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Local topological analysis at the distal radius by HR-pQCT: Application to in vivo bone microarchitecture and fracture assessment in the OFELY study

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ABSTRACT

High-resolution peripheral quantitative computed tomography (HR-pQCT) is an in-vivo technique used to analyze the distal radius and tibia. It provides a voxel size of 82 μm. In addition to providing the usual micro-architecture parameters, local topological analysis (LTA) depicting rod- and plate-like trabeculae may improve prediction of bone fragility. Thirty-three women with prevalent wrist fractures from the OFELY cohort were compared with age-matched controls. Bone microarchitecture, including the structural model index (SMI), was assessed by HR-pQCT, and micro-finite element analysis (μFE) was computed on trabecular bone images of the distal radius (XtremeCT, Scanco Medical AG). A new LTA method was applied to label each bone voxel as a rod, plate or node. Then the bone volume fraction (BV/TV*), the rod, plate and node ratios over bone volume (RV/BV*, PV/BV*, NV/BV*) or total volume (RV/TV*, PV/TV*, NV/TV*) and the rod to plate ratio (RV/PV*) were calculated. Associations between LTA parameters and wrist fractures were computed in a conditional logistic regression model. Multivariate models were tested to predict the μFE-derived trabecular bone stiffness. RV/TV* (OR = 4.41 [1.05–18.62]) and BV/TV* (OR = 6.45 [1.06–39.3]), were significantly associated with prevalent wrist fracture, after adjustment for ultra distal radius aBMD. Multivariate linear models including PV/TV* or BV/TV* + RV/PV* predicted trabecular stiffness with the same magnitude as those including SMI. Conversion from plates into rods was significantly associated with bone fragility, with a negative correlation between RV/PV* and trabecular bone stiffness ($r = -0.63$, $p < 0.0001$). We conclude that our local topological analysis is feasible for a voxel size of 82 μm. After further validation, it may improve bone fragility description.

Introduction

The measurement of areal bone mineral density (aBMD) has been the cornerstone of fragility fracture evaluation over the last 20 years. However, recent literature has suggested that in vivo evaluation of bone microarchitecture using high resolution peripheral quantitative computed tomography (HR-pQCT) may improve fracture risk prediction. With this technique, some microarchitectural parameters are associated with prevalent fracture independently of aBMD [1–5]. Assessment of microarchitectural parameters is also emerging as a surrogate marker of bone strength [6–10]. There is a growing interest in the morphological aspects of the trabeculae, as postmenopausal osteoporosis is associated with the distribution of plate-like to rod-like changes [11], which can influence the mechanical strength of the trabecular component of the bone [12,13]. The trabecular network can be described by indirect global indices, e.g., the structural model index [14], but these exclude the local analysis of an individual trabecula. In addition to morphological assessment, topological analysis of the trabecular network has also been developed to explore the structural connectivity and the local shape of trabeculae [15,16], with the goal of superseding the gold standard of histomorphometry, which is limited to 2D analysis. These techniques imply high resolution images; they have thus been performed

Abbreviations: aBMD, areal bone mineral density; BV/TV*, total bone volume fraction calculated from local topological analysis; Ct.Ar, cortical area; Ct.vBMD, cortical volumetric bone mineral density; Ct.Th, cortical thickness; HR-pQCT, high-resolution peripheral quantitative computed tomography; K, total bone stiffness; LTA, local topological analysis; NV/TV*, node volume to total volume ratio; NV/BV*, node volume to bone volume ratio; PV/BV*, plate volume to bone volume ratio; PV/TV*, plate volume to total volume ratio; RV/BV*, rod volume to bone volume ratio; RV/PV*, rod volume to plate volume ratio; RV/TV*, rod volume to total volume ratio; SMI, structural model index; Tb.Ar, trabecular area; Tb.K, trabecular bone stiffness; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Sp.SD, intra-individual distribution of separation; Tb.Th, trabecular thickness; Tb.vBMD, trabecular volumetric bone mineral density; UDR aBMD, ultra distal radius areal bone mineral density; vBMD, volumetric bone mineral density.

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historically on ex-vivo bone samples using μCT [15,17–19], although clinical evaluation via in-vivo μMR imaging [20–22] and more recently HR-pQCT [23–25] has also been attempted.

In earlier works, an alternative approach based on the medial axis of the trabeculae was developed to identify the local geometry of bone structures from very high-resolution images [15]. The classification is based not only on the skeleton but also on an adaptive neighborhood around each voxel of the medial axis. It can then be extended to the entire volume using the reversibility property of the medial axis, and furthermore provides parameters such as the percentages of plate-like and rod-like shapes [19]. The precision of non metric indexes is affected by voxel size resolution [26,27]. The resolution of in-vivo HR-pQCT images is relatively coarse, with a voxel size of 82 μm but a measured spatial resolution barely reaching the average size of trabecula, on the order of 100 to 150 μm. Despite this, the proposed method may extract topological parameters in addition to the usual morphometric parameters. The purpose of the present study was two-fold: 1) to evaluate the feasibility of our topological analysis with HR-pQCT images, and 2) to test its association with prevalent fracture in a case–control setting.

Material and methods

Subjects

All subjects included in the present study were participants in the OFELY cohort. The latter is a prospective study on the determinants of bone loss in 1039 volunteer women, launched in February 1992 and described elsewhere [28]. The present nested case–control analysis included 33 women who sustained a forearm fragility fracture during the follow-up of the study and age-matched controls. This subset has been described in a previous analysis [29]. Briefly, only low-trauma fractures (i.e., those occurring in falls from standing height or less) were included. The use of treatments affecting bone metabolism (bisphosphonates, hormone replacement therapy, selective estrogen receptor modulator, tibolone, or aromatase inhibitors) was recorded every year and taken into account in that study if the duration of treatment was 1 year or more at the time (or within 6 months before) of architectural evaluation.

Areal bone mineral density (aBMD)

The aBMD (g/cm^2) at the ultra distal radius (UDR aBMD) was measured using dual-energy X-ray absorptiometry (DXA) with either a QDR 1000+ (Hologic, Bedford, MA, USA) for 9 women with fracture and 7 without, or a QDR 4500 (Hologic) for 24 women with fracture and 26 without.

HR-pQCT image acquisition

The study subjects were assessed with HR-pQCT (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland) from September 2004 to June 2006 to determine volumetric BMDs and trabecular microstructure in vivo at preferably the non-dominant distal radius [30]; if the non-dominant arm had a history of fracture, measures were taken on the other arm. A region spanning 9.02 mm was acquired over 110 slices, 9.5 mm proximally from the endplate of the distal radius. The 12.6 cm field of view was reconstructed across a 1536×1536 matrix leading to an isotropic voxel size of 82 μm. Acquisition time was 3 min with an effective dose of approximately 3 μSv. Attenuation data were converted to equivalent hydroxyapatite (HA) densities. Quality control was monitored by daily scans of a phantom containing cylinders of HA (densities of 0, 100, 200, 400, and 800 mg HA/cm^3) embedded in a soft-tissue equivalent resin (QRM, Moehrendorf, Germany).

Image processing

To outline the periosteal surface, a semi-automated edge-defining algorithm was applied to the original grayscale image using the software delivered with the HR-pQCT device (IPL 5.08b, Scanco Medical AG, Brüttisellen, Switzerland). Binarization of the selected region of interest was obtained using a thresholding technique. Voxels were considered as bone if their density was 40% of the maximum measured value or above. Complementary to the manufacturer's detection of the cortical shell, a custom script specifying a minimum cortical thickness of 6 voxels was used to differentiate cortical and trabecular bone. The process resulted in a volume of binarized images with cortical and trabecular components that could be analyzed together or separately.

Bone microarchitectural measurement and micro-finite element analysis

Volumetric BMD and microarchitecture parameters were measured using the standard evaluation program delivered with the HR-pQCT device (IPL 5.08b, Scanco Medical AG, Brüttisellen, Switzerland). Total volumetric BMD (total vBMD, mg HA/cm^3), trabecular volumetric BMD (Tb.vBMD, mg HA/cm^3) and trabecular area (Tb.Ar, mm^2) were measured. A mid-axis transformation method was used to identify trabecular elements and the distance between them was assessed three dimensionally using the distance transform method [31]. Trabecular number (Tb.N, mm^{-1}) was defined as the inverse of the mean spacing of the mid-axes. Trabecular thickness (Tb.Th, μm) and trabecular separation (Tb.Sp, μm) were derived from Tb.vBMD and Tb.N, using standard methods from histomorphometry (i.e., $Tb.Th = (Tb.vBMD/1200)/Tb.N$, and $Tb.Sp = (1-(Tb.vBMD/1200))/Tb.N$) based on the assumption of a fixed model of plate-like trabeculae [32]. Intra-individual distribution of separation (Tb.Sp.SD, μm) was measured as the standard deviation of the Tb.Sp.

Bone strength was assessed by micro-finite element analysis (μFEA). Briefly, a compression test was simulated in which a load in the longitudinal direction was applied at one end while the other end was fully constrained to simulate a fall from standing height on an outstretched hand [33]. Details of this μFEA simulation have been provided previously [29]. Finite element analyses were performed using the FE-solver included in the IPL software (IPL 1.13, Scanco Medical AG, Brüttisellen, Switzerland). FE models were created by converting each voxel to an equally sized brick element [34].

A first FE analysis was performed on the whole radius; cortical bone elements were assigned a Young's modulus of 20 GPa, whereas trabecular tissue elements were assigned a Young's modulus of 17 GPa [35] and for all elements a Poisson's ratio of 0.3 was specified. A second analysis was performed only on the trabecular compartment with the same settings as for the whole analysis (i.e. Young's modulus of 17 GPa and Poisson's ratio of 0.3). Total and trabecular bone stiffnesses (Tb.K, kN/mm) were assessed as the index for total and trabecular bone strength respectively (K and Tb.K, kN/mm).

Topological analysis

Global topological analysis: the structure model index

To assess trabecular network organization, the structure model index (SMI, no unit) was added to the basic analysis of the HR-pQCT device. SMI values ranged from 0 for an ideal plate structure to 3 for an ideal rod structure [14].

Local topological analysis (LTA)

Local topological analysis was operated on the trabecular compartment after binarization of the bone. The first step consisted in the extraction of the medial axis defined as the local maxima of a discrete distance map [15]. Each point of the medial axis was then classified as a rod, plate, node, or boundary according to the calculation