

RESEARCH ARTICLE

Effect of Low-Dose MDCT and Iterative Reconstruction on Trabecular Bone Microstructure Assessment

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Abstract

We investigated the effects of low-dose multi detector computed tomography (MDCT) in combination with statistical iterative reconstruction algorithms on trabecular bone microstructure parameters. Twelve donated vertebrae were scanned with the routine radiation exposure used in our department (standard-dose) and a low-dose protocol. Reconstructions were performed with filtered backprojection (FBP) and maximum-likelihood based statistical iterative reconstruction (SIR). Trabecular bone microstructure parameters were assessed and statistically compared for each reconstruction. Moreover, fracture loads of the vertebrae were biomechanically determined and correlated to the assessed microstructure parameters. Trabecular bone microstructure parameters based on low-dose MDCT and SIR significantly correlated with vertebral bone strength. There was no significant difference between microstructure parameters calculated on low-dose SIR and standard-dose FBP images. However, the results revealed a strong dependency on the regularization strength applied during SIR. It was observed that stronger regularization might corrupt the microstructure analysis, because the trabecular structure is a very small detail that might get lost during the regularization process. As a consequence, the introduction of SIR for trabecular bone microstructure analysis requires a specific optimization of the regularization parameters. Moreover, in comparison to other approaches, superior noise-resolution trade-offs can be found with the proposed methods.

Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing an individual to an increased risk for fracture [1]. Osteoporotic fractures not only

considerably reduce quality of life but are also associated with an increased mortality. Due to the aging population, the prevalence of osteoporosis and accordingly the incidence of osteoporotic fractures are expected to increase. Therefore, osteoporosis is classified as a public health problem. The socio-economic burden is expected to rise dramatically, e.g. in the United States from \$17 billion in 2005 by almost 50% until 2025 [2].

The assessment of osteoporosis associated fracture risk has traditionally relied on dual-energy X-ray absorptiometry (DXA) for the measurement of bone mineral density (BMD) at the spine and hip. However, BMD values of patients with and without osteoporotic fractures statistically overlap [3–5]. Therefore, the Fracture Risk Assessment Tool (FRAX) has been introduced which uses easily obtainable clinical risk factors to estimate a 10-year fracture probability in order to provide a better clinical guidance for treatment decisions. Furthermore, considerable research effort has been undertaken to develop non-invasive imaging techniques focusing on the assessment of cortical and trabecular bone microstructure to improve fracture risk predictions [6]. These imaging techniques include high-resolution magnetic resonance imaging (MRI), high-resolution peripheral quantitative computed tomography (hr-pQCT) and high-resolution multi-detector computed tomography (MDCT) [6–8]. However, hr-pQCT and MRI are limited to peripheral sites and cannot be applied to the spine, which is one of clinically most relevant fracture sites. It has been demonstrated that MDCT-based bone microstructure parameters and finite element models (FEM) improved the prediction of bone strength beyond BMD [6, 9–12]. However, in-vivo MDCT imaging for bone microstructure analysis and FEM at the spine is associated with an effective dose of estimated 3 mSv for one vertebra [13]. This dose is close to the diagnostic reference value of medically indicated radiation exposure and not acceptable for longitudinal assessment of fracture risk and therapy monitoring. Unfortunately these measurements are—so far—not clinical routine and thus are limited to research trails. Clearly a reduction of radiation exposure is needed; however, such a reduction would cause a significant increase in image noise and reduction in diagnostic image quality. On the contrary, advanced reconstruction algorithms, such as iterative approaches, are well known to reduce image noise and improve the diagnostic quality [14–19].

The purpose of our study was to investigate the effects of low-dose MDCT and in-house developed fully statistical iterative reconstruction (SIR) algorithms on trabecular bone microstructure parameters. We hypothesized that trabecular bone microstructure parameters assessed by low-dose MDCT in combination with SIR algorithms adequately predict vertebral bone strength in-vitro as compared to bone microstructure measurements based on established standard-dose MDCT protocols.

Materials and Methods

Specimens

The human donors had dedicated their bodies for educational and research purposes to the local Institute of Anatomy prior to death, in compliance with local institutional and legislative requirements. Written informed consent was obtained from the donors. The study was reviewed and approved by the local institutional review boards (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Munich, Germany). 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). The donors had no history of pathological bone changes other than osteoporosis, i.e. bone metastases, hematological, or metabolic bone disorders. The surrounding muscle, fat tissue, and intervertebral discs were completely removed. 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. The resin fixation was performed with parallel alignment of the upper and lower endplate of the vertebrae with the outer surface of the resin chock to guarantee strict axial loading conditions of the vertebrae during the uniaxial biomechanical test. Specimens were stored in a refrigerator at +10°C between preparation and testing in sealed plastic bags. Mechanical testing was performed at room temperature (+19°C, moisture ~ 55%). All vertebrae were in sodium chloride solution at least 3 h before imaging to prevent air artifacts. During imaging the vertebrae were sealed in vacuum plastic boxes filled with sodium chloride solution.

MDCT Imaging

MDCT imaging was performed with a 64-row MDCT scanner (Somatom Definition AS, Siemens Medical Solutions, Erlangen, Germany). Each vertebra stored in a plastic box filled with sodium chloride solution as outlined above was placed in a plastic container filled with water to simulate an in-vivo examination. 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. The routine radiation exposure used in our department (standard-dose, SD) and a low-dose protocol (LD) were applied to each vertebra. The SD and LD protocol had both a pitch factor of 0.8, tube voltage of 120 kV, and tube current of 220 mA and 70 mA, respectively. Voxel size and slice thickness were 300 x 300 μm² and 600 μm in both protocols. That amounts to an estimated effective dose of 2.5 mSv for SD and 0.79 mSv for LD for one vertebra.

Image Reconstruction

All datasets were reconstructed with filtered backprojection (FBP) and SIR. The implementation of SIR is based on separable paraboloidal surrogates (SPS) with ordered subsets [20]. A Poisson distribution is used to model the noise of the measurement. Paraboloidal surrogates are used to find the maximum of the log-likelihood:

$$L(\mu) = \sum_i y_i \log(b_i e^{-[A\mu]_i}) - b_i e^{-[A\mu]_i}, \tag{1}$$

where the sum runs over all measured rays i , y is the measurement, A is the system matrix, μ 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.

Statistical iterative reconstruction algorithms are ill-posed in nature and thus a penalty function (regularization) is necessary to control image noise. We employed

$$\Delta(\mu) = L(\mu) - \beta R(\mu), \tag{2}$$

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

$$R(\mu) = \sum_j \sum_{k \in N_j} v_k \psi(\mu_j - \mu_k), \tag{3}$$

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 ψ is the potential function. We used Lange's potential function [21]:

$$\psi(x) = \delta[|t/\delta| - \log(1 + |t/\delta|)]. \tag{4}$$

This potential function belongs to the group of edge-preserving regularization. δ 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. This number was used for all SIR in this work.

SIR was performed without regularization (SIR w/o reg.) and with different regularization parameters. Regularization parameters were chosen by extensive testing of the data from one osteoporotic and one healthy bone. We started with values $\beta = 0.0001$ and $\delta = 0.00001$ and increased them stepwise by a factor of ten until we reached $\beta = 0.1$, $\delta = 0.01$ and having used all different (β, δ) -combinations in between. Trabecular microstructure parameters were assessed for each reconstruction and compared to the parameters from SD-FBP by computing the average relative error. Additionally, images were compared visually. Based on the extensive testing, best results in this work were reconstructed with $\beta = 0.001$, $\delta = 0.0001$. Moreover, we present results for reconstructions with $\beta = 0.1$, to show the effect of a stronger regularization, and $\beta = 0$ (SIR w/o reg.) to show the effect of no regularization.

MDCT Image Analysis

One person performed all steps of the MDCT image analysis. MDCT images were loaded into an in-house developed program based on IDL (Interactive Data Language, Research Systems, Bolder, CO, USA). According to QCT-based BMD measurements [22], 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 MDCT images. The circular ROI had a diameter of 10 mm. Furthermore, ROIs were drawn in the phases of the calibration phantom in the MDCT images. BMD in the ROIs was calculated by converting the pixel attenuations in Hounsfield Units [HU] into calcium hydroxyapatite [mg/cm^3] by using the calibration phantom. Afterwards, MDCT images were binarized to calculate trabecular bone microstructure parameters. An optimized global threshold was applied to all MDCT images. Similar to previous studies, $200 \text{ mg}/\text{cm}^3$ calcium hydroxyapatite was identified as optimized global threshold [9, 23]. Four morphometric parameters were calculated in the ROIs in analogy to standard histomorphometry using the mean intercept length method [24]: bone volume divided by total volume (BV/TV), trabecular number (TbN; [mm^{-1}]), trabecular separation (TbSp; [mm]), and trabecular thickness (TbTh; [mm]). Parameters were labeled as apparent (app.) values, since they cannot depict the true trabecular structure due to the limited spatial resolution [13]. In addition, fractal dimension (FD) as texture measurement of the trabecular bone structure was determined in the MDCT images using a box counting algorithm [25].

Biomechanical Testing

The biomechanical testing was performed similar to previous studies [23, 26, 27]. The resin embedded vertebrae were fixed in a mechanical testing system (Wolpert Werkstoffprüfmaschinen AG, Schaffhausen, Switzerland). A ball joint was used for the mechanical testing to guarantee axial loading. Ten pre-conditioning cycles with uniaxial tension-compression up to a load between 10 N and 400 N with a rate of 5 mm/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 in force $>10\%$ (Fig 1). The setup for biomechanical testing is shown in Fig 2.

Statistical Analysis

The statistical analysis was performed with SPSS software package (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

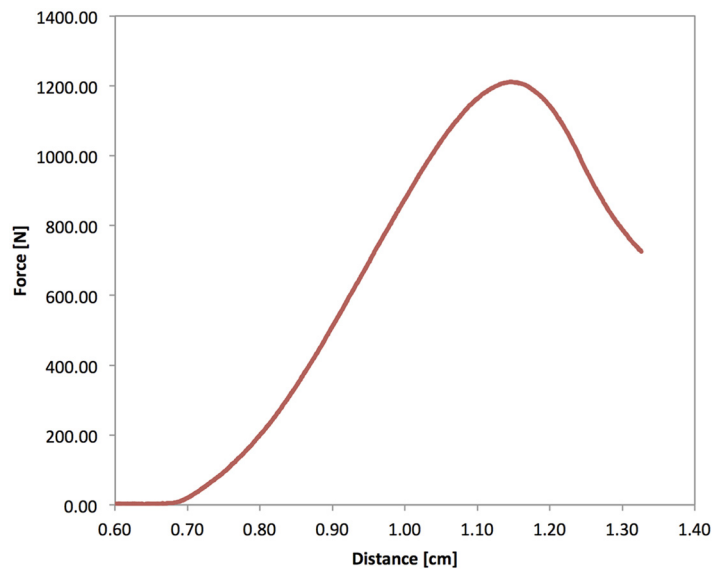


Fig 1. Sample load-displacement curve. Load-displacement curve from the biomechanical testing of a vertebra (ID: OPS004_1). FL was defined as the first peak of the load-displacement curve with a subsequent drop in force >10%.

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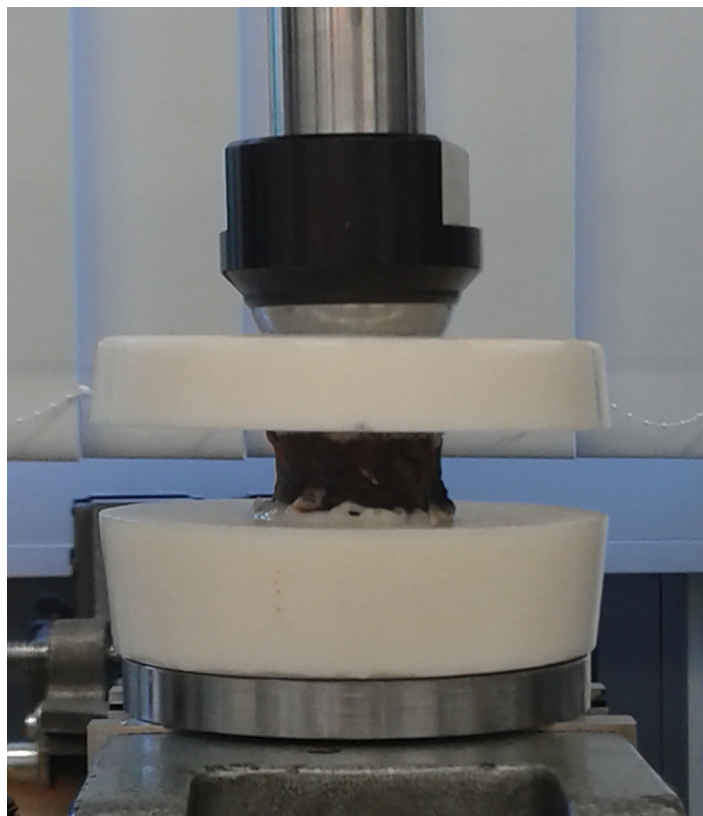


Fig 2. Setup of the biomechanical testing. Setup of the biomechanical testing to determine FL. The vertebra is fixed in a mechanical testing system.

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Table 1. Correlation coefficients versus FL.

	SD-FBP	LD-FBP	LD-SIR		
			w/o reg.	$\beta = 0.1, \delta = 0.0001$	$\beta = 0.001, \delta = 0.0001$
app.BV/TV	0.90 ($p < 0.001$)	0.85 ($p < 0.001$)	0.93 ($p < 0.001$)	0.81 ($p = 0.002$)	0.90 ($p < 0.001$)
app.TbN	0.88 ($p < 0.001$)	0.77 ($p = 0.003$)	0.87 ($p < 0.001$)	0.67 ($p = 0.020$)	0.91 ($p < 0.001$)
app.TbSp	-0.90 ($p < 0.001$)	-0.85 ($p < 0.001$)	-0.90 ($p < 0.001$)	-0.67 ($p = 0.020$)	-0.91 ($p < 0.001$)
app.TbTh	0.91 ($p < 0.001$)	0.85 ($p = 0.001$)	0.92 ($p < 0.001$)	0.58 ($p = 0.046$)	0.84 ($p = 0.001$)
FD	0.89 ($p < 0.001$)	0.62 ($p = 0.031$)	0.69 ($p = 0.014$)	0.65 ($p = 0.024$)	0.89 ($p < 0.001$)

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 -value < 0.05) with FL.

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showed for most parameters a significant difference from 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 Friedman test was used to compare the whole set of microstructure parameters. Moreover, the parameters assessed from each reconstruction were compared to the parameters as assessed with SD-FBP using the Wilcoxon rank sum test.

Results

The absolute values of the trabecular microstructure parameters are noted together with the measured FL and BMD in the supporting information (S2 Table).

According to the Friedman test, the absolute values of the trabecular bone microstructure parameters as assessed with SD-FBP, LD-FBP and LD-SIR with and without regularization were significantly different ($p < 0.05$). 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). Fig 3 visualises the correlation between app.BV/TV and FL exemplarily for our reference reconstruction (SD-FBP; Fig 3a) and for the best LD result (LD-SIR $\beta = 0.001, \delta = 0.0001$; Fig 3b).

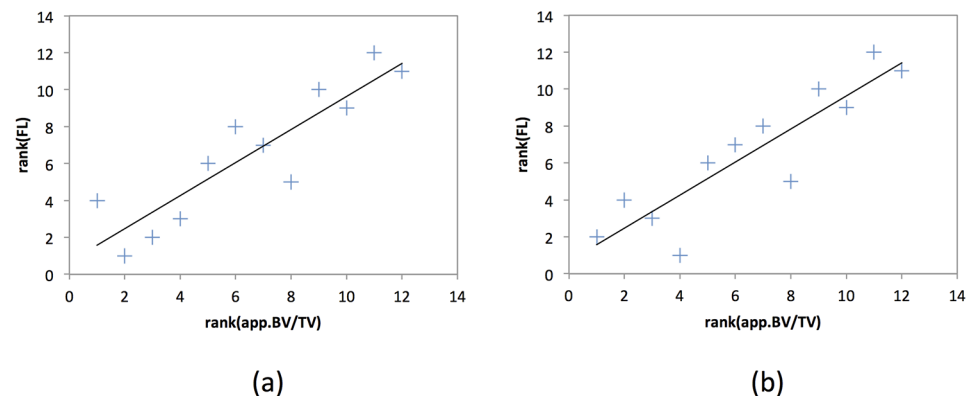


Fig 3. Correlation app.BV/TV versus FL. Sample correlation plots for app.BV/TV vs. FL ((a) SD-FBP, (b) LD-SIR $\beta = 0.001, \delta = 0.0001$). Note that the correlation plots show the ranked values for app.BV/TV and FL because we used Spearman’s rank correlation coefficient.

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Table 2. Wilcoxon rank sum test against standard-dose FBP data.

	LD-FBP	LD-SIR		
		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	$p = 0.046$	$p = 0.285$	$p = 0.014$	$p = 0.236$

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

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Comparing all parameters to the values assessed with SD-FBP using the Wilcoxon rank sum test showed significant differences for the following values ($p < 0.05$; Table 2): TbN, FD for LD-FBP; TbN, TbSp, TbTh, FD for LD-SIR with $\beta = 0.1, \delta = 0.0001$. There was no significant difference between SD-FBP and LD-SIR w/o reg. and between SD-FBP and LD-SIR with $\beta = 0.001, \delta = 0.0001$.

Fig 4 shows images acquired with LD and SD reconstructed with different settings and algorithms. Clearly, images reconstructed with FBP are noisier than images reconstructed with SIR. The results of Table 2 show that we can reach the same quality as with SD-FBP for the structure parameters using LD-SIR. But the regularization parameters have to be chosen carefully. A relative strong regularization ($\beta = 0.1, \delta = 0.0001$) resulted in significant differences for the microstructure parameters.

Discussion

The purpose of this study was to investigate the diagnostic quality, at two different radiation dose levels, of FBP and SIR for the calculation of trabecular bone microstructure parameters. Radiation exposure associated with CT diagnostics is a relevant challenge in the day-to-day clinical routine. The number of CT examinations is increasing with the rising number of indications and applications. The growing challenge of fulfilling the ALARA principle remains the major task for clinicians as well as for the research community. For example, at the same time microstructure parameters and FEM improve the prediction of bone strength. Thus, with advanced reconstruction algorithms becoming clinically available clinicians have the opportunity to introduce new metrics (such as microstructure assessment) while keeping the radiation dose at a low level.

Trabecular bone microstructure parameters significantly correlated with FL for all reconstructions. However, the absolute values showed significant differences. One can observe that parameters assessed for LD-FBP caused the majority of absolute values to drift towards the range of healthy bone. Hence, we can come to the conclusion that image noise is partly counted as bone-tissue. This behavior of LD (noisy) FBP reconstructions could lead to wrong results in the structure analysis. These observations lead to the conclusion that by using SIR, the noise level decreases while maintaining the anatomical and pathological information of bones.

Previous studies performed in-vitro vertebral MDCT imaging and reconstruction based on SD-FBP. Baum et al. [23] reported correlation coefficients up to $r = 0.79$ between bone microstructure parameters and FL, and Dall'Ara et al. [27] up to $r = 0.89$ between finite element models and FL. We observed correlation coefficients in a similar range.

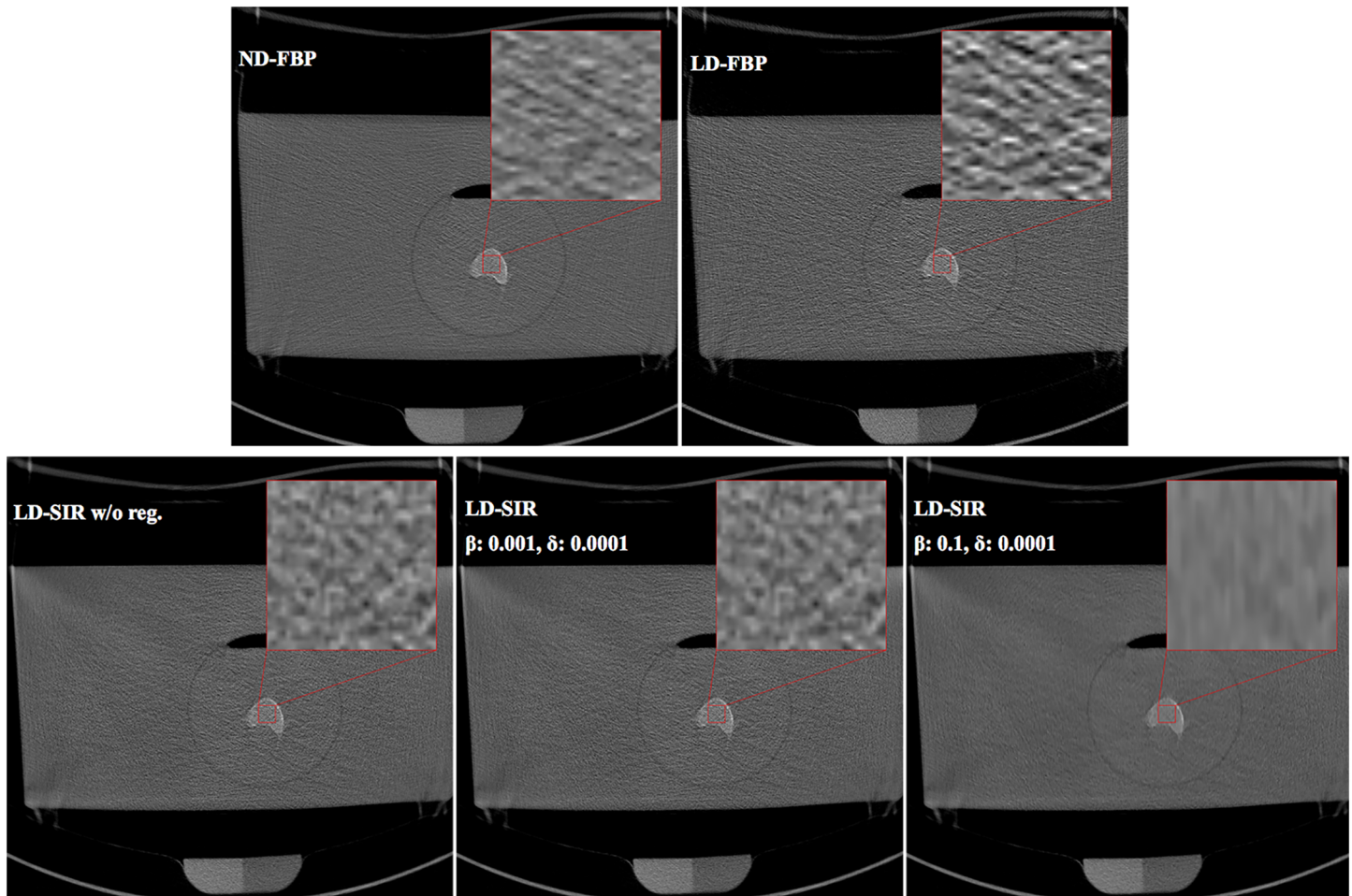


Fig 4. Comparison of CT images from different doses. MDCT images of a representative vertebra in a water bath to simulate an in-vivo examination. For visual comparison of the bone microstructure, it is magnified by a factor of 10. Scans were performed with SD and LD protocols and images were reconstructed with FBP and SIR. (Level 300 HU, window 2000 HU).

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The results of the Wilcoxon rank sum tests reveal that LD-SIR yield in equal prediction of the bone strength as SD-FBP. However, the results revealed a strong dependency on the regularization strength. We demonstrated that regularization might corrupt the microstructure analysis. The ultra small trabecular bone microstructure is just small detail in the images and will therefore be lost when applying too much regularization. As a consequence, the introduction of SIR for trabecular bone microstructure analysis requires a specific optimization of the regularization parameters and number of iterations.

Automated parameter selection for iterative reconstructions is still subject of ongoing research. In this work, we chose the parameters for iterative reconstruction based on extensive testing on two datasets—one with high and one with low bone strength.

On this note, for SIR type algorithms such a parameter search has only to be done once for a specific diagnostic question and radiation dose level. An optimization for different radiation exposures could be done with a low-dose simulation tool [28, 29]. For the future, with such a

tool not only the parameter optimization but additionally the lowest possible dose level can be determined.

One drawback in our study design is the relatively small sample size of twelve vertebrae from three different donors. However, the goal of this work was to investigate the effect of LD protocols and SIR on the measurement of trabecular bone microstructure parameters. For this technical driven purpose of this study the sample size may be considered as sufficient.

With respect to radiation exposure reduction our work illustrated the possibility to employ advanced reconstruction algorithms to assess structural bone information under low dose situations. Other investigators have illustrated that there is a spectrum of other techniques which reduces dose within a given range [30]. For example with regard to osteoporosis assessment of the spine, one could foresee to use region-of-interest techniques to reduce the dose in the peripheral [31–33]. Further, the introduction of single photon-counting detectors will enable the clinician to reduce dose and improve the spatial resolution [34, 35], which could generate high interest for osteoporosis screening. Further, the additional information, which are made available via spectral imaging, can be used to improve task driven reconstruction algorithms [36].

Conclusion

It was shown that trabecular bone microstructure parameters as assessed by LD-SIR significantly correlated with vertebral bone strength. The parameters were not significantly different to parameters assessed by SD-FBP. Therefore, LD protocols and SIR algorithms may allow the clinical use of MDCT-based trabecular bone microstructure analysis at the spine with an acceptable radiation exposure. This would allow for the future to improve fracture risk prediction and therapy monitoring in the context of osteoporosis. However, absolute values of the trabecular bone microstructure parameters are dependent on the MDCT protocol and reconstruction algorithm. This has to be considered when translating advanced algorithms into the clinical area. In conclusion, our results showed that SIR with properly tuned parameters—for regularization and number of iterations—allows the usage of MDCT based trabecular bone microstructure assessment at significantly reduced radiation dose.

Supporting Information

S1 Table. Abbreviations and acronyms.

(PDF)

S2 Table. Measured trabecular bone microstructure parameters and fracture load for each vertebra. Vertebrae with the same 3-digit number are from the same donor. The FD parameter value for LD-SIR $\beta = 0.1$, $\delta = 0.0001$ of vertebra OPS004_2 could not be determined. The correlation FD vs. FL for LD-SIR $\beta = 0.1$, $\delta = 0.0001$ was computed without consideration of vertebra OPS004_2.

(PDF)

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Author Contributions

Conceived and designed the experiments: FKK KH TB JSK PBN EJ. Performed the experiments: FKK KH TB JSK EGG RB. Analyzed the data: FKK KH TB. Contributed reagents/materials/analysis tools: FKK KH TB RAN KM JSK RB EJ. PBN. Wrote the paper: FKK KH TB PBN.

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