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SHORT COMMUNICATION

Individual site-specific bone mineral density gain in normocalcemic primary hyperparathyroidism

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Abstract
Summary In this study, we show that successful parathyroidectomy is followed at 1 year by a significant individual bone mineral density (BMD) gain in nearly half of normocalcemic PHPT patients with reduced bone mass. Alkaline phosphatase levels above median were identified as an independent predictor of individual BMD gain in normocalcemic PHPT patients.
Introduction The aims of this study were to assess bone mineral density (BMD) gains after parathyroidectomy (PTX) in normocalcemic primary hyperparathyroidism (PHPT) at the individual level and to identify predictors of BMD gain after PTX in this context.
Methods Longitudinal cohort study of 55 PHPT patients referred for low bone mass and mild abnormalities of calcium/phosphorus metabolism, and successfully treated by PTX. BMD gain at 1 year was considered significant if ≥0.030 g/cm^2 at one site or more, without any equivalent BMD loss at another site. A logistic regression analysis was performed to identify predictive factors of individual BMD gain.
Results Among the 55 PHPT patients included, 29 patients with hypercalcemia, 36 patients with normocalcemic PHPT, defined by normal pre-PTX serum total (albumin-corrected) calcium (tCa), including 15 patients with normal ionized calcium (iCa), were identified. At 1 year of PTX, an individual BMD gain was observed in 73.7 % of hypercalcemic, 44.4 % of normocalcemic, and 46 % of PHPT patients with both normal tCa and iCa. Site-specific BMD gains were most important at the spine and hip in all subgroups including patients with normal iCa. Alkaline phosphatase activity above median, which reflects high bone turnover, was predictive of individual BMD gain, both in the overall cohort (OR=4.9, 95 % CI 1.3–18.9), and in the normocalcemic group: OR=8.4, 95 % CI 1.4–56.6.
Conclusions Successful PTX is followed at 1 year by a significant individual BMD gain in nearly half of normocalcemic PHPT patients with osteoporosis. ALP levels above median could contribute to the therapeutic decision in this context.

Keywords Bone mineral density · Normocalcemia · Osteoporosis · Parathyroidectomy · Primary hyperparathyroidism · Vitamin D

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Introduction

Normocalcemic primary hyperparathyroidism (PHPT) is characterized by normal serum calcium levels, and the exclusion of causes of secondary hyperparathyroidism [1]. Normocalcemic calcium levels also require normal ionized calcium levels [1]. However, mainly due to the difficulties relative to the measurement of ionized calcium in practice and to the low prevalence of such an entity, pivotal studies on normocalcemic primary hyperparathyroidism have used normal serum total calcium (tCa) to define normocalcemic

patients [2–4]. Skeletal involvement, especially on cortical bone, is a hallmark of primary hyperparathyroidism (PHPT), including normocalcemic forms of PHPT [2, 5–7]. Following parathyroidectomy (PTX), increases in bone mineral density (BMD) have been demonstrated, both at the spine and hip in symptomatic [5, 8–11], in mild asymptomatic PHPT [12–14], and recently by our group in normocalcemic PHPT patients with low bone mass 1 year after successful PTX [15]. Indeed, the BMD gains observed at the spine and hip did not significantly differ from those observed in hypercalcemic PHPT patients and were similar to those observed in osteoporotic postmenopausal women treated with oral bisphosphonates during 1 year [16]. However, in this same study by our group that included 39 patients with normal tCa, BMD tended to decrease at the distal third of the radius (1/3 radius) at 1 year of PTX, contrasting with significant improvements at the femoral neck and spine [15]. Moreover, this BMD loss at the 1/3 radius was significant in the normocalcemic group (−1.5±3.5 %, p=0.02). Thus, although significant increases in mean BMD were observed at the spine and hip, these results may not reflect the impact of PTX on BMD for an individual patient.

This discrepancy between hip and spine vs forearm results made us ask the following questions: (1) what is the benefit of PTX for an individual patient with normocalcemic PHPT if the increase in BMD at the spine and hip in patients is counterbalanced by a loss at the distal third radius or at another site? and (2) are there any baseline biochemical and/or parameters able to identify those patients most likely to display a significant individual BMD gain after PTX?

The aims of this study were thus to investigate the impact of PTX at the individual patient level on BMD parameters at all sites (i.e., spine, hip, and radius) and to identify predictors of BMD gain after PTX in the specific context of normocalcemic PHPT.

Materials and methods

Patient selection

Patients were recruited from the Metabolic Bone Disease Unit at Cochin Hospital (Paris, France) between 2008 and 2010, as previously described [15]. Briefly, all patients met the following criteria: (1) biological confirmation of PHPT diagnosis and (2) indication for PTX; (3) successful PTX as defined by normal post-PTX serum tCa and ionized calcium (iCa) levels; (4) histopathological confirmation of PHPT; (5) longitudinal follow-up with clinical, biochemical, and BMD assessment before and after PTX. The biological diagnosis of normocalcemic PHPT was based on elevated PTH levels with normal albumin-adjusted tCa, and no cause of secondary hyperparathyroidism. ICa was documented for all patients, allowing the characterization of a subgroup of patients with both normal tCa and normal iCa.

Among the 60 patients studied in Koumakis et al. [15], those whose BMD follow-up was lacking for one of the three investigated sites (spine, hip, and forearm) were excluded from the analyses (N=5) to include only patients with complete BMD data including at the radius.

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

Bone mineral density assessment and definition of BMD gain at the individual level

BMD was measured before and 12 months after PTX by dual-energy X-ray absorptiometry (QDR-4500; Hologic) at the lumbar spine (L1-L4), hip, non-dominant ultradistal (UD) radius, and 1/3 radius, on the same instrument. To calculate a significant increase in BMD for an individual patient, we used the least significant change (LSC) formula: $1.96\times\sqrt{2}\times$ CV (coefficient of variance). We considered that a BMD gain was significant for an individual patient if it was ≥0.030 g/cm^2 at any site, without any loss of BMD of ≥0.030 g/cm^2 at another site during the same period of time. This value of 0.030 g/cm^2 is a rounded value of the least significant change (LSC) based on a precision error of 0.01 g/cm^2 in our facility.

Biochemical and clinical variables

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

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

Statistical analysis

Statistical analyses were performed using the MedCalc software (MedCalc® v11.6.1). Descriptive statistics were performed to characterize the study population. For categorical data, statistical significance was analyzed by Fisher's exact test. A p value <0.05 was considered significant. A multiple variable logistic regression analysis was performed to determine whether an individual BMD gain as defined above was associated with pre-PTX characteristics in the total PHPT population and in the normocalcemic group. We included in our model all variables identified with a p value ≤0.2 in the univariate analysis and calculated odds ratio (OR) and 95 % confidence intervals.

Results

In all, 55 PHPT patients were included in the study. All patients displayed normal tCa at 3 months. No recurrence of PHPT was observed during the study period. The pre-PTX characteristics of these patients are detailed in Table 1. Among these, 21 patients with mild hypercalcemia and 36 patients with normocalcemic PHPT as defined by a normal pre-PTX albumin-corrected serum tCa, including 15 patients with normal iCa, were identified.

Individual BMD gain in the overall cohort

Prevalence of individual BMD gain at 1 year of PTX

An individual BMD gain at one site at least without loss at any other site was observed at 1 year in 30/55 patients (54.5 %) of the overall cohort. Site-specific individual BMD gains (without loss at any other site) were as follows: 21/55 (38.2 %) of patients at the spine, 12/55 (21.8 %) at the femoral neck, 15/55 (27.3 %) at the total hip, 4/55(7.3 %) at the UD radius, and 2/55 (3.6 %) at the 1/3 radius.

Comparison of patients with and without individual BMD gain in the overall PHPT cohort and prediction of BMD gain after PTX in the overall cohort (Table 1)

In order to identify factors associated with a significant individual gain 1 year after PTX, we compared, in our overall PHPT cohort, the subset of patients who experienced a BMD gain as defined above (n=30) with those who did not (n=25).

In univariate analysis, PHPT patients with a significant individual BMD gain (n=30) were more likely to have lower pre-PTX eGFR, tended to have higher pre-PTX serum tCa and ALP than patients who did not (n=25). Patients with a significant BMD gain also tended to have a greater, although not significantly, adenoma weight (279.0 vs 202.8 mg, p=0.07) than patients who did not display an increase in BMD.

In multivariate analysis, pre-PTX ALP above the median of the observed values (>66 UI/L) was the only variable identified as an independent predictor for BMD gain (OR=4.9, 95 % CI 1.3–18.9).

Individual BMD gain in the normocalcemic group

In all, 36 normocalcemic PHPT patients were included (Table 2). Mean serum pre-PTX tCa was 2.51±0.08 mmol/l, iCa was 1.32±0.05 mmol/l, and pre-PTX PTH was 65.03±20.0 pg/ml. As defined by the inclusion criteria, all normocalcemic PHPT patients had a pre-PTX 25OHD level above 20 ng/ml (mean 25OHD 34.3±7.4 ng/ml). Out of the 36 normocalcemic PHPT patients, 15 had a pre-PTX iCa below 1.30 mmol/L and 21 had pre-PTX iCa >1.30 mmol/L. Among the 15 patients with pre-PTX normal iCa, mean serum pre-PTX tCa was 2.43±0.09 mmol/l, iCa was 1.28±0.03 mmol/l, and pre-PTX PTH was 64.5±13.08 pg/ml.

Prevalence of individual BMD gain in the normocalcemic group in comparison with the hypercalcemic group

Individual site-specific BMD gains in the normocalcemic group in comparison with hypercalcemic patients were as follows: 27.8 vs 57.9 % (p=0.042) at the spine, 16.7 vs 31.6 % (p=0.30) at the femoral neck, 22.2 vs 36.8 % (p=0.34) at the total hip, 5.6 vs 10.5 % (p=0.6) at the UD radius, and none vs 10.5 % (p=0.11) at the 1/3 radius. Individual site-specific BMD gains among normocalcemic patients with both normal tCa and iCa were as follows: 33.3 % at the spine, 33.3 % at the femoral neck, 20 % at the total hip, 6.7 % at the UD radius, and none at the 1/3 radius. An individual BMD gain whatever the site (spine, hip, forearm) without loss at any other site was observed at 1 year in 16/36 (44.4 %) of the normocalcemic group, vs 14/19 (73.7 %) of hypercalcemic patients (p=0.049). An individual BMD gain was observed in 9/21 (42.8 %) patients with pre-PTX iCa >1.30 mmol/L and 7/15 (46.7 %) of patients with normal pre-PTX iCa (p=1).

Comparison of normocalcemic patients with and without individual BMD gain and prediction of BMD gain after PTX in the normocalcemic group (Table 2)

In univariate analysis, normocalcemic patients who gained BMD after PTX (n=16) displayed a higher pre-PTX ALP compared to patients who did not (n=20): 89.2±44.0 vs 65.3±36.0 UI/L (p=0.0098). The frequency of patients with eGFR lower than 60 ml/min/1.73 m^2 tended to be higher among patients who gained BMD at the individual level (non significant).

In multivariate analysis, pre-PTX ALP value above the median was confirmed as a predictive factor of BMD gain (OR=8.4, 95 % CI 1.4–56.6). No association was identified with any other pre-PTX characteristic.

Discussion

In the present work, we sought to determine the impact of PTX for an individual patient following our recent study showing significant BMD improvements at the spine and hip both in hypercalcemic and normocalcemic PHPT, but on the other hand, a decrease in 1/3 radius BMD, especially in the normocalcemic group [15]. This unexpected BMD decrease at the 1/3 radius lead to the concern that the BMD gain observed at the group level might not reflect the impact of PTX for an individual patient. For this purpose, we chose the less favorable situation which consisted in the inclusion of only those

Table 1 Pre-PTX characteristics of patients with (*N*=30) and without individual BMD gain (*N*=25) after PTX in the overall PHPT cohort (*N*=55)

Pre-PTX characteristics	Total PHPT cohort (*N*=55)	BMD gain at 1 year (*N*=30)	No BMD gain at 1 year (*N*=25)	Univariate analysis (*p*)
Age, years	64.5±9.8	64.1±11.2	65.0±8.0	0.8
Women, %	94.5	93.3	96.0	1
VAS fatigue ≥6/10 (median in total group), %	60.6	70.6	53.3	0.5
History of kidney stone, %	14.5	10.0	20.0	0.4
Chondrocalcinosis, %	3.6	3.3	4.0	1.0
History of fracture, %	33.3	33.3	33.3	1.0
Osteoporosis[a],%	87.3	83.3	88.0	0.7
Osteoporosis at the spine, %	54.7	44.8	66.7	0.2
Osteoporosis at the hip, %	39.6	30.0	52.0	0.1
Osteoporosis at the radius, %	56.6	51.7	62.5	0.6
Serum total calcium (2.20–2.60 mmol/L)	2.59±0.14	2.56±0.14	2.51±0.12	0.07
Pre-PTX serum corrected calcium >2.60 mmol/l, %	*34.5*	*46.7*	*20.0*	*0.049*
Ionized calcium (1.17–1.30 mmol/L)	1.35±0.07	1.36±0.07	1.34±0.06	0.2
Pre-PTX serum phosphate <0.8 mmol/l, %	30.9	40.0	20.0	0.19
PTH (10–46 pg/ml)	70.3±27.95	75.1±33.9	64.6±17.5	0.9
eGFR (ml/min/1.73 m^2)	*76.0±16.7*	*72.8±18.6*	*79.9±13.4*	*0.02*
eGFR <60 ml/min (ml/min per 1.73 m2),%	*10.9*	*20.0*	*0*	*0.005*
ALP (30–120 UI/L)	73.3±28.1	79.1±30.7	65.1±23.1	0.06
ALP above median (67–161 UI/L), %	*48.1*	*62.1*	*30.4*	*0.03*
Osteocalcin (ng/ml)	33.5±13.4	31.8±14.6	34.9±12.4	0.3
Serum CTX (pmol/ml)	5501.5±3078.6	5843±2589	5118±3569	0.1
CTX in the upper median, %	49.0	59.3	45.8	0.4
25OHD (30–60 ng/ml)	33.0±8.7	31.9±9.8	34.4±7.2	0.3
25OHD between 20–30 ng/ml, %	20	26.7	12.0	0.3
25OHD <20 ng/ml, %	9.9	13.3	4.0	0.4
Adenoma weight, mg	242.8±239.6	279.0	202.8	0.07
Multiple adenomas or hyperplasia, %	21.8	13.3	32.0	0.17

An individual gain was defined as a BMD change ≥0.030 g/cm^2 at the lumbar spine and/or hip and/or forearm, without any equivalent BMD loss at another site during the same period of time. All variables with a *p* value ≤0.2 in univariate analysis were included in the logistic regression model. Continuous variables are presented as mean±standard deviation (SD), and categorical data are presented as the percentage of analyzed patients (%)

Values in italics indicate statistical significance ($p<0.05$)

25OHD 25-hydroxy-vitamin D, *ALP* alkaline phosphatase activity, *BMD* bone mineral density, *CTX* carboxy-terminal telopeptide of type 1 collagen, *eGFR* estimated glomerular filtration rate, *SD* standard deviation, *VAS* visual analog scale

[a] T-score ≤−2.5 DS at the spine, hip or forearm, and/or fragility fracture

patients with complete data for all sites including the radius and the definition of an individual BMD gain taking into account the possible changes at the radius.

Our study revealed that successful PTX was followed by a significant individual BMD gain at1 year in three out of four hypercalcemic PHPT patients, which confirms the well-known benefit of PTX on bone involvement in the classical form of PHPT. Interestingly, we found that approximately one out of two osteoporotic patients with biologically and surgically proven normocalcemic PHPT also experienced significant individual improvements in BMD, in normocalcemic patients defined by normal tCa (44.4 %) as well as in normocalcemic patients defined by normal tCa and normal iCa (46.7 %). This finding is important because it suggests that although a slight decrease in 1/3 radius BMD is observed at 1 year at the group level, a large proportion of these patients has a rapid improvement in overall BMD with no significant loss. Individual site-specific BMD gain without loss was more frequent at the spine and hip than at the radius, both in hypercalcemic and in normocalcemic PHPT patients, including those with normal iCa. In fact, the BMD change at the forearm after PTX is inconsistent in available studies [5, 9, 12–14, 17, 18]. Indeed, some studies reported a BMD increase at the radius after PTX [9, 17, 18], while others reported no change, including a 10-year follow-up study [5] and three randomized controlled trials that evaluated BMD change after

Table 2 Pre-PTX characteristics of patients with (*N*=16) and without individual BMD gain (*N*=20) after PTX in the normocalcemic group (*N*=36)

Pre-PTX characteristics	Normocalcemic group (*N*=36)	BMD gain at 1 year (*N*=16)	No BMD gain at 1 year (*N*=20)	Univariate analysis (*p*)
Age, years	66.0±8.8	66.0±10.3	66.1±7.5	0.95
Women, %	91.6	87.5	95.0	0.6
VAS fatigue ≥6/10 (median in total group), %	60.0	72.7	50.0	0.5
History of kidney stone, %	19.4	12.5	25.0	0.4
Chondrocalcinosis, %	2.8	0	5.0	1.0
History of fracture, %	37.1	37.5	36.8	0.7
Osteoporosis[a],%	91.6	87.5	95.0	0.6
Osteoporosis at the spine, %	65.7	56.3	73.7	0.3
Osteoporosis at the hip, %	47.2	31.3	60.0	0.1
Osteoporosis at the radius, %	55.6	43.8	65.0	0.3
Serum total calcium (2.20–2.60 mmol/L)	2.51±0.08	2.51±0.098	2.52±0.07	0.9
Ionized calcium (1.17–1.30 mmol/L)	1.32±0.05	1.32±0.05	1.32±0.05	0.9
Pre-PTX serum phosphate <0.8 mmol/l, %	16.7	18.8	15.0	1.0
PTH (10–46 pg/ml)	65.0±20.0	67.0±26.3	63.6±13.5	0.9
eGFR (ml/min/1.73 m^2)	80.1±17.5	78.4±22.2	81.5±13.1	0.3
eGFR <60 ml/min (ml/min per 1.73 m^2),%	8.3	18.8	0	0.08
ALP (30–120 UI/L)	*76.2±30.8*	*89.2±44.0*	*65.3±36.0*	*0.0098*
ALP above median (67–161 UI/L), %	*48.6*	*75.0*	*26.3*	*0.007*
Osteocalcin (ng/ml)	32.7±13.1	34.1±12.3	31.6±13.9	0.4
Serum CTX (pmol/ml)	4697.7±2041.1	4949.9±2101.2	4485.3±2021.3	0.4
CTX in the upper median, %	45.7	50.0	42.1	0.7
25OHD (ng/ml), mean±SD	34.3±7.4	34.4±9.1	34.2±5.9	0.9
25OHD between 20–30 ng/ml, %	25.0	37.4	15.0	0.2
Adenoma weight, mg	197.8±185.7	231.4±220.4	172.7±156.1	0.2
Multiple adenomas or hyperplasia,%	27.8	18.8	35.0	0.5

Values in italics indicate statistical significance ($p<0.05$)

[a] T-score ≤−2.5 DS at the spine, hip or forearm and/or fragility fracture

PTX in mild asymptomatic PHPT [12–14]. It seems, therefore, that the short-term BMD change at the radius does not reflect appropriately the global change in BMD after PTX.

We next attempted to identify baseline patients' characteristics that could predict individual BMD gain without loss after PTX. The only variable identified as an independent predictor of BMD gain was a pre-PTX ALP value above median (≥ 67 UI/L). Indeed, patients from the total PHPT cohort with ALP above median were 4.9 times more likely to have a significant BMD gain at the individual level (OR=4.9, 95 % CI 1.3–18.9); similarly patients from the normocalcemic group were 8.4 times more likely to have a BMD gain when their pre-PTX ALP value was above median (OR=8.4, 95 % CI 1.4–56.6). Although a change in bone turnover markers such as ALP is known to be associated with an improvement in BMD after PTX in classic PHPT [19], this is the first time this is reported in normocalcemic PHPT. This also lends support for similar bone mineral recuperation capacities between normocalcemic and hypercalcemic PHPT after PTX. It should be noted that in the present study, pre-PTX ALP levels tended to be in the normal high range compared to previous work where preoperative ALP levels were clearly above normal [19]. Nevertheless, since PAL values follow a normal distribution in the general population, and that the median PAL value in our cohort (66 UI/L) was close to the median PAL of the laboratory (reference range 30–120), our results indicate that normocalcemic PHPT patients with osteoporosis and a PAL value above the mean of the laboratory may have an improvement of BMD after PTX [20]. On the other hand, serum tCa, iCa, and serum PTH did not predict individual BMD gain in our total PHPT cohort, further supporting the potential benefit of PTX in normocalcemic patients as well as in the hypercalcemic subtype.

This study is not without limitations. As already discussed elsewhere [15], the proportion of normocalcemic PHPT patients and patients with both normal tCa and normal iCa in our cohort is important compared to the proportion of hypercalcemic PHPT patients, due to the referral bias in our department, dealing with patients addressed for the investigation of low bone mass with very mild abnormalities of calcium,

phosphorus, and/or PTH. This may have biased the results obtained in the overall PHPT cohort. Secondly, although we used the BMD change as main outcome measure, we did not investigate the impact of PTX on subsequent fracture risk, which is essential and needs to be investigated. Indeed, whether the BMD change at the forearm after PTX has any influence on bone strength is yet to be determined.

Altogether, the present study shows that successful PTX is followed at 1 year by a significant individual BMD gain in approximately half of normocalcemic PHPT patients with osteoporosis, which may help in the clinical management of biologically proven normocalcemic PHPT with low bone mass. Normal high to high ALP levels may also contribute to the decision of PTX in this context.

Conflicts of interest None.

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