CLINICAL STUDY

The risk of fractures in postmenopausal women with primary hyperparathyroidism

Simona De Geronimo*, Elisabetta Romagnoli*, Daniele Diacinti, Emilio D'Erasmo and Salvatore Minisola

Department of Clinical Sciences, University of Rome 'La Sapienza', Viale del Policlinico 155, 00161 Rome, Italy

(Correspondence should be addressed to E Romagnoli; Email: elisabetta.romagnoli@libero.it)

*(S De Geronimo and E Romagnoli contributed equally to this work)

Abstract

Objective: To evaluate the prevalence of vertebral (vFr) and non-vertebral (nvFr) fractures in postmenopausal women with primary hyperparathyroidism (PHPT).

Materials and Methods: We studied 98 patients with PHPT, divided into 'mild' (M, $n=25$) and 'non-mild' (NM, $n=73$) sub-groups, according to recently published guidelines (2002), and 89 healthy women (C) matched for age, years since menopause and body mass index. vFr was evaluated according to a visual semiquantitative method; bone mineral density (BMD) at the lumbar spine (LS), and femoral sites (femoral neck, FN and total femur, FT) was measured by dual energy X-ray absorptiometry. Volumetric BMD of the third lumbar vertebra (vBMDL3) was also calculated.

Results: The prevalence of vFr was significantly higher ($P<0.001$) in both M and NM PHPT patients compared with C; this prevalence did not differ between M and NM patients. BMD was significantly lower ($P<0.05$) in NM patients compared with both C and M patients. BMD at LS in M patients was also significantly higher with respect to C. Similar results were also obtained for vBMDL3; in M patients, vBMDL3 was also significantly higher compared to C. When M and NM patients were subdivided according to the presence or lack of vFr, no difference was found between fractured and unfractured patients for either BMD or vBMDL3 values.

Conclusions: The risk of vFr is higher in postmenopausal patients with mild PHPT even if BMD appears well preserved. This finding suggests that other factors, such as bone quality, seem to be relevant in determining fracture risk, especially when gonadal function is lacking.

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Introduction

Fracture risk in patients with asymptomatic primary hyperparathyroidism (PHPT) is still a controversial issue, which is difficult to work out on the basis of available data (1, 2). Based upon the densitometric and histomorphometric findings, it may be expected that the cortical skeleton would be at greater risk of fracture with respect to the cancellous skeleton (3, 4). In fact, it has been shown that bone mineral density (BMD) is lower at the cortical site, whereas bone mass is relatively well preserved in trabecular bone (5). Similarly, bone biopsy shows cortical thinning but maintenance of cancellous bone volume (6). These findings suggest that the effect of endogenous parathyroid hormone (PTH) excess is different in trabecular and cortical bones (7). However, a discrepancy between BMD measurement and histology on one hand, and the distribution of fractures on the other had been demonstrated by several retrospective and case-control studies. In fact, some authors have found no increase in the risk of appendicular or

vertebral fractures (8, 9), whereas others have (10–13). Methodological problems could be partially responsible for these conflicting results, since many studies are limited by their design, inadequate control groups, ascertainment biases and, most importantly, imprecise definitions of fracture. This is particularly true regarding the definition of vertebral fracture. In fact, several epidemiological studies have demonstrated that the majority of these fractures are asymptomatic (14); many cases may be treated as 'simple' back pain by general practitioners and X-rays may never be taken. However, morphometric vertebral deformities also increase the risk of both vertebral and non-vertebral fractures and are associated with significant morbidity and mortality (15). The aim of this study was to evaluate the prevalence of vertebral and appendicular fractures in a group of 98 postmenopausal women with PHPT. Female patients should be at higher risk of vertebral fractures because estrogen deficiency would be expected to be associated with the preferential reduction of cancellous bone. If the risk of fractures, particularly subclinical vertebral fractures, is

higher in patients with PHPT, then the evaluation of skeletal involvement, as is presently proposed, needs to be revised.

Materials and methods

Ninety-eight consecutive postmenopausal patients with PHPT (age (mean $\pm$ s.d.), 61.44 ± 8.0 years; years since menopause (YSM), 13.18 ± 9.62), from our Mineral Metabolism Center, were enrolled in the study. They were grouped as 'mild' (M) or 'non-mild' (NM) according to the criteria established by the Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism, recently reviewed by Bilezikian *et al.* (16) as follows: (i) serum calcium greater than 1 mg/dl above the upper limits of normal; (ii) 24-h total urine calcium excretion of more than 400 mg; (iii) creatinine clearance reduced by more than 30% compared to age-matched persons; (iv) bone density at the lumbar spine (LS), hip or distal radius that is more than 2.5 s.d. below peak bone mass (T score < -2.5) (however, for technical reasons we were not able to measure the forearm BMD at the start of the study); and (v) patients under 50 years of age. Based on these widely accepted criteria, only 25 of the 98 patients were considered as suffering from mild disease. In particular, in this group of patients, hypercalcemia was occasionally detected in the course of the standard biochemical evaluation performed in our center on all subjects undergoing BMD measurement. None of the M patients reported either height loss or clinical vertebral fractures at history. In the remaining 73 patients, a severe disease was present; in particular, 13 of them had a history of clinical non-vertebral fractures for minimal/moderate trauma (by convention, falls from standing height or less were considered moderate trauma); 7 and 21 patients were referred to our center by their general practitioners for a comprehensive clinical evaluation of nephrolithiasis and osteoporosis respectively; in 15 patients renal stones were shown by ultrasonography; three were referred for etiologic definition of hypercalcemia; two had a life-threatening episode of pancreatitis. The remaining 12 patients complained of bone pain and/or neuromuscular symptoms. Diagnosis of PHPT was made according to the conventional clinical and laboratory data, including a history of at least 1 year of prolonged hypercalcemia without evidence of a non-parathyroid etiology and unsuppressed serum levels of immunoreactive PTH. Familial hypocalciuric hypercalcemia was excluded because in all cases the ratio of calcium to creatinine clearance was > 0.01 . Clinical diagnosis was confirmed in 61 patients during surgery and by histological examination (removal of a parathyroid adenoma). During the period of the study, no patients took medications (including estrogen) known to influence mineral metabolism.

Eighty-nine healthy postmenopausal women, matched for age, YSM and body mass index (BMI) were concomitantly studied as a control group (C). They were randomly selected from ambulatory postmenopausal women sent by their general practitioners to our hospital as a part of a menopause-screening program. In each woman, medical history, physical examination, and laboratory tests excluded disorders of bone and mineral metabolism. All patients and normal subjects had standardized lateral radiographs in antero-posterior and left lateral projections of the thoracic and LS, centered at T8 and L3 respectively, at a film-focus distance of 115 cm. The radiographs were examined first for quality and then for fractures by an experienced skeletal radiologist. Vertebral deformity was defined, according to the visual semiquantitative method, when anterior, middle, or posterior height loss was more than 20% with respect to the adjacent vertebra (17). This criterion for defining vertebral fracture had a relatively high true-positive rate and low false-positive rate based on the classifications from previous reports (18). None of the patients or normal subjects showed evidence of fracture of the third lumbar vertebra. BMD at the LS in posterior–anterior projection (L1–L4) (LS-BMD) and femoral sites (femoral neck, FN-BMD and total hip, FT-BMD) was measured in each patient and healthy subject by dual energy X-ray absorptiometry (DEXA) technique using a QDR 4500A (Hologic, Inc., Bedford, MA, USA). In order to recognize the influence of bone size on bone fragility, we also calculated volumetric BMD of the third lumbar vertebra (vBMD-L3) according to the method described by Duan and coworkers (19). Vertebral body volume (V) was estimated as $V = A^{3/2}$, where A is the projected area of the third lumbar vertebra obtained by posterior–anterior scanning; $vBMD = BMC/V$. The metabolic study included a 24-h urine collection, followed by a fasting short urine collection (from 0800 to 1100 h) along with a blood sample, in order to measure the main parameters of calcium metabolism, as well as PTH and 25-hydroxy-vitamin D (25OHD) serum levels, according to the method described previously (20). All patients and healthy subjects were called together for metabolic evaluation between March and May 2005, in order to minimize the seasonal variation of vitamin D status. The study was approved by the local Ethics Committee. All subjects gave informed consent.

Statistical analysis

Descriptive statistics are expressed as the mean $\pm$ s.d. for each index. After a test for normality, comparisons between groups were performed by t -test or one-way ANOVA, as appropriate. Differences between frequencies were assessed by χ^2 -analysis. Statistical significance was set at $P < 0.05$.

Results

Main demographic and biochemical variables observed in all the groups examined are reported in Table 1. As can be seen, no difference was found between M and NM PHPT patients and C in age, YSM, height, and BMI. As expected, in NM patients, serum total and ionized calcium, PTH levels and fasting urinary calcium/creatinine excretion were significantly higher compared with M patients. Renal function was also reduced in NM patients. However, serum levels of 25OHD did not differ among the three groups. Values regarding BMD, vBMD-L3, and related variables (bone mineral content, BMC and volume) are reported in Table 2. As shown, in M patients, BMD values were higher compared with C; this difference was significant for LS-BMD ($P < 0.05$). Moreover, M patients show significantly higher values of vBMD-L3 with respect to C because of a significant increase in BMC ($P < 0.05$). In NM patients, BMD at any site and vBMD were significantly lower with respect to both M patients and C. Furthermore, when classifying patients by quartiles of PTH serum levels, vBMD values significantly decreased from the lowest to the highest quartile of PTH ($P = 0.033$ by ANOVA). In Table 3, the distribution of vertebral (vFr) and non-vertebral (nvFr) fractures in the two subgroups of patients is reported, compared with that found in healthy women. M patients had a significantly higher percentage of vFr (44%) than C ($P < 0.001$). The percentage of vFr was also significantly higher in NM patients compared with C (47 vs 9%, $P < 0.001$). However, the percentage of vertebral fractures did not differ between M and NM patients. As far as nvFr are concerned, no difference was found between NM patients and C. When M and NM patients were subdivided according to the presence or lack of vertebral fractures, no difference was found

between fractured and unfractured patients in BMD, vBMD-L3, and related variables (Table 4). However, as far as M patients are concerned, those without vertebral fractures show significantly higher values of LS-BMD, BMC, and vBMD compared with C; on the contrary, these variables were not different from C in M patients with vFr. In patients with more severe disease, independent of the presence or absence of vertebral fractures, BMD at both LS and femoral sites was significantly lower compared with C. However, only in fractured NM patients were BMC and vBMD values significantly lower than in C.

Discussion

Few studies have focused on the issue of fracture risk in patients with PHPT. Patients with mild disease should have a reduction in the risk of vertebral fractures due to the anabolic action of the PTH in the cancellous bone. On the contrary, appendicular fractures should be more common, since PTH is catabolic for the cortical skeleton (21). However, these findings are not supported by the two most important epidemiological studies on fracture risk: the study of Koshla *et al.* (11), which enrolled patients with mild PHPT, and the study of Vestergaard and coworkers (10), which was carried out on patients before and after parathyroidectomy, both demonstrated an increase in fracture risk at all the examined sites. Several explanations are plausible for this unexpected increase in vertebral fractures: (i) surveillance bias; (ii) thinning of the cortical rim of the vertebral bodies; (iii) generally higher bone turnover; and (iv) inclusion of patients with lower LS BMD, thus at higher risk. Our study focused on postmenopausal women with PHPT in which, fracture risk should be higher and the disease

Table 1 Main demographic and biochemical variables of healthy postmenopausal women and patients grouped according to the severity of the disease.

	Healthy women (C)	Mild PHPT patients (M)	Non-mild PHPT patients (NM)	P*
n	89	25	73	
Age (years)	60.65 ± 6.92	60.84 ± 6.82	61.65 ± 8.40	n.s.
YSM (years)	11.15 ± 8.99	13.44 ± 10.44	13.09 ± 9.40	n.s.
Height (cm)	159.1 ± 5.9	161.6 ± 6.1	159.9 ± 6.3	n.s.
BMI	24.8 ± 3.1	26.2 ± 3.5	25.1 ± 3.9	n.s.
sCa (mg/dl)	9.53 ± 0.51	10.66 ± 0.39†	11.14 ± 0.96†‡	<0.001
iCa (mmol/l)	1.24 ± 0.02	1.44 ± 0.06†	1.50 ± 0.145†‡	<0.001
P (mg/dl)	3.64 ± 0.49	2.92 ± 0.38†	2.81 ± 0.56†	<0.001
ALP (U/l)	74.04 ± 19.49	106.96 ± 28.49§	171.89 ± 279.19§	<0.001
sCr (mg/dl)	0.84 ± 0.13	0.81 ± 0.13	0.95 ± 0.45	n.s.
ClCr (ml/min)	90.3 ± 18.7	82.8 ± 20.2	69.7 ± 22.4§†	<0.001
25OHD (ng/ml)	19.1 ± 9.5	18.4 ± 5.8	18.0 ± 8.7	n.s.
PTH (pg/ml)	28.8 ± 9.3	82.9 ± 36.7§	168.5 ± 211.1§†	<0.001
u Fasting Ca/Cr (mg/mg)	150.3 ± 80.5	183.0 ± 97.4	263.3 ± 149.6§†	<0.001
u Ca (mg/24h)	158.7 ± 83.0	228.1 ± 90.9§	286.7 ± 135.5§	<0.001

YSM, years since menopause; BMI, body mass index; s, serum; i, ionized; Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; Cr, creatinine; Cl/Cr, clearance creatinine; 25OHD, 25-hydroxy-vitamin D; PTH, parathyroid hormone; u, urinary. *Comparisons were performed by one-way ANOVA. §Significantly different from C, $P < 0.05$; †significantly different from C, $P < 0.001$; ‡significantly different from M patients, $P < 0.05$.

Table 2 Mean $\pm$ s.d. values of bone mineral density and of volumetric bone mineral density, bone mineral content and volume of the third lumbar vertebra in healthy postmenopausal women and patients grouped according to the severity of the disease.

	Healthy women (C)	Mild PHPT patients (M)	Non-mild PHPT patients (NM)	P*
n	89	25	73	
LS-BMD (mg/cm ²)	839.0 $\pm$ 109.8	916.1 $\pm$ 100.4†	765.4 $\pm$ 156.6†‡	<0.001
FN-BMD (mg/cm ²)	690.6 $\pm$ 109.1	709.0 $\pm$ 92.7	601.3 $\pm$ 102.5†‡	<0.001
FT-BMD (mg/cm ²)	802.2 $\pm$ 116.0	823.4 $\pm$ 116.2	699.7 $\pm$ 126.0†‡	<0.001
Volume (cm ³)	51.22 $\pm$ 7.91	51.48 $\pm$ 5.99	51.56 $\pm$ 9.14	n.s.
BMC (g)	11.89 $\pm$ 2.25	13.25 $\pm$ 2.11†	10.93 $\pm$ 3.04†‡	<0.001
vBMD-L3 (g/cm ³)	0.235 $\pm$ 0.031	0.257 $\pm$ 0.025†	0.213 $\pm$ 0.040†‡	<0.001

BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; FT, total femur; v, volumetric; BMC, bone mineral content; *Comparisons were performed by one-way ANOVA. †Significantly different from C, $P < 0.05$; ‡significantly different from M patients, $P < 0.05$.

was more frequent. We also analyzed patients grouped according to the severity of the disease, thus limiting methodological problems arising from the analysis of non-homogenous series. This also allowed us to hypothesize that an increase in fragility fracture in patients with mild PHPT should be considered as a new indication for surgery. In fact, according to 2002 guidelines, skeletal involvement in M PHPT patients is only evaluated by BMD measurement. As expected, in patients with more severe disease, BMD values were significantly lower at any site compared with both M patients and C. However, confirming our previous results (22), in M patients BMD values at the LS were significantly higher than C, supporting the hypothesis of an anabolic action of PTH on cancellous bone in postmenopausal women with mild disease. To define this action better, we also calculated volumetric BMD of the third lumbar vertebra according to an accepted and widely used method (19). In fact, neither BMC nor areal BMD, as assessed by DEXA, fully account for bone size. Bone size is an independent determinant of bone strength, which may be influenced by excessive concentrations of PTH by virtue of its role in eroding subcortical bone and stimulating periosteal bone formation (23, 24). Our M patients not only have higher BMD values, but also show significantly higher vBMD-L3 compared with C. The increase in vBMD seems to be dependent on the increase in BMC, since the volume of the vertebrae did not differ among the three groups. Interestingly, by classifying patients according to quartiles of PTH levels, we found that vBMD significantly decreased from the lowest to the highest quartile of PTH; this finding again supports the hypothesis of anabolic action of PTH on cancellous bone in mild disease. Our results are original, because very few studies have addressed the issue of volumetric BMD in patients with PHPT. In the study of Chen and coworkers (25), trabecular BMD measured by peripheral quantitative computed tomography was significantly lower in patients with PHPT compared with controls. However, in this study, no information about the severity of the disease was made and no analysis on weight-bearing bone, such as the spine, was performed.

If the relationship between bone density and fracture risk, clearly shown for postmenopausal women, is applicable in the same manner to PHPT, a reduction in vertebral fractures is expected. However, our M patients show a percentage of vertebral fractures significantly higher (44%) than C (9%) but not different compared with that observed in patients with more severe disease (47%). Therefore, BMD does not seem to be the only factor determining fracture risk in PHPT. In fact, bone strength is affected by BMD as well as bone quality, which includes bone structure, the accumulation of microdamage and bone turnover rate. Subdividing M and NM patients according to the presence or lack of vertebral fractures, no difference was found between fractured and unfractured patients in BMD or in variables related to volumetric BMD. Moreover, when comparing these subgroups of patients with healthy women, we observed that in fractured M patients, BMD values and parameters related to volumetric BMD were not different from C. On the contrary, in NM patients, BMD at any site was lower than in C, independently from the presence or lack of vertebral fractures. Our data clash with those recently published by Kaji and coworkers (26), whose data demonstrate that only LS BMD was lower in postmenopausal women with PHPT and vertebral fractures. However, in this study, patients were not separated according to the severity of disease and this could have influenced the results obtained. Our data seem to suggest that in patients with PHPT, BMD measurement

Table 3 Distribution of vertebral and non-vertebral fractures in healthy postmenopausal women and patients grouped according to the severity of the disease.

	Healthy women (C)	Mild PHPT patients (M)	Non-mild PHPT patients (NM)
n	89	25	73
vFr	n=8 (9%)	n=11* (44%)	n=35* (47%)
Non-vFr	n=17 (19.1%)	0	n=13 (17.8%)

vFr, vertebral fractures; n, number of controls and patients with fractures; in brackets percentage of controls and patients with fractures. * $P < 0.001$ vs controls by χ^2 -analysis.

Table 4 Mean $\pm$ s.d. values of bone mineral density and of volumetric bone mineral density, bone mineral content and volume of the third lumbar vertebra in healthy postmenopausal women and patients grouped according to the severity of the disease and to the presence or lack of vertebral fractures.

	Healthy women (C)	Mild PHPT patients (M)			Non-mild PHPT patients (NM)		
		Fractured	Unfractured	P*	Fractured	Unfractured	P*
n	89	11	14		35	38	
LS-BMD (mg/cm ²)	839.0 $\pm$ 109.8	887.5 $\pm$ 77.4	938.5 $\pm$ 113.0†	<0.01	761.8 $\pm$ 144.3†	768.89 $\pm$ 168.9†	<0.001
FN-BMD (mg/cm ²)	690.6 $\pm$ 109.1	716.0 $\pm$ 113.3	703.5 $\pm$ 76.8	n.s.	579.6 $\pm$ 88.1†	621.3 $\pm$ 111.6†	<0.001
FT-BMD (mg/cm ²)	802.2 $\pm$ 116.0	835.5 $\pm$ 137.0	813.8 $\pm$ 101.4	n.s.	681.3 $\pm$ 111.3†	716.6 $\pm$ 137.5†	<0.001
BMC (g)	11.89 $\pm$ 2.25	12.49 $\pm$ 1.49	13.83 $\pm$ 2.38†	<0.05	10.46 $\pm$ 3.37†	11.35 $\pm$ 2.71	<0.05
Volume (cm ³)	51.22 $\pm$ 7.91	50.39 $\pm$ 6.02	52.31 $\pm$ 6.08	n.s.	51.47 $\pm$ 10.50	51.63 $\pm$ 7.94	n.s.
vBMD-L3 (g/cm ³)	0.235 $\pm$ 0.031	0.248 $\pm$ 0.016	0.264 $\pm$ 0.029†	<0.01	0.203 $\pm$ 0.049†	0.221 $\pm$ 0.043	<0.001

BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; FT, total femur; v, volumetric; BMC, bone mineral content; *Comparisons were performed by one-way ANOVA. †Significantly different from C, $P < 0.05$.

is not specific to fracture sites and a different relationship exists between fracture risk and BMD. Furthermore, data on volumetric BMD found in M patients should be consulted. In fact, it has been demonstrated that women with spine fractures have smaller vertebrae with less bone in the smaller bone (19). On the contrary, in our sample, fractured M patients show both BMD and vBMD values not different from C; furthermore, these parameters were found to be increased in unfractured M patients. This finding further supports the anabolic action of the PTH in mild disease and the fact that other factors could be relevant in determining fracture risk in PHPT. For example, it is now known that PTH may increase the cross-sectional area of bone and therefore strengthen it, despite a reduction in BMD (27). We found that in M patients, no appendicular fractures were registered, while in NM patients, the percentage of these fractures was not higher compared with C, even if BMD was lower. Data on the risk of non-vertebral fractures in patients with PHPT are uncertain, perhaps because fractures are not always classified according to the circumstances of the injury and, therefore, also traumatic fractures may be included in some case studies. Moreover, metabolic parameters related to the disease could modify skeletal (28) as well as non-skeletal risk factors for fractures, such as the tendency to fall. Regarding this, it is now known that vitamin D influences not only bone metabolism, but also muscle strength and function (29). We found that serum levels of 25OHD were similar among the three groups studied. Moreover, confirming our previous results (20), no correlations were found between 25OHD serum levels and BMD in both M and NM patients (data not shown). Therefore, we can hypothesize that, at least in our population, the susceptibility to falls is not different between patients and controls. There are some limitations in the present study. First, compared with other case studies, the proportion of M patients is smaller (25 of 98 patients); since our patients were recruited from a referring center for osteoporosis and do not represent the general population, some selection

bias might be included in the cases. Secondly, for technical reasons we were not able to measure the forearm BMD at the start of the study. Therefore, we may have underestimated the proportion of patients with osteoporosis and their need for parathyroidectomy according to the current criteria. However, according to Kaji's results (26), radial BMD measurement is not predictive of vertebral fracture risk in PHPT patients, so the lack of forearm BMD data should not jeopardize the main results of the study. In conclusion, the risk of vertebral fractures is higher in postmenopausal women with PHPT, independently of the severity of the disease, even if BMD appears well preserved in M patients. These findings strongly indicate that X-ray examination of the thoracic and LS is mandatory, especially in M patients. Our results also suggest that other factors, such as bone quality, seem to be relevant in determining fracture risk. Finally, the current guidelines for surgery in asymptomatic patients based only on the T-score may be considered insufficient; the evaluation of vertebral fractures could be proposed among the criteria for parathyroidectomy in these patients.

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