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Significant bone microarchitecture impairment in premenopausal women with active celiac disease

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ABSTRACT

Patients with active celiac disease (CD) are more likely to have osteoporosis and increased risk of fractures. High-resolution peripheral quantitative computed tomography (HR-pQCT) permits three-dimensional exploration of bone microarchitectural characteristics measuring separately cortical and trabecular compartments, and giving a more profound insight into bone disease pathophysiology and fracture. We aimed to determine the volumetric and microarchitectural characteristics of peripheral bones—distal radius and tibia—in an adult premenopausal cohort with active CD assessed at diagnosis. We prospectively enrolled 31 consecutive premenopausal women with newly diagnosed CD (median age 29 years, range: 18–49) and 22 healthy women of similar age (median age 30 years, range 21–41) and body mass index. Compared with controls, peripheral bones of CD patients were significantly lower in terms of total volumetric density mg/cm^3 (mean ± SD: 274.7 ± 51.7 vs. 324.7 ± 45.8, p 0.0006 at the radius; 264.4 ± 48.7 vs. 307 ± 40.7, p 0.002 at the tibia), trabecular density mg/cm^3 (118.6 ± 31.5 vs. 161.9 ± 33.6, p < 0.0001 at the radius; 127.9 ± 28.7 vs. 157.6 ± 15.6, p < 0.0001 at the tibia); bone volume/trabecular volume ratio % (9.9 ± 2.6 vs. 13.5 ± 2.8, p < 0.0001 at the radius; 10.6 ± 2.4 vs. 13.1 ± 1.3, p < 0.0001 at the tibia); number of trabeculae 1/mm (1.69 ± 0.27 vs. 1.89 ± 0.26, p 0.009 at the radius; 1.53 ± 0.32 vs. 1.80 ± 0.26, p 0.002 at the tibia); and trabecular thickness mm (0.058 ± 0.010 vs. 0.071 ± 0.008, p < 0.0001 at the radius with no significant difference at the tibia). Cortical density was significantly lower in both regions (D comp mg/cm^3 860 ± 57.2 vs. 893.9 ± 43, p 0.02; 902.7 ± 48.7 vs. 932.6 ± 32.6, p 0.01 in radius and tibia respectively). Although cortical thickness was lower in CD patients, it failed to show any significant inter-group difference (a—8% decay with p 0.11 in both bones). Patients with symptomatic CD (n = 22) had a greater bone microarchitectural deficit than those with subclinical CD. HR-pQCT was used to successfully identify significant deterioration in the microarchitecture of trabecular and cortical compartments of peripheral bones. Impairment was characterized by lower trabecular number and thickness—which increased trabecular network heterogeneity—and lower cortical density and thickness. In the prospective follow-up of this group of patients we expect to be able to assess whether bone microarchitecture recovers and to what extend after gluten-free diet.

1. Introduction

Celiac disease (CD) is a gluten-dependent systemic disorder characterized by an autoimmune damage initiated in the small bowel of predisposed individuals [1]. Previous studies have shown that osteopenia and osteoporosis are well-recognized complications in CD patients [2–9]. Bone disease constitutes a major problem through the association with an increased risk of bone fractures, predominantly in the peripheral skeleton and often produced by minimal or moderate trauma [10]. In such context, former studies have shown that the distal radius is the most common fractured site corresponding to more than 50% of events in CD cases [10–14]. Although controversial, some studies suggest that the increased risk can be reverted by strict adherence to a specific treatment, the gluten-free diet (GFD) [11,12,15].

Bone health, characterized by its mass, density, and micro-architectural and material properties, is maintained by a balanced system of remodeling [9,16,17]. The deterioration of any of those parameters or an uncoupling of the remodeling process, leads to bone fragility and an increased risk of fractures. Osteoporosis is characterized

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by low bone mass, thin porous cortices and decreased trabecular number and connectivity [17]. It may be diagnosed before fractures occur by measuring areal bone mineral density (aBMD) using dual energy X-ray absorptiometry (DXA) [18]. Thus, DXA has been considered the gold standard for predicting osteoporotic fractures. Despite the ability of DXA to assess bone mass (BMC, BMD), the inherent planar nature of the measurements makes geometric assessment of a bone impossible and bone strength estimation very limited. Furthermore, the method is unable to discriminate between trabecular and cortical bone tissues, which have been shown to be differentially affected by many conditions [19,20]. Furthermore, DXA cannot assess the microarchitectural structure of bones and, therefore, explore the intimate pathogenesis of osteoporotic fractures. High resolution peripheral quantitative computed tomography (HR-pQCT), which is a non-invasive method for volumetric three-dimensional characterization of peripheral skeletal sites, allows quantification of bone microarchitecture parameters and permits the assessment of bone mechanical properties by FEA (Finite element analysis) [21–23]. For this purpose, the resolution of HR-pQCT (82 μm) permits the direct and reliable assessment of microarchitectural parameters which are relevant to bone strength. Hence, HR-pQCT has shown to provide better prediction of bone strength when compared with DXA [24].

Some years ago, our group conducted a longitudinal analysis of bone structure and strength in a series of newly diagnosed CD patients using peripheral and axial quantitative computerized tomography (QCT) [25]. That seminal study allowed us to speculate about the pathogenesis of bone weakening in CD patients. There, we suggested that secondary hyperparathyroidism and the inflammatory process of CD would enhance bone remodeling inducing trabecular thinning, cortical–subcortical bone mass loss, increase of intracortical porosity and impairment of bone mechanical quality.

To our knowledge, no studies have assessed the microarchitectural quality of bones in CD patients. Therefore, our aims in this study were: 1—to determine the microarchitectural characteristics of peripheral bones in a consecutive series of adult premenopausal women with active CD assessed at the time of diagnosis using HR-pQCT and 2—to compare these results with those of healthy women of similar age and body mass index (BMI). Secondary aims of the study were to assess the association of the clinical phenotype at diagnosis with the severity of bone impairment.

2. Materials and methods

2.1. Patients and controls

Female patients with newly diagnosed CD were recruited at a single center (Sección Intestino Delgado, Hospital de Gastroenterología "Dr. C. Bonorino Udaondo"). Between May 2011 and November 2012, 67 consecutive female patients with recent diagnosis of CD were screened for inclusion and exclusion criteria. We defined premenopausal status on a clinical basis: less than one year since last menstrual cycle. Patients with a concomitant known disorder affecting bone metabolism (thyroid disease, pregnant at the time of diagnosis, breast feeding, etc.) or consuming medications potentially affecting bones were excluded from the study. Patients having former diagnosis of CD and those having performed any kind of dietary gluten restriction were also excluded. During the enrolment period, 31 consecutive premenopausal patients fulfilled these criteria and were finally enrolled in the study. Twenty two healthy premenopausal women of comparable age and BMI were used as a control group. Diagnosis of CD was based on well-established criteria as are the concurrent evidence of positive CD serology tests and abnormal duodenal histology (IIIa or greater damage according to Marsh's modified criteria) [26]. Exclusion of CD in healthy control females was exclusively based on a negative CD-specific serology. The categorization of the clinical picture at the time of diagnosis was established according to the Oslo's nomenclature [1]. Patients were categorized as having symptomatic CD (gastrointestinal and/or extra-intestinal symptoms) or subclinical CD. At the enrolment interview, patients and controls were requested to report known risk factors for osteoporosis (smoking, alcohol consumption, parent hip fracture history and menstrual cycles). Excessive alcohol consumption was defined according to FRAX: 3 or more units of alcohol daily. History of fractures, if present and intensity of trauma were also recorded.

2.2. Study design

The present study reports cross-sectional results obtained at the time of diagnosis of CD compared with a control group. The overall study was designed as a prospective assessment of patients before and after one year of treatment (gluten free diet).

2.3. HR-pQCT: bone microarchitecture assessment

Bone microarchitectural parameters for patients and healthy controls were determined at the distal non-dominant radius and tibia using HR-pQCT (XtremeCT; Scanco Medical AG, Bassersdorf, Switzerland). Scans were performed by a specialized technologist. The arm and leg of the subject were positioned in the scanner and were immobilized during the examination in an anatomical carbon fiber shell. Scans were repeated in the event of significant motion. The region of interest was defined by manual placement of a reference line at the endplate of the radius or tibia, with the first slice 9.5 and 22.5 mm proximal to the reference line at the radius and tibia, respectively. A stack of 110 parallel CT slices was obtained at the distal end of both sites with a nominal voxel size of 82 μm. This provided a three-dimensional image of approximately 9 mm in the axial direction. Image processing and calculation of numerical values were performed using Scanco software. The analysis methods had been previously described, validated ex vivo against the gold standard μ-CT at the radius and tibia and applied in various clinical studies [27–30]. Briefly, the volume of interest was automatically separated into cortical (Ct.BMD) and trabecular (Tb.BMD) regions. Cortical Thickness (Ct.Th) was defined as the mean cortical volume divided by the outer bone surface. The high isotropic resolution of HR-pQCT permitted direct 3D assessment of trabecular number (Tb.N) but all other trabecular microarchitecture parameters required calculation. Trabecular bone volume to tissue volume ratio (BV/TV) (%) was derived from trabecular density (Tb. BMD), assuming the density of fully mineralized bone to be 1.2 g HA/cm^3 (BV/TV = 100 × Tb. BMD/1200 mg HA/cm^3). Trabecular thickness (Tb. Th.), spacing (Tb. Sp.) and the intra-individual distribution of separation (Tb. Sp.SD), a parameter that reflects the heterogeneity of the trabecular network, were derived from BV/TV and Tb. N. using formulas from traditional quantitative histomorphometry.

Quality control of the scanner was performed on a daily basis before the measurement of the first patient and using a phantom provided by the manufacturer. The coefficient of variation (CV) of the method had been previously published by our group [31], performing two consecutive measurements with full repositioning in 56 women. Reproducibility of volumetric BMD measurements ranged from 0.5 to 0.8% in premenopausal women. Reproducibility of structural parameters was slightly lower ranging from 0.4% to 3.1%, which was similar to what others had published for this method [30].

HR-pQCT scans were performed in the period of time between diagnosis and up to one month after Gluten Free Diet initiation.

2.4. Areal bone density

Areal BMD at the lumbar spine (L1 to L4), femoral neck and distal radius was measured in all patients and controls by DXA (Lunar Prodigy Advance-Soft 13.6. GE Healthcare; USA). Bone mineral density was reported as g/cm^2 and z-score as recommend by the International Society for Clinical Densitometry (ISCD) for premenopausal women [32]. A negative z-score below 2 or lower was defined as ¨ below the expected