Idiopathic osteoporosis in premenopausal women. Clinical characteristics and bone remodelling abnormalities

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Abstract

Objective

Osteoporosis is infrequent in young premenopausal women and is often associated with secondary disorders. However, idiopathic osteoporosis may be found in this setting and few data are known on this condition. Therefore, the aim of this study was to analyse the clinical characteristics and bone remodelling abnormalities in premenopausal women with idiopathic osteoporosis.

Methods

28 premenopausal women with idiopathic osteoporosis (aged 38.3±7.6 years) were included. The patients had one or more fragility fractures and/or decreased bone mass (z-score < -2 in the lumbar spine or femur). In all patients, secondary causes of osteoporosis were excluded and previous skeletal fractures, family history and risk factors for osteoporosis were recorded. In addition, bone mineral density at the lumbar spine and hip, spinal x-rays, and laboratory tests including PTH, 25-hydroxyvitamin D, 1,25 (OH)₂ vitamin D and urinary calcium excretion were measured. Bone markers such as serum bone alkaline phosphatase (bone AP) and P1NP, and urinary hydroxyproline (HYP), NTx and CTx were measured and results were compared with those observed in a control group of 28 healthy premenopausal women.

Results

46% of the patients had previous fragility fractures, 53% had family history of osteoporosis, 36% had associated hypercalciuria and 30% had a BMI <20 Kg/m². Patients with idiopathic osteoporosis had increased bone resorption markers (NTx and HYP) but normal bone formation markers when compared with healthy controls. No significant differences in the clinical and biochemical parameters were observed between patients with or without hypercalciuria.

Conclusion

Young women with idiopathic osteoporosis have an increased bone resorption without changes in bone formation when assessed by biochemical markers.

Key words

Primary osteoporosis, premenopausal osteoporosis, bone turnover, low bone mass, bone markers.
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Introduction
Osteoporosis is an uncommon disorder in young individuals. Nevertheless, because of the Gaussian distribution of bone mineral density (BMD) values, it could be expected that nearly 0.5% of this population would have low densitometric values, that is, a bone mass below 2.5 T-score (1). Indeed, in our country 0.34% of women aged 20 to 44 years have a lumbar T-score of -2.5 or less (2). In young individuals osteoporosis is frequently associated with secondary disorders. However, idiopathic disease is also a common cause of osteoporosis in these patients (3-6). Although little is known about this process it is likely that its pathogenesis is heterogeneous. In fact, findings such as low levels of IGF-I, increased interleukin 1, decreased β-estradiol levels, history of delayed puberty or an osteoblastic dysfunction, among others, have been reported (7-11). In addition, we have previously described some clinical characteristics in patients with idiopathic osteoporosis such as younger age, frequent association with hypercalciuria and family history of osteoporosis, the latter further suggesting a genetic role in some of these patients (3, 6). Moreover, few studies have focused on the characteristics of bone turnover in this process, and when assessed, they showed variable results. Thus, in some cases a decrease in bone formation parameters has been reported (9, 10, 12, 13), whereas in others an increase in bone resorption has been indicated (14).

Therefore, the aim of this study was to analyse the clinical features and bone remodelling characteristics in premenopausal women with idiopathic osteoporosis.

Patients and methods
Twenty-eight premenopausal Caucasian women with idiopathic osteoporosis aged 20-50 years (mean age±standard deviation (SD) 38.3±7.6 years) were included in the study. The patients had one or more fragility fractures and/or decreased bone mass, i.e., a Z-score <-2 in the lumbar spine or femur (15). In all patients secondary causes of osteoporosis were excluded and previous skeletal fractures, renal lithiasis, weight, height, body mass index (BMI), and family history of osteoporosis were recorded, as well as dietary calcium intake and current and past consumption of alcohol and tobacco. Daily dietary calcium intake was based on a food frequency questionnaire and alcohol consumption was recorded as number of drinks per week. No patient reported delayed menarche or menstrual irregularities. Standard radiographs of the spine were obtained in all patients to evaluate the presence of vertebral fractures as well as BMD measurements at the lumbar spine and femoral neck (Lunar DPX-L). The coefficients of variation were 0.8% and 2.3% for lumbar spine and femoral neck, respectively. Vertebral fracture was defined as a reduction ≥20% in the anterior, middle, or posterior height of the vertebral body when compared with the adjacent, undeformed vertebra. Idiopathic osteoporosis was diagnosed after excluding secondary causes for low bone mass and fragility fractures.

Informed consent was obtained from all the subjects, and the study was approved by the Ethics Committee of the Hospital.

Biochemical determinations and markers of bone turnover
Blood and second morning urine samples were obtained between 8:00 and 10:00 a.m after an overnight fast. Automated biochemical profile and complete blood cell count were determined in all patients, as well as serum calcium, phosphate, 25-hydroxyvitamin D (25-OHD), 1,25-dihydroxyvitamin D (1-25OH,D) and parathyroid hormone (PTH), and 24-hour urinary calcium excretion. Hypercalciuria was defined as a urinary calcium excretion >4mg/kg/day.

The bone formation markers measured were: serum bone alkaline phosphatase (bone AP) (Tandem-R Ostase; Beckman Coulter, Fullerton, CA, USA) and procollagen type I N propeptide (P1NP) (Intact PINP; Orion, Espoo, Finland). The markers of bone resorption measured were: N-terminal cross-linking telopeptide of type I collagen (NTx) and C-terminal cross-linking telopeptide (β-CTX), both measured in urine by enzyme immunoassays (Osteomark;
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Ostex International Inc, Seattle, WA, USA and CrossLaps ELISA; and urinary hydroxyproline (HYP), which was measured by high-performance liquid chromatography. Urine determinations were expressed in relation to creatinine excretion.

Reference values of markers of bone turnover were obtained from 28 healthy premenopausal women of similar ages (control group).

Statistical analysis
All data are expressed as mean±SD (standard deviation of the mean). To analyse differences between continuous variables, the Wilcoxon test was used. Differences between proportions were assessed by the Chi square test. The Spearman’s rank correlation test was used for correlation studies. A p-value of <0.05 was considered statistically significant.

Results
Fourteen patients (50%) had previous skeletal fractures (12 had peripheral fractures, 4 had vertebral fractures; 2 patients presented with both peripheral and vertebral fractures), 53% had family history of osteoporosis, 30% had a BMI <20 kg/m², 36% of the patients had associated hypercalciuria and 25% had previous renal lithiasis (most of these patients, 5 out of 7 (71%), had associated hypercalciuria). The clinical characteristics of the patients are shown in Table I. The mean calcium intake was 761.2±334 mg/day, but 35% of the patients had calcium intake lower than 500 mg/day, and only 39% of them had a dietary calcium intake higher than 1000 mg/day. Alcohol consumption was reported in 10% of the patients, but in all of them alcohol consumption was one drink or less per week. Eleven patients (39%) were smokers.

Patients with idiopathic osteoporosis showed an increase in bone resorption markers with significantly higher urinary values of NTx (42.7±23 vs. 28.5±14.2 nM BCE/mM, p<0.05) and HYP (121.1±104 vs. 63.4±23 mmol/mg, p=0.007) when compared to controls (Table II and Fig. 1); conversely, urinary β-CTX (another bone resorption marker) and bone formation markers, P1NP and bone AP, were similar to controls (Table II). When patients with idiopathic osteoporosis were compared according the presence or absence of hypercalciuria, no significant differences were observed in lumbar or femoral BMD between either group of patients. In addition, when patients with idiopathic osteoporosis were compared, classified according to the presence or absence of skeletal fractures, no significant differences in clinical, densitometric and biochemical parameters (including bone markers)
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were observed between either group of patients (Table II).

When correlations among biochemical markers were evaluated, NTx and β-CTx were the only bone markers that showed a significant correlation ($r=0.762$, $p=0.028$) in women with idiopathic osteoporosis (Table III).

### Discussion

This study shows that young women with idiopathic osteoporosis may present various clinical features, such as frequent family history of osteoporosis, low BMI and calcium intake and, in a subset of patients, hypercalciuria. In addition, the bone turnover in these patients is characterized by an increase in bone resorption markers.

Idiopathic osteoporosis is a relatively common cause of osteoporosis in young individuals, constituting in some series nearly 50% of the cases (2-6). However, although there are few studies focusing on the pathogenesis of this disorder, it is likely that there are various mechanisms related to this condition. Indeed, family history of osteoporosis was observed in more than 50% of our patients, and idiopathic hypercalciuria and low BMI were observed in more than 30% of them; Most of these findings have been previously described (3, 4, 16, 17).

The features of bone remodelling in idiopathic osteoporosis in previous studies are variable and mostly described in men, with some patients having evidence of a defect in osteoblast function, whereas others having increased bone resorption (9-14). Thus, studies including histomorphometric analysis showed heterogeneous findings with a predominance of impaired osteoblast function with low bone formation rate and increased eroded surface, both suggesting that these patients have uncoupling between resorption and formation. Because an increase in bone formation...
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would be expected, in order to balance increased bone resorption, these studies suggested that this would be indicative of an osteoblastic dysfunction (10, 13, 32). These results were similar in both genders (9, 12).

When bone turnover markers have been analysed, either non significant changes (21, 33) or an increase in bone resorption have both been observed (7, 14). Similarly, in our patients we have observed an increase in bone resorption markers. Thus, patients with idiopathic osteoporosis showed increased NTx and HYP values when compared to controls. Conversely, bone formation markers, such as bone AP and P1NP, were similar to controls and no correlations were observed between bone formation and bone resorption markers, further suggesting that there is an imbalance in bone remodelling in these patients. In addition, we did not observe significant differences in bone markers when patients were analysed according to the presence of associated hypercalciuria or previous skeletal fractures. Interestingly, urinary β-CTX, another bone resorption marker, though positively correlated with NTx, was not increased in these patients. Although the reasons for such discrepancies are not completely known, the special characteristics of this marker may partly explain this finding. Thus, the type I collagen C-telopeptide, CTx, contains a site, the aspartic acid residue which is susceptible to undergoing a β-isomerization. This spontaneous nonenzymatic post-translational modification results in a structural perturbation of the peptide backbone, which is believed to be associated with the ageing of proteins. So, in healthy adults, the isomerization process seems to reach an equilibrium, and nearly 70% of the type I collagen molecules from normal bone are isomerized (34). However, in some clinical conditions such as growing children, fractures and Paget’s disease among others, the nonisomerized (α-CTX) molecule is the predominant collagen form (34-37). We hypothesize that the age of our patients could have influenced these results. In fact, it is possible that in this group of patients, the determination of α-CTX instead of β-CTX could be more appropriate for evaluating bone resorption due to the younger age of patients and, consequently, of the bone. Indeed, premenopausal women have higher α-CTX/β-CTX ratios (>1) that postmenopausal women, who showed ratios below 1 (35, 38), and this ratio tends to be higher in younger people (36, 38). Unfortunately, we did not determine the urinary levels of α-CTX in order to confirm this hypothesis. Nevertheless, it should be noted that the reference values of bone markers from control premenopausal healthy women used in this study are very close to those recently reported in the same group of population (39), further supporting the value of our results.

All these data indicate that the evaluation of bone turnover markers in premenopausal women with osteoporosis should be cautiously analysed taking into account the special characteristics of this population.

In conclusion, bone turnover in young women with idiopathic osteoporosis is characterized by an increase in bone resorption. In this condition, associated factors such as family history of osteoporosis, hypercalciuria and low BMI are frequent.

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