

# The Impact of Baseline Intact Parathyroid Hormone Levels on Severity of Primary Hyperparathyroidism and Outcomes in Patients Undergoing Surgery

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**Objective:** To determine the impact of intact parathyroid hormone (iPTH) baseline levels on severity of primary hyperparathyroidism (PHPT) and outcomes following parathyroidectomy for PHPT.

**Design:** Single institution retrospective review.

**Setting:** Academic tertiary care center.

**Patients:** A total of 447 consecutive patients undergoing parathyroid surgery for PHPT.

**Main Outcome Measures:** Comparison of patients with high ( $\geq 150$  pg/mL) and low ( $< 150$  pg/mL) baseline iPTH values; preoperative serum calcium, alkaline phosphatase, and 25-hydroxyvitamin D levels; and 6-month postoperative serum calcium and iPTH levels.

**Results:** A total of 304 patients had baseline iPTH values of at least 150 pg/mL (high baseline group), and 143 patients had baseline iPTH values lower than 150 pg/mL (low baseline group). Patients in the high baseline group had significantly higher levels of preoperative serum calcium, serum alkaline phosphatase, and adenoma weights

( $P < .001$  for all comparisons). Serum 25-hydroxyvitamin D levels were significantly lower in patients in the high baseline group ( $P < .001$ ). Sestamibi scans were more likely to localize an adenoma in the high baseline group (83.7%) than in the low baseline group (68.9%) ( $P < .01$ ). There were no differences in the serum calcium and iPTH levels between the 2 groups 6 months after surgery.

**Conclusions:** Patients in the high baseline group undergoing surgery for PHPT had higher baseline levels of serum calcium, serum alkaline phosphatase, and parathyroid adenoma weights and lower serum 25-hydroxyvitamin D levels compared with the lower baseline group. Sestamibi scans were more likely to localize an adenoma in the high baseline group (83.7%) than in the low baseline group (68.9%) ( $P < .01$ ). Despite an apparently lower rate of positive preoperative sestamibi scans for the low baseline group, patients were able to achieve a similar rate of disease cure as other patients with higher baseline iPTH levels. It seems that baseline iPTH level should not be used as a criterion to perform surgery or not perform surgery for patients with PHPT.

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**P**RIMARY HYPERPARATHYROIDISM (PHPT) is a common disorder characterized by chronically elevated serum calcium and serum intact parathyroid hormone (iPTH) concentrations and has an estimated incidence of 1 in every 500 women and 1 in every 2000 men older than 40 years.<sup>1</sup> Intraoperative parathyroid (IOPTH) monitoring has facilitated more directed surgical approaches, smaller incisions, and shorter operative times in appropriately selected cases.<sup>2</sup> The “50% rule,” commonly attributed to George Irvin III, MD, has been used for defining biochemical cure intraoperatively but continues to be adjusted according to experience.<sup>3-6</sup> These criteria were originally defined with clearly abnormal

baseline IOPTH levels. However, the correct interpretation of IOPTH levels remains an understudied topic in relation to iPTH baseline levels.

As awareness of mild hyperparathyroidism has increased and indications for parathyroidectomy have been clarified and liberalized,<sup>7</sup> patients are increasingly referred with biochemically subtle disease. Many patients are noted to have low baseline iPTH levels and mild indices of disease. Our goal in this study was to determine the relationship of iPTH baseline levels with severity of PHPT and outcomes of surgery. We hypothesized that baseline iPTH levels correlate with severity of PHPT and can predict the degree of a successful surgical outcome in patients undergoing surgery.

**Table. Clinical Characteristics of the Study Population by Low and High Baseline iPTH Levels<sup>a</sup>**

Characteristic	Group <sup>b</sup>		P Value <sup>c</sup>
	Low Baseline (n=304)	High Baseline (n=143)	
Adenoma weight, mg	415 (15 to 6100)	910 (60 to 3300)	<.001
25-hydroxyvitamin D level, ng/dL	23 (4 to 78)	16 (4 to 49)	<.001
<25 ng/dL	133 (53.6)	89 (79.5)	
≥25 ng/dL	115 (46.4)	23 (20.5)	
Alkaline phosphatase level, U/L	87 (28 to 244)	104 (45 to 329)	<.001
Calcium level, preop, mg/dL	11.0 (8.5 to 12.7)	11.4 (9.4 to 14.7)	<.001
iPTH level, preop, pg/mL	100 (16 to 149)	197 (150 to 1023)	<.001
Sestamibi scans			.001
Positive for adenoma	204 (68.9)	118 (83.7)	
Nonpositive	92 (31.1)	23 (16.3)	
IOPTH level change, after 5 min, %	63.2 (-178.5 to 92.3)	70.7 (-246.4 to 96.5)	<.001
IOPTH level, after 10 min, pg/mL	16 (5 to 200)	28 (10 to 147)	<.001
IOPTH level change, after 10 min, %	82.0 (-700.0 to 95.9)	87.3 (26.1 to 96.1)	<.001
Calcium level, 6-mo postop, mg/dL	9.6 (8.6 to 10.8)	9.5 (8.8 to 10.3)	.46
iPTH level, 6-mo postop, pg/mL	39 (5.7 to 129)	46 (6.6 to 167)	.09

Abbreviations: IOPTH, intraoperative parathyroid hormone; iPTH, intact parathyroid hormone; postop, postoperative measurement; preop, preoperative measurement.

SI conversion factors: To convert alkaline phosphatase to microkatal per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert parathyroid hormone levels to nanograms per liter, multiply by 1; to convert 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.

<sup>a</sup>Data are reported as median (range) or number (percentage).

<sup>b</sup>High baseline was defined as baseline iPTH values of at least 150 pg/mL, and low baseline was defined as iPTH values lower than 150 pg/mL.

<sup>c</sup>P values are from Wilcoxon rank sum tests.

## METHODS

This was a single institution retrospective review of a database of 447 consecutive patients who underwent parathyroidectomy for PHPT from July 2002 to November 2006. Johns Hopkins institutional review board approval was obtained. Each patient's medical record was reviewed for demographic information; preoperative and baseline serum iPTH, serum calcium, serum 25-hydroxyvitamin D, and serum alkaline phosphatase levels; and operative details. The pathology reports were reviewed for excised parathyroid adenoma weights. Preoperative sestamibi scans were reviewed. Treatment outcomes included calcium and iPTH levels at 1 week and 6 months following surgery. Patients with familial hyperparathyroidism (HPT), secondary and/or tertiary HPT, multiple endocrine neoplasia, and parathyroid carcinoma were not included in this study.

Demographic and clinical characteristics, preoperative laboratory results, and IOPTH kinetics were summarized using appropriate descriptive statistics. Categorical data were summarized with frequencies and percentages, and continuous data were summarized with medians and ranges because many of the measures were not normally distributed. Patients were divided into 2 groups according to their baseline iPTH values; iPTH levels of 150 pg/mL or higher (hereinafter, high baseline group) and iPTH levels lower than 150 pg/mL (low baseline group), and the groups were compared using  $\chi^2$  tests for categorical data and Wilcoxon rank sum tests for continuous data. (To convert PTH levels to nanograms per liter, multiply by 1.) Analysis was performed using SAS statistical software (version 9.1.3; SAS Institute Inc, Cary, North Carolina). All reported P values are 2-sided, and  $P < .05$  was considered significant.

## RESULTS

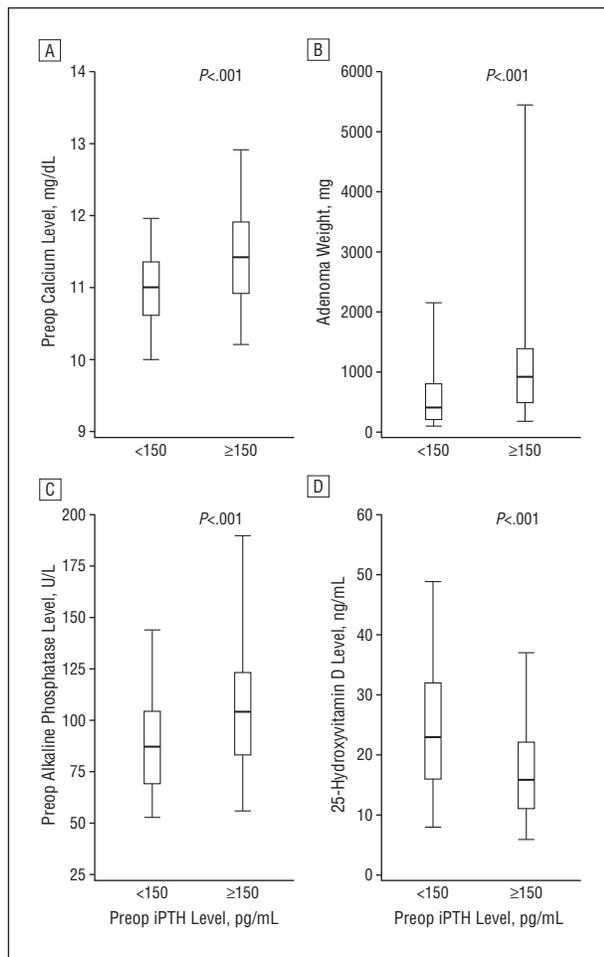
A total of 447 consecutive patients were included in the study. The median age of the patients was 61 years (range,

23-94 years). Most of the patients (74.5%) were female, 74.5% were white, and 19.9% were African American. The patients were classified by baseline level of iPTH into 2 groups and the groups were compared; 304 patients were in the high baseline group and 143 patients in the low baseline group. The demographic and clinical characteristics, preoperative laboratory results, and IOPTH kinetics for both groups are shown in the **Table**. Patients in the high baseline group had significantly higher levels of preoperative serum calcium, serum alkaline phosphatase, and adenoma weights and significantly lower levels of serum 25-hydroxyvitamin D (**Figure 1**) ( $P < .001$  for all comparisons).

Median baseline iPTH and IOPTH levels taken at 5 and 10 minutes after resection are shown by baseline iPTH group in **Figure 2**. Sestamibi scans were positive for adenoma more often in the high baseline group (83.7%) than in the low baseline group (68.9%) ( $P < .01$ ). There was no difference in the calcium and iPTH levels between the 2 groups 6 months after surgery.

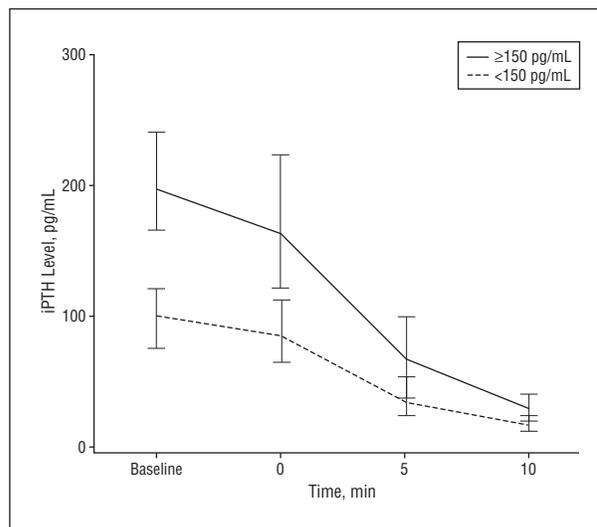
## COMMENT

Primary hyperparathyroidism, once the disease of "bones, stones, abdominal groans, and psychic overtones," has become largely a biochemical disorder in the asymptomatic or mildly symptomatic patient. Although operative excision of the offending gland or glands is mandatory in symptomatic patients, the benefit of surgery in certain asymptomatic patients has been debated.<sup>8,9</sup> Intraoperative PTH monitoring with preoperative localization studies has enabled success rates as high as 98% with minimally invasive parathyroidectomy for PHPT.<sup>10</sup> Multiple studies have shown



**Figure 1.** Group comparisons. Box and whisker plots showing the median (horizontal line), interquartile range (outside of box), and fifth and 95th percentiles (top and bottom of whiskers) of data comparing the low baseline intact parathyroid hormone (iPTH) level group (<150 pg/mL) with the high baseline iPTH group (≥150 pg/mL) for preoperative (preop) (A) calcium, (B) adenoma weight, (C) alkaline phosphatase, and (D) 25-hydroxyvitamin D levels. The *P* values are from the Wilcoxon rank sum test. To convert alkaline phosphatase to microkatal per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert parathyroid hormone levels to nanograms per liter, multiply by 1; to convert 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.

variable degrees of correlation between several preoperative serum chemistry levels and parathyroid adenoma size and weight. A recent retrospective study<sup>11</sup> of 155 patients with parathyroid adenomas suggests that preoperative PTH levels may alert the surgeon to the likelihood of small or large parathyroid adenomas. Previous studies using different methods for PTH measurement have found mild to moderate correlation between iPTH and gland weight.<sup>12,13</sup> Parathyroid tumor weight is a significant determinant of disease severity, as reflected by serum levels of iPTH, serum calcium, serum 25-hydroxyvitamin D, and serum alkaline phosphatase. Rao et al<sup>14</sup> indicated a significant negative correlation between serum 25-hydroxyvitamin D (the best parameter of vitamin D nutritional status) and parathyroid gland weight (the best parameter of parathyroid tumor cell number). Previous reports by us and others indicated that vitamin D deficiency leads to more severe clinical forms of PHPT.<sup>14-16</sup>



**Figure 2.** Group comparisons. Median and interquartile range of intact parathyroid hormone (iPTH) levels at baseline (prior to surgery) and intraoperative parathyroid level (PTH) levels at 0, 5, and 10 minutes after surgery by high (≥150 pg/mL) or low (<150 pg/mL) baseline iPTH group. (To convert PTH levels to nanograms per liter, multiply by 1.)

Our current study found a positive association between baseline iPTH levels and adenoma weight. In addition, our study demonstrated that patients in the high baseline group had more advanced indices of PHPT. Median preoperative serum calcium levels were significantly higher ( $P < .001$ ) in the high baseline group. Patients in the high baseline group also had higher serum alkaline phosphatase activity, reflecting the increased severity of bone turnover. The 25-hydroxyvitamin D levels were significantly lower in patients in the high baseline group. The cause of these findings is uncertain but likely multifactorial. Despite these findings, there was no significant difference between the 2 groups when comparing the serum calcium ( $P = .46$ ) and iPTH ( $P = .09$ ) values measured 6 months after surgery. While baseline iPTH may correlate with severity of PHPT based on the disease parameters we analyzed, it does not distinguish the cure rate between the 2 groups based on serum calcium and iPTH levels measured 6 months after surgery. Although the clinical relevance of our study should be validated by additional prospective studies, we believe that patients with low baseline PTH levels are likely to achieve a similar cure rate, with serum calcium and iPTH levels similar to those of the high baseline group at 6 months after surgery that may further justify surgical intervention.

In conclusion, patients in the high baseline group had higher levels of serum calcium, serum alkaline phosphatase, and parathyroid adenoma weights and lower serum 25-hydroxyvitamin D levels compared with the low baseline group. Sestamibi scans were more likely to localize an adenoma in the high baseline group (83.7%) than the low baseline group (68.9%) ( $P < .01$ ). Despite an apparently lower rate of positive preoperative sestamibi scans for the low baseline group, patients were able to achieve serum calcium and iPTH levels 6 months after surgery that were similar to those of other patients undergoing surgery in the high baseline group.

It seems that baseline iPTH is not helpful in predicting cure from surgery and should not be used as a criterion to perform surgery or not perform surgery for patients with PHPT.

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**Author Contributions:** All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kandil and Tufano. *Acquisition of data:* Kandil. *Analysis and interpretation of data:* Kandil, Alabbas, Tufano, Carson, and Tufano. *Drafting of the manuscript:* Kandil, Alabbas, and Carson. *Critical revision of the manuscript for important intellectual content:* Tufano and Tufano. *Statistical analysis:* Carson. *Administrative, technical, and material support:* Kandil and Alabbas. *Study supervision:* Kandil and Tufano.

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