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Changes in cortical microarchitecture are independent of areal bone mineral density in patients with fragility fractures

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ABSTRACT

Dual-energy X-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography (HR-pQCT) are commonly used to assess the areal bone mineral density (aBMD) and peripheral microstructure, respectively. While DXA is the standard to diagnose osteoporosis, HR-pQCT provides information about the cortical and trabecular architecture. Many fragility fractures occur in patients who do not meet the osteoporosis criterion (i.e., T-score ≤ -2.5). We hypothesize that patients with T-score above -2.5 and fragility fracture may have abnormal bone microarchitecture. Therefore, in this retrospective clinical study, HR-pQCT data obtained from patients with fragility fractures and T-scores ≥ -2.5 ($n = 71$) were compared to corresponding data from patients with fragility fractures and T-scores ≤ -3.5 ($n = 56$). Types of secondary osteoporosis were excluded from the study. To verify the dependency of alterations in bone microarchitecture and T-score, the association between HR-pQCT values and aBMD as reflected by the T-score at both proximal femora, was assessed. At the distal tibia, cortical thickness was lower ($p < 0.001$), cortical porosity was similar ($p = 0.61$), trabecular number was higher ($p < 0.001$), and bone volume fraction (BV/TV) was higher ($p < 0.001$) in patients with T-scores ≥ -2.5 than in patients with T-scores ≤ -3.5. Trabecular number and BV/TV correlated with T-score ($r = 0.68$, $p < 0.001$; $r = 0.61$, $p < 0.001$), whereas the cortical values did not. Our results thus demonstrate the importance of bone structure, as assessed by HR-pQCT, in addition to the standard DXA T-score in the diagnosis of osteoporosis.

Introduction

Osteoporosis is a critical problem for health care policy and an economic problem for our aging society. In Germany, 6.3 million individuals have osteoporosis [1]. The incidence of osteoporosis is 885,000 cases per year, and over 50% of new patients suffer from a fragility fracture [1]. Osteoporosis is defined as decreased areal bone mineral density (aBMD), measured using dual-energy X-ray absorptiometry (DXA), with a T-score ≤ -2.5. Nevertheless, about 50% of all fragility fractures are observed in patients with a T-score ≥ -2.5 who do not meet the osteoporosis criterion [2].

Since DXA is a planar technology, which only measures areal BMD, insights about changes in bone are not accessible with this method. One way to permit the in vivo assessment of trabecular and cortical architecture at the distal tibia is the use of high-resolution peripheral quantitative computed tomography (HR-pQCT) [3]. Many studies have documented that bone microstructure is an important factor in fracture risk [4,5]. For instance, the Rotterdam study demonstrated that only 44% of all non-vertebral fractures appeared in women with a T-score ≤ -2.5 [6]. The OFELY study compared postmenopausal women with fractures to age-matched women without fractures and showed that 50% of the fragility fractures occurred at a T-score ≥ -2.5 [7].

The measurement of aBMD by DXA combined with the assessment of bone microstructure by HR-pQCT have recently improved our understanding of the pathogenesis of osteoporosis and our understanding of the mechanism of action of osteoporosis drugs [8]. Predicting the risk for fragility fractures in osteoporosis is of high clinical importance for treatment decisions, yet the

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apparent lack of association between T-score and fragility fractures makes this prediction difficult. The primary goal of this retrospective clinical study was to compare patients with different aBMD and fragility fractures in terms of peripheral bone microarchitecture. The secondary goal was to assess which peripheral bone changes are associated with the occurrence of fragility fractures in patients who do not meet the osteoporosis criterion, i.e. T-score ≤ -2.5.

Material and methods

Study design and patients

This retrospective clinical study was based on 127 patients with fragility fractures who underwent aBMD measurements by DXA (DXA Lunar Prodigy, GE Healthcare, UK) and assessment of bone microstructure by HR-pQCT (XtremeCT®, Scanco Medical AG, Brüttisellen, Switzerland) between September 2010 and February 2016 in the Department of Osteology and Biomechanics at the University Medical Center of Hamburg-Eppendorf in Germany. Based on the records, patients with fragility fractures and both available measurements with DXA and HR-pQCT were included. Patients with a medical history of vertebral or femoral bone implants, treatment with glucocorticoids lasting over 3 months, terminal renal insufficiency, diabetes mellitus type 1, prolonged immobilization (over 6 weeks), or tumors were excluded from the study. Included were low-energy vertebral fractures confirmed with X-ray in patients with back pain, hip, wrist and subcapital humeral fractures, the skeletal site of fractures are shown in Table 1. Patients with a medical history of traumatic vertebral fracture were excluded from the study.

Patients were assigned to either one of two groups based on their DXA T-score value. For this study, 71 patients with a T-score <0 and -2.5 and a history of fragility fracture (first group) were found in our internal database and 56 patients with a T-score ≤ -3.5 and a history of fragility fracture (second group).

Biochemical analyses of bone metabolism markers including serum levels of, 25-OH-D3, serum calcium, phosphate, osteocalcin, bone alkaline phosphatase, parathormone and creatinine were analyzed.

Bone densitometry and microarchitecture

DXA scans were acquired at both proximal femora. The detected aBMD of the projected bone area was expressed in grams per square centimeter (g/cm2), and the corresponding T-Score was calculated. T-scores compared the values to young-normal populations with the same race, height, weight, and gender, as provided by the manufacturer. The lowest T-score was used for group assignment. Based on the records, patients with high risk of further fractures received a HR-pQCT, usually on the same day DXA was performed. HR-pQCT scans were acquired on the dominant distal tibia (in case of previous fracture, the contralateral limb was scanned). The measurement region was manually defined by a trained operator by placing a reference line at the endplate of the tibia on a preliminary performed scout view. The same operator generates semiautomatic contours around the periosteal surface and the entire volume of interest is thereafter automatically separated into a cortical and trabecular region. A quality scan for calibration of the CT system was performed each day using a phantom provided by the manufacturer. The scanning settings used were 60 kV/40 k_eV at a current of 900 μA. Each image comprised 110 slices with an isotropic voxel size of 82 μm. Data with motion artifacts in the HR-pQCT were excluded from evaluation. The following parameters were acquired using the HR-pQCT system: cortical thickness (Ct.Th), cortical porosity (Ct.Po), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and bone volume to tissue volume ratio (BV/TV). HR-pQCT values were compared to gender specific reference values of 20–29 years old subjects as previously described [9]. The advanced analysis mode was described by Burghardt et al. in 2010 [10].

Table 1
Demographic characteristics of patients with fragility fractures.

BMD		
Parameter	T-score $\geq$ -2.5	T-score $\leq$ -3.5
Number (n)	71	56
Male/female	16/55	16/40
Age (years)	69.3 ± 10.2	65.2 ± 14.1
Total number of fractures (n)	161	155
Vertebral fractures (n)	143	132
Hip fractures (n)	8	5
Wrist fractures (n)	8	12
Humeral fractures (n)	2	6
Specific treatment	30	36

Statistical analysis

The biometric characteristics of individuals are reported as mean values ± standard deviations. For group comparing the *t*-test was used. To report association between continuous variables Pearson's respectively Spearman's rank correlation coefficient was calculated. If appropriate logarithmic transformation was done.

A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed with statistical software R [R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/], version 3.3.2., and the package ggplot2 [H. Wickham. ggplot2: elegant graphics for data analysis. Springer New York, 2009].

Results

The data of hundred twenty-seven individuals were examined (95 women and 32 men) with a mean age of 69.3 years in the first group and of 65.2 years in the second group ($p = 0.072$). The total number of fractures was 161 compared with 155 between both groups. From these fractures 143 in the first and 132 in the second group were vertebral fractures, therefore the measurement of aBMD by DXA at the lumbar spine was not included. General characteristics including all fractures are shown in Table 1. Patients with antiresorptive treatment with bisphosphonates were 30 cases in the first and 36 cases in the second group (Table 1).

The assessment of the bone structure showed for the trabecular compartment higher BV/TV ($p < 0.001$) and higher trabecular number ($p < 0.001$) in the first compared to the second group (Fig. 1A-B). The trabecular separation ($p < 0.001$) was lower in the first compared to the second group, indicating a deterioration in trabecular microarchitecture in the group of patients with a T-score ≤ -3.5 (data not shown). Both groups presented similar values for trabecular thickness ($p = 0.29$) (Fig. 1C).

The cortical compartment showed a lower cortical thickness ($p < 0.001$) and similar cortical porosity ($p = 0.61$) in the first compared to the second group (Fig. 1D-E).

A sample image of tibial bone microstructure in patients with fragility fracture and T-score ≥ -2.5 (Fig. 3A) and patients with fragility fracture and T-score ≤ -3.5 (Fig. 3B) shows the difference in trabecular and cortical structure.