Bone Mineral Density Evolution After Successful Parathyroidectomy in Patients With Normocalcemic Primary Hyperparathyroidism

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Context: It is unclear whether bone mineral density (BMD) improves in patients with normocalcemic primary hyperparathyroidism (PHPT) after parathyroidectomy (PTX).

Objective: The objective of the study was to evaluate and compare the impact of PTX on BMD change at 1 year in normocalcemic vs hypercalcemic PHPT.

Design: This was a longitudinal cohort study.

Setting: The study took place at a referral center.

Patients: We included 60 PHPT patients (mean age 64.0 ± 10.1 years), successfully treated by PTX by the same surgeon. Two groups were individualized according to baseline serum total (albumin corrected) calcium: 39 patients with normal baseline serum total calcium (normocalcemic group) and 21 patients with hypercalcemia at baseline (hypercalcemic group).

Main Outcome Measure: BMD changes 1 year after PTX were measured.

Results: In the normocalcemic group, BMD increased significantly by +2.3 ± 5.0% at the spine (*P* = .016) and +1.9 ± 5.7% at the hip (*P* = .048). In the hypercalcemic group, BMD increased significantly by +4.0 ± 3.8% at the spine (*P* = .0003) and +3.2 ± 4.2% at the hip (*P* = .003). There was no difference in these BMD gains between both groups (*P* > .1). The presence of multiple adenomas or hyperplasia was more frequent in the normocalcemic group than in the hypercalcemic group (*P* = .04).

Conclusion: Our results indicate for the first time that successful PTX in normocalcemic PHPT patients with osteoporosis is followed with mild but significant BMD improvement at the spine and hip at 1 year, comparable with that observed in hypercalcemic PHPT, suggesting that PTX may be beneficial in normocalcemic PHPT. (*J Clin Endocrinol Metab* 98: 3213–3220, 2013)

Skeletal involvement, especially on cortical bone, is a hallmark of primary hyperparathyroidism (PHPT) (1–3). After successful parathyroidectomy (PTX), increases in bone mineral density (BMD), both in symptomatic (4–8) and in mild asymptomatic PHPT have been demonstrated (9–11). The general consensus is to recom-

Abbreviations: BMD, bone mineral density; CTX, carboxy-terminal telopeptide of type 1 collagen; eGFR, estimated glomerular filtration rate; iCa, ionized calcium; 25OHD, 25-hydroxyvitamin D; PHPT, primary hyperparathyroidism; PTX, parathyroidectomy; 1/3 radius, distal third of the radius; tCa, total calcium; UD, ultradistal.

mend PTX for symptomatic PHPT patients (12, 13) and asymptomatic PHPT patients with significant hypercalcemia (>2.85 mmol/L) and/or BMD T-score less than −2.5 at any site, or previous fragility fracture, and/or age younger than 50 years, and/or impaired renal function [estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2] (13).

Recently normocalcemic PHPT, characterized by normal serum total (tCa) and ionized calcium (iCa) concentrations and elevated PTH levels in the absence of any cause of secondary hyperparathyroidism, has emerged as a new clinical entity (13–16). This is mainly due to the wider PTH measurement during the evaluation of osteoporosis, even when serum tCa is normal (14). Indeed, with the improvement in the knowledge on the risks of osteoporosis, the proportion of PHPT patients diagnosed with very mild calcium and phosphorus abnormalities is increasing, whereas the proportion of patients diagnosed with the classic form of PHPT is decreasing. Authors have raised the possibility that normocalcemic PHPT may represent a variant of the more usual form of the disease, featuring stability of serum calcium and possible bone involvement, whereas others consider that it may be an early form of asymptomatic disease with progressive increase in serum calcium over time (13, 15, 16). To date, this entity remains poorly described in terms of pathophysiology, natural history, and therapeutic management. In particular, the BMD outcome after PTX in normocalcemic PHPT patients remains unreported, rendering their management particularly complex and challenging in clinical practice.

Accordingly, we conducted a longitudinal study of PHPT patients who underwent PTX to determine the benefit of surgery on BMD in patients with normocalcemic PHPT as compared with classical PHPT.

Materials and Methods

Patient selection

Between 2008 and 2010, 413 consecutive patients were referred to our tertiary Metabolic Bone Disease Unit because of low BMD and mild abnormalities of calcium, phosphorus, and/or PTH concentrations. Among these, 193 met the biological criteria for PHPT, and 220 were diagnosed with secondary hyperparathyroidism. The data were prospectively collected.

Diagnosis of PHPT

The biological diagnosis of PHPT was based on one of the following: 1) elevated (>46 pg/mL) or inappropriately normal PTH levels with increased albumin-corrected serum tCa (>2.60 mmol/L) or iCa (>1.30 mmol/L) or 2) elevated PTH levels with normocalcemia and no cause of secondary hyperparathyroidism (14).

Diagnosis of normocalcemic PHPT

All patients with elevated PTH and normal tCa levels underwent extensive investigations aiming at excluding causes of secondary hyperparathyroidism, including a thiazide diuretic test (17, 18) in those with hypercalciuria. They all underwent oral ± iv calcium load test to confirm the biological diagnosis of PHPT (19). The diagnosis of normocalcemic PHPT was established when, during the calcium load test described below, serum tCa and/or iCa concentrations increased to supranormal values, and only a minimal reduction in PTH concentration was seen (16, 19, 20). Among those with a diagnosis of PHPT, we included only patients who met the following criteria: baseline serum 25-hydroxyvitamin D (25OHD) levels greater than 20 ng/mL (15), absence of bisphosphonate use, thiazides, anticonvulsants or lithium (21), an eGFR greater than 40 mL/min per 1.73 m^2 (Modification of Diet in Renal Disease Study formula), and the absence of gastrointestinal diseases associated with malabsorption or liver disease (14, 15, 22, 23).

Calcium load test

Patients were on a low-calcium diet for 3 days before the test (<300 mg per 24 hours) and collected 24-hour urine samples the day before the test. Fasting blood and urine samples were collected on the day of the test. Patients were administered 1 g oral calcium. Blood was drawn at 2 hours of calcium administration. For patients who did not exhibit iCa greater than 1.42 mmol/L, a 20-minute iv infusion of 2 mg/kg elemental calcium (in the form of calcium gluconate) was performed. Blood was drawn 10 and 40 minutes after the end of the infusion to measure serum tCa and iCa, albumin, phosphorus, and PTH levels (16). Insufficient decrease in serum PTH level defined by a PTH concentration that did not decrease below 20 pg/mL when iCa increased greater than 1.40 mmol/L was in favor of the diagnosis of PHPT. It must be noted that this threshold (20 pg/mL) is based on our experience and is applicable only with the PTH kit that we use routinely.

Inclusion and exclusion criteria (Figure 1)

Inclusion criteria were as follows: 1) a diagnosis of PHPT as detailed above; 2) indication for PTX (see above); 3) successful PTX as defined by normal post-PTX serum tCa and iCa levels; 4) histopathological confirmation of PHPT; and 5) longitudinal follow-up with clinical, biochemical, and BMD assessments before and after PTX, entirely performed in our unit.

Exclusion criteria were as follows: 1) the absence of BMD follow-up (n = 98); 2) persistent hypercalcemia after PTX (n = 11), and 3) normal parathyroid gland on histopathological analysis (n = 2). Some patients had more than 1 exclusion criterion.

The study was approved by the local institutional review board. Written informed consent was obtained from all patients.

Study design

All PTXs were performed by the same single experienced parathyroid surgeon (E.S.). The surgical procedure was as follows: bilateral neck exploration is the standard surgical procedure to ensure that all parathyroid glands were visualized during the surgical procedure; when 1 abnormal gland was identified (single adenoma), it was excised and confirmed by frozen section examination, and a biopsy was performed on a second gland; when 2 or more abnormal parathyroid glands (double adenoma or multiple adenomas) were identified, the abnormal glands were
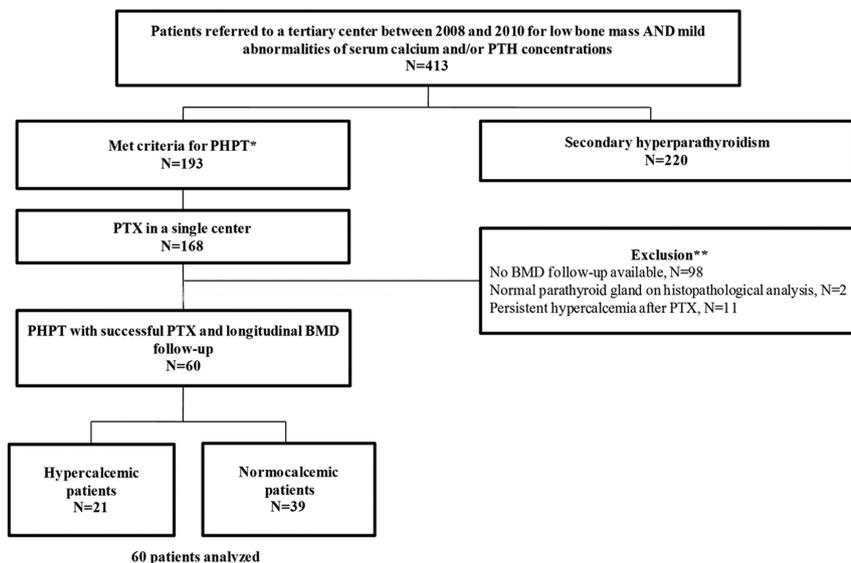
Figure 1. Flow diagram of patient recruitment and population for analysis. *, Defined by elevated (>46 pg/mL) or inappropriately normal PTH levels with increased albumin-corrected serum tCa (>2.60 mmol/L) or iCa (>1.30 mmol/L) or elevated PTH levels with normocalcemia and no causes of secondary hyperparathyroidism; **, some patients had more than 1 exclusion criteria.

removed, and a biopsy was performed on a remaining normal gland; when all the parathyroid glands were abnormal (hyperplasia), a subtotal parathyroidectomy (3 parathyroid glands and three fourths of the fourth gland) was performed. Transcervical thymectomy was performed with both the second and third situations.

The data of 60 patients were analyzed. We divided our cohort into 2 groups according to baseline albumin-corrected serum tCa concentration: a normocalcemic group defined by normal baseline serum tCa (n = 39) and a hypercalcemic group defined by elevated serum tCa (>2.60 mmol/L) at baseline (n = 21). All patients received oral vitamin D supplementation before and after PTX.

The primary end point was a comparison of BMD changes 1 year after PTX between patients with normocalcemic and hypercalcemic PHPT.

A biochemical evaluation performed before PTX included serum albumin-corrected tCa, iCa, phosphorus, PTH, 25OHD, eGFR, alkaline phosphatase activity, osteocalcin, carboxy-terminal telopeptide of type 1 collagen (CTX), and fasting and 24-hour urine calcium, sodium, phosphorus, and creatinine. Resolution of biological PHPT after PTX was checked in all patients at 3 months by the normalization of serum tCa and iCa.

BMD was measured before and 12 months after PTX by dual-energy X-ray absorptiometry (QDR-4500; Hologic, Bedford, Massachusetts) at the lumbar spine (L1-L4), hip, nondominant ultradistal (UD) radius, and distal third of the radius (1/3 radius), on the same instrument.

The history of fragility fractures, nephrolithiasis, and chondrocalcinosis was recorded.

The results of the histopathological analysis of the parathyroid glands were also available. The diagnosis of a single adenoma was based on the surgical finding of only 1 enlarged gland with histological confirmation of an adenoma and the biopsy of a second gland showing normal parathyroid gland. The diagnosis of multiadenomas or diffuse hyperplasia was based on the surgical finding of more than 1 abnormally enlarged gland or all abnormal glands, with histological confirmation of at least 2 abnormal excised glands.

Laboratory methods

Serum tCa, phosphorus, creatinine, urinary calcium, alkaline phosphatase, and creatinine were measured using standard methods. iCa was measured by a specific electrode (Rapidlab 855 blood gas analyzer; Siemens, Holliston, Massachusetts). Serum 25OHD was measured by RIA (Diasorin, Sallugia, Italy). Serum PTH, osteocalcin, and CTX were measured by means of immunochemoluminescent assays on the ELECSYS automated platform (Roche Diagnostics, Meylan, France).

Statistical analysis

Statistical analyses were performed using the MedCalc software (MedCalc version 11.6.1; Ostend, Belgium). Descriptive statistics were performed to characterize the study population. Differences between pre- and post-PTX values were assessed using Wilcoxon rank test for paired data. Comparisons between the normocalcemic and hypercalcemic groups were assessed with the Mann-Whitney test. Differences in frequency were calculated using a Fisher-exact test. A value of $P < .05$ was considered significant.

Results

Baseline characteristics (Table 1)

Baseline clinical and biochemical characteristics of the study group are shown in Table 1. Most patients had a T-score of −2.5 or less at any site (80%) and/or had a history of fragility fracture(s) (35%). Eight patients (13.3%) had a history of nephrolithiasis.

Of the 60 analyzed patients, 39 met the criteria for normocalcemic PHPT, defined by normal levels of serum tCa (2.51 ± 0.08 mmol/L), the absence of secondary hyperparathyroidism, and an insufficient decrease in the PTH level during the calcium load test. In addition, 16 of 39 of these patients (41.0%) had both normal serum tCa and iCa. All 39 patients had a 25OHD level greater than 20 ng/mL, 30 of 39 (76.9%) of whom having a level greater than 30 ng/mL. BMD assessment showed that 35 of the 39 normocalcemic subjects (89.7%) had a T-score less than −2.5 SD in at least 1 site, a proportion that was significantly higher than in the hypercalcemic group (13 of 21, 61.9%, $P = .02$). There was no significant difference in demographic characteristics between hypercalcemic and normocalcemic PHPT patients. Serum CTX was sig-

Table 1. Baseline Clinical, Biochemical, and Bone Densitometric Parameters of the 60 Patients Enrolled in the Study and Comparison of Baseline Parameters Between Normocalcemic and Hypercalcemic Individuals

Baseline Characteristics	Total PHPT Cohort (n = 60)	Normocalcemic (n = 39)	Hypercalcemic (n = 21)	P Value
Clinical				
Age, y	64.0 ± 10.1	66.1 ± 9.1	61.4 ± 11.3	.1
Women, n, %	57/60 (95.0)	36/39 (92.3)	21/21 (100)	.5
VAS fatigue	6.2 ± 2.0	6.2 ± 2.1	6.4 ± 1.9	.8
History of nephrolithiasis, n, %	8/60 (13.3)	7/39 (17.9)	1/21 (4.8)	.2
Chondrocalcinosis, n, %	2/60 (3.3)	1/39 (2.6)	1/21 (4.8)	1.0
Biochemical				
Serum total calcium, 2.20–2.60 mmol/L	2.53 ± 0.13	2.51 ± 0.08	2.69 ± 0.10	<.0001
Ionized calcium, 1.17–1.30 mmol/L	1.35 ± 0.07	1.32 ± 0.05	1.41 ± 0.06	<.0001
PTH, 10–46 pg/mL	68.9 ± 27.8	63.2 ± 20.9	79.6 ± 35.7	.08
Serum phosphorus, 0.80–1.40 mmol/L	0.89 ± 0.16	0.93 ± 0.16	0.82 ± 0.13	.01
24-Hour urinary calcium, n < 4 mg/k g ·d	4.62 ± 2.55	4.20 ± 2.31	5.39 ± 2.83	.07
eGFR, mL/min per 1.73 m^2	77.2 ± 17.0	80.7 ± 17.9	70.6 ± 13.3	.03
Alkaline phosphatase activity, 30–120 IU/L	72.7 ± 27.0	75.7 ± 29.7	66.7 ± 20.1	.4
Osteocalcin, ng/mL	32.6 ± 13.2	31.8 ± 13.0	34.0 ± 13.8	.4
Serum CTX, pmol/mL	5363 ± 2985	4651 ± 1997	6868 ± 4075	.02
25OHD, 30–60 ng/mL	33.0 ± 8.4	34.3 ± 7.2	30.4 ± 10.1	.1
Bone assessment				
History of fracture, n, %	21/60 (35)	15/38 (39.5)	6/21 (28.6)	.6
Osteoporosis, n, %[a]	52/60 (86.7)	36/39 (92.3)	16/21 (76.2)	.2
T-score ≤ −2.5 in at least 1 site, n, %	48/60 (80)	35/39 (89.7)	13/21 (61.9)	.02
T-score between −1 and −2.5 in at least 1 site, n, %	12/60 (20)	4/39 (10.3)	8/21 (38.1)	.02
Lumbar spine T-score (SD)	−2.4 ± 1.3	−2.5 ± 1.3	−2.1 ± 1.2	.1
Femoral neck T-score (SD)	−2.3 ± 0.7	−2.5 ± 0.6	−2.0 ± 0.7	.01
Distal third of the radius T-score (SD)	−2.5 ± 1.6	−2.6 ± 1.6	−2.1 ± 1.7	.3

Abbreviation: VAS, visual analog scale. Continuous variables are presented as mean ± SD, and the categorical data are presented as the percentage of analyzed patients (n, %).

[a] T-score −2.5 SD or less at the spine, hip, or forearm and/or fragility fracture.

nificantly lower in the normocalcemic group than in the hypercalcemic group (P = .02). Baseline eGFR and serum phosphorus were higher in the normocalcemic group than in the hypercalcemic group. The other biochemical parameters did not differ between the 2 groups.

Histopathological findings

The presence of parathyroid hyperplasia or of multiple adenomas was more frequent in the normocalcemic group (11 of 39, 28.2%) than in hypercalcemic patients (1 of 21, 4.8%) (P = .04). Adenoma weight was lower in the normocalcemic group (189.9 ± 181.5 mg) than in the hypercalcemic group (354.4 ± 296.8 mg) (P = .03).

Longitudinal follow-up after PTX

Patients were followed up for 12.9 ± 3.6 months after PTX.

Biochemical assessment

Serum tCa, iCa, and PTH significantly decreased 3 months after surgery in all groups (P < .005). In all 21 hypercalcemic patients, data obtained 3 months after PTX showed the normalization of serum tCa (2.35 ± 0.08 mmol/L) and iCa (1.22 ± 0.035 mmol/L) and a significant

decrease in PTH (44.2 ± 18.5 pg/mL vs 79.6 ± 35.7 pg/mL at baseline, P < .0001).

In the normocalcemic group (n = 39), significant decreases in serum tCa (2.32 ± 0.08 vs 2.51 ± 0.08 mmol/L at baseline, P < .0001), iCa (1.23 ± 0.03 vs 1.32 ± 0.05 mmol/L at baseline, P < .0001), and PTH (43.9 ± 18.7 vs 63.2 ± 20.9 pg/mL at baseline, P < .0001) were observed after PTX. In the 23 of 39 patients of the normocalcemic group with baseline iCa greater than 1.30 mmol/L, we observed a post-PTX normalization of iCa (1.23 ± 0.03 vs 1.35 ± 0.03 mmol/L at baseline, P < .0001). 25OHD remained stable after PTX in all groups (P > .1). No patient had recurrence of PHPT during the study period. On evaluation at 3 months after PTX, 21 patients from the total cohort displayed PTH levels above our upper normal value (46 pg/mL), which was related to 25OHD insufficiency and/or low calcium intake after PTX. Among these 21 PHPT patients, 8 patients were normocalcemic patients with both normal baseline tCa and normal iCa. In these 8 patients, iCa decreased significantly after PTX (1.22 ± 0.04 vs 1.27 ± 0.04 before PTX, P = .03) suggesting a cure of PTX. Moreover, the follow-up of these 8 patients revealed a total normalization of PTH, although delayed in

time, in all cases. Interestingly, among these 8 patients, 2 had post-PTX 25OHD less than 20 ng/mL, 4 had 25OHD between 20 and 30 ng/mL, and 2 had 25OHD greater than 30 ng/mL. Both patients with 25OHD greater than 30 ng/mL after PTX had a daily calcium intake less than 500 mg/d. All 8 patients had normal levels of 25OHD level when normalization of PTH was confirmed.

BMD change after PTX (Figure 2)

In the total cohort (n = 60), BMD increased significantly by +2.9% ± 2.3% at the spine ($P < .0001$) and +2.4% ± 2.7% at the femoral neck ($P = .0008$) at 1 year. BMD remained stable at the UD radius (+1.4% ± 8.1%, $P = .67$) and tended to decrease at the 1/3 radius (−1.1% ± 4.8%, $P = .08$).

In the normocalcemic group (n = 39), BMD increased significantly by +2.3% ± 5.0% at the spine ($P = .016$) and by +1.9% ± 5.7% at the femoral neck ($P = .048$). The increase at UD radius was not significant: +0.6% ± 5.8%, $P = .64$. BMD declined significantly by −1.5% ± 3.5% at the 1/3 radius ($P = .02$). Within the normocalcemic group, those with baseline iCa greater than 1.30 mmol/L (n = 23) had a BMD change of 0.3% ± 4.0% at the femoral neck (not significant), +2.5% ± 5.2% at the spine ($P = .048$), and a loss of −1.8% ± 3.6% at the 1/3 radius ($P = .032$), whereas those with a normal baseline iCa (n = 16) had a BMD gain of +4.1% ± 6.9% at the femoral neck ($P = .044$) and no significant gain at the spine (+2.0% ± 4.7%, $P = .18$) or loss at the 1/3 radius (−1.0% ± 3.3%, $P = .3$). BMD gain was greater at the femoral neck ($P = .02$) in those with normal baseline iCa than in those with elevated baseline iCa. BMD gain at the spine was not different between these 2 subgroups.

In the hypercalcemic group (n = 21), BMD increased significantly by +4.0% ± 3.8% at the spine ($P = .0003$) and by +3.2% ± 4.2% at the femoral neck ($P = .003$). BMD remained stable at the UD radius (+2.8% ± 11.5%, $P = .92$) and at the 1/3 radius (−0.5% ± 6.9%, $P = .98$).

At 1 year, the percentage change in BMD at the lumbar spine, femoral neck, and 1/3 radius did not significantly differ between the normo- and hypercalcemic groups ($P = .1, P = .2$, and $P = .4$, respectively).

Discussion

To our knowledge, this is the first study to report BMD change after PTX in a defined group of normocalcemic PHPT patients. We observed significant BMD gains at 1 year at both the spine and femoral neck, which did not significantly differ from those observed in the hypercalcemic group. The magnitude of BMD improvement in our normocalcemic group was similar to that observed in osteoporotic postmenopausal women treated with oral bisphosphonates during 1 year (24) and also after PTX in nonnormocalcemic PHPT patients (25) and greater than that observed by Rao et al (11) at the spine and hip in mild PHPT. Our findings therefore support that the benefit of PTX previously reported in mild asymptomatic PHPT might be extended to the specific group of osteoporotic normocalcemic PHPT patients. However, concluding definitely whether these positive changes in BMD may translate into a reduction in the risk of fracture deserves further studies of longer duration, including a larger number of patients.

Noteworthily, the high proportion of normocalcemic patients in our study may be due to a selection bias related to the fact that our unit is specialized in the exploration of calcium/phosphorus metabolism in patients with bone disease. Indeed, most patients were referred because of osteoporosis with very mild calcium, phosphate, and/or PTH abnormalities, which does not reflect the whole PHPT population. In fact, although the estimated prevalence of PHPT in the general population is 0.1%–0.5% in the United States, the prevalence of normocalcemic PHPT is difficult to evaluate (15, 26, 27). In a recent study, it was reported that among 771 patients with sporadic PHPT who underwent PTX in a single center during a 9-year period, 93 (12%) had a normal preoperative serum tCa level (28). Interestingly, recent studies assessing the causes of bone loss in postmenopausal women found that normocalcemic PHPT represented 3.0% and 3.1% of secondary causes of bone loss in 2 independent breast cancer populations from Australia and the United States (29, 30). These data, as well as the findings of the present study, raise the question on whether every patient with normocalcemia and osteoporosis should have the PTH checked.

One of the major issues in the diagnosis of normocalcemic PHPT is to rule out causes of secondary hyperparathyroidism. For this purpose, all normocalcemic patients underwent extensive biochemical investigations, which included search for vitamin D insufficiency, renal impairment, and hypercalciuria. Moreover, all normocalcemic patients underwent a calcium load test to confirm inappropriate parathyroid response to hypercalcemia, whereas those who had hypercalciuria underwent a thiazide test to rule out an increased PTH secretion due to a renal calcium leak. Although one of the major requirements for the definition of normocalcemic PHPT should be that iCa is in the normal range (13), the measurement of iCa is not an easy task in routine practice and is not available everywhere. Thus, normal serum tCa on its own has previously been used to distinguish normocalcemic
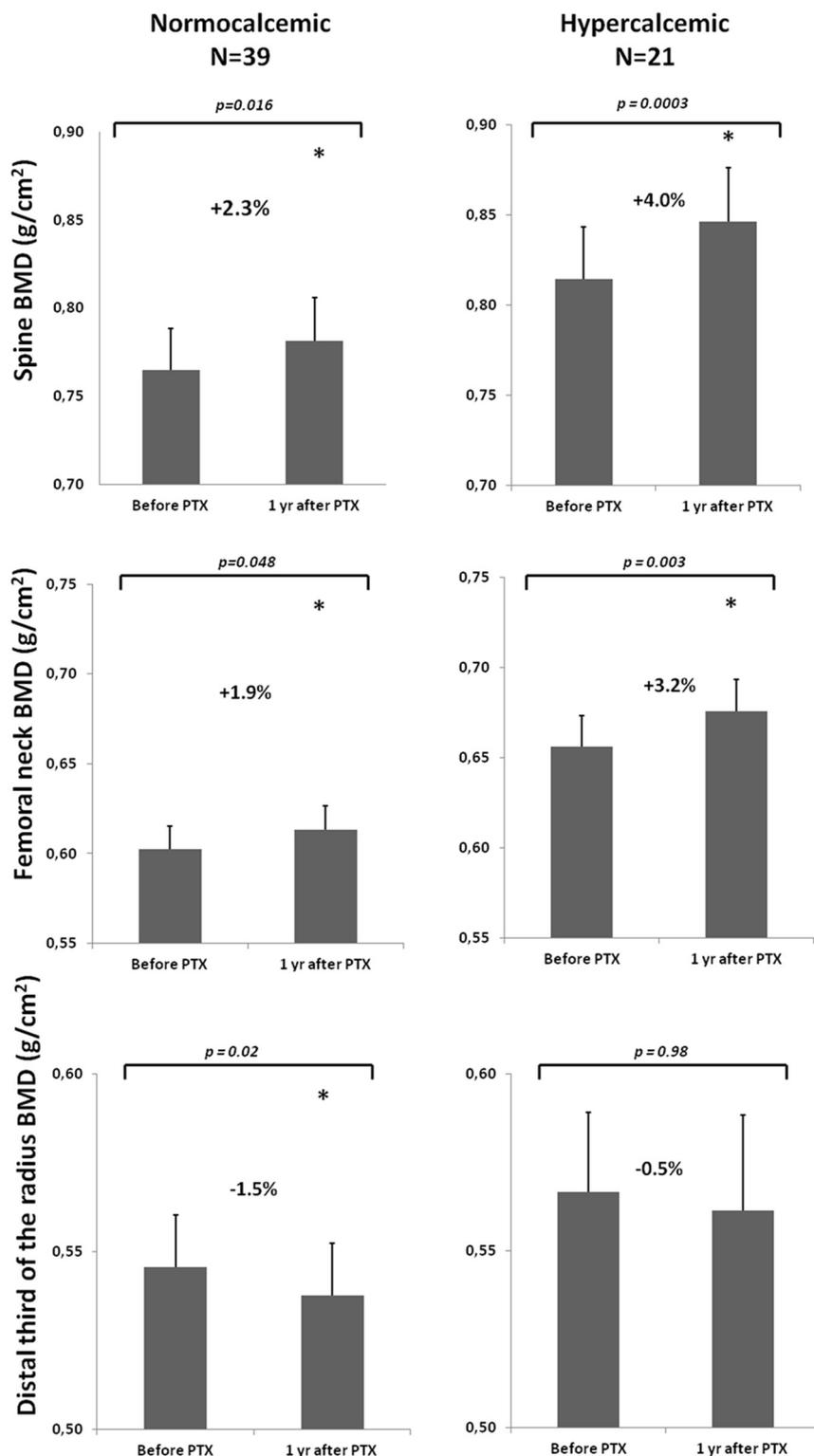
Figure 2. Mean (±SEM) BMD before and 1 year after PTX at the lumbar spine, femoral neck, and distal third of the radius in patients classified at baseline as normocalcemic (left panels) and hypercalcemic (right panels). *, *P* value of Wilcoxon test between pre- and post-PTX BMD values < 0.05.

In agreement with the study by Lowe et al (15) that included 37 normocalcemic PHPT patients, the normocalcemic patients in our study displayed substantial skeletal involvement as shown by low T-scores before PTX. Moreover, the prevalence of fragility fractures was similar in both the normocalcemic and hypercalcemic groups, and densitometric osteoporosis was more frequently encountered in the normocalcemic group. However, this higher prevalence of osteoporosis is likely due to the referral bias because the reason for referral to our unit and the discovery of a high PTH was the evaluation of reduced bone mass in all our patients. It must thus not be concluded from the present study that normocalcemic PHPT patients have a lower BMD than hypercalcemic PHPT patients.

Predominant cortical bone involvement is frequent in PHPT (31). In the present study, a surprising discrepancy was observed between the BMD changes at the 1/3 radius and at the femoral neck. Indeed, we observed a decline in the BMD at the 1/3 radius at 1 year, whereas an improvement was observed at the femoral neck. In the classical form of PHPT, results concerning BMD change at the forearm after PTX are variable. Some studies reported an increase (5, 8, 32), and others reported no change, including a 10-year follow-up study (1) and 3 randomized controlled trials that evaluated BMD change after PTX in mild asymptomatic PHPT (9–11). However, whether the absence of BMD change at the forearm after PTX has any influence on bone strength and fracture risk is essential and remains to be determined in longer studies including comparison with a control group of PHPT patients without PTX.

Multigland adenomas are found in 2%–12% of PHPT cases, and hyperplasia in 15%–25% of PHPT cases (33). Hyperplasia is a classic consequence of secondary hyper-

from hypercalcemic subtypes both in clinical studies (15) and in general practice. Therefore, although this may be a limitation to our study, we believe that our normocalcemic group reflects what is seen in routine practice.

parathyroidism that is evolving into an autonomous process leading to tertiary hyperparathyroidism. The fact that hyperplasia and multiple adenomas were more frequent in the normocalcemic group leads to suggest that this entity may have a different pathophysiological origin, sharing characteristics with secondary and tertiary hyperparathyroidism. Importantly, as detailed in *Material and Methods*, we excluded normocalcemic patients who displayed causes of secondary hyperparathyroidism such as vitamin D insufficiency and renal failure at the time of the study, but one cannot exclude that these patients may have had longstanding periods of hypocalcemia or intermittent hypocalcemia that could have led to a state of secondary and then tertiary hyperparathyroidism.

In our cohort, no patient had a recurrence of PHPT during the study period. The persistence of elevated PTH after PTX in normocalcemic patients may raise the question of persistent PHPT in the normocalcemic subgroup. However, a complete normalization of PTH was observed, although delayed in time, in all 8 normocalcemic patients (with both normal baseline tCa and iCa). This normalization generally occurred concomitantly with the normalization of the 25OHD level, supporting the fact that elevated post-PTH levels were due to secondary hyperparathyroidism.

This study has several strengths: 1) it is one of the rare studies assessing a large number of surgically proven normocalcemic PHPT patients with longitudinal follow-up after PTX performed by the same surgeon, including clinical, surgical, and biochemical assessment in a single center; 2) it is the first study reporting BMD change after PTX in the specific context of normocalcemia. This study also has limitations: 1) the study did not include a control group, and therefore, further studies would be useful to confirm the effects of PTX vs no PTX in normocalcemic patients; 2) the referral bias, responsible for the higher proportion of normocalcemic patients, makes that our total PHPT population does not reflect PHPT patients in general. However, this same referral bias allowed us to study the characteristics of a large number of normocalcemic patients; 3) the follow-up period was limited to 1 year, and therefore, the long-term change in BMD remains to be determined, in particular with regard to the decrease in BMD at the 1/3 radius; and 4) the small number of normocalcemic patients having both normal serum tCa and iCa (n = 16) did not enable us to examine this phenotype separately, using the exact definition of normocalcemic PHPT. Therefore, controlled studies with a longer study period including more normocalcemic subjects and assessing fracture incidence would allow definite clinical conclusions.

In conclusion, our results indicate for the first time that successful PTX in normocalcemic PHPT with osteoporosis at presentation is followed by mild but significant BMD improvement at the spine and hip at 1 year, comparable with that observed in hypercalcemic PHPT, suggesting that PTX may also be beneficial in normocalcemic PHPT. It must be underlined that the diagnosis of normocalcemic PHPT is challenging and requires the exclusion of all potential causes of secondary hyperparathyroidism and to perform a calcium load test showing that PTH is not sufficiently repressed when serum calcium level is clearly above normal. Further studies, including longitudinal prospective randomized controlled studies with long-term follow-up, may be useful to confirm these data.

Acknowledgments

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