought of more advanced regularizers, like dictionary learning, to better distinguish between image noise and trabecular microstructure.

We chose SD-FBP data as reference because previous studies showed good results for this setting. For future work, finite element analysis (FEA) could be applied to the data. This way FL can be simulated and correlated to the biomechanical experiments.

5. CONCLUSION

In conclusion it was demonstrated that trabecular bone microstructure parameters as assessed by low-dose CT and SIR significantly correlated with vertebral bone strength. The parameters were not significantly different to
parameters assessed by SD-FBP. Therefore, low-dose CT protocols and SIR algorithms may allow the clinical use of CT-based trabecular bone microstructure analysis at the spine with an acceptable radiation exposure to improve fracture risk prediction and therapy monitoring in the context of osteoporosis. However, microstructure analyses are very sensitive to regularization. It was observed that only a very low regularization induced superior results while stronger regularizations corrupted the microstructure parameters. For the future one can foresee a specific SIR protocol, as proposed in this work, to clinically assess the osteoporotic status with a clinically justifiable radiation exposure.
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