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ORIGINAL SCIENTIFIC REPORT

Surgery for Primary Hyperparathyroidism with Normal Non-suppressed Parathyroid Hormone can be Both Challenging and Successful

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Abstract

Background Criteria for diagnosing primary hyperparathyroidism (PHPT) include hypercalcemia in the presence of parathyroid hormone (PTH) levels that are either elevated (classic PHPT) or normal but non-suppressed. However, there is no standard definition of what constitutes normal non-suppressed levels, and data are lacking regarding the potential for surgical cure in these patients.

Methods A retrospective review of patients undergoing parathyroidectomy for sporadic PHPT between 2012 and 2014 was performed. Patients with normal PTH were compared to classic PHPT patients to assess demographics, imaging, operative findings, and outcomes.

Results In total, 332 patients met study criteria, and 60 (18%) had normal PTH levels. Negative sestamibi scans were seen more often with normal PTH levels (18.3 vs. 4.8%, $p < 0.001$). Patients with normal PTH were more likely to have ≥2 glands removed (26.7 vs. 14.3%, $p = 0.02$), and the specimens were more likely to be classified as only mildly hypercellular or normocellular (20 vs. 2.9%, $p < 0.001$). Average follow-up was 24 months (range 6–55). Cure rate was 88% in the normal PTH group, compared to 96% in classic PHPT ($p = 0.02$). Among patients with normal PTH, those with PTH ≤ 55 pg/mL had an 83% cure rate, whereas those with PTH 56–65 had a 96% cure rate ($p = 0.12$).

Conclusions Parathyroidectomy can have a high cure rate in the context of normal PTH levels despite an increased likelihood of negative imaging and multigland resection. Operative success is equivalent to classic PHPT when PTH levels are > 55 pg/mL.

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder defined by excessive secretion of parathyroid hormone (PTH) from one or more abnormal parathyroid glands. A diagnosis is made when hypercalcemia is observed in the setting of elevated or normal but non-suppressed levels of PTH [1]. However, there is no guideline for determining whether a PTH level in the normal range is in fact appropriately suppressed relative to the serum calcium or is non-suppressed. Additionally, authors have described a variant form of hyperparathyroidism in which PTH levels are elevated but calcium levels are normal [2–7]. Many patients with PHPT may be asymptomatic or have non-specific symptoms, leading to diagnostic uncertainty when only PTH or calcium is elevated.

The mainstay of treatment and the only definitive therapy for PHPT is surgical resection of adenomatous or

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hyperplastic parathyroid glands. Parathyroidectomy has proven benefits for PHPT and is recommended for a specified set of indications [1]. Surgical cure, characterized by normocalcemia at 6 months after parathyroidectomy, is seen in 95–99% of patients [1, 8].

Few studies have examined postoperative outcomes in patients who undergo parathyroidectomy for PHPT with normal PTH levels. There is some evidence that surgery may be successful in this subset of patients, with cure rates of 93–100% [4, 9–11]. These studies have relatively small numbers of patients and short follow-up, some without the 6-month calcium levels necessary to determine cure. Others fail to specify the range of PTH values in operative patients. The purpose of this study is to analyze long-term outcomes following parathyroidectomy in patients with normal PTH values and to identify factors associated with success in this challenging group of patients, for which diagnostic uncertainty still arises. Secondarily, we examined the demographics and disease-specific characteristics in patients undergoing surgery with normal PTH compared to patients with classic PHPT.

Materials and methods

Following institutional review board approval, a retrospective review of 411 adult patients undergoing initial parathyroidectomy for hyperparathyroidism between January 2012 and March 2014 at Mayo Clinic was performed. Patients with multiple endocrine neoplasia (MEN) syndromes, secondary hyperparathyroidism, or tertiary hyperparathyroidism were excluded, leaving only patients with primary hyperparathyroidism available for analysis. Additionally, patients were excluded if they were normocalcemic preoperatively or if they had <6 months of biochemical follow-up postoperatively.

Variables examined were age, gender, indications for surgery, preoperative imaging results, preoperative laboratory values (serum calcium, PTH, phosphorous, creatinine, 25-hydroxyvitamin D, and 24-h urine calcium and creatinine), intraoperative PTH (IOPTH) levels, histology findings, parathyroid gland weight, and postoperative serum calcium. Indications included osteoporosis or osteopenia, neurocognitive symptoms (such as fatigue or memory problems), significantly elevated calcium levels (serum calcium > 1 mg/dL above upper limit of normal [normal 8.9–10.1 mg/dL] or 24-h urine calcium > 400 mg), nephrolithiasis, or age < 50 years at diagnosis. For cases in which multiple sets of preoperative laboratory studies were drawn, only the most recent value for each variable was recorded. Patients were divided into two subgroups on the basis of having normal preoperative PTH or elevated preoperative PTH (classic PHPT group), with the reference range for normal PTH at our institution being 15–65 pg/mL. A monoclonal PTH-specific antibody sandwich immunoassay was used with *Cobas*® e602 or 8000 (Roche Diagnostics, Indianapolis, IN) modular analyzers to process the samples.

All patients had one or more imaging studies performed preoperatively. In nearly all cases, preoperative localization was attempted with sestamibi subtraction scintigraphy, in which an I-123 thyroid scan (1.0 mCi) was subtracted from a technetium sestamibi (20 mCi) scan with anterior, right oblique, and left oblique views. A minority of patients underwent neck ultrasound with high-resolution and high-frequency (10–13 MHz) scanners and color Doppler imaging, in addition to or in place of sestamibi scintigraphy.

IOPTH samples were collected in 3-mL aliquots from an arterial line, a peripheral venous line located in a different extremity than other functioning lines, or an internal jugular vein. In most cases, only a focused cervical exploration was performed if IOPTH levels declined appropriately, which was generally defined as a ≥50% decrease in PTH level from baseline with a normal or near-normal value.

Surgical cure was defined by a total calcium level less than or equal to the upper limit of normal (≤10.1 mg/dL at our institution), at 6 months or later after surgery. Persistent disease was defined by ongoing hypercalcemia more than 6 months postoperatively. A patient was said to have recurrent disease if calcium levels normalized over 6 months after surgery but subsequently became elevated again.

Continuous variables were analyzed with a Student's *t* test. Categorical variables were compared using a Chi-square test. A p value of <0.05 was considered to be statistically significant.

Results

Of the 411 patients who underwent parathyroidectomy during the study period, 332 patients met study criteria. There were 64 patients excluded for insufficient follow-up. The remaining excluded patients consist of 7 with multiple endocrine neoplasia type 1 (MEN1) syndrome, 4 with secondary or tertiary hyperparathyroidism, and 4 who underwent parathyroidectomy for normocalcemic hyperparathyroidism. The average age of study patients was 62 years (range 19–89) with a female predominance (76.2%). Multiple indications for surgery were present in 49.4% of patients. For the cohort as a whole, the most common surgical indication was osteoporosis or osteopenia (63.3%), followed by significantly elevated calcium levels (32.5%), neurocognitive symptoms (31.9%),

nephrolithiasis (21.0%), and age $\leq$ 50 (6.3%). Sestamibi scans were obtained in 98.8% of patients, and 32.8% underwent ultrasound examination preoperatively.

The normal PTH group consisted of 60 patients (18%) with PTH values ranging from 33 to 65 pg/mL with a mean of 52.5 pg/mL (normal 15–65 pg/mL). PTH levels in the classic PHPT group ranged from 66 to 641 with a mean of 122.8 pg/mL. The normal PTH and classic PHPT groups did not differ significantly in terms of age or sex (Table 1). Preoperative indications were also similar for both groups, except that significantly elevated calcium levels, defined by serum calcium > 1 mg/dL above normal or 24-h urine calcium > 400 mg, were observed less often in the normal PTH group (18 vs. 36%, $p = 0.01$). However, mean serum calcium levels were the same in both groups, 10.9 mg/dL. Preoperative sestamibi imaging was more likely to be negative in the normal PTH group (18.3 vs. 4.8%, $p < 0.001$). Among the 11 patients with normal PTH and negative sestamibi scans, 9 patients also had a neck ultrasound, which was able to localize disease in 2 cases (22%). In the classic PHPT group, 13 patients had negative sestamibi scans, and 9 of these patients had a neck ultrasound, which accurately localized disease in 6 cases (67%).

Focused cervical exploration was performed in the majority of cases. In the classic PHPT group, 79% of patients underwent focused cervical exploration, compared to 50% of the normal PTH group ($p < 0.0001$). The proportion of patients who underwent a focused-converted-to-bilateral exploration was 9.2% for the classic PHPT group and 20% for the normal PTH group ($p = 0.016$) (Fig. 1). In the classic PHPT group, focused exploration was performed in 7 of the 11 patients who went on to have persistent disease, compared to 2 of 7 patients who went on to have persistent disease in the normal PTH group ($p = 0.15$).

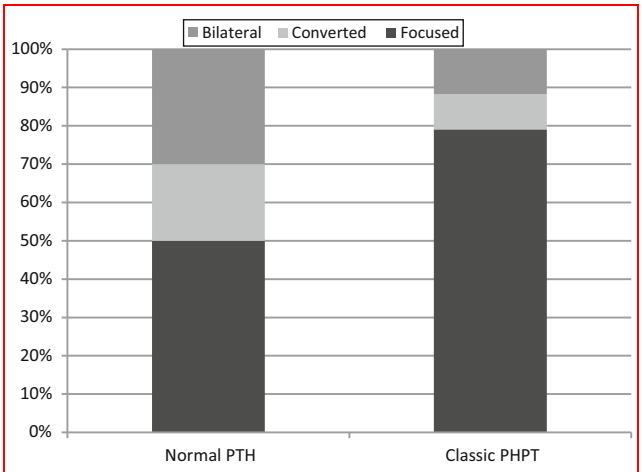

Fig. 1 Rates of focused parathyroid exploration, focused-converted-to-bilateral parathyroid exploration, and bilateral parathyroid exploration in patients with primary hyperparathyroidism (PHPT) undergoing surgery with normal PTH compared to classic PHPT

Intraoperative findings differed significantly between the two groups (Table 2). The average weight of resected parathyroid tissue, as a sum of all glands removed, was 286 mg in the normal PTH group (range 0–1150 mg) versus 706 mg in classic PHPT (range 10–6070 mg) ($p < 0.0001$). Furthermore, patients with normal PTH levels were more likely to have 2 or more glands removed (26.7 vs. 14.3%, $p = 0.02$). On final pathology, the specimens were described as only normocellular or mildly hypercellular (as opposed to hypercellular) in 20% of

Table 1 Preoperative characteristics of patients with primary hyperparathyroidism (PHPT) undergoing parathyroidectomy in normal PTH and classic PHPT groups

	Normal PTH ($n = 60$)	Classic PHPT ($n = 272$)	P
Age (years)	60.9	62.1	0.43
Sex			0.41
Female	48 (80%)	204 (75%)	
Male	12 (20%)	68 (25%)	
Preoperative indications			
Osteoporosis or osteopenia	38 (63%)	172 (63%)	0.99
Significantly elevated calcium	11 (18%)	97 (36%)	0.01
Neurocognitive symptoms	16 (27%)	86 (32%)	0.45
Nephrolithiasis	15 (25%)	56 (21%)	0.45
Age < 50 years	5 (8%)	16 (6%)	0.49
Preoperative calcium (mg/dL)	10.9	10.9	0.27
Negative sestamibi scan	11 (18%)	13 (5%)	<0.001

Table 2 Intraoperative findings for patients with primary hyperparathyroidism (PHPT) undergoing surgery with normal PTH compared to classic PHPT

	Normal PTH ($n = 60$)	Classic PHPT ($n = 272$)	P
Total gland weight (mg)	286	706	<0.0001
Multiple glands resected	16 (27%)	39 (14%)	0.02
Normocellular or mildly hypercellular	12 (20%)	8 (3%)	<0.001

Table 3 Results following parathyroidectomy in patients with primary hyperparathyroidism (PHPT) undergoing surgery in normal PTH and classic PHPT groups

	Normal PTH ($n = 60$)	Classic PHPT ($n = 272$)	P
Follow-up (months)	22	24	0.35
Cure rate	53 (88%)	261 (96%)	0.02

patients with normal PTH, compared to 2.9% of patients with classic PHPT ($p < 0.001$).

Higher cure rates were achieved in the classic PHPT group (Table 3). An 88% cure rate was seen among patients with normal preoperative PTH levels with an average follow-up of 22 months (range 6–55 months). Patients with classic PHPT had a 96% cure rate with an average follow-up of 24 months (range 6–54). The difference between the two groups was statistically significant ($p = 0.02$). When patients in the normal PTH group were divided into subgroups based on PTH $\leq$ 55 pg/mL versus PTH 56–65 pg/mL, the former had a cure rate of 83% (29/35), whereas the latter exhibited a 96% cure rate (24/25) ($p = 0.12$). Among the patients with normal PTH and negative sestamibi scans, the cure rate was 82%. Among the 13 patients in the classic PHPT group with negative sestamibi scans, the cure rate was 85% ($p = 0.85$).

IOPTH was examined with regard to its sensitivity and accuracy in predicting 6-month cure in the normal PTH group. IOPTH declined $\geq$50% in 45/60 patients (75%), $\geq$40% in 50/60 (83%), and $\geq$30% in 50/60 (83%). Using either the $\geq$40 or $\geq$30% decline criterion to predict cure proved equally sensitive and accurate (90% sensitive and 86% accurate for both), which was superior to using a $\geq$50% decline criterion (81% sensitive and 78% accurate).

Complications were rare. Cervical hematoma requiring reoperation occurred in 3 patients (0.9%). One recurrent laryngeal nerve was sacrificed out of concern for involvement by parathyroid carcinoma, but no unintentional injuries occurred. One stroke and one deep vein thrombosis occurred. All of these complications occurred in the classic PHPT group. No patients in either group demonstrated permanent hypoparathyroidism.

Discussion

While the success and durability of parathyroidectomy for PHPT have been widely reported, it is unclear how effective surgery is for patients who present with normal non-suppressed PTH levels and on what grounds surgery should be offered to these patients. In fact, there are no established criteria for defining normal non-suppressed levels as opposed to appropriately suppressed. The few previous studies that have examined this specific population found success rates upward of 93%, suggesting that patients with normal non-suppressed PTH levels are appropriate candidates for surgery. This study represents one of the largest cohorts of patients undergoing parathyroidectomy with normal PTH values. Furthermore, all of our patients had the minimum 6 months of follow-up necessary to determine whether cure was achieved.

Analysis of preoperative patient characteristics reveals that patients with normal PTH were being offered surgery for similar symptomatology as patients with classic PHPT. However, a higher percentage of patients with classic PHPT had biochemical criteria for surgery in the form of significantly elevated calcium levels. Indeed, a normal PTH may be correlated with a milder or early stage of the disorder, which could nonetheless be symptomatic. However, it should be noted that the average serum calcium levels were the same between the two groups at 10.9 mg/dL. There may also be a selection bias to consider in regard to symptomatic patients receiving surgical referrals more frequently, and thus, we do not know the true denominator of this patient population. Additionally, it is difficult to capture how many patients were not referred to surgery because of negative imaging or because a provider did not recognize that patients with PHPT may indeed have PTH levels within the normal range. Finally, although we

excluded patients with MEN1, it is important to recognize that these individuals often present with a lower PTH with associated hypercalcemia at a younger age (<50 years), and in such patients, one may consider MEN1 screening [12].

This study echoes some findings seen in previous studies of patients with normal PTH levels undergoing parathyroidectomy. Specifically, Amin et al. [9] and Bergenfelz et al. [13] observed that patients with normal PTH had significantly smaller adenomas than patients with classic PHPT, as was seen in our data. Indeed, there is a significant correlation between parathyroid tumor mass and degree of PTH suppression, such that PTH secretion is less suppressible with larger parathyroid adenomas [14]. Amin et al. also found a trend toward decreased sensitivity of preoperative imaging in the normal PTH group, though, unlike our study, they did not find this to be statistically significant [9]. A recent study by Applewhite et al. [15] similarly found a higher incidence of multigland disease and significantly lower gland weights. The implication of having smaller glands and a higher likelihood of multigland resection, as well as more frequently having negative localization studies, may be that patients with normal PTH are less likely to undergo minimally invasive parathyroidectomy and may present more of a challenge in the operating room. Thus, these patients may be at a risk of multigland resection because of the challenge of identifying a solitary adenoma when it is small, as opposed to truly having multigland disease. This is supported by our finding that there were a larger number of normocellular or mildly hypercellular parathyroid glands resected in the normal PTH group (20 vs. 2.9%).

Studies of patients with normocalcemic primary hyperparathyroidism (normal serum calcium and elevated PTH levels) have found similar differences between these patients and classic PHPT. Carneiro-Pla et al. [4] observed multigland disease in 6 of 14 patients (43%) undergoing parathyroidectomy for normocalcemic PHPT. Lim et al. [16] examined 72 patients with normocalcemic primary hyperparathyroidism and found multigland disease in 45%, compared to 9% in the classic PHPT group. Interestingly, in contrast to our study, they found multigland disease in only 10% of 96 patients with normal PTH.

Previous studies have demonstrated that IOPTH levels can be used to predict a surgical cure [17]. Alhefdhi et al. [11] specifically examined IOPTH decline in patients with normal baseline PTH levels and found that 96.5% of patients had >50% decline in IOPTH by the end of the operation, with 36% of patients having multiple glands resected and 100% going on to cure. However, the range of preoperative PTH values was not stated, only the mean, which was 59.1 pg/mL. Javid et al. [18] studied 114 patients with normal baseline IOPTH levels and found that a ≥50% decline in IOPTH was 75.4% accurate. They reported a 99.1% cure rate with a high incidence of multigland disease at 58.8%. However, the mean preoperative PTH level in these patients was 68 ± 26 pg/ml. Therefore, many of these patients did not have a non-suppressed normal PTH level preoperatively. In our study, 75% of patients had ≥50% decline in IOPTH, 83% had ≥40% decline, and the same 83 had ≥30% decline. Multiple glands were resected in 27% of cases. Based on our data, using a 30 or 40% decline was equally sensitive and accurate (90% sensitive and 86% accurate for both vs. 81 and 78 for ≥50% decline). Because the range of normal preoperative PTH values in our study was 33–65 pg/mL, it is possible that PTH values toward the lower end of that range are less likely to decline by 50% given the low starting point, or alternatively that these patients may have a lower potential for cure.

As suggested by Mischis-Troussard et al. [19], patients with normal PTH may be experiencing a delay in diagnosis or lack of referral to surgeons due to the uncertainty surrounding this diagnostic entity. Our study shows that cure rates are reasonable with surgery (88%), albeit not as high as observed in the classic PHPT patients (96%). If the subset of patients with PTH 56–65 pg/mL is considered, cure rates are equivalent to classic PHPT (96%). Thus, a PTH level of >55 pg/mL is a potential target for predicting success on par with classic PHPT patients, keeping in mind that PTH levels ≤ 55 pg/mL were still associated with an acceptable 83% success rate which was not significantly different. It is yet unclear what the reason for failure is in these cases and whether the cause of the patient's hypercalcemia was misdiagnosed or perhaps adenomas were missed during operation. Future studies will be needed to address whether the biochemical cure produced with parathyroidectomy has a quantifiable effect on quality of life measures and prevention of adverse health consequences in patients with normal preoperative PTH as has been shown for classic PHPT.

Compliance with ethical standards

Conflict of interest None.

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