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/m^2. 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-dyhydroxyvitamin D (1-25OH_2D) 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;

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 Willcoxon 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/m^2, 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 nmol/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 in the analysed clinical (BMI, family history of osteoporosis, skeletal fractures, calcium intake, renal lithiasis, lifestyle habits) and biochemical parameters (PTH, 25-OHD, 1-25 OHD, bone markers) were found between both groups of patients, except for a higher urinary calcium excretion in hypercalciuric patients (147±56 *vs.* 276±63 mg/24h, $p<0.001$). Nor were significant differences 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)

Table I. Clinical characteristics of the patients.

	Patients with idiopathic osteoporosis n=28
Age (years)	38.3 ± 7.6
Age at menarche (years)	12.9 ± 1.3
BMI (kg/m^2)	21.7 ± 2.9
Weight (kg)	54.9 ± 9
Height (cm)	158,9 ± 7.6
Calcium intake (mg/day)	761.2 ± 334
Family history of osteoporosis (%)	53 %
Current smokers (%)	39 %
Alcohol intake (%)	
≤1 drink per day	10%
>1 drink per day	–
Renal lithiasis (%)	25 %
Previous fracture (%)	
Any site	50 %
Peripheral	43 %
vertebrae	14 %

Data are expressed as means±SD.
BMI: body mass index.

Table II. Bone mass, biochemical parameters and bone markers in women with idiopathic osteoporosis.

	Normal values	Idiopathic OP n=28	With HYPC n=10	Without HYPC n=18
Lumbar Z-score	-	-2.3 ± 0.4	-2.4 ± 0.5	-2.2 ± 0.4
Femur Z-score	-	-1.3 ± 0.4	-1 ± 0.8	-1.5 ± 0.6
PTH pg/ml	10-65	33.6 ± 10	30 ± 8	35.3 ± 11
25-OHD ng/ml	15-42	21.8 ± 7.7	23.4 ± 8.2	20.8 ± 7.5
1-25 OHD pg/ml	18-70	32.5 ± 14	35.2 ± 12	30.1 ± 16
Bone AP ng/ml	11.9 ± 4	10.3 ± 6.7	8.5 ± 3	11.7 ± 8.5
P1NP ng/ml	30 ± 11	36 ± 13.7	38.6 ± 9.6	33.8 ± 16.9
HYP nmol/mg	63.4 ± 23	121.1 ± 104*	141.9 ± 133*	110.7 ± 92*
NTx nM BCE/mM	28.5 ± 14.2	42.7 ± 23*	51.6 ± 29*	36.1 ± 15
β-CTx mg/mM	130.5 ± 54	113.9 ± 68	103.9 ± 4	117.3 ± 80

Data are expressed as mean±SD
*$p<0.05$ compared to control group.
HYPC: hypercalciuria; 25-OHD: 25-hydroxyvitamin D; 1-25OH$_2$D: 1.25-dyhydroxyvitamin D; PTH: parathyroid hormone; HYP: hydroxyproline; Bone AP: bone alkaline phosphatase; P1NP: procollagen type I N propeptide; NTx: N-terminal cross-linking telopeptide of type I collagen; β-CTx: C-terminal cross- linking telopeptide of type I collagen.

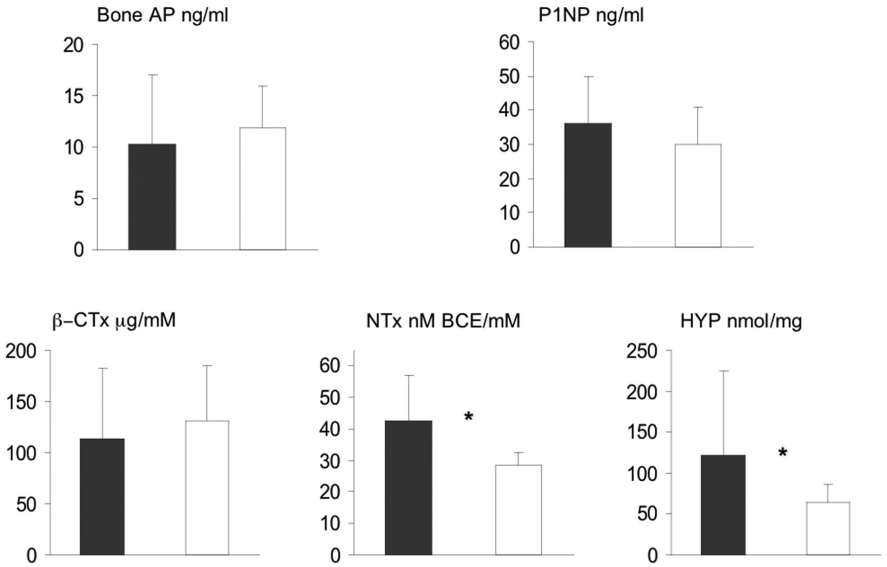

Fig. 1. Bone markers of bone turnover in patients and controls. The grey bars show the values of patients with idiopathic osteoporosis and the white bars show the values of controls. *p<0.05 patients *vs*. controls. For other abbreviations see Table II.

Table III. Correlations between markers of bone turnover in women with idiopathic osteoporosis.

	P1NP	Bone AP	NTx	β-CTx
Bone AP	0.446 (0.268)			
NTx	0.356 (0.282)	0.423 (0.223)		
β-CTx	0.509 (0.243)	0.705 (0.051)	0.902 (0.002)	
HYP	0.327 (0.474)	0.244 (0.470)	0.373 (0.410)	0.606 (0.202)

Spearman rank correlation coefficients. Significance level in parentheses.
For other abbreviations see Table II.

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 hypercalcuria and low BMI were observed in more than 30% of them; Most of these findings have been previously described (3, 4, 16, 17).

The strong family history of osteoporosis in premenopausal osteoporotic women provides further support for current theories of genetic predisposition to osteoporosis. Indeed, previous reports indicated a high frequency of low bone mass in the relatives of individuals with idiopatic osteoporosis (18, 19) and nearly 50% of young women with maternal history of osteoporosis had low bone mass (20). In addition, recent findings point towards a major contributory role of a genetically determined maturational defect in bone acquisition in the pathogenesis of idiopathic osteoporosis (21). Additional contributing factors, such as low calcium intake, tobacco consumption and low body weight, frequently observed in our patients, may favour the development of osteoporosis in these individuals. Thus, only 39% of the women in the present study had an acceptable dietary calcium intake, nearly 40% of them were current smokers and 30% had a BMI lower than 20. All these factors have been previously related to low bone mass and fractures in young premenopausal women (22-26).

Hypercalciuria and renal lithiasis have also been associated with bone loss and osteoporosis in some, but not all studies (27-29). Although hypercalciuria could be considered as a secondary cause of osteoporosis, the mechanism of bone loss in this process is still unclear, this fact probably explains the inclusion of this disorder in the subgroup of patients with idiopathic disease (10, 30) and was the cause of the inclusion of these patients in our study. Thus, several factors may be involved in bone loss in idiopathic hypercalciuria, including increased prostaglandin E2 production, a negative calcium balance due to a reduction in renal tubular calcium resorption and an increased activity of cytokines, including tumour necrosis factor α, interleukin 1 and granulocyte macrophage stimulating factor (8, 31).

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

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 nonenzimatic 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 postmenopusal 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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References

1. KANIS JA, DELMAS P, BURCKHARDT P, COOPER C, TORGERSON D: Guidelines for diagnosis and management of osteoporosis. *Osteoporos Int* 1997; 7: 390-406.
2. DÍAZ CURIEL M, GARCÍA JJ, CARRASCO JL *et al*.: Prevalencia de osteoporosis determinada por densitometría en la población femenina española. *Med Clin* (Barc) 2001; 116: 86-8.
3. PERIS P, GUAÑABENS N, MARTÍNEZ DE OSABA MJ *et al*.: Clinical Characteristics and etiologic factors of premenopausal osteoporosis in a group of Spanish women. *Semin Arthritis Rheum* 2002; 32: 64-70.
4. MOREIRA KULAK CA, SCHUSSCHEIM DH, MCMAHON DJ *et al*.: Osteoporosis and low bone mass in premenopausal and perimenopausal women. *Endocr Pract* 2000; 6: 296-304.
5. KAUFMAN JM, JOHNELL O, ABADIE E *et al*.: Background for studies on the treatment of male osteoporosis: state of the art. *Ann Rheum Dis* 2000; 59: 765-72.
6. PERIS P, MARTÍNEZ MA, MONEGAL A *et al*.: Etiology and clinical characteristics of male osteoporosis: have they changed in the past few years? *J Bone Miner Res* 2006; 21 (Suppl. 1): S177.
7. PIETSCHMANN P, KUDLACEK S, GRISAR J *et al*.: Bone turnover markers and sex hormones in men with idiopathic osteoporosis. *Eur J Clin Invest* 2001; 31; 444-51.
8. GHAZALI A, FUENTES V, DESAINT C *et al*.: Low bone mineral density and peripheral blood monocyte activation profile in calcium stone formers with idiopathic hypercalciuria. *J Clin Endocrinol Metab* 1997; 82: 32-8.
9. JOHANSSON AG, ERIKSEN EF, LINDH E *et al*.: Reduced serum levels of growth hormone-dependent insulin-like growth factor binding protein and a negative bone balance at the level of individual remodelling units in idiopathic osteoporosis in men. *J Clin Endocrinol Metab* 1997; 82: 2795-88.
10. KHOSLA S, LUFKIN EG, HODGSON SF, FRITZPATRICK LA, MELTON LJ 3RD: Epidemiology and clinical features of osteoporosis in young individuals. *Bone* 1994; 15: 551-5.
11. CALÒ L, CASTRIGNANO R, DAVIS PA *et al*.: Role of insulin-like growth factor-I in primary osteoporosis: a correlative study. *J Endocrinol Invest* 2000; 23: 223-7.
12. CIRIA-RECASENS M, PEREZ-EDO L, BLANCH-RUBIO J *et al*.: Bone histomorphometry in 22 male patients with normocalciuric idiopathic osteoporosis. *Bone* 2005; 36: 926-30.
13. DONOVAN MA, DEMPSTER D, ZHOU H, MCMAHON DJ, FLEISHER J, SHANE E: Low bone formation in premenopausal women with idiopathic osteoporosis. *J Clin Endocrinol Metab* 2005; 90: 3331-6.
14. RUBIN MR, SCHUSSHEIM DH, KULAK CAM *et al*.: Idiopathic osteoporosis in premenopausal women. *Osteoporos Int* 2005; 16: 526-533.
15. LEIB ES, LEWIECKI EM, BINKLEY N, HAMDY RC: Official positions of the International Society for Clinical Densitometry. *J Clin Densitom* 2004; 7: 1-5.
16. PERIS P, GUAÑABENS N, MONEGAL A *et al*.: Aetiology and presenting symptoms in male osteoporosis. *Br J Rheumatol* 1995; 34: 936-41.
17. GOURLAY ML, BROWN SA: Clinical considerations in premenopausal osteoporosis. *Arch Intern Med* 2004; 164: 603-14.
18. COHEN-SOLAL ME, BAUDOIN C, OMOURI M, KUNTZ D, DE VERNEJOUL MC: Bone mass in middle-aged osteoporotic men and their relatives: familial effect. *J Bone Miner Res* 1998; 13: 1909-14.
19. ERBAS B, RISTEVSKI S, POON C, YEUNG S, EBELING PR: Decreased spinal and femoral neck volumetric bone mineral density (BMD) in men with primary osteoporosis and their first-degree male relatives: familial effect on BMD in men. *Clin Endocrinol* 2007; 66: 78-84.
20. DANIELSON ME, CAULAY JA, BAKER CE *et al*.: Familiar resemblance of bone mineral density (BMD) and calcaneal ultrasound attenuation: the BMD in mothers and daughters study. *J Bone Miner Res* 1999; 14: 102-10.
21. VAN POTTELBERGH I, GOEMAERE S, ZMIERCZAK H, DE BACQUER D, KAUFMAN JM: Deficient acquisition of bone during maturation underlies idiopathic osteoporosis in men: evidence from a three-generation

family study. *J Bone Miner Res* 2003; 18: 303-11.
22. MEIN AL, BRIFFA NK, DHALIWAL SS, PRINCE R: Lifestyle influences on 9-year changes in BMD in young women. *J Bone Miner Res* 2004; 19: 1092-8.
23. LLOYD T, ANDON M, ROLLINGS N *et al*.: Calcium supplementation and bone mineral density in adolescent girls. *JAMA* 1993; 270: 841-4.
24. BARAN D, SORENSEN A, GRIMES J *et al*.: Dietary modification with dairy products for preventing vertebral bone loss in premenopausal women: a three-year prospective study. *J Clin Endocrinol Metab* 1990; 70: 264-70.
25. BLUMM M, HARRIS SS, MUST A, PHILLIPS SM, RAND WM, DAWSON-HUGHES B: Weight and body mass index at menarche are associated with premenopausal bone mass. *Osteoporos Int* 2001; 12: 588-94.
26. HAWKER GA, JAMAL SA, RIDOUT R, CHASE C: A clinical prediction rule to identify premenopausal women with low bone mass. *Osteoporos Int* 2002; 13: 400-6.
27. HELLER HJ, ZERWEKH JE, GOTTSCHALK FA, PAK CYC: Reduced bone formation and relatively increased bone resorption in absortive hypercalciuria. *Kidney Int* 2007; 71: 808-15.
28. GARCÍA-NIETO V, NAVARRO JF, MONGE M, GARCÍA RODRÍGUEZ VE: Bone mineral density in girls and their mothers with idiopathic hypercalciuria. *Nephon Clin Pract* 2003; 94: c89-93.
29. CAUDARELLA R, VESCINI F, BUFFA A *et al*.: Bone mass loss in calcium stone disease: Focus on hypercalciuria and metabolic factors. *J Nephrol* 2003; 16: 260-6.
30. JP BILEZIKIAN, ES KURLAND, CJ ROSEN: Idiopathic osteoporosis in men. *In* ES ORWOLL (Ed.) *Osteoporosis in men. The effects of gender on skeletal health. Academic Press*, San Diego 1999, 395-416.
31. PACIFICI R: Idiopathic hyercalciuria and osteoporosis-Distinct clinical manifestations of increased cytokine-induced bone resorption? *J Clin Endocrinol Metab* 1997; 82: 29-31.
32. PERNOW Y, GRANBERG B, SÄÄF M, WEIDENHIELM L: Osteoblast dysfunction in male idiopathic osteoporosis. *Calcif Tissue Int* 2006; 78: 90-7.
33. LORMEAU C, SOUDAN B, D' HERBOMEZ M, PIGNY P, DUQUESNOY B, CORTET B: Sex hormone-binding globulin, estradiol, and bone turnover markers in male osteoporosis. *Bone* 2004; 933-9.
34. FLEDELIUS C, JOHNSEN AH, CLOOS PAC, BONDE M, QVIST P: Characterization of urinary degradation products derived from type I collagen. *J Biol Chem* 1997; 272; 9755-63.
35. PERIS P, ALVAREZ L, MONEGAL A *et al*.: Effects of surgical menopause and Paget's disease of bone on the isomerization of type I collagen carboxyterminal telopeptide: evolution after antiresoptive therapy. *J Bone Miner Metab* 2002; 20: 117-21.
36. DE LA PIEDRA C, CALERO JA, TRABA ML, ASENSIO MD, ARGENTE J, MUÑOS MT: Urinary α and β C-telopepetides of collagen I: clinical implications in bone remodeling in patients with anorexia nervosa. *Osteoporos Int* 1999; 10: 480-6.
37. ALEXANDERSEN P, PERIS P, GUAÑABENS N *et al*.: Non-isomerized C-telopeptide fragments are highly sensitive markers for monitoring disease activity and treatment efficacy in Paget's disease of bone. *J Bone Miner Res* 2005; 20: 588-95.
38. HOSHINO H, TAKAHASHI M, KUSHIDA K, OHISHI T, INOUE T: The relationships between the degree of β-isomerization of type I collagen degradation products in urine and aging, menopause and osteoporosis with fractures. *Osteoporos Int* 1999; 9: 405-9.
39. DE PAPP AE, BONE HG, CAULFIELD MP, KAGAN R, BUINEWICZ A, CHEN E: A cross-sectional study of bone turnover markers in healthy premenopausal women. *Bone* 2007; 40: 1222-30.