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Bone turnover markers are associated with higher cortical porosity, thinner cortices, and larger size of the proximal femur and non-vertebral fractures

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ABSTRACT

Bone turnover markers (BTM) predict bone loss and fragility fracture. Although cortical porosity and cortical thinning are important determinants of bone strength, the relationship between BTM and cortical porosity has, however, remained elusive. We therefore wanted to examine the relationship of BTM with cortical porosity and risk of non-vertebral fracture.

In 211 postmenopausal women aged 54–94 years with non-vertebral fractures and 232 age-matched fracture-free controls from the Tromsø Study, Norway, we quantified femoral neck areal bone mineral density (FN aBMD), femoral subtrochanteric bone architecture, and assessed serum levels of procollagen type I N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX).

Fracture cases exhibited higher PINP and CTX levels, lower FN aBMD, larger total and medullary cross-sectional area (CSA), thinner cortices, and higher cortical porosity of the femoral subtrochanter than controls ($p \le 0.01$). Each SD increment in PINP and CTX was associated with 0.21–0.26 SD lower total volumetric BMD, 0.10–0.14 SD larger total CSA, 0.14–0.18 SD larger medullary CSA, 0.13–0.18 SD thinner cortices, and 0.27–0.33 SD higher porosity of the total cortex, compact cortex, and transitional zone (all $p \le 0.01$). Moreover, each SD of higher PINP and CTX was associated with increased odds for fracture after adjustment for age, height, and weight (ORs 1.49; 95% CI, 1.20–1.85 and OR 1.22; 95% CI, 1.00–1.49, both $p < 0.05$). PINP, but not CTX, remained associated with fracture after accounting for FN aBMD, cortical porosity or cortical thickness (OR ranging from 1.31 to 1.39, p ranging from 0.005 to 0.028).

In summary, increased BTM levels are associated with higher cortical porosity, thinner cortices, larger bone size and higher odds for fracture. We infer that this is produced by increased periosteal apposition, intracortical and endocortical remodeling; and that these changes in bone architecture are predisposing to fracture.

1. Introduction

Bone fragility is a worldwide public health problem due to the increased morbidity, mortality, and financial costs associated with osteoporotic fractures, in particular non-vertebral and hip fractures [1–3]. To reduce the burden of fragility fractures, a better understanding of the mechanisms that influence bone loss and result in fracture is needed.

All factors influencing bone loss and strength express their effects through modulation of bone remodeling [4–6]. The bone volume deficits produced by each remodeling event and the intensity of remodeling increase after menopause [7,8]. These changes result in structural decay produced by cortical thinning, increased porosity, and loss of trabeculae [6,9,10]. Although all women become estrogen-deficient after menopause, a significant proportion do not exhibit accelerated bone loss, structural decay, or sustain low-energy fractures [9,11,12].

Elevated levels of bone turnover markers (BTM) are associated with increased risk of both vertebral and non-vertebral fracture [12–15]. This effect is independent of areal bone mineral density (aBMD) in some, but not all studies [14–16]. In a meta-analysis, there was a moderate but

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significant association between serum procollagen type I N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX) and risk of fracture [17]. Further studies are required to better evaluate the independent role of BTM in fracture risk prediction.

Few studies have examined the association between BTM and bone architecture. In women, BTM are associated with higher cortical porosity of the distal tibia, but not of the distal radius [9]. To the best of our knowledge, there have been no studies on the effect of BTM on the architecture of the proximal femur assessed *in vivo*, or whether the effect of BTM on risk of fracture is dependent on bone architecture such as cortical porosity.

We therefore wanted to examine the relationship of BTM with cortical porosity and risk of non-vertebral fracture. We quantified in standard CT images the subtrochanteric architecture *in vivo*, using StrAx1.0, a new image analysis algorithm [18], to test the hypothesis that (i) BTM are associated with cortical porosity of the proximal femur and (ii) BTM are associated with non-vertebral fractures, and whether this relationship is dependent on cortical porosity or aBMD.

2. Materials and methods

2.1. Study population

The Tromsø Study is a single-center population-based health study in Northern Norway, which conducted six surveys in 1974, 1979–80, 1986–87, 1994–95, 2001–02, and 2007–08 [19]. During the Tromsø 4 survey in 1994–95, all 37,558 eligible inhabitants in Tromsø over 24 years old were invited and 27,158 subjects (72%) participated. All their non-vertebral fractures were registered from the x-ray archives of the University Hospital of North Norway, Tromsø between 1994 and 1 January 2010 [20,21].

In 2011, we designed a nested case–control study and identified 1250 women participating in Tromsø 4, who suffered a fracture at the hip, wrist, or proximal humerus after the age of 50 years, during the 15-year registry of fractures (1994–95 to 2010). We invited all 760 who still were alive and living in Tromsø. After excluding those who were premenopausal, received bisphosphonates for osteoporosis, had hip prostheses, metal screws, or pathological fractures, 264 fracture cases attended. The women with hip prostheses or metal screws in the hip region were excluded because metal on one side can make noise in the CT images at both hip sites, and therefore many women with hip fractures could not be included. Age-matched fracture-free women were randomly selected among the Tromsø 4 participants, 1186 were invited, and after the same exclusion criteria, 260 controls attended. Of these 524 participants, we excluded 15 currently receiving hormone replacement therapy and 66 with movement artifacts during CT scanning. This left 443 women in the final analyses; 232 controls and 211 fracture cases (4 hip, 181 wrist, and 26 proximal humeral). The median time since their last fracture was 6.6 years (range, 1–25). All measurements were performed from November 2011 through January 2013. All participants gave written informed consent. The study was approved by the Regional Committee of Research Ethics and was conducted in accordance with the World Medical Association Declaration of Helsinki.

2.2. Variables

A self-administered questionnaire included information concerning all fractures after the age of 50 years, diseases, use of medication, and lifestyle. Height and weight were measured in light clothing without shoes. Femoral neck (FN) aBMD was measured at the non-dominant proximal femur using dual-energy x-ray absorptiometry (DXA, GE Lunar Prodigy, Lunar Corporation, Madison, WI, USA), and at the opposite side in those with a hip fracture at the non-dominant side, and the coefficient of variation (CV) was 1.7% [22]. Fasting blood samples were collected between 8 a.m. and 10 a.m. and assayed for serum PINP and CTX using electrochemiluminescence immunoassay (Elecsys 1010 Analytics, Roche Diagnostics, Germany), with a CV of 3%–8%.

CT scans (Siemens Somatom Sensation 16, Erlangen, Germany) of the non-dominant hip were performed at the Department of Radiology, University Hospital of North Norway. The CT machine had an in-plane resolution of 0.74 mm, the slice thickness was 0.6 mm, the hip was scanned from just above the femoral head to 2 cm below the lesser trochanter, and the exposure dose of radiation was ~1.5 mSv. Images were analyzed in Melbourne, Australia using StrAx1.0 software [23]. As cortices are thin at the proximal femur (femoral head, neck, and trochanter), analyses were confined to a region of interest (ROI) where the cortices are thicker. This 3.7 mm subtrochanteric region starts at the tip of the lesser trochanter.

The subtrochanteric region within the ROI of low-resolution CT images was segmented into the compact-appearing cortex, transitional zones, and trabecular compartment using StrAx1.0, a non-thresholding method. Segmentation was achieved by automatically selecting attenuation profile curves perpendicular to the periosteal surface, as reported using high-resolution peripheral quantitative computed tomography (HR-pQCT) images [23]. Local bone edges are identified as the beginning and the end of the rising and falling S-shaped portions of the curve enabling the delineation of the compartments. Bone was segmented by analyzing ~3600 consecutive overlapping profiles around the perimeter of each cross-sectional slice as previously described [23]. The density profile curve produced had two plateaus: one corresponding to the compact-appearing cortex and one corresponding to the trabecular compartment. Between these plateaus is a descending S-shaped curve or transition between the two plateaus. This is the transitional zone. The density profile curve is expressing the mineralized bone area as the percentage of total area within each column.

Porosity within each cortical compartment was also quantified automatically throughout the entire ROI, and similarly in CT images as reported in HR-pQCT images [18,23]. Porosity presented in this study is the average void volume fraction from all voxels within the total cortex (compact cortex, outer, and inner transitional zones). The porosity quantified by this algorithm is the proportion of emptiness within each voxel, or the fraction of the bone volume occupied by void (porosity). The accuracy of porosity measurements using CT, with a voxel size of 740 μm, was validated *ex vivo* by testing the agreement with HR-pQCT measurements, voxel size 82 μm, of the same ROI at the femoral subtrochanter in 5 cadaveric specimens [18]. The correlation (R^2) between porosity of compact-appearing cortex, outer and inner transitional zones, and total cortex, quantified by these two methods was 0.96, 0.87, 0.87 and 0.94, respectively. The error (difference between measurements by CT and HR-pQCT scanning) ranged from 0% to 10%, depending on the compartment, and agreement between both measurements exceeded 90% [18]. In addition, validation of the StrAx 1.0 software analyses of the femoral subtrochanter cortical porosity as well as all standard CT parameters was performed by repositioning and rescanning a human hip phantom 10 times, and CVs were between 0.3% and 2.3%. The CT imaging of bone parameters was phantom-calibrated at the time of the examination.

In this study, we present femoral subtrochanteric porosity of the total cortex, the compact cortex, and the transitional zone (the outer and inner transitional zones combined), total and cortical vBMD, trabecular bone volume/tissue volume (BV/TV), the total, medullary and cortical cross-sectional area (CSA), and cortical thickness. In addition, we used the cortical CSA/total CSA ratio as a measure of relative cortical thickness because cortical thickness varies around the perimeter of the bones. A smaller cortical area relative to the total area reflects greater excavation upon the endocortical surfaces relative to periosteal apposition, which enlarges the medullary canal area, while producing a smaller cortical area and so a thinner cortex *relative* to the total area [24,25].