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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Biochemical and Skeletal Outcomes of Parathyroidectomy for Normocalcemic (Incipient) Primary Hyperparathyroidism

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ABSTRACT

Background. Normocalcemic (incipient) primary hyperparathyroidism (PHPT) is characterized by inappropriately elevated parathyroid hormone (PTH) levels in the setting of normal serum calcium. The biochemical and skeletal outcomes after parathyroidectomy for normocalcemic PHPT are not well-described.

Methods. All patients who underwent parathyroidectomy for normocalcemic PHPT at a single institution were retrospectively reviewed (2006–2016). Pre- and postoperative calcium, PTH, and bone mineral density (BMD) were compared between patients with normalized versus persistently elevated PTH levels $>$ 6 months after parathyroidectomy. Multivariable Cox regression was used to identify risk factors associated with persistently elevated PTH levels after parathyroidectomy.

Result. Parathyroidectomy was performed in 71 patients with normocalcemic PHPT, of whom 38 (53.5%) had multi-gland disease. No patients became hypercalcemic, with a median follow-up of 23.1 months. Persistently elevated PTH levels were noted in 33 (46.5%) patients. In multivariable analysis, preoperative PTH $>$ 100 pg/mL was associated with persistently elevated PTH levels after parathyroidectomy. In 38 patients with available pre- and postoperative BMD measurements, the mean preoperative BMD improved + 5.6% ($p < 0.01$) in patients with normalized PTH, while no significant change was observed in patients with persistently elevated PTH levels (− 2.2%, $p = 0.47$).

Conclusions. Elevated PTH levels are common after parathyroidectomy for normocalcemic PHPT. Improvements in BMD may be predicated on long-term normalized PTH levels following surgery.

Keywords Parathyroidectomy · Hyperparathyroidism · Osteoporosis · Normocalcemic hyperparathyroidism

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with an estimated prevalence in the United States of between 0.1 and 0.5%.[1] The classic presentation of PHPT includes hypercalcemia with an inappropriately increased serum parathyroid hormone (PTH) level. Normocalcemic hyperparathyroidism is a variant of PHPT in which the serum calcium remains normal despite excess PTH, after the exclusion of secondary causes, including vitamin D deficiency and chronic kidney disease. Patients with normocalcemic PHPT are identified primarily through screening for secondary causes of osteoporosis.[2]

Normocalcemic PHPT, alternatively termed incipient PHPT, was formally recognized in 2008 at the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.[3] Although now a well-recognized variant of PHPT, outcomes following parathyroidectomy for normocalcemic PHPT are not well-described.[2,4,5] Parathyroidectomy for classic PHPT has a 95% long-term cure rate when performed by experienced surgeons, and reduces the incidence of end-organ complications (predominantly fractures and kidney stones).[6,7] Whether patients with normocalcemic PHPT derive similar benefits from parathyroidectomy has not been clarified.

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In the current study, we analyzed the biochemical and skeletal outcomes of parathyroidectomy for normocalcemic PHPT. We also evaluated risk factors associated with PTH elevation following parathyroidectomy in patients with normocalcemic PHPT.

METHODS

Study Subjects

With approval from the Institutional Review Board, we retrospectively reviewed records of patients who underwent parathyroidectomy for PHPT within the University of California, Los Angeles Medical Center between 1 January 2006 and 31 December 2016. Patients with normocalcemic PHPT were defined as having serum calcium levels within the reference range, with concurrent elevated PTH levels above the reference range (17–55 pg/mL). Given multiple sources of laboratory testing, the upper limit of normal for serum calcium concentration ranged between 10.2 and 10.6 mg/dL. However, only patients with peak serum calcium levels within the reference range for the testing laboratory within 1 year prior to surgery were included. Patients with vitamin D deficiency (25-hydroxyvitamin D < 20 nmol/L) or renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) were excluded.

Clinical, pathological, and biochemical data abstracted included age, sex, preoperative localization study results, the presence of single-gland disease (SGD) versus multigland disease (MGD) found intraoperatively, visual or pathologic confirmation that all four glands were identified, surgical approach (focused vs. four-gland exploration), intraoperative PTH (ioPTH) levels, pre- and postoperative peak PTH and calcium levels, and bone mineral density (BMD). BMD data were obtained preoperatively and > 2 years postoperatively through dual-energy x-ray bone densitometry (DXA). The site with the lowest DXA T-score (spine, femoral neck, or hip) preoperatively was chosen as the site where the pre- and postoperative bone mineral densities were compared.

Study Protocol

The surgical approach was chosen at the discretion of the operating surgeon. In patients with adequate preoperative localization who underwent a focused parathyroidectomy, the ipsilateral parathyroid gland was routinely inspected. ioPTH levels were routinely measured pre-incision, pre-excision, 10 min post-excision, and 30 min postoperatively. Intraoperative determination of successful parathyroidectomy was defined by a decreased in ioPTH levels $> 50\%$ from pre-incision or pre-excision baseline. The percentage of decrease in ioPTH levels was analyzed at 10 min post-excision and 30 min postoperatively. In patients who did not satisfy the ioPTH criteria, procedures were terminated when the risk–benefit ratio of further exploration or resection of additional glands was deemed unfavorable. Particularly in normocalcemic PHPT, our experience is that due to the high prevalence of MGD with minimally enlarged glands, coupled with the limited evidence for improved outcomes after parathyroidectomy, our threshold to continue parathyroid exploration at the expense of patient safety was high. Determination of SGD or MGD (two or more abnormal glands, including four-gland hyperplasia) was made based on intraoperative findings (size, color, and overall appearance of the parathyroid glands) in conjunction with an adequate decrease in ioPTH levels ($> 50\%$). All patients with MGD underwent four-gland exploration.

Patients were divided into two groups based on the peak PTH level > 6 months following parathyroidectomy. Patients whose PTH level normalized and remained within the normal reference range (17–55 pg/mL) after parathyroidectomy were assigned to the 'normalized PTH' group, while those with a peak PTH above the reference range > 6 months following parathyroidectomy were assigned to the 'persistently elevated PTH' group.

Statistical Analysis

Demographic and clinical factors were compared between patients with normalized versus persistently elevated PTH levels after parathyroidectomy. Continuous variables (age, calcium, PTH levels, creatinine, phosphorus, and BMD) were analyzed using Student's *t* test or the Wilcoxon rank-sum test, while categorical variables (sex, preoperative localization study results, SGD vs. MGD, and surgical approach) were evaluated using the Chi square test. The cumulative proportion of patients with elevated PTH levels following surgery at various postoperative time points was estimated using the Kaplan–Meier analysis. Univariable and multivariable Cox regression analyses were performed to identify factors associated with recurrence/persistence of PHPT. The optimal cut-off point was determined for continuous variables where clinically useful (i.e. laboratory values). This was performed by fitting the dichotomized variable to a Cox proportional hazard model, and then determining the cut-off point with the most significant split in recurrence-free survival as defined by the log-rank test. *P*-values < 0.05 were defined as statistically significant. All statistical analyses were performed using the R program version 2.12.0 (www.r-project.org).

RESULTS

Baseline Characteristics

Of 2055 patients who underwent parathyroidectomy for PHPT between 2006 and 2016, 90 had normocalcemic PHPT. Biochemical follow-up at > 6 months was available for 71 patients, with a median postoperative follow-up of 23.1 months (range 10.7–518). The frequency of parathyroidectomy performed for normocalcemic PHPT increased over the course of the study, with 57% of cases performed in the last 3 years. The median patient age was 67 years (interquartile range [IQR] 62–72 years) and 88.7% of patients were female (Table 1). The median preoperative calcium and PTH levels were 10.2 mg/dL and 92.0 pg/mL, respectively. All patients had calcium levels within the normal range for the year preceding parathyroidectomy. Twenty-nine of 71 (40.8%) patients had a prior history of hypercalcemia > 1 year preceding parathyroidectomy, and 59 of 71 (83.1%) patients had ionized calcium measured preoperatively (median 1.25, range 1.1–1.49 mmol/L, reference 1.09–1.29 mmol/L). All 10 of 71 patients with elevated preoperative ionized calcium had normal total serum calcium with normal serum albumin, and these patients were included in our cohort due to questionable reliability and pH dependency of ionized calcium measurements.[8]

Four-gland exploration was performed in 47 of 71 (66.2%) patients, while the remaining 24 patients underwent focused parathyroidectomy. In the patients who underwent focused parathyroidectomy, the ioPTH criteria were met in 22 of 24 (91.7%) patients at 10 min post-excision, and 22 of 24 (91.7%) patients at 30 min postoperatively. In patients who underwent four-gland exploration, four parathyroid glands were identified in 38 of 47 (80.5%) patients, while three or fewer glands were identified in the remaining 9 of 47 (14.9%) patients. The ioPTH criteria were met in 27 of 47 (57.4%) patients at 10 min post-excision and 39 of 47 (83.0%) patients at 30 min postoperatively. In patients who underwent four-

TABLE 1 Demographic, imaging, and biochemical characteristics of patients with normalized versus persistently elevated PTH levels following parathyroidectomy

Characteristics	Patient groups			*p* value
	Total [*N* = 71]	Postoperative PTH elevated [*N* = 33]	Postoperative PTH normal [*N* = 38]	
Age, years [median (IQR)]	67 (62–72)	66 (64–73)	65 (59–71)	0.21
Sex [*n* (%)]				0.34
Female	63 (88.7)	28 (84.8)	35 (92.1)	
Male	8 (11.3)	5 (15.2)	3 (7.9)	
Preoperative imaging localization [*n* (%)]				0.48
Single-gland disease	35 (49.3)	15 (45.5)	20 (52.6)	
Multi-gland disease	13 (18.3)	8 (24.2)	5 (13.2)	
Negative	23 (32.4)	10 (30.3)	13 (34.2)	
Preoperative biochemical values[a] [median (IQR)]				
Calcium (mg/dL)	10.2 (9.7–10.4)	10.3 (9.9–10.4)	10.2 (9.6–10.4)	0.17
PTH (pg/mL)	92 (68–109)	103 (77–133)	79.5 (65–98)	< 0.01
Creatinine (mg/dL)	0.8 (0.7–1.0)	0.9 (0.8–1.1)	0.8 (0.7–0.9)	0.03
Phosphorus (mg/dL)	3.3 (3.0–3.5)	3.4 (3.1–3.5)	3.2 (2.7–3.5)	0.10
History of hypercalcemia[b] [*n* (%)]	29 (40.8)	15 (45.5)	14 (36.8)	0.46
Bone marrow density[c] (g/cm^2)	0.705	0.704	0.706	0.59
Postoperative biochemical value [median (IQR)]				
Calcium (mg/dL)	9.5 (9.1–9.8)	9.6 (9.2–10.0)	9.3 (9.1–9.8)	0.16
PTH (pg/mL)	51 (39–66)	71.3 (61–78)	39.5 (36–47)	< 0.01
% PTH decrease	43.5 (28.2–56.8)	31.0 (10.9–46.6)	52.6 (38.6–63.4)	< 0.01

PTH parathyroid hormone, *IQR* interquartile range

[a]Based on the highest value obtained within 1 year prior to parathyroidectomy

[b]History of calcium levels above the normal range more than 1 year prior to parathyroidectomy

[c]Applies to patients with available pre- and postoperative BMD results

gland exploration and did not satisfy the ioPTH criteria, the exploration was concluded if the risk–benefit ratio associated with additional exploration became unfavorable. MGD was identified in 38 of 71 patients (53.5%), of whom 23 of 38 (60.5%) had hyperplasia and 15 of 38 (39.5%) had double adenomas.

Subtotal parathyroidectomy was performed in 25 of 71 (35.2%) of patients. Of the 22 patients who did not achieve a drop in ioPTH levels of > 50% at 10 min, 16 underwent subtotal parathyroidectomy. In the remaining six patients who did not undergo subtotal thyroidectomy, the 10-min ioPTH values ranged between 42 and 61 pg/mL. The decision not to pursue subtotal parathyroidectomy in these cases was made based on the normal appearance of the remaining parathyroid glands in the setting of a drop in ioPTH level to a normal/near-normal PTH value. Removal of additional parathyroid glands in these cases was not performed because the perceived risk of hypoparathyroidism was too high.

Biochemical Outcomes

Normalized PTH levels were observed > 6 months after parathyroidectomy in 38 (53.5%) patients, while the remaining 33 (46.5%) patients had elevated PTH levels. Patients with normalized PTH after parathyroidectomy had significant reductions in median calcium and PTH levels (pre- vs. postoperative values: calcium, 10.2 vs. 9.3 mg/dL; PTH, 79.5 vs. 39.5 pg/mL; $p < 0.001$ for both). Patients with persistently elevated PTH levels also had significant reductions in calcium and PTH levels (pre- vs. postoperative values: calcium, 10.3 vs. 9.6 mg/dL; PTH, 103 vs. 71.3 pg/mL; $p < 0.001$ for both); however, the median postoperative PTH level remained above the reference range. Our institutional cure rate for patients with classic hyperparathyroidism during the same period was 97.5% (unpublished data).

The cumulative incidence of developing elevated PTH levels after parathyroidectomy is shown in Fig. 1. The median time to detection of elevated PTH after parathyroidectomy was 7.7 months (IQR 2.3–35.5). No patients developed hypercalcemia in the postoperative period in either the normalized or persistently elevated PTH groups.

Risk Factors Associated with Persistently Elevated Parathyroid Hormone Levels Following Parathyroidectomy

No significant differences were observed between patients with normalized versus persistently elevated PTH levels with respect to age, sex, or preoperative localization (Tables 1 and 2). Patients with elevated PTH had higher median preoperative PTH levels compared with patients

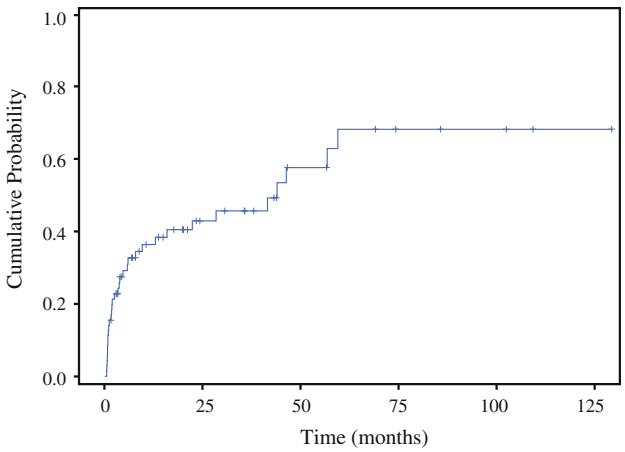

FIG. 1 Cumulative incidence of developing elevated parathyroid hormone following parathyroidectomy for normocalcemic primary hyperparathyroidism ($n = 71$)

with normalized PTH (median [IQR] 103 [77–133] vs. 79.5 [65–98] pg/mL, $p < 0.01$), as well as higher median 10-min ioPTH levels (66 [50–103] vs. 44 [36–84] pg/mL, $p = 0.02$), higher 30-min postoperative PTH levels (50 [39–73] vs. 35.5 [19–52] pg/mL, $p < 0.01$), and lower rate of drop in ioPTH levels into the normal PTH-level range (30.3 vs. 57.9%, $p = 0.02$). Furthermore, the persistently elevated and normalized PTH groups had similar rates of MGD (60.6 vs. 47.4%, $p = 0.265$), four-gland exploration (66.7 vs. 65.8%, $p = 0.938$), subtotal parathyroidectomy (36.4 vs. 34.2%, $p = 0.85$), visual or pathologic confirmation of four parathyroid glands identified (51.5 vs. 55.3%, $p = 0.75$) and > 50% drop in ioPTH levels at 10 min (70 vs. 66.4%, $p = 0.91$).

In univariate analysis, factors associated with elevated PTH after parathyroidectomy included preoperative PTH level > 100 pg/mL (odds ratio [OR] 3.73, 95% confidence interval [CI] 1.84–7.55, $p \leq 0.001$), postoperative PTH level at 30 min > 30 pg/mL (OR 2.05, 95% CI 1.03–4.07, $p = 0.04$), and failure of the ioPTH level to drop into the normal PTH-level range (OR 2.09, 95% CI 1.01–4.40, $p = 0.045$). Preoperative calcium level, history of hypercalcemia > 1 year prior to parathyroidectomy, MGD, surgical approach, and subtotal parathyroidectomy were not predictive of persistently elevated PTH levels after parathyroidectomy (Table 3). Of 47 patients who underwent four gland exploration, 17 of 38 (44.7%) patients who had four glands identified intraoperatively had persistently elevated PTH levels, compared with 5 of 9 (55.6%) patients with three or less glands identified intraoperatively ($p = 0.830$). No ioPTH cut-off (level or percentage drop) at 10 min post-excision predicted long-term PTH normalization. In multivariable analysis, preoperative PTH level > 100 pg/mL (OR 3.24, 95% CI 1.55–6.8, $p = 0.001$) and postoperative PTH level at 30 min > 30 pg/mL (OR

TABLE 2 Operative characteristics of patients with normalized versus persistently elevated PTH levels following parathyroidectomy

Characteristics	Total [$N = 71$]	Postoperative PTH elevated [$N = 33$]	Postoperative PTH normal [$N = 38$]	p value
Surgical approach [n (%)]				0.94
Focused	24 (33.8)	11 (33.3)	13 (34.2)	
Four-gland exploration	47 (66.2)	22 (66.7)	25 (65.8)	
Single versus multi-gland disease [n (%)]				0.27
Single-gland	33 (46.5)	13 (39.4)	20 (52.6)	
Multi-gland	38 (53.5)	20 (60.6)	18 (47.4)	
Four glands identified [n (%)]				0.75
Yes	38 (53.5)	17 (51.5)	21 (55.3)	
No	33 (46.5)	16 (48.5)	17 (44.7)	
Subtotal parathyroidectomy [n (%)]				
Yes	25 (35.2)	12 (36.4)	13 (34.2)	0.85
No	46 (64.7)	21 (63.6)	25 (65.8)	
ioPTH [median (IQR)]				
Baseline ioPTH (pg/mL)	149 (106–197)	171 (120–215)	137 (104–171)	0.05
ioPTH at 10 min (pg/mL)	57 (38–99)	66 (50–103)	44 (36–84)	0.02
Percentage of ioPTH decrease at 10 min	55.6 (41.5–73.0)	54.2 (44.7–67.5)	59.4 (39.1–73.7)	0.34
Percentage of patients with > 50% drop in ioPTH levels at 10 min	69.0%	70.0%	68.4%	0.91
Percentage of patients with > 50% drop in ioPTH levels *and* into the normal range at 10 min	45.1%	30.3%	57.9%	0.02
Postoperative PTH at 30 min [median (IQR)]				
PTH (pg/mL)	44 (26–62)	50 (39–73)	35.5 (19–52)	< 0.01
Mean percentage PTH decrease	71.4 (56.7–79.7)	67.4 (54.9–74.2)	74.4 (58.3–84.9)	0.04

PTH parathyroid hormone, *ioPTH* intraoperative PTH

3.44, 95% CI 1.6–11.19, $p = 0.040$) remained predictive of persistently elevated PTH levels after parathyroidectomy.

Skeletal Outcomes

Preoperative BMD data were available for 63 of 71 (88.7%) patients, of whom 58 (92.1%) had either osteopenia (32 patients) or osteoporosis (26 patients). Osteopenia was present in 32 patients, while osteoporosis was present in 26 patients. A complete set of pre- and postoperative BMD data was available for 38 patients. For patients for whom both the pre- and postoperative BMD data were available, the mean pre- and postoperative BMD was 0.705 ± 0.026 (mean ± standard error) g/cm^2 and 0.723 ± 0.030 g/cm^2, respectively, representing an overall +2.6% improvement in BMD ($p = 0.15$). In patients with normalized PTH ($n = 23$), mean preoperative BMD improved + 5.6%, from 0.706 ± 0.036 g/cm^2 to 0.745 ± 0.037 g/cm^2 postoperatively ($p = 0.006$). Patients in the persistently elevated PTH group ($n = 15$) had no significant change in mean BMD (preoperative BMD 0.704 ± 0.038 g/cm^2, postoperative BMD 0.688 ± 0.052 g/cm^2, change − 2.2%, $p = 0.475$) (Fig. 2).

DISCUSSION

Our results indicate that persistently elevated PTH levels are common following parathyroidectomy for normocalcemic PHPT. Although no patients progressed to hypercalcemia following surgery, only patients with normalized PTH levels (54% of the cohort) had improved BMD > 2 years after parathyroidectomy. None of the following clinical factors were predictive of cure, including (1) positive imaging; (2) focused versus four-gland exploration; (3) identification of all four parathyroid glands; and (4) ioPTH decrease of > 50% at 10 min.

Normocalcemic PHPT is an increasingly recognized entity, and, indeed, the annual frequency of parathyroidectomy for normocalcemic PHPT at our institution more than doubled over the study period. Although the surgical cure rate for classic PHPT is > 95% (defined as long-term eucalcemia),[9,10] biochemical outcomes after parathyroidectomy for normocalcemic PHPT are not well-described. In a previous study of 93 patients who underwent surgery for normocalcemic PHPT, 25% of patients had persistently elevated PTH levels postoperatively.[4] In a similar study including 39 patients with normocalcemic

TABLE 3 Univariate analysis of factors associated with persistently elevated PTH levels after parathyroidectomy for normocalcemic PHPT

Characteristics	Odds ratio	*p*-Value
Preoperative biochemical values		
Calcium[a] (mg/dL)	2.12 (0.90–5.0)	0.086
PTH[a] (pg/mL)	1.01 (1.01–1.02)	< 0.001
PTH level ≤ 100	1 (reference)	< 0.001
PTH level > 100	3.73 (1.84–7.55)	
History of hypercalcemia[b]		
Yes	1.27 (0.64–2.52)	0.51
No	1 (reference)	
Number of abnormal glands		
Single-gland disease	1 (reference)	
Multi-gland disease	1.71 (0.66–4.40)	0.27
Approach		
Focused	1 (reference)	0.47
Four-gland exploration	1.32 (0.63–2.76)	
Four glands identified		
No	1 (reference)	
Yes	0.860 (0.34–2.19)	0.75
Subtotal parathyroidectomy		
Yes	1 (reference)	0.98
No	1.01	
Intraoperative PTH		
ioPTH at 10 min	1.00 (1.00–1.01)	0.36
Postoperative 30-min PTH[a]	1.01 (1.01–1.03)	0.001
> 30 pg/mL	2.05 (1.03–4.07)	
≤ 30 pg/mL	1 (reference)	0.041
Percentage decrease in ioPTH at 10 min[a]	0.55 (0.14–2.31)	0.42
≤ 50%	1.03 (0.50–2.13)	
> 50%	1 (reference)	0.93
Percentage decrease in PTH at 30 min postoperatively[a]	0.14 (0.018–1.00)	0.057
≤ 50%	1.34 (0.51–3.48)	
> 50%	1 (reference)	0.55
Drop in ioPTH value by > 50% *and* into the normal range		
No	2.09 (1.01–4.40)	0.045
Yes	1 (reference)	

PTH parathyroid hormone, *PHPT* primary hyperparathyroidism, *ioPTH* intraoperative PTH

[a]Analyzed as a continuous variable

[b]History of calcium levels above the normal range more than 1 year prior to parathyroidectomy

PHPT, 21% of patients had elevated PTH levels 3 months postoperatively, although most were found to be vitamin D deficient and had subsequent normalization of PTH levels after vitamin D repletion.[5] Our study confirms that elevated PTH levels are common after parathyroidectomy for normocalcemic PHPT.

The clinical significance of persistently elevated PTH levels after parathyroidectomy is unclear. Normocalcemic elevations in PTH levels after parathyroidectomy for classic PHPT have been reported in 20% of patients, but few of these patients developed recurrent hypercalcemia.[11–14] As defined by the American Association of Endocrine Surgeons (AAES) guidelines, surgical cure for normocalcemic PHPT includes normalization of PTH levels postoperatively.[15] This criterion follows from the decreased utility of following serum calcium in patients who were normocalcemic preoperatively, and is a stricter definition of cure than that applied to patients with classic PHPT, in which the serum calcium alone is considered.

Patients with normocalcemic PHPT have an increased rate of MGD,[2,4] as confirmed in our study (53.5%). Thus, failure to normalize the PTH postoperatively may be a

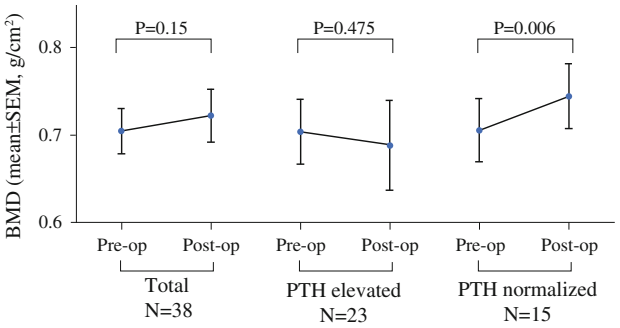

FIG. 2 Pre- and postoperative BMD measurements in patients with normalized versus elevated postoperative PTH. *BMD* bone mineral density, *PTH* parathyroid hormone, *SEM* standard error of the mean, *Pre-op* preoperative, *Post-op* postoperative

consequence of inadequate surgery. For this reason, a priority in our analyses was to scrutinize the adequacy of parathyroidectomy. In our study, two-thirds of patients underwent routine four-gland exploration, which reflects our high vigilance towards MGD in this patient population. More aggressive surgery, consisting of subtotal parathyroidectomy with visual or pathologic confirmation of all four parathyroid glands, was not protective against elevated postoperative PTH levels. Lastly, a $> 50\%$ decrease in ioPTH levels at 10 min was also unreliable in predicting normalization of PTH long-term. Interestingly, however, a $> 50\%$ decrease in ioPTH level *and* a drop in ioPTH level into the normal range, combined, was predictive of long-term PTH normalization. The PTH level at 30 min following surgery was also predictive of long-term cure. Although higher preoperative PTH levels were associated with a higher rate of postoperative PTH elevation, this likely reflects positive covariance related to the biological capacity to produce a given level of PTH.

Most patients with normocalcemic PHPT are identified and referred for surgery due to osteopenia/osteoporosis. In our small subset of patients with complete pre- and postoperative BMD data, improvement in BMD was predicated on normalized PTH levels postoperatively. In a prior study of 38 patients with long-term PTH normalization after parathyroidectomy, the BMD increased by $+ 2.3\%$ and $+ 1.9\%$ at the lumbar spine and hip, respectively, 1 year after surgery.[5] In our study, with a median follow-up of 23.1 months, we observed a higher magnitude of increase in BMD ($+7.9\%$) in patients with normalized PTH levels, which is comparable to increases in BMD observed in patients with classic PHPT.[6] This emphasizes that normalization of PTH levels may be critical to achieve optimal skeletal outcomes after surgery.

This study has several limitations. Our median follow-up was limited to 23 months. Defining baseline ioPTH as the higher of pre-incision or pre-excision values may allow an increased number of patients to satisfy the ioPTH criteria based on a stimulated pre-excision value. However, redefining baseline ioPTH as the unstimulated, pre-incision value did not change our results. Although parathyroidectomy for normocalcemic PHPT was performed at our institution with increasing frequency over the study period, our sample size was limited to only 71 patients, which is consistent with prior studies.[4,5] BMD data were available in a minority of patients, and our analysis of skeletal outcomes may be underpowered. This may be due to our significant referral population, who may be receiving follow-up outside of our health system. However, differences in BMD between patients with normalized or elevated PTH were evident despite the relatively small sample size, which is comparable with the sample size of patients with PHPT from other referral centers.[16]

CONCLUSIONS

Almost half of normocalcemic PHPT patients had persistently elevated PTH levels after parathyroidectomy. This occurred even in patients who had undergone the most aggressive possible parathyroidectomy: histologically confirmed subtotal resection to 25 mg of vascularized parathyroid tissue. Patients with normocalcemic PHPT may have disease biology less amenable to surgical cure, as evidenced by prior work suggesting end-organ resistance to PTH in patients with this biochemical profile.[17] A subpopulation of patients with normocalcemic PHPT did exhibit improved BMD with normalization of PTH after surgery. However, given the high rates of elevated PTH levels after parathyroidectomy observed in our study, we recommend a selective approach to surgery and a detailed discussion with patients regarding the goals and expected outcomes.

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