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VOXEL-BASED DENSITY REGISTRATION OF TRABECULAR BONE: A LONGITUDINAL HR-PQCT STUDY OF POSTMENOPAUSAL WOMEN

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Abstract. Bone mineral density (BMD) is one of the important parameters used to characterise bone quality. Clinically, the only recommended method - dual X-ray absorptiometry - can only evaluate a two-dimensional areal BMD. Currently, three-dimensional localised BMD information is absent. HR-pQCT enables the assessments of 3D microstructure down to trabecular bone. Therefore, in this study, a voxel-based density registration (VDR) method is proposed to analyse the longitudinal changes of trabecular-bone density distribution. The VDR techniques were evaluated based on a six-month longitudinal study of five postmenopausal women. The time effect on localised changes of trabecular-bone mineral density was visualized and variations between different anatomical regions were quantified for the first time. Different distributions between anatomical regions were found in bone mineral density of trabecular bone ($vBMD_{trab}$), with a change of $vBMD_{trab}$ at medial region (-0.56%) significantly higher than anterior (-1.58%) ($p = 0.032$). This study indicates that localised density changes might be used as a prior indicator for the effect of aging or other interventions.

1 INTRODUCTION

Diagnosis and treatment of bone-related diseases, such as osteoporosis, depend heavily on the quality of bone [1], which is commonly described by its physical and mechanical properties[2]. These properties, such as bone mineral density (BMD), structural parameters and the Young's modulus, were easy to measure ex-vivo from cadaver bone [3]. However, clinical interventions require non-invasive and in-vivo examination of bone qualities. Currently, dual X-ray absorptiometry (DXA) is the only recommended method by World Health Organization to

assess BMD for the diagnosis of osteoporosis and fracture risk [4, 5]. Despite the widespread clinical use and low radiation dose of DXA, it can only evaluate a two-dimensional areal BMD based on the single value [6]. However, the disorder of bone properties due to diseases often lead to a heterogeneous and regional pattern [7, 8]; DXA is unable to provide this three-dimensional (3D) information for BMD.

Computational tomography (CT) is able to provide 3D structural properties; therefore, it has been widely used in clinical and research as a tool to evaluate the bone quality and generate geometrical models for finite-element analysis [9, 10]. Previous studies proved that a 3D distribution of X-ray attenuation (Hounsfield units, HU) can be used to estimate the volumetric bone mineral content (vBMD) accurately [11], according to a phantom - a solid calibrated standard with known density [12]. However, due to the limitation of the resolution of clinical CT, CT-based vBMD studies can only assess cortical bone [13] although trabecular bone (TB) was shown to correlate better with fracture risk rather than cortical bone [14]. Studies also demonstrated a regional variation of vBMD distribution in human (cadaver) TB [15], while CT studies are still unable to provide information for trabecular bone.

The development of high-resolution peripheral quantitative computed tomography (HR-pQCT) enables an in-vivo assessment of 3D distribution of vBMD [16]. This imaging modality offers a range of data sets with resolution of 82 μm, which is high enough to capture a structure of trabecular bone [17]. A wide-ranging of studies based on HR-pQCT were conducted to investigate the pathology on TB [18]. However, in most of the HR-pQCT studies, a homogenised structure was assumed in a standard analysis protocol provided by the manufacturer [19]. Although previous studies demonstrated that the structure of TB varies significantly at different anatomical cites, with anterior exhibiting significantly less structure than medial and lateral ones [7, 20], the in-vivo assessment of regional variation of trabecular bone $vBMD_{trab}$ has not been reported.

In this study, a voxel-based density registration (VDR) method is presented to evaluate the TB mineral-density features. A six-month HR-pQCT study was designed to investigate the reliability of VDR in longitudinal studies. The aim of this work was to develop a method to measure the spatial distribution of TB based on the in-vivo HR-pQCT images of postmenopausal women and the time effect on the regional variation of $vBMD_{trab}$.

2 METHOD

2.1 Participants and Imaging

The study was a six-month longitudinal study to compare the bone mineral density (vBMD) of TB at pre (baseline) and post (follow-up) time interventions. Five healthy women aged between 55-70 years-old with more than one-year post menopause from a cohort of local dwelling were recruited into the study. HR-pQCT scans were performed at the beginning of the study; after six months the participants were invited back to the repeated HR-pQCT scan. This study was registered at clinicaltrials.gov: NCT03225703 and approved by the National Research Ethics Service (16/EM/0460).

Baseline and follow-up HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland) scans were performed for all the recruited participant using the manufacturer's standard protocol (60 kVp, 1000 mA, 100-ms integration time) at the NIHR Clinical Research Facility, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. Briefly, before the scanning process,

tibia of a participant was immobilized and fixed in a carbon-fibre cast in the scanner to ensure a correct position upon entry. A volume of interest (VOI) combining 110 parallel CT slices was defined from a reference line from 22.5 mm proximal to distal tibia endplate. The quality of image based on motion-induced artifacts was defined by the manufacturer's qualitative grading system to ensure the use of images above grade 4 in the analysis procedures [21]. To monitor the stability of the XtremeCT, a manufacturer device-specific phantom was scanned daily and, most importantly, converted the linear attenuation values (Hounsfield Unit, HU) to concentration of hydroxyapatite (HA) mineral densities (vBMD).

Four anatomical regions were defined (anterior, lateral, posterior, and medial) to observe the region-specific data (Fig. 1), according to the previously published study [7]. A developed procedure was performed to extract the trabecular bone for four anatomical regions. Briefly, a horizontal line was drawn through the centre of trabecular area, four regions were separated based on two lines rotated ± 45º to the horizontal line (Fig. 1). The regions were than cropped along the inner surface of cortical bone. Vision inspections were performed for each participant to ensure that no cortical bone was included.

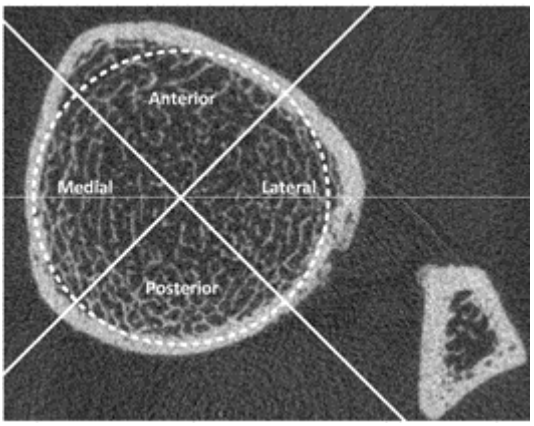

Figure 1. : Definition of four anatomical regions

2.2 VDR

An in-house program based on MATLAB (2020b) was designed to visualise and analyse the spatial variation of TB at distal tibia. A five-step VDR process was suggested to visualise and quantitatively measure the evolution of vBMD (Fig. 2). First, according to the manufacturer recommendation, HR-pQCT images were pre-processed with a Laplace-Hamming filter to balance the sensitivity and noise presented in the measurements. Then, a previously published three-dimensional (3D) rigid registration algorithm was implemented to determine the common VOI for the images before and after six months [22]. The registration process involved pre-aligning the centroids of the scanned images, then the pre-aligned follow-up images were registered to the baseline ones according to the normalized mutual information metric [23] and resampled using the Lanczos interpolator [24]. After that, a calibration of HU was performed according to the QC1 phantom [25] provided by the manufacturer. The phantom contained four rods with known HA mineral density (100, 200, 400, 800 mg HA/cm^3); therefore, a regression equation was computed, with HU converted into the corresponding HA. A color map linked to the vBMD value for each voxel on the registered images was mapped based on the regression equation. Finally, to measure the vBMD changes after six-month (ΔvBMD), differences of each

voxel value (density) between the follow-up ($vBMD_f$), and baseline ($vBMD_b$) images were computed and presented by a color contour.

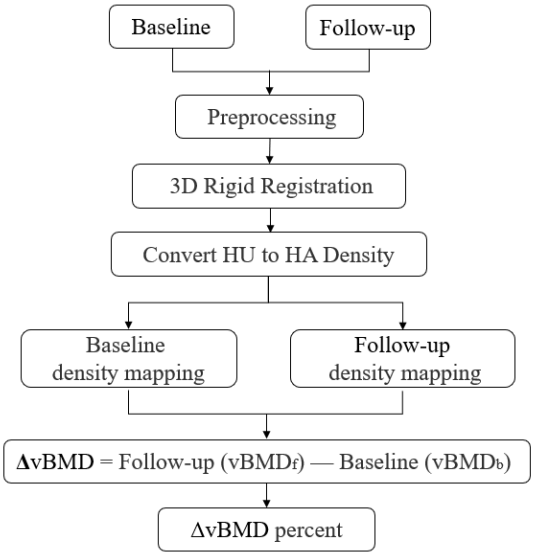

Figure 2. : Schematic of VDR process.

2.3 Statistical Analysis and Reproducibility Test

To evaluate the statistically significant differences ($p < 0.05$) of vBMD for the four anatomical regions before and after 6 months, repeated measures ANOVA (RM-ANOVA) were performed using SPSS 20.0 software (IBM Corp., NY, USA).

The short-term reproducibility tests were implemented based on the data set from the previous study of ten participants of a 70-years-old cohort with two repeated scans taken on the same day [26]. A root mean square coefficient of variance (RMSCV%) was used to calculate the short-term reproducibility of $vBMD_{trab}$. Its level was between 1.6-3.3% for the four anatomical regions.

3 RESULTS AND DISCUSSION

Five pairs of HR-pQCT images at distal tibia from five postmenopausal women (mean ± std age = 62.4 ± 1.2 years) were analysed in the study at two time points. An example of BMD maps presented by a cross-section for baseline, follow-up and over-lapping images after VDR are shown in Fig. 2. It was noteworthy that vBMD of cortical bone at distal tibia was dramatically higher than that of TB (Fig. 3a); besides, no obvious changes were observed over 6 months (Figs. 3a and 3b). However, a different distribution of vBMD between anatomical regions was observed in trabecular bone. By quantifying $vBMD_{trab}$ at four regions (A, P, L, M) of distal tibia, the absolute value and changes ($\Delta vBMD_{trab}$) after 6 months are presented in Table1.

Table 1. : Values of $vBMD_{trab}$ at different anatomical regions

Regions	Baseline (mg/cm^3)	Follow-up(mg/cm^3)	$\Delta vBMD_{trab}$ (%)
Anterior	377.56±15.6	371.60±20.1	**-1.58***
Lateral	391.94±23.4	423.12±11.3	-0.27
Posterior	417.64±18.8	415.10±25.8	-0.61
Medial	414.24±21.1	411.93±.9.4	-0.56

Data are expressed as mean ± SD, $\Delta vBMD_{trab}$ - percentage change of $vBMD_{trab}$ after 6 months;

*significant difference between baseline and follow-up

A significant decrease of 1.58% at the anterior region (from 377.56 ± 15.6 to 371.60 ± 20.1 mg/cm3) was found due to the six-month time effect ($p = 0.04$). Controversially, no significant differences were found at other regions. The differences in changes between the anatomical regions were analysed as well, with $\Delta vBMD_{trab}$ at the medial region (-0.56%) significantly higher than that at the anterior one (-1.58%) ($p = 0.032$), while no significant differences were found between the posterior and the medial regions. These regional variations of TB mineral density were consistent with data on its microstructure and stiffness from the previous study [7], with BV/TV (bone volume/tissue volume), Tb.N (trabecular number), and Tb.Th (trabecular thickness) being significantly lower (up to 52.8%) at the anterior region than the medial one.

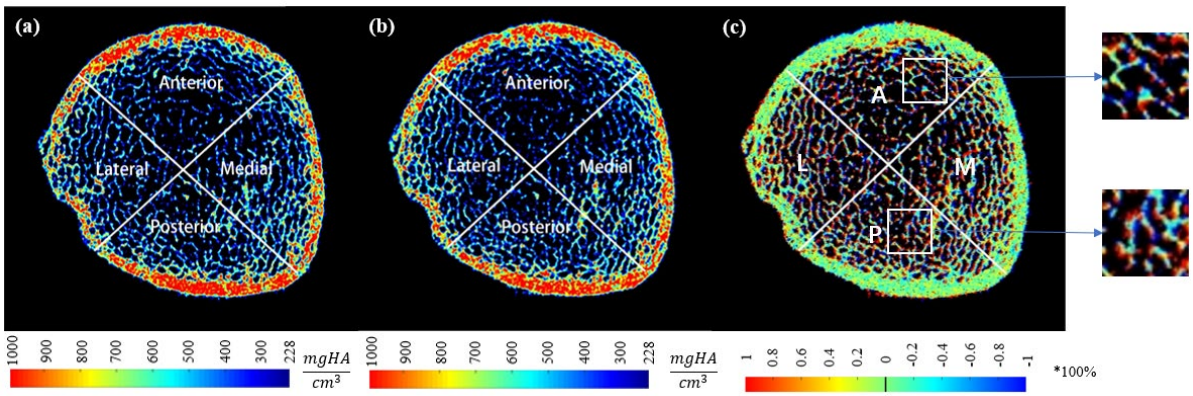

Figure 3. : Examples of cross-sectional density map for baseline (b) follow-up scans; (c) absolute vBMD changes after 6 months.

Comparing with our previously reported results about no significant changes (both global and regional) after 6 months of microstructure, BMD at the anterior region exhibited a significant change. It indicated that localised density changes might be used as a prior indicator of the effect of aging or other interventions. Such anatomical variations of bone mineral density (as well as microstructure) may be explained by the fact that, in the distal tibia, the maximum variation of the internal load along the axis was as high as 1.5 times the body weight [27]. During

the habitual gait, the size and pattern of load varies for the sites, especially the medial and posterior portions of the distal tibia are subjected to substantial pressure and shear [28-32]. This opinion was supported by an identical 6-month longitudinal study for the control leg, with the level of TB resorption rate in the anterior and lateral regions of tibia being significantly higher than that in the medial region [23]. The presented study showed a potential of the VDR technique for visualizing and monitoring the time-lapsed localised changes of TB BMD.

4 CONCLUSION

In this study, a novel VDR method was proposed to analyse the longitudinal changes of trabecular bone density distribution. The time effect on localised changes of TB mineral density was visualized and variations between different anatomical regions were quantified for the first time. Our research proved that the VDR technique might provide a new way to non-invasively examine the spatial distribution of vBMD in TB. This technique shows a potential for clinical application to monitor the skeleton health including osteoporosis, fracture and treatment effects in the future.

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