

# Persistent Elevation of Parathormone Levels after Surgery for Primary Hyperparathyroidism

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## Abstract

**Background:** Persistent elevation of serum parathyroid hormone (PTH) despite normocalcemia have been documented in 8- 40% of patients after parathyroidectomy. We hereby report our experience from different centers across India to determine clinical significance of postoperatively elevated PTH levels and review relevant literature. **Methods:** We conducted a retrospective case series study and reviewed all the patients who underwent surgery for primary hyperparathyroidism (PHPT) from April 2010 to January 2020. **Results:** Total of 201 patients was diagnosed as PHPT. Out of available follow-up data of 180 patients, a total of 54 patients (30%) had persistently elevated PTH (PePTH) at 1 month. Patients with PePTH were older with higher preoperative serum calcium, iPTH, alkaline phosphatase and lower serum phosphate and 25-hydroxy vitamin D3 levels. Creatinine clearance was found to be significantly lower in patients with PePTH. Multiple linear regression analysis revealed that preoperative 25-OH D3 concentration, creatinine clearance and iPTH are the factors influencing persistent elevation of PTH levels. Significantly lower serum calcium and higher alkaline phosphatase levels were observed in PePTH patients with preoperative 25-OH D3 levels <20 ng/mL. Thirty patients at 6 months, 24 patients at 1 year, 18 patients at 2 years and 9 patients at 3 years had eucalcemic PTH elevation. Nine out of 126 (7%) patients with normal initial postoperative calcium and iPTH levels developed PePTH, with none culminating into recurrent hyperparathyroidism. **Conclusion:** Though the pathogenesis of such a phenomenon still remains to be elucidated, a multifactorial mechanism appears to play a role.

**Keywords:** Normocalcemia, parathormone, parathyroidectomy, primary hyperparathyroidism

## INTRODUCTION

Primary Hyperparathyroidism (PHPT) is a generalized disorder of calcium metabolism resulting from abnormally high levels of serum calcium and non suppressed/increased level of parathyroid hormone (PTH). It is one of the most common causes of hypercalcemia and the goal of surgical treatment is restoration of calcium homeostasis by removal of all hyperfunctioning glands. The conventional surgical treatment of primary hyperparathyroidism has been bilateral exploration with identification of all 4 parathyroid glands. The extent of surgical resection is based on the gross appearance of each gland as well as the results of intraoperative pathologic evaluation. Recently, more limited, minimally invasive surgical approaches have become increasingly popular.<sup>[1]</sup> Functional determination of the adequacy of parathyroidectomy is done by intraoperative

measurement of parathyroid hormone (IOPHT), rather than the actual visualization of all glands, to determine the extent of surgery. Preoperative imaging studies are required to identify abnormal parathyroid glands. Parathyroidectomy is successful in more than 95% of patients with PHPT.<sup>[2-11]</sup> The success rate of these minimally invasive parathyroidectomies (MIP) is greater than 95% comparable to that of bilateral exploration.<sup>[12-16]</sup>

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Persistently elevated PTH (PePTH) levels in the setting of normocalcemia after successful parathyroidectomy for PHPT have been reported with an incidence ranging from 8%- 40%.<sup>[17-27]</sup> Some authors believe that elevated PTH levels is a transient phenomenon<sup>[19,21,28,29]</sup> whereas others assert that this presentation is a dynamic process in which PTH levels normalize 1 year postoperatively or fluctuate with the occasional development of recurrent disease.<sup>[30]</sup> Advanced age, ethnicity, disease severity, osteoporosis, adenoma size, multigland disease, decreased peripheral sensitivity to PTH, renal failure, and vitamin D deficiency, osteomalacia, diminished calcium reserve from excessive bone demineralization, secondary adaptive physiology related to bone remineralization have also been described as possible underlying causes in the development of postoperative elevated PTH levels in eucalcemic patients.<sup>[20,23,30-35]</sup>

Indian data pertinent to persistent PTH elevation after parathyroidectomy (PePTH) is scant. Patients coming from Indian subcontinent are likely to be younger, vitamin D deficient and have more severe skeletal manifestations. They tend to have larger glands during surgery. Postoperatively patients are more likely to suffer with hungry bone disease.<sup>[36]</sup> The aim of this study was to present our experience with surgical treatment of PHPT in Indian patients, to compare our findings with results of similar such studies and review relevant literature.

## METHODS

### Patients' selection

The medical records of all patients who underwent surgery for PHPT at our respective centers from April 2010 to January 2020 were retrospectively reviewed. All patients included were diagnosed as having sporadic PHPT. Patients with familial hyperparathyroidism, persistent or recurrent hyperparathyroidism after previous parathyroid surgery, Patients who underwent hemodialysis or renal transplant and patients taking any medication known to interfere with calcium or vitamin D metabolism for at least 3 weeks before surgery, were excluded. The study protocol was approved by our respective hospital ethical committees and all subjects were asked to provide informed consent after being explained about the study.

### Preoperative biochemical and radiographic evaluation

Blood and urine samples were collected after an overnight fast. Serum activity of alkaline phosphatase and serum concentrations of total calcium, albumin, blood urea nitrogen, creatinine, and inorganic phosphate were measured by routine automated laboratory procedures. The corrected calcium concentration was calculated as {calcium concentration (mg/dL) + [4- albumin (g/dL)] X 0.8}. The preoperative and IOPTH level was determined by means of a 2-site immunochemiluminometric assay.<sup>[37]</sup> The serum 25-hydroxyvitamin D (25OHD) concentration was measured by competitive protein-binding assay involving the use of

high-performance liquid chromatography, with intra-assay and inters assay coefficients of variation of 5.8% and 12.6%, respectively.<sup>[38]</sup> Vitamin D deficiency was defined as a serum 25OHD concentration <20 ng/mL.<sup>[39]</sup>

All patients had preoperative ultrasonography and 99m technetium sestamibi scans were performed using the following protocol. Patients were injected with 925 to 1,110 MBq (25 to 30 mCi) of technetium 99m-Sestamibi. Early, late, and 3-dimensional SPECT images were obtained. Patients were also injected with 185 MBq (5 mCi) of 99mTc-pertechnetate for thyroid imaging. The early and late sestamibi images and the thyroid images were background subtracted and normalized. The thyroid image was then subtracted from the late Sestamibi image.

### Surgical procedure and the accompanying intraoperative PTH

Parathyroidectomy was performed through a mini-incision with patients under general anesthesia. Bilateral exploration was carried out in patients without preoperative localization, sestamibi scan suggestive of 1 abnormal gland in those requiring total thyroidectomy for unrelated coexisting thyroid pathologies like thyroid cancer and multinodular goiter, in those with preoperatively suspected parathyroid hyperplasia and in patients who's IOPTH did not fall adequately after removal of significant mass. Parathyroidectomy was terminated on the basis of positive IOPTH assay results.

IOPTH levels were measured in all patients using the QuiCK-Intra Operative Intact PTH Assay (Nichols Institute Diagnostics-San Juan Capistrano, Calif). Blood samples were drawn from an indwelling intravenous or radial arterial catheter. Samples were taken at the following times: baseline-1 (before skin incision or induction of anesthesia), baseline-2 (after identification but before removal of gland), at 5 and 10 minutes after gland excision and at variable intervals thereafter. In patients with more than 1 enlarged parathyroid, samples were drawn generally at 10-minute intervals after each gland was excised. A decrease in the IOPTH by 50% from baseline-1 and into the normal range (<65 pg/mL) was used to indicate successful removal of all abnormal parathyroid tissue.<sup>[37,40]</sup>

### Postoperative laboratory monitoring

Calcium and PTH levels were measured preoperatively and then postoperatively the day after operation, at 1 week, within 1 to 3 months, between 4 to 6 months, and 7 to 12 months. Medical records were reviewed retrospectively. Primary endpoints were postoperative serum calcium and PTH levels, cure and failure rates, and the incidence of eucalcemic postoperative PTH elevation. Curative parathyroidectomy was defined as normocalcemia (serum calcium level of less than 10.2 mg/dl at 6 months or longer postoperatively. Recurrence was defined as hypercalcemia (serum calcium > 10.2 mg/dL) 6 months after operation.<sup>[41,42]</sup> Eucalcemic PTH elevation was defined as elevated serum PTH (>65 pg/mL) in combination with normal serum calcium. Biochemical hypoparathyroidism was considered to be a low or undetectable PTH level in the

setting of a low serum calcium level. Patients were considered to have multigland disease if more than one abnormal gland was excised or if a single gland parathyroidectomy resulted in surgical failure.

### Statistical analysis

Data are expressed as mean  $\pm$  SD unless otherwise indicated. The student t test was used to compare laboratory data. Categorical data were analyzed with the Pearson Chi-square test. Multivariate analysis was performed with a multiple logistic model. All statistical analyses were done with online graphpad quickcalc software (available at (<http://www.graphpad.com/quickcalcs/index.cfm>)). *P* value of less than 0.05 was considered significant.

## RESULTS

Diagnosis of PHPT was made in total of 201 subjects based on elevated calcium levels with unsuppressed PTH levels. In 189 patients, abnormal gland was localized in at least one of the imaging. Sixty three subjects (34%) presented with fractures and significant bone disease. Nephrolithiasis in 54 (25.5%) and peptic ulcer in 27 (13.5%) patients was observed. The remaining 57 patients (27%) had asymptomatic PHPT. Bone disease manifestations included subperiosteal resorption of terminal phalanges in 36, lesions in skull in 15, knee in 6 and pubic symphysis in 2. Brown tumors could be identified in lower end of humerus and maxillary sinus in 2 each subjects. One patient declined surgery. One hundred ninety eight patients underwent neck exploration. Out of the 198 patients subjected to parathyroidectomy, hyperplasia was shown in 15 patients. Out of these 15 patients, one patient was subsequently detected to harbor multiple endocrine neoplasia-1 (MEN-1). In 183 patients, single adenoma was removed, which was confirmed by histopathology study of the biopsy specimen. Mean parathyroid gland weight was  $1235.6 \pm 684.5$  mg. In the postoperative period, all subjects had significant hypocalcemia because of hungry bone disease. They were treated with oral and intravenous calcium infusions. Activated vitamin D3 (Calcitriol) had to be used to varying periods of interval. Follow-up data of 18 patients were not available. Ultimately data of data of 180 patients (men: women = 45: 135) were retrospectively analyzed, including 15 patient with parathyroid hyperplasia. The mean age of the study population was  $55.5 \pm 12.3$  years. Table 1 depicts the baseline biochemical data of the study population.

Out of 180 patients, a total of 54 (30%) had persistently elevated parathormone (PePTH) levels and 126 (70%) had normal serum calcium and iPTH postoperatively. Baseline characteristics of the whole study population are mentioned in Table 1. Table 2 depicts the preoperative profile of patients under both the subgroups. Of the 54 patients, 39 had PePTH at 1 week and 54 had PePTH at 4 weeks. It was found that patients with PePTH were older with larger gland size, higher baseline serum calcium, iPTH, alkaline phosphatase and lower serum phosphate and 25-hydroxy vitamin D3 levels, lower creatinine

**Table 1: Baseline biochemical data for the study population (n=180)**

Biochemical parameters (units)	Value	Reference range
Serum corrected calcium (mg/dL)	12.1 $\pm$ 0.8	9.5-10.5
Serum phosphate (mg/dL)	2.9 $\pm$ 0.5	2.5-4.5
Serum creatinine	0.86 $\pm$ 0.34	0.5-1.1
Serum alkaline phosphatase (IU/L)	175.6 $\pm$ 96.7	45-155
iPTH (pg/mL)	350.5 $\pm$ 153.6	10-65
25 OHD (ng/mL)	22.3 $\pm$ 4.5	40-60

Data expressed as mean $\pm$ SD. iPTH=intact parathormone, 25OHD=25 hydroxy vitamin D, n=number of patients, SD=standard deviation

clearance. Though none of our patient had renal insufficiency, creatinine clearance was found to be significantly lower in patients with PePTH. Multiple linear regression analysis revealed that 25-OH D3 concentration, creatinine clearance and iPTH (*P* < 0.05 for all 3 variables) are the factors influencing re elevation of PTH levels.

Based on preoperative 25-OH D3 levels, the 54 patients with PePTH were divided into 2 groups (Group 1: <20 ng/mL and group 2:  $\geq$ 20 ng/mL). Table 3 shows that there were statistically significant lower serum calcium and higher alkaline phosphatase levels in PePTH patients with preoperative 25-OH D3 levels <20 ng/mL.

None of the patients with an elevated iPTH level at 1 week after surgery had a normal iPTH levels at 1 month. But 12 patients with normal PTH at 1 week after surgery had elevated iPTH levels at 1 month. Out of the 54 patients with PePTH at 1 month, we have follow-up data of 45 patients for 6 months and 36 patients for 1 year. Thirty patients (66%) at 6 months and 24 patients (70%) at 1 year had PePTH with normal serum calcium patients. Eighteen subjects at 24 months and 3 at 36 months had PePTH even on calcium and vitamin D supplements. Alkaline phosphatase levels declined but they were hovering at upper border of normal range. None developed recurrent hyperparathyroidism. Nine out of 126 (7%) patient with normal initial postoperative calcium (at both 1 week and 1 month) and iPTH levels developed PePTH, with none culminating into recurrent hyperparathyroidism.

## DISCUSSION

Elevated PTH levels after parathyroidectomy may represent persistent/recurrent hyperparathyroidism. The reported incidence of normocalcemic elevation of PTH after parathyroidectomy for PHPT is 12% to 43%.<sup>[43]</sup> Its incidence in our series was 20% at 1 week and 30% at 4 weeks after parathyroidectomy. Table 4 presents incidence from various studies. Bone hunger, vitamin D deficiency, inadequate calcium intake/absorption, reduced peripheral sensitivity to parathyroid hormone, chronic kidney disease and renal leak of calcium are the proposed etiologies of such a normocalcemic hyperparathyroidism.<sup>[20,22,24,27, 32,34,44,45]</sup>

Factors found to be consistently associated with persistent PTH elevation after surgical resection includes higher initial

**Table 2: Baseline biochemical data for the study population grouped according to postoperative PTH levels**

	PePTH	Normal Post-op PTH	P
Number of patients*	54 (30%)	126 (70%)	
Age (years)	65.3±8.3	52.5±8.2	<0.001 <sup>#</sup>
Gender (female/male)	36/18	90/36	0.45
Serum Ca <sup>2+</sup> (mg/dL)	11.6±1.1	10.9±0.7	<0.001 <sup>#</sup>
Serum phosphorus (mg/dL)	2.8±0.3	3.1±0.5	0.03 <sup>#</sup>
25 OHD (ng/mL)	16.3±8.5	22.3±9.6	<0.001 <sup>#</sup>
Prevalence of Vitamin D deficiency (25 OHD <20 ng/mL)*	24/54 (62%)	61/126 (50%)	<0.001 <sup>#</sup>
Serum alkaline phosphatase (IU/L)	207.9±101.5	135.5±53.6	<0.001 <sup>#</sup>
iPTH (pg/mL)	395.5±153.3	142.2±74.1	<0.001 <sup>#</sup>
Serum creatinine (mg/dL)	1.2±0.3	0.9±0.4	0.04 <sup>#</sup>
Creatinine clearance <sup>#</sup>	111.8±21.3	123.3±18.5	0.008 <sup>#</sup>
Parathyroid gland weight (mg)	1348.6±723.5	1143.5±598.7	0.007 <sup>#</sup>

Data expressed as mean±SD, \*data expressed as proportion (percentage). iPTH=intact parathormone, PePTH=persistently elevated PTH, 25OHD=25 hydroxy vitamin D, SD=standard deviation. <sup>#</sup>Statistically significant

**Table 3: Baseline biochemical data for the patients with PePTH grouped according to preoperative 25 OHD levels**

	Group 1 (serum 25 OHD <20 ng/mL)	Group 2 (Serum 25 OHD ≥20 ng/mL)	P
Number of patients*	36 (67%)	18 (33%)	
Age (years)	55.5±10.2	57.5±9.5	0.09
Gender (female/male)	24/12	12/6	0.65
Serum Ca <sup>2+</sup> (mg/dL)	9.3±3.4	10.8±3.9	0.04 <sup>#</sup>
Serum phosphorus (mg/dL)	2.8±0.4	3.0±0.6	0.72
Serum alkaline phosphatase (IU/L)	190.5±85.7	180.7±80.3	0.02 <sup>#</sup>
iPTH (pg/mL)	355.6±134.5	295.5±123.9	0.86
Serum creatinine (mg/dL)	0.91±0.32	0.92±0.29	0.81
Creatinine clearance	120.3±22.3	129.4±25.1	0.52

iPTH=intact parathormone, 25OHD=25 hydroxy vitamin D, SD=standard deviation. Data expressed as mean±SD. \*Data expressed as proportion (percentage). <sup>#</sup>Statistically significant

**Table 4: Incidence of persistent parathyroid hormone elevation after parathyroidectomy for primary hyperparathyroidism (in comparison to our study)**

Author(s)	No. patients in study	Incidence of persistent PTH, No. patients (%)
Westerdahl <i>et al.</i> <sup>[22]</sup>	98	34 (35%)
Vestergaard <i>et al.</i> <sup>[52]</sup>	103	23 (22%)
Nordenström <i>et al.</i> <sup>[30]</sup>	99	40 (40%)
Solorzano <i>et al.</i> <sup>[26]</sup>	505	168 (33%)
Ning <i>et al.</i> <sup>[27]</sup>	611	111 (18%)
Mittendorf <i>et al.</i> <sup>[19]</sup>	85	23 (27%)
Carty <i>et al.</i> <sup>[20]</sup>	380	105 (28%)
Dhillon <i>et al.</i> <sup>[32]</sup>	49	21 (43%)
Beyer <i>et al.</i> <sup>[25]</sup>		
Routine supplementation	26	3 (12%)
Discretionary supplementation	60	22 (37%)
Wang <i>et al.</i> <sup>[24]</sup>	816	114 (15%)
Yamashita <i>et al.</i> <sup>[23]</sup>	90	39 (43%)
Our study	180	54 (30%)

preoperative PTH levels and lower 25-hydroxyvitamin D3 levels. Older age, black race, greater gland volume, higher alkaline phosphatase, higher final intraoperative PTH levels, and lower initial postoperative calcium levels, higher preoperative serum creatinine were thought to be associated as well, although not consistently throughout all

studies.<sup>[18,20,24,26,27,29,30-33]</sup> In our study, patients with PePTH were older with high PTH levels, larger gland size and lower creatinine clearance [Table 2].

Vitamin D deficiency is defined as serum 25-OHD concentration below 20 ng/mL.<sup>[39]</sup> Vitamin D deficiency was one of the factors

significantly influencing persistently elevated PTH with normocalcemia in previously reported data.<sup>[23,24,31,33,46]</sup> This is because of vitamin D deficiency induced hypocalcemia and secondary hyperparathyroidism. Wang *et al.* have shown lower levels of vitamin D in patients with PePTH having postoperative serum calcium <9.6 mg/dL.<sup>[24]</sup> Vitamin D deficiency is highly prevalent worldwide<sup>[47]</sup> and is increasing more prevalent in India.<sup>[48,49]</sup> Carty *et al.* evaluated the impact of postoperative calcium supplementation.<sup>[20]</sup> Calcium supplementation in the first 6 months after parathyroidectomy was associated with a significantly lower incidence of PTH elevation. Some authors suggest that primary HPT may coexist with secondary HPT that is unmasked after surgical cure of serious and neglected HPT that should have been treated sooner.<sup>[32]</sup> In our study population, prevalence of vitamin D deficiency at the baseline was 46%.

Several studies<sup>[19,24,50]</sup> have suggested that patients with musculoskeletal symptoms preoperatively had higher incidence of PePTH postoperatively. This group of patients also had higher preoperative blood urea nitrogen, serum creatinine, alkaline phosphatase and lower bone mineral density reflecting a state of bone hunger. In our patients with PPTH serum creatinine was significantly higher resulting in lower creatinine clearance values.

Secretory recovery of the suppressed parathyroid glands for restoration of circulating iPTH levels requires about 30 hours.<sup>[51]</sup> This observation suggests that the main cause of the transient postoperative rebound increase in PTH secretion results from a decrease in the serum calcium concentration due to increased deposition of calcium in bone. Some have been the transient phenomenon as a compensatory response to relative hypocalcemia and bone remineralization<sup>[19,28,29]</sup> and also to lower calcium absorption.<sup>[22]</sup> Patients who take calcium and vitamin D supplements immediately after surgery may be less likely to have postoperative elevation of PTH levels.<sup>[20,22,52]</sup> Another study has shown that elevated PTH levels after successful parathyroidectomy seems to be a dynamic phenomenon, not a transient one. Levels of PTH fluctuated from normal to elevated over time, with some patients showing signs of renal impairment and disease recurrence.<sup>[30]</sup> Therefore, the investigators concluded that elevated PTH levels postoperatively may not be a transient phenomenon, and that there may be an increased risk of recurrent disease with low 25(OH) D levels contributing to prolonged PePTH. Our patients were on postoperative calcium and Vitamin D supplementation, the compliance of which was strictly ensured by the investigators from time to time. This probably helped us rule out possible role of vitamin D deficiency in causation of PePTH.

Recurrent PHPT is implied in the event of an initial successful operation followed by maintenance of normal serum PTH and calcium levels for at least 6 months postoperatively, subsequently leading to development of PHPT.<sup>[53]</sup> This occurs because of 1) non localization of incident parathyroid adenoma, 2) Inadequate resection of multigland hyperplasia, 3) presence of familial disease, 4) a left over second occult parathyroid

adenoma in situ; or 5) Remnant hyperfunctioning parathyroid tissue in rare cases of parathyromatosis or parathyroid carcinoma. Additionally a greater percentage decrease in IOPTH (>63%) and lesser postoperative PTH (<48 pg/mL) at 1-2 weeks is protective against recurrent PHPT.<sup>[54]</sup> Thorough preoperative work up and localization, exclusion of familial cases and good surgical clearance by experienced surgeon might have resulted in lack of any recurrence in our series. All these series have large number of patients enrolled, to the tune of 845-1386 cases with a reported small prevalence of recurrent HPT between <1%- 2.2%.<sup>[54]</sup> And our series comprised of very small number of patients compared to the ones cited. That probably is one more explanation for absence of recurrence in our series.

The disadvantages of our study include

1. Fractional excretion of calcium excretion in urine was not calculated in the study patients to rule out familial hypocalciuric hypercalcemia
2. Lack of evaluation of PePTH on long term morbidity and mortality
3. Lack of study of effect of calcium and vitamin D supplementation on outcome.
4. No separate analysis was done for serum calcium and PTH levels in the 15 patients with hyperplasia.

*However, we have some novelties in our favor*

1. Multicentric data collection
2. Analysis of data from large number of patients (n-180)
3. To the best of our knowledge, this is the first such Indian study look at this aspect of Persistently elevated PTH (PePTH) and having analysis of 180 patients with PHPT.

We strongly believe that our preliminary results would pave way for large scale multicenter study involving larger number of patients with longer follow-up to confirm or refute our data on Indian patients.

## CONCLUSION

The factors predicting PePTH with normocalcemia appear to be multifactorial. The elevated PTH calls for more aggressive and prolonged doses of vitamin D and calcium supplements. This would help to recover the skeletal mineralization in patients with PHPT from Indian subcontinent. Although not necessarily predictive of persistent or recurrent PHPT, PTH elevation after parathyroidectomy may potentially be an early indicator of autonomous parathyroid secretion. Therefore, PTH elevation should be monitored over time for PHPT recurrence and for other concerns such as cardiovascular disease.

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## Conflict of interest

It is submitted with the full knowledge and approval of our institutes and there is no conflict of interest to disclose from any of the authors with regards to publication of the manuscript or an institution or product that is mentioned in the manuscript. There are no competing interests to disclose, due to any reasons, with whom so ever concerned.

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