

CALCIUM, PARATHYROID HORMONE, AND VITAMIN D IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM: NORMOGRAMS DEVELOPED FROM 10000 CASES

James Norman, MD, FACS, FACE; Arnold Goodman, MD, FACS;
Douglas Politz, MD, FACS, FACE

ABSTRACT

Objective: To better define the typical and atypical biochemical profiles of patients with surgically proven primary hyperparathyroidism.

Methods: In this single-center, prospectively conducted study of consecutive patients with surgically proven primary hyperparathyroidism over a 7-year period, we analyzed serum calcium, parathyroid hormone, and 25-hydroxyvitamin D concentrations.

Results: A total of 10000 patients were included, and more than 210000 calcium, parathyroid hormone, and 25-hydroxyvitamin D values were evaluated. Both calcium and parathyroid hormone levels demonstrated a Gaussian distribution with the average calcium concentration being 10.9 ± 0.6 mg/dL and the average parathyroid hormone concentration being 105.8 ± 48 pg/mL. The average highest calcium and parathyroid hormone concentrations were 11.4 ± 0.7 mg/dL and 115.3 ± 50 pg/mL, respectively. At least 1 calcium value of 11.0 mg/dL was seen in 87% of patients, but only 21% had 1 or more calcium value above 11.5 mg/dL. Only 7% had a single serum calcium level reaching 12.0 mg/dL. Normocalcemic hyperparathyroidism was seen in just under 3% of patients who had identical

findings at surgery. An average parathyroid hormone concentration less than 65 pg/mL was seen in 16%, with 10% of patients who had no high parathyroid hormone values. The average 25-hydroxyvitamin D concentration was 22.4 ± 9 ng/mL, with levels decreasing as calcium levels increased ($P < .001$); 36% had 25-hydroxyvitamin D levels below 20 ng/mL.

Conclusions: Patients with PHPT present with a number of distinct biochemical profiles, but as a group, they present with a near-normal Gaussian distribution of both calcium and parathyroid hormone levels. Either serum calcium or parathyroid hormone remained normal in 13% of patients, yet the findings at surgery are similar to those of patients with elevated calcium or parathyroid hormone. Low 25-hydroxyvitamin D is an expected finding in patients with PHPT, decreasing as serum calcium levels increase. (*Endocr Pract.* 2011;17:384-394)

Abbreviations:

PHPT = primary hyperparathyroidism; PTH = parathyroid hormone

INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most common endocrine diagnoses (1,2). The hallmark of the disease is elevated blood calcium levels, which are in turn caused by inappropriate overproduction of parathyroid hormone (PTH), most commonly by a single benign parathyroid tumor. The diagnosis of PHPT is classically based on the finding of hypercalcemia in the presence of high (or nonsuppressed) PTH levels. Unfortunately, the diagnosis is not always so simple and a number of other factors must be considered.

The biochemical spectrum of PHPT has a great deal of individual variation, from patients with normocalcemia to patients presenting with hypercalcemic crisis. Similarly, PTH levels in these patients are often variable and frequently normal despite high calcium levels (3-5).

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From the Norman Parathyroid Center, Tampa, Florida.

Address correspondence to Dr. James Norman, Norman Parathyroid Center, 2400 Cypress Glen Dr, Wesley Chapel, FL 33544. E-mail: jnorman@parathyroid.com (for reprints: reprints@parathyroid.com).

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This variability in presentation often leads to a workup of many other potential, but much less common, causes of hypercalcemia and often a delay in diagnosis because the classic presentation of high calcium with a simultaneous high PTH value is not observed. Further complicating the interpretation of laboratory values in patients with elevated calcium and/or PTH levels is the well-known role vitamin D has in calcium absorption, use, and excretion (2,6,7).

The knowledge of the variability of hypercalcemia associated with PHPT has come from hundreds of studies that were typically undertaken with some other endpoint as the focus. These studies include patients with high calcium levels who have an offending parathyroid gland removed at surgery, as well as studies of patients with normocalcemic PHPT who have not undergone surgery (8-16). Some studies examine differences in various populations such as age (9-13) or race (5-8). Almost all studies in the literature on the biochemical profile of this very diverse group of patients are on populations of 200 persons or fewer, often collected at multiple centers over many years' time, but designed to look at a particular aspect of parathyroid disease, its symptoms, complications, and various methods of surgical treatment.

Despite the large number of patients afflicted, no large-scale study has analyzed calcium levels in patients with PHPT along with a detailed look at PTH and vitamin D levels. Normograms for these interrelated molecules have not been established in a large population with surgically proven—and cured—disease. This prospective study was designed to provide an accurate picture of the biochemical profile of PHPT, so that the treating physician has a reference from which to compare patients with presumed PHPT with respect to 10 000 others with surgically proven disease.

PATIENTS AND METHODS

A prospectively maintained database of calcium, PTH, and 25-hydroxyvitamin D levels and 24-hour urinary calcium excretion was established for patients who underwent operation for PHPT at a single center during a 7-year period ending June 2010. Patients with renal failure or who were renal transplant recipients were excluded. To be included in this analysis, patients were required to have laboratory data consistent with PHPT, and 1 or more parathyroid adenomas (or more uncommonly, 4 hyperplastic glands) had to be found at surgery. The diseased glands had to be overproducing hormone at least 4-fold greater than normal—proven by intraoperative hormone assessments of individual gland activity as described previously (17-20) and established as a diseased gland(s) by histologic examination. All removed tumors were photographed, and photos became part of the permanent records. The laboratory values indicating the presence of PHPT must have been reversed and normal values reestablished postoperatively

for patients to be included. Postoperative laboratory analysis was established immediately after the operation, at 1 month, and then for a minimum of 3 months. All patients were prescribed our postoperative oral calcium protocol as described in detail elsewhere (21). All data were collected in a nonidentifiable fashion in accordance with the principles outlined in the Declaration of Helsinki (22) and as required for our institutional review board approval.

An effort was made to obtain as many serum calcium, serum intact-PTH, and vitamin D levels on every patient as possible, and laboratory test results were obtained from all physicians that the patient had seen in the past decade whenever feasible. 25-Hydroxyvitamin D levels obtained while a patient was taking 1000 IU of vitamin D per week or more were excluded. None of the calcium, PTH, or vitamin D levels were obtained at our facility; all values were obtained from referring physicians and the laboratory tests were conducted in standard laboratories throughout the nation.

If there was an obvious point in a patient's past where normal calcium levels were typical and this was followed by an obvious change into the high range, the normal lower levels were not included in the calculations of hypercalcemia associated with PHPT. This was done to ensure that the calcium levels obtained before developing PHPT were not included in our analysis (21,23-25). The highest calcium level for each patient was used in the calculation for highest calcium; however, when it was apparent that a very high calcium level was significantly out of range for a particular patient given previous and subsequent values, further investigations were undertaken to see if this was associated with a dehydration episode that led to a hospital emergency department visit. If so, that value was discarded. Similarly, if a patient had a history of infusion of an intravenous bisphosphonate in an attempt to decrease serum calcium levels, those subsequent lower calcium levels were disallowed in our calculations.

Patient location was included in the study data. The potential bias from regional differences in referral patterns was examined by subdividing the population into 3 groups according to the distance they (and their physicians) lived from our center in Tampa, Florida. Normograms and statistical analysis were compared for each group (less than 50 miles, 51 to 500 miles, and more than 500 miles).

RESULTS

A total of 10 000 patients were included in the study. Average patient age was 59.9 ± 13.0 years (range, 13-105 years). Of the 10 000 patients, 7511 (75%) were women and 2489 (25%) were men. The average duration of follow-up was 3.7 years (range, 3 months to 7 years). In an effort to establish the duration of the disease, laboratory values were obtained for at least 10 years before the date of operation in 3944 patients (39%) and for at least 5 years

in 8639 patients (86%). Eight thousand nine hundred thirty patients (89%) were seen by 1 or more of 1328 different endocrinologists who assisted in establishing the diagnosis of PHPT. The other 1070 (11%) were referred for surgery by a primary care physician. Patients were from all 50 states, with 4209 (42%) from Florida (all counties) and 5791 (58%) from all other 49 states.

Serum Calcium Levels in PHPT

A total of 116337 calcium values were included in this study (average, 11.6 per patient; mode, 9; range, 2-41). The distribution of average calcium levels in the population of 10000 patients with PHPT is shown in Figure 1. To ensure that calcium levels obtained before developing PHPT were not included in the analysis, more than 22000 normal calcium levels were excluded. A total of 289 inappropriately high calcium levels were eliminated after review to determine whether the very high calcium level was associated with a dehydration episode that led to a hospital emergency department visit. Less than 0.5% of patients were given an intravenous bisphosphonate for the purpose of lowering serum calcium levels. The statistical analysis of this population is shown in Table 1 where average and highest calcium levels are further broken down into groups by age: 25 years or younger, between 26 and 50 years, and older than 50 years. Calcium levels for the total PHPT patient population represented a Gaussian distribution with the mean concentration of each patient's average serum calcium concentration being 10.9 mg/dL. The most frequent (mode) average calcium value was 10.8 mg/dL, and the median calcium concentration was 10.9 mg/dL. Interestingly, 8534

patients (85%) had average serum calcium concentrations below 11.5 mg/dL—the level that has often been quoted as being an indication for surgical referral (1,25,27-29). Furthermore, 6922 patients (69%) never had a single calcium concentration of 11.5 mg/dL or greater (Fig. 2). When teenagers are eliminated, 72% of adults never had a single calcium concentration reach 11.5 mg/dL. Only 413 patients (4%) had an average calcium concentration of 12.0 mg/dL or greater, with 9338 patients (93%) never having a single calcium value this high.

Figure 2 shows the highest serum calcium level seen within the population of patients with PHPT, and Table 1 shows the statistical analysis of the highest calcium levels according to age group. The mean value of the highest serum calcium concentration observed was 11.4 mg/dL, which was 0.5 mg/dL higher than each patient's average calcium level. Virtually all patients with PHPT had variable calcium levels. Seventy-four percent of patients had 1 or more normal calcium concentration (<10.0 mg/dL) within the previous year, scattered among the other higher levels.

Patients with an average calcium concentration of 10.0 mg/dL or lower comprised 2.5% of the population. A more strict definition of normocalcemic PHPT where every measurement of an individual patient's serum calcium concentration was less than 10.0 mg/dL was seen in only 114 patients (1.1%). Each of these patients had high PTH levels, 78% had high urinary calcium excretion (>250 mg/24 h) and, as required to be in this study, all had 1 or more parathyroid tumors at surgery with resolution of the pre-operative high PTH level. Kidney stones and osteoporosis

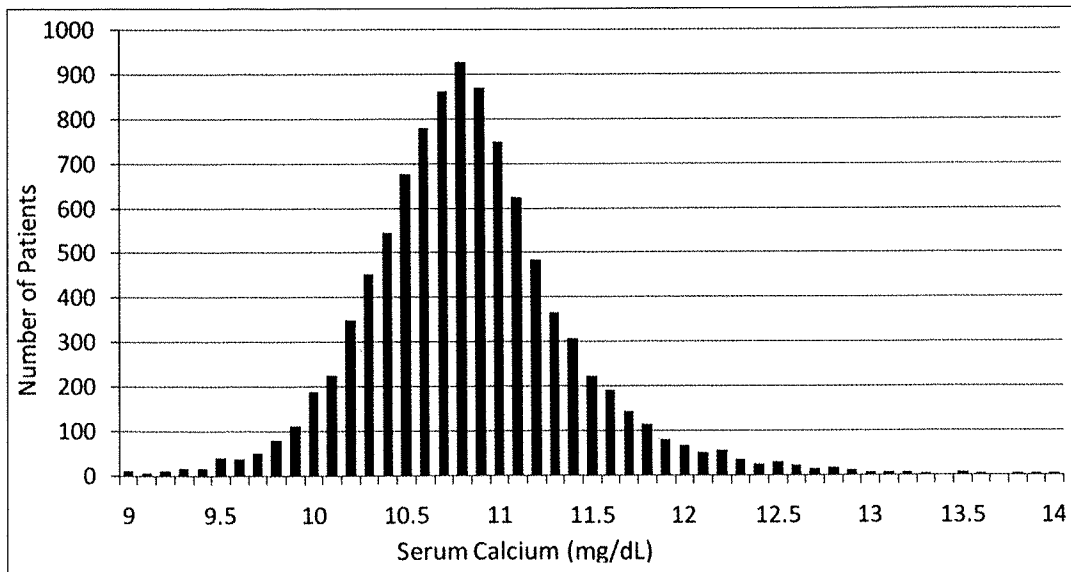


Fig. 1. Normogram of average serum calcium concentration in 10000 patients with primary hyperparathyroidism. The mean is 10.9 ± 0.6 mg/dL, the median is 10.9 mg/dL, and the mode is 10.8 mg/dL. Patients with an average calcium concentration of 10.0 mg/dL or lower comprised 2.5% of the population, while only 15% of the patients had average calcium concentrations above 11.5 mg/dL. Most patients with primary hyperparathyroidism had average calcium concentrations below 11 mg/dL.

Table 1
Serum Calcium Concentration in 10 000 Patients
With Surgically Proven Primary Hyperparathyroidism According to Age^{a,b}

Calcium and age category	Mean (SD) serum calcium, mg/dL	Median serum calcium, mg/dL	Mode serum calcium, mg/dL
Average calcium (all ages)	10.9 (0.6)	10.9	10.8
Highest calcium (all ages)	11.4 (0.7)	11.2	11.2
Average calcium (≤ 25 years)	11.6 (0.9) ^c	11.3	11.2
Average calcium (26-50 years)	10.9 (1.2)	10.9	10.8
Average calcium (> 50 years)	10.9 (0.6)	10.9	10.8
Highest calcium (≤ 25 years)	11.9 (1.0) ^c	11.7	11.4
Highest calcium (26-50 years)	11.3 (0.7)	11.2	11.1
Highest calcium (> 50 years)	11.3 (0.7)	11.1	11.1

Abbreviation: SD, standard deviation.

^a Patients older than 25 years had identical average and highest calcium levels regardless of how this group was subdivided into smaller age groups.

^b Eighty-five percent of all patients had average calcium levels less than 11.5 mg/dL, with 72% of adults never having a single calcium value of 11.5 mg/dL or higher.

^c Average and highest calcium levels for patients 25 years or younger are higher than those for patients older than 25 years (both $P < .001$).

resistant to medical therapy were overwhelmingly cited as the causes for surgical referral in this group. As reported previously (17,20), findings at surgery (single vs multiple adenomas vs hyperplasia) were identical in patients with normocalcemic PHPT and in patients with PHPT who had higher calcium levels; however, on average, their tumors were smaller and weighed less.

Patients 25 years or younger who had PHPT comprised 1.4% of the study group ($n = 144$), and they typically presented with higher average calcium levels (11.6 mg/dL) than those older than 25 years (10.9 mg/dL) ($P < .001$) as seen in Table 1. The degree of calcium elevation associated with any particular PTH level was also higher in patients 25 years or younger than in patients older than 25 years ($P < .001$). Similarly, the highest observed calcium value associated with PHPT in patients 25 years or younger (11.9 mg/dL) was higher ($P < .001$) than in those older than 25 years (11.3 mg/dL) (Table 1). All age groups older than 25 years (regardless of breakdown) had similar average and high calcium levels.

Serum calcium levels were more variable in patients with PHPT than they were in those same patients before development of PHPT. Before the first calcium measurement over 10.2 mg/dL (before the development of hypercalcemic PHPT), patients showed little differences from one calcium measurement to another (mean variability 0.19 ± 0.09 mg/dL). This variability more than doubled to 0.4 ± 0.33 mg/dL in those same patients when PHPT was evident ($P < .001$). Calcium levels occasionally varied by more than 1 mg/dL from month to month in patients with PHPT, a phenomenon that is almost never seen in patients

without PHPT where differences of more than 0.4 mg/dL are rare ($P < .001$). Patients with normocalcemic PHPT are the exception to this rule, and they typically present with very little variability in serum calcium levels, like their normal counterparts without parathyroid pathology.

Twenty-four-hour urinary calcium excretion showed tremendous variability at all levels of serum calcium and PTH. The average 24-hour urinary calcium measurement was 297.7 ± 174 mg/24 h (standard deviation). A detailed look at 24-hour urinary calcium measurements will be a part of an upcoming report.

Serum PTH Levels in PHPT

A total of 40 882 PTH values were included (average, 4.1 per patient; mode, 3; range, 1-15). The distribution of average PTH levels in the population of 10 000 patients with PHPT is shown in Figure 3; the distribution of highest PTH levels seen in these patients is shown in Figure 4, both figures representing a near-Gaussian distribution. The mean PTH concentration was 105.8 pg/mL (± 48.2 pg/mL), the median was 95 pg/mL, and the mode was 84 pg/mL. The average of the highest PTH values seen in each of these patients was 115.3 pg/mL (± 50.0 pg/mL) with the median and mode of the highest PTH levels being 104 pg/mL and 95 pg/mL, respectively.

PTH levels remained (on average) within the reference range in 16.5% of patients, with 10.5% having zero PTH levels above 65 pg/mL (no high levels). Similar to that seen for calcium levels, patients 25 years or younger had significantly higher PTH levels than patients older than 25 years ($P < .001$) (Table 2). In contrast to serum calcium

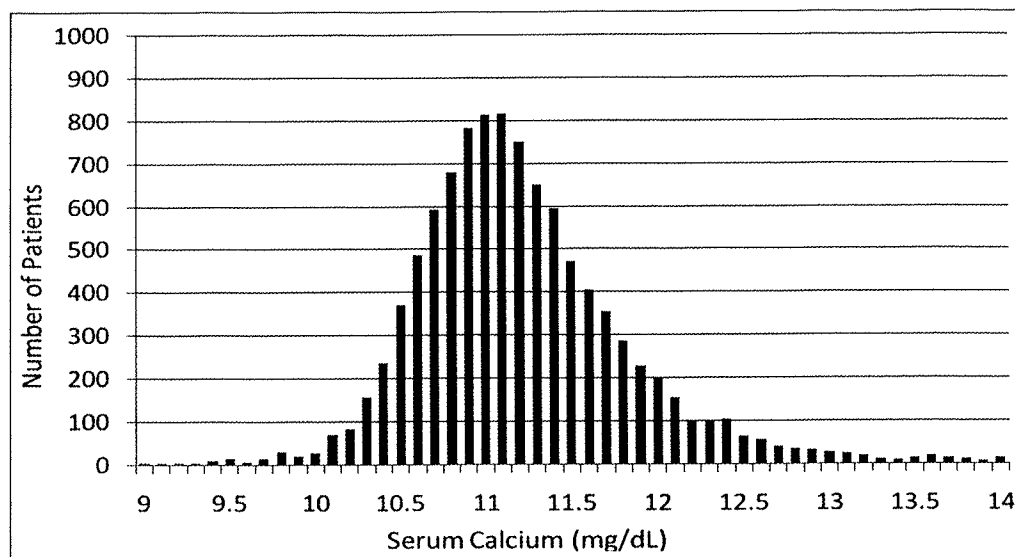


Fig. 2. Normogram of the highest serum calcium concentration observed in 10,000 patients with primary hyperparathyroidism. The mean is 11.4 ± 0.7 mg/dL, the median is 11.2 mg/dL, and the mode is 11.2 mg/dL. Just over 1% of patients never had a single calcium measurement above 10.0 mg/dL, while 69% of patients never had a single calcium measurement of 11.5 mg/dL or higher.

levels, however, PTH values in patients older than 80 years were also higher than those of patients between 26 and 79 years ($P < .001$) despite no differences in peak or average calcium levels.

The relationship between serum calcium and PTH is shown in Figure 5. There is a great deal of variation at all calcium and PTH levels, with little correlation between the average calcium level and the average PTH level ($R^2 =$

0.139). As a general rule, higher PTH levels were associated with higher serum calcium levels (a positive slope) ($P < .001$). However, as demonstrated by the scatter of the data, there is tremendous variability in this relationship; thus, a high PTH level does not necessarily dictate a high calcium level, and vice versa, in any individual patient.

When the degree of PTH elevation was compared with the duration of hypercalcemia, several observations were

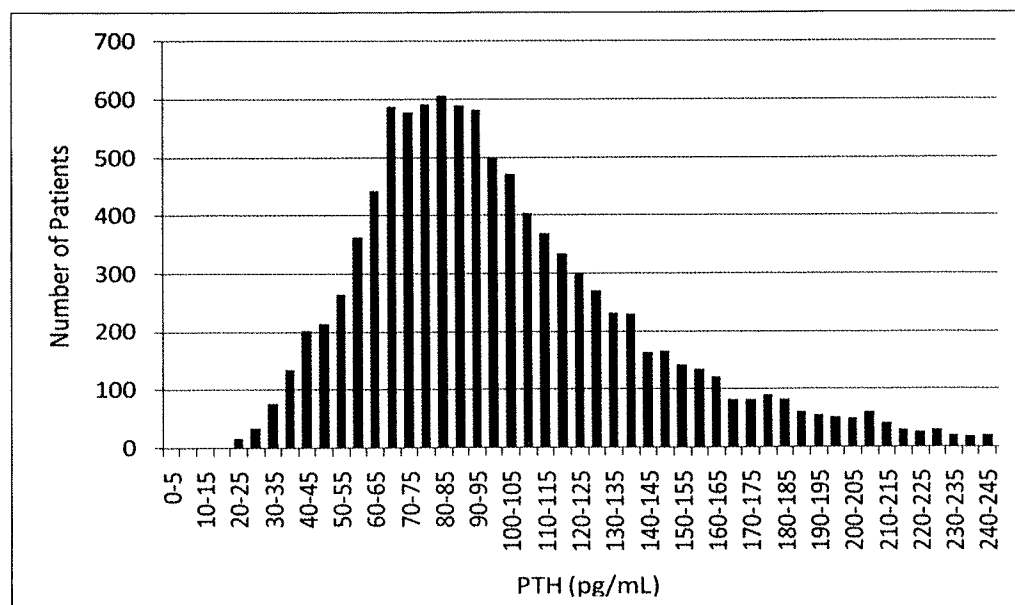


Fig. 3. Normogram of average serum parathyroid hormone (PTH) concentration in 10,000 patients with primary hyperparathyroidism. The mean is 105 ± 48.2 pg/mL, the median is 95 pg/mL, and the mode is 84 pg/mL. Average PTH concentrations remained in the reference range (below 65 pg/mL) in 15% of patients.

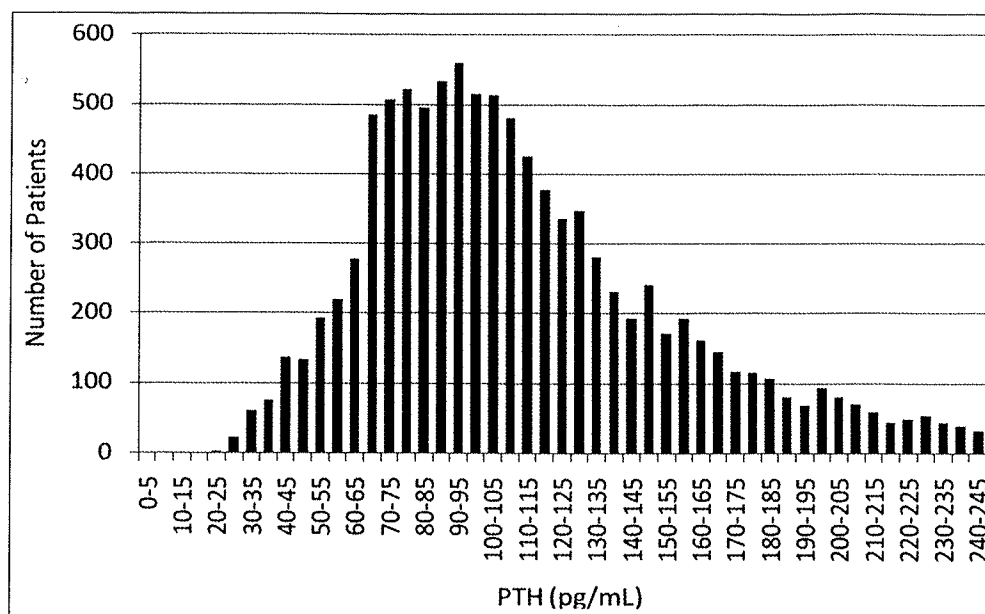


Fig. 4. Normogram of the highest serum parathyroid hormone (PTH) concentration in 10,000 patients with primary hyperparathyroidism. The mean is 115.3 ± 50.0 pg/mL, the median is 104 pg/mL, and the mode is 95 pg/mL. Ten-and-a-half percent of patients had no PTH measurement above 65 pg/mL.

made. Adults (older than 25 years) with hypercalcemia due to PHPT for 6, 8, or even 10 years or more can occasionally have PTH levels that are only mildly elevated or even in the high-normal range. However, the opposite (very high PTH in a patient with recent-onset PHPT) is quite uncommon. When the PTH concentration was over 150 pg/mL, the duration of hypercalcemia was longer than 6 years in adults (78%). Similarly, 86% of those with PTH levels over 180 pg/mL had hypercalcemia (10.2 mg/dL) for 6 years or longer; 75% had hypercalcemia for 8 years or longer.

Patients referred for surgery were identical in all aspects of their calcium and PTH levels whether they saw an endocrinologist or not. There was no difference in the calcium or PTH normograms or their means, medians, or modes when the data were examined according to the distance the patient lived from our center, indicating no regional treatment differences and no discernable bias in the population of 10,000 patients in terms of our local community.

25-Hydroxyvitamin D Levels in Primary Hyperparathyroidism

25-Hydroxyvitamin D levels obtained before the administration of vitamin D were available in 4758 patients. The 25-hydroxyvitamin D levels averaged 22.4 ng/mL (± 9.4 ng/mL) for the entire population (lower limit of normal = 20 ng/mL). Figure 6 shows the relationship between vitamin D levels and average serum calcium level. Although there is tremendous variability as demonstrated by the scatter and poor correlation coefficient of the trend line ($R^2 = 0.059$), it demonstrates that

Table 2
Average Serum Parathyroid Hormone Concentrations in 10,000 Patients With Primary Hyperparathyroidism According to Age^a

Age group	Mean (SD) parathyroid hormone concentration, pg/mL
≤25 years	148 (113)*
26-75 years	112 (73)
>76 years	133 (80)*

Abbreviation: SD, standard deviation.

^a Patients 25 years or younger and older than 75 years present with significantly higher parathyroid hormone levels than patients between these 2 age extremes. The asterisks denote $P < .001$ compared with parathyroid hormone levels in the age group of 26 to 75 years.

25-hydroxyvitamin D levels decrease as the average serum calcium level increases ($P < .001$). Of all 10,000 patients undergoing surgery for PHPT, 7681 (77%) had preoperative 25-hydroxyvitamin D concentrations below 30 ng/mL and 3640 (36%) had concentrations below 20 ng/mL.

DISCUSSION

The purpose of this study was to show the tremendous variability in the biochemical profile of PHPT while developing normograms for calcium and PTH for a very large population with surgically proven PHPT. Our intention was

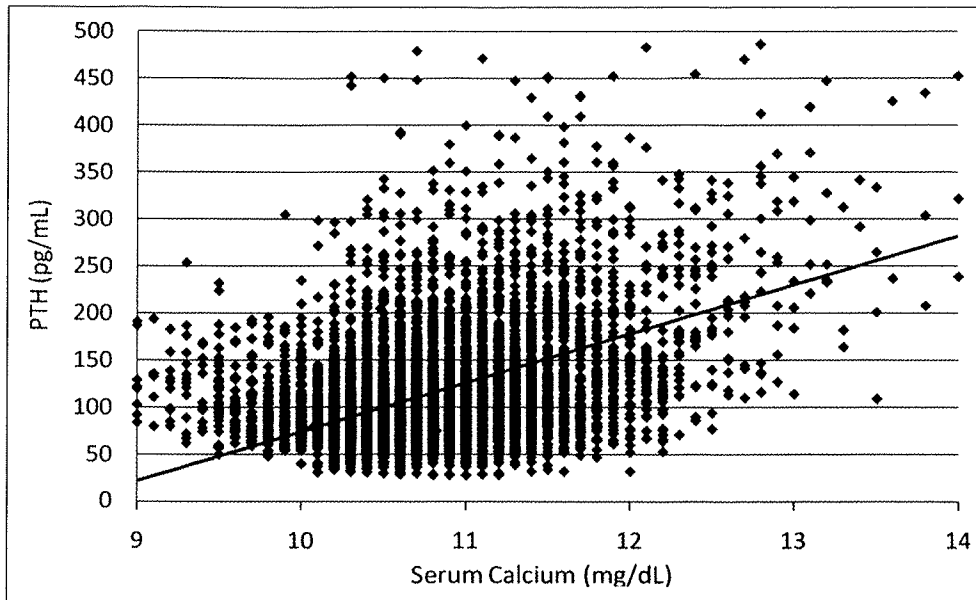


Fig. 5. Average serum calcium concentration vs average parathyroid hormone (PTH) concentration in patients with primary hyperparathyroidism. The relationship between serum PTH levels and their corresponding serum calcium levels is shown for 10 000 patients, demonstrating a positive slope, but a very poor correlation ($R^2 = 0.139$) signifying the tremendous variability in calcium levels associated with any particular PTH level, and vice versa.

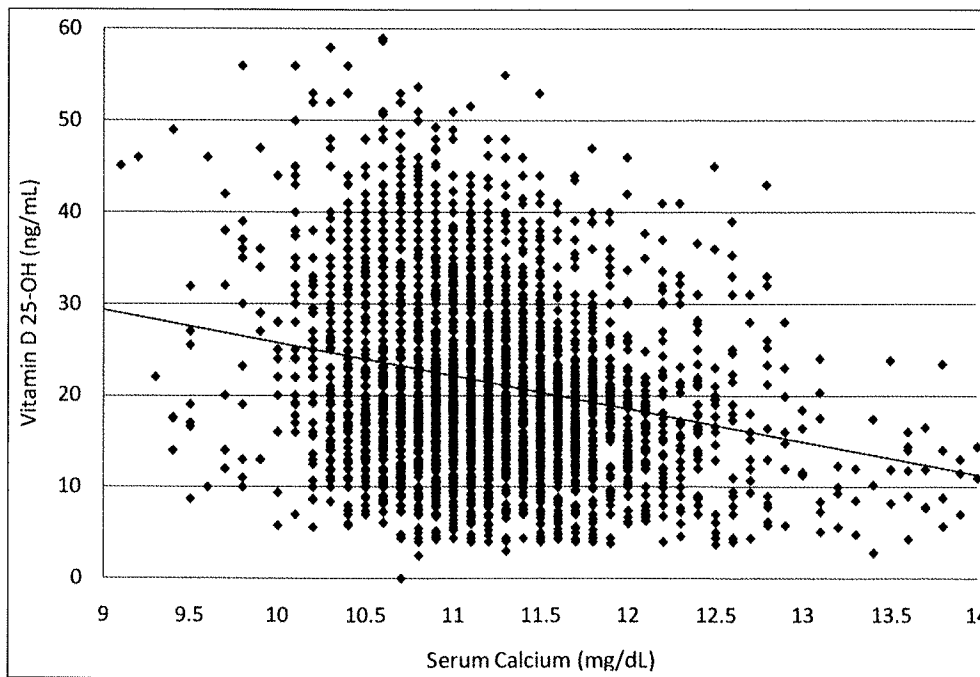


Fig. 6. 25-Hydroxyvitamin D (vitamin D 25-OH) concentration according to average serum calcium concentration in 10 000 patients with primary hyperparathyroidism. Values of vitamin D 25-OH were obtained before administration of exogenous vitamin D in 4 758 patients who subsequently underwent operation and were cured of primary hyperparathyroidism. Vitamin D 25-OH levels decrease as calcium levels increase ($P < .001$) despite significant individual variation ($R^2 = 0.066$).

to better understand the many ways a patient with a parathyroid tumor may present, providing physicians a means by which they can compare their patient with 10000 others. By including only patients who had parathyroid tumor(s) surgically removed, which resolved the biochemical profile of PHPT, we aimed to provide an accurate picture and eliminate bias that could be introduced if patients who had not undergone surgery were included.

Taken as a population, patients with PHPT present with elevated serum calcium levels that have a near-normal Gaussian distribution centered on the mode value of 10.8 mg/dL, with a mean value of 10.9 mg/dL. When the highest serum calcium levels are plotted, the near-normal distribution is maintained, just shifted to the right by 0.5 mg/dL. Both the average and highest calcium levels in this study are consistent with those documented in most other smaller series. Bilezikian et al (25) noted that most patients with PHPT have average serum calcium levels less than 1 mg/dL above normal as was confirmed here. Others have shown slightly higher calcium levels among certain populations, presumably because access to health care was limited (5,8).

We found that patients with PHPT who were 25 years or younger presented with significantly higher average calcium and highest calcium levels than patients older than 25 years. Other authors have previously reported this phenomenon (9-12). Thus, a normogram of serum calcium levels in patients 25 years or younger is different from that of any other age group—being shifted to the right 0.5 mg/dL—with all other age groups having identical normograms. This lack of difference in calcium levels in adult patient populations is consistent with findings in previous studies (5).

Of significant interest are the lower and upper ends of the bell-shaped calcium normograms. At the lower end of the curve, approximately 2% of patients have average calcium concentrations that are 10.2 mg/dL or lower, with 1.1% having *all* calcium measurements (typically 8 or more in this study) below this level. These patients have normocalcemic hyperparathyroidism as described elsewhere and defined as patients with normal calcium and elevated PTH in the absence of a secondary cause (13-16). This study confirms observations by our group that adults do not normally have *persistent* calcium levels above 10.2 mg/dL, regardless of the upper limit of normal, which can be as high as 10.6 mg/dL in some laboratories. Many of the previously reported patients with normocalcemic PHPT have been followed up clinically and have not had their disease proven at surgery. Yet, in this study, the findings at surgery are identical to those of patients with a classic presentation of PHPT with elevated calcium levels. It is likely that this area of the bell-shaped curve may actually be larger, because there are probably more patients with normocalcemic PHPT who were not referred for surgery and instead

elected to be followed up nonsurgically, or their PHPT has gone undetected.

At the upper end of the bell-shaped curve, only 7% of patients ever have a single calcium level above 12.0 mg/dL, with only 4% having average calcium levels this high. On occasion, we still see physicians waiting to refer patients for surgery until the serum calcium reaches the “magical” number of 12 mg/dL, but this study clearly demonstrates that few patients ever reach this degree of hypercalcemia. Waiting for this to occur is not the criterion standard among American endocrinologists. Again, our review of 10 or more years of calcium levels in almost 4000 patients shows that patients do not necessarily develop higher calcium levels as time passes. That is, patients observed for years do not necessarily develop higher calcium as the years go by, and therefore, the philosophy of observing a patient with modestly elevated calcium and waiting for higher calcium levels to develop must be reconsidered. Fifty-eight percent of patients with calcium concentrations above 12 mg/dL had PHPT for 5 or fewer years, while only 23% of patients with hypercalcemia for more than 10 years presented with even a single calcium value of 12 mg/dL. The severity of PHPT is much more closely related to the duration of the disease or the associated signs and symptoms, rather than to the degree of calcium elevation. Several upcoming articles from this large database (now more than 15000 patients) will help delineate clearly that the degree of calcium elevation is not a good marker of parathyroid disease severity. In most cases, disease duration is much more predictive of the types and severity of complications that arise from PHPT.

It is important to note that 8534 patients (85%) had average serum calcium concentrations below 11.5 mg/dL, the level that has often been quoted as being an indication for surgical referral in both the 2002 and 2009 versions of the National Institutes of Health consensus statement regarding surgical treatment of asymptomatic PHPT (1,25,26-28). An upcoming study from our group will examine the symptoms in these patients, reflecting our belief that few patients are without symptoms. However, it is important to note that 69% of patients never had a single calcium value of 11.5 mg/dL or higher. This is clear evidence that practicing endocrinologists consider many variables when assessing a patient’s need for surgical removal of the offending parathyroid tumor(s) and that most of the 1328 endocrinologists represented in this study favor surgical treatment once PHPT is diagnosed, regardless of the degree of elevation of a patient’s serum calcium.

Our review of more than 150000 calcium values has revealed that the hypercalcemia associated with PHPT is typically variable for each patient from month to month, week to week, and even day to day. Most patients with PHPT have 1 or more normal calcium value(s) (below 10.0 mg/dL) scattered among elevated levels. In contrast, before developing PHPT, these same patients had normal

calcium levels that showed very little variability, typically within 0.2 mg/dL between individual measurements. Thus, the variability in serum calcium levels can be used to help diagnose PHPT, noting that changes from 0.5 to 1.2 mg/dL are often seen from month to month, indicating a loss of calcium homeostasis by a parathyroid tumor(s) that is not responding to appropriate feedback. Normocalcemic PHPT is the exception to the rule, where less variability exists from one calcium measurement to the next, mimicking patients with normal parathyroid function in whom calcium levels show little change over time.

There is a great deal of individual variation among calcium levels observed at a particular PTH level (Fig. 5), but as expected, there is a positive correlation between these 2 variables regardless of age. Higher PTH levels typically, but not always, result in higher serum calcium levels, confirming observations from smaller series (29). Therefore, the assumption that a very high calcium level must be associated with a very high PTH level, and vice versa, does not hold. The scattergram shown in Figure 5 illustrates this well.

As seen with serum calcium, serum PTH levels in patients with PHPT represent a Gaussian distribution centered at about 105 pg/mL for the average PTH concentration and 115 pg/mL for the highest PTH concentration. Several findings are important to note, such as the fact that 16.5% of patients has an average PTH level that is in the reference range and that 10.5% never have a single high PTH level (with a minimum of 3 measurements). This represents the classic "inappropriately normal" and "nonsuppressed" PTH levels known to be associated with PHPT (4). We often see a delay in PHPT diagnosis by physicians who wait for the PTH to be elevated at the same time that the calcium is elevated. The data here clearly show that a high PTH and high calcium occurring at the same time is not a requirement for the diagnosis of PHPT.

Variability is the rule for PTH elevation as it is for calcium elevation. Parathyroid adenomas that have been associated with hypercalcemia for more than 8 years can present with PTH levels that are only modestly elevated or very high. However, PTH levels above 180 pg/mL are associated with hypercalcemia (and PHPT) for more than 8 years 84% of the time. Thus, not all patients demonstrate a continuous rise in PTH levels as their tumor increases in age, but a high level almost always indicates an old tumor and disease that has been present for a number of years.

This study shows that a difference exists in PTH levels associated with PHPT according to the patient's age. PHPT was associated with higher PTH levels at the extremes of life, with patients younger than 20 years having the highest levels. Our group (23) and others (9-11) have previously noted this difference. Higher average PTH levels were also noted in the older population despite calcium levels that are not different from those of younger patients (23,29). This elevation in PTH levels in the elderly population

has not been previously described; however, it might be predicted based on the work of others who have demonstrated that aging is associated with an increased secretory response for PTH for any given calcium level in patients without hyperparathyroidism (30,31). Interestingly, this upward trend in PTH levels does not become apparent until the seventh decade of life and does not subside as age increases.

Low vitamin D levels have been reported to be present in patients with PHPT in smaller studies (6-7). This study is the first to show that 25-hydroxyvitamin D decreases as average serum calcium levels rise (Fig. 6). Physicians frequently attempt to assign a diagnosis of secondary hyperparathyroidism to patients with high serum calcium and high PTH when these findings are associated with low vitamin D levels. Some authors have suggested this phenomenon (2,6,25,32), but it is our opinion that this mechanism occurs very rarely if ever. Although it is possible for a low vitamin D level to slightly increase PTH levels, these parathyroid glands do not become hyperplastic, leading to autonomous PTH secretion that then could lead to high serum calcium. Within our current prospective analysis of 10 000 patients, the incidence of hyperplasia (and multiple adenomas) decreases as serum calcium levels increase ($P < .001$), while 25-hydroxyvitamin D levels are decreasing to very low levels. An upcoming publication from our group looks at vitamin D levels (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) in great detail; however, the current study shows clearly that a low 25-hydroxyvitamin D level is an expected finding in patients with PHPT due to a parathyroid tumor. As the duration of the disease increases, or the degree of hypercalcemia increases, vitamin D levels decrease. A low vitamin D level does not mean secondary hyperparathyroidism is the diagnosis, and a low vitamin D level will rarely, if ever, elevate serum calcium levels.

Aside from the very large numbers of patients, the participation of 1328 board-certified endocrinologists in the diagnosis and referral of these patients for surgery is important for the validity of the results, eliminating selection bias and regional differences in practices. Although our center is located in Florida, 62% of the study patients reside in other states, with all 50 states being represented. Eighty-nine percent of the referring endocrinologists ($n = 1187$) practice outside of Florida, with more than 1000 located more than 500 miles away. It was interesting to find, however, that patients who did not see an endocrinologist, but were instead referred by their primary care physician or gynecologist, had nearly identical biochemical profiles regarding serum calcium and PTH.

CONCLUSION

PHPT presents with serum calcium and PTH levels within predictable, near-normal Gaussian distributions. Patients with PHPT can be expected to have variable

calcium levels that fluctuate as much as 1 mg/dL up and down from week to week and month to month. Most patients will have occasional normal calcium levels scattered among elevated levels. Eighty-eight percent of patients will have at least 1 calcium measurement above 11.0 mg/dL, but 12% have persistent calcium concentrations between 10 and 11 mg/dL, never reaching 11.0 mg/dL. Just over half of patients with PHPT have average serum calcium concentrations below 11 mg/dL, illustrating that persistent calcium concentrations between 10 and 11 mg/dL in an adult are highly suggestive of a parathyroid tumor. Eighty-five percent of patients with PHPT will have average serum calcium concentrations below 11.5 mg/dL, with nearly 70% never having a single measurement reaching 11.5 mg/dL. Calcium levels of 12 mg/dL or higher are uncommon and often represent larger tumors that have gone undiagnosed or untreated for many years. Teens and young adults present with higher serum calcium levels for a given PTH level than older patients, while patients with PHPT who are older than 25 years present with nearly identical calcium normograms through all decades of life. Although most patients are located within the center of these normograms, there are patients on the extreme left who present with consistently normal calcium levels (2.5% with normocalcemic hyperparathyroidism) and another 10.5% who present with consistently normal PTH levels. Low 25-hydroxyvitamin D is the rule and not the exception in patients with PHPT, with levels decreasing as calcium levels increase or the duration of the disease becomes longer. Most of the more than 1300 endocrinologists representing the 10 000 patients in this study referred the patient for surgery on the basis of many factors without regard for their degree of serum calcium elevation once PHPT was diagnosed.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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