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A case–control study of fractures in men with idiopathic osteoporosis: Fractures are associated with older age and low cortical bone density

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ABSTRACT

Objectives: To determine biochemical, radiological and micro-architectural bone factors related to fragility fractures in idiopathic male osteoporosis (IMO) patients. IMO is a rare disorder characterized by low areal bone mineral density (aBMD) (Z-score < -2) occurring in men after excluding secondary causes of low BMD.
Methods: We conducted a case–control study in 31 patients with fragility fracture (IMO F+) that had occurred after the age of 40 years and 37 without fracture (IMO F–). We first compared IMO group to 40 age-matched disease-free men. We measured aBMD and bone micro-architectural indices at distal radius and tibia sites with a HR-pQCT scan (XtremeCT) using standard and extended cortical analysis. Urine and blood samples were collected in order to determine the levels of bone-turnover markers and the potential determinant of bone fragility. Models of analysis of covariance, including age, height and weight as adjustment factors, were used to compare the groups.
Results: Compared to their controls, IMO patients showed marked disturbance of their micro-architectural parameters at tibia and radius affecting both trabecular and cortical parameters. IMO F+ subjects were significantly older than IMO F− subjects (58 ± 8 vs. 53 ± 9 yrs, $p = 0.01$). BMD Z-score at the total-hip was significantly lower in IMO F+ (-1.3 ± 0.5 vs. -0.9 ± 0.8 g/cm^2, $p = 0.01$). After adjustment, trabecular micro-architectural parameters, biochemical markers and hormonal parameters were not different in the 2 groups. At distal tibia, cortical v-BMD was significantly lower in IMO F+ patients (799 ± 73 vs. 858 ± 60 mg/cm^3, $p = 0.03$), while cortical thickness was not different.
Conclusion: Our results show that patients with IMO display a marked disturbance of trabecular and cortical bone micro-architecture, and that age and low cortical density are determinants of the fracture occurrence.
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Introduction

Among the young and middle-aged men referred for the investigation of osteoporosis, no secondary cause of osteoporosis can be identified in some of them by relevant clinical and biological investigations. These men are considered to have idiopathic male osteoporosis (IMO), on the basis of a low areal bone mineral density (aBMD) defined by a Z-score below-2 [1–3]. Idiopathic male osteoporosis is a multifactorial condition [4]. Bone histomorphometry [5], molecular biology [5] and osteoblast cultures [6] point to decreased bone formation. Familial investigations emphasize that deficiency in bone mass acquisition might be genetically determined [1]. It has been suggested that the role of IGF1, a significant determinant of peak bone mass attainment in men [7], may be a major factor [8]. Other studies have suggested that decreased free estradiol may be responsible for the decreased cortical thickness of patients with IMO [9,10].

Only some of these patients would go on to experience fragility fractures [1,2] and it is not clear what underlying difference this reflects. The determinants of fragility fractures in these men with IMO are poorly understood. Furthermore, so far there is no consensus about the clinical management of men with idiopathic osteoporosis without fractures [11]. Indeed, it is not clear to what extent such patients should be treated with bisphosphonate or teriparatide, which have been reported to decrease the fracture rate in older men [4].

Therefore, our aim in this study was to identify the factors associated with fragility fractures in order to improve the clinical management of these IMO patients. We hypothesized that IMO patients with prevalent fractures would have more severe disturbance of their bone architecture and/or higher bone remodeling, both parameters being possibly responsible for fragility fractures. We therefore performed a case–control

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study to find out whether there were any biochemical or structural differences between idiopathic osteoporosis with or without fractures. We had previously found that IMO patients with vertebral fractures had trabecular and cortical micro-architectural changes at the iliac crest using bone histomorphometry. Interestingly, we observed no change in cortical thickness, but did observe an increase in cortical porosity [12]. Bone biopsy is an invasive procedure that cannot be used to decide what treatment is appropriate. Consequently, we used XtremeCT Scanco Medical AG, an instrument that can be used to investigate the micro-architecture at the peripheral bones, and also provides further information about bone fragility in postmenopausal osteoporosis [13] and older men [14]. We therefore recruited patients with IMO, and decided to compare biochemical and micro-architectural parameters in patients with and without prevalent fragility fractures.

Material and methods

Patients

This was a non-interventional, cross-sectional study with no individual benefit. The patients were recruited at Lariboisière Hospital (Paris France) by physician referral. The inclusion criteria for IMO were male gender, age between 40 and 70 years, with a Z-score <-2 at one of the 3 sites measured: ultradistal radius, lumbar spine or femoral neck. The patients underwent a detailed historical, physical and biochemical evaluation to exclude secondary cause of osteoporosis. The exclusion criteria were treatment with corticosteroids for more than 3 months, known HIV positivity, a chronic inflammatory condition (rheumatoid arthritis, inflammatory colitis). Patients who had received bisphosphonate treatment for more than 3 years or during the last 6 months before the inclusion were excluded as we expected that this delay would attenuate interference of the treatment with the BMD measurement. Patients that had received teriparatide were excluded. Patients were included if they were Caucasian, had normal basal biochemical screening results, including serum calcium, phosphate, alkaline phosphatase, gammaglutamyl transferase, T4 and TSH and testosterone in order to exclude osteomalacia, chronic liver disease and overt hypogonadism and thyrotoxicosis. All the patients had a measurement of urinary cortisol to exclude Cushing syndrome. All the patients signed an informed consent form. The study obtained authorization from the local Ethics Committee (CPP Ile de France III), and was performed in accordance with the current Helsinki Declaration. The patients also completed a questionnaire about family history of fractures, and nutritional habits.

Patients completed a questionnaire about previous fractures. All fractures were to be reported, irrespective of site, with the date and the circumstances. Peripheral fractures were ascertained by review of radiograph reports. All the patients underwent a lateral X-ray of the spine at inclusion. Vertebral fractures (VFx) were assessed blindly by two physicians according to the Genant classification, and only grade-2 fractures and above were considered [15]. We classified patients according to the presence (IMO F+, $n=31$) or absence (IMO F−, $n=37$) of a low-trauma fragility fracture (i.e. a fracture at femoral neck, wrist, humerus, rib or a VFx) occurring after age 40 years. Patients were included in the study at least 3 months after a fracture in order not to interfere with bone markers measurements.

We also recruited 40 age- and sex-matched control subjects ($n=40$) who were current or former employees of our hospital (physicians, researchers etc…) or members of their families. To qualify as normal controls, these volunteers were required to have normal aBMD by DEXA (Z-score >-1) at each site measured, and no history of low-trauma fracture. They did not have a systematic X-ray of the spine. The same exclusion criteria were used as for the IMO patients. The controls underwent bone densitometry and micro-architectural (XtremeCT, Scanco Medical AG) measurements, and filled out the same questionnaire as the IMO patients.

Dual-energy X-ray absorptiometry (DXA)

BMD was measured at the femoral neck, at the lumbar spine (L1–L4) and at the distal radius at the inclusion visit using the same Lunar DPX-L (Lunar Corp., Madison, WI, USA) densitometer operated by the same technician. Age-adjusted values were based on a French reference population between 20 and 89 years of age from several centers (provided by Lunar France).

Bone micro-architecture measurements

Image registration

Volumetric BMD (vBMD) and micro-architectural parameters were assessed at the nondominant distal radius and right distal tibia by HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). The arm or leg of the patient was immobilized in a carbon fiber shell. An anteroposterior scout view was used to define the measured volume of interest (VOI) [13]. At each site, a stack of 110 parallel CT slices with an isotropic voxel size of 82 μm was obtained, thus delivering a three dimensional representation of ~9 mm in the axial direction. The most distal CT slice was located 9.5 mm and 22.5 mm proximal to the endplate of the radius and tibia, respectively. Quality control was performed by daily scans of a phantom containing rods of HA (densities of 0 to 800 mg HA/cm^3) embedded in a soft-tissue equivalent resin (QRM, Moehrendorf, Germany).

Standard analysis

The VOI was separated into cortical and trabecular regions using a threshold-based algorithm. This threshold was set automatically to one third of cortical vBMD (Dcort). Cortical thickness (Ct.Th) was defined as the mean cortical volume divided by the outer bone surface. Trabecular vBMD (Dtrab, mg HA/cm^3) was computed as the average vBMD in the trabecular VOI. The trabecular bone volume (BV) fraction [BV/trabecular volume (TV), %] was derived from Dtrab, assuming fully mineralized bone to have a mineral density of 1200 mg HA/cm^3 [i.e. BV/TV (%) $=100\times$(Dtrab (mg HA/cm^3)/1.2 g HA/cm^3)]. Trabecular elements were identified by the mid-axis transformation method, and the distance between them assessed 3-dimensionally by the distance transform method. The trabecular number (Tb.N, mm^{-1}) was defined as the inverse of the mean spacing of the mid-axes. Trabecular thickness (Tb.Th, mm) and separation (Tb.Sp, mm) were derived from BV/TV and Tb.N: Tb.Th $=$ (BV/TV)/Tb.N and Tb.Sp $=(1-$BV/TV)/Tb.N). CV for parameters at the radius and tibia were respectively as follows: cortical area (Ct.Ar) 0.7% and 0.5%, trabecular area (Tb.Ar) 0.2% and 0.4%, total vBMD (Dtot) 0.8% and 0.5%, Dcort 0.8% and 0.4%, cortical perimeter (Ct.Pm) 0.4% and 0.2%, Ct.Th 1% and 0.6%, Dtrab 0.8% and 0.6%, BV/TV 0.8% and 0.7%, Tb.N 5.8% and 4.9%, Tb.Th 5.6% and 4.4%, Tb.Sp 5.6% and 5.2%, and Tb.N.SD 10.9% and 5.3%.

Extended cortical analysis

In order to measure the cortical parameters more accurately, we used the software collaboratively developed and implemented in the scanner Manufacturer's Image Processing Language (IPL v5.08b, Scanco Medical AG) and incorporated via extension into the Manufacturer's visualization and analysis software (μCT Evaluation v6.0, Scanco MedicalAG, Brüttisellen, Switzerland). In this technique [16,17], the image-processing algorithms applied automatically segment the cortical compartment and intracortical pore volume. Quantitative measures of cortical thickness, geometry, density, and porosity are also performed. The cross sectional area of the total (Tt.Ar, mm^2) and cortical areas (Ct.Ar, mm^2) are calculated on a slice-by-slice basis. The mineral volume density of the cortical tissue (Dcort mg HA/cm^3) is the apparent density of the cortex including the pore spaces. A 3D calculation of

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