

***Calcium, Parathyroid Hormone, and Vitamin D in
Patients with Primary Hyperparathyroidism.
Normograms Developed from 10,000 Cases***

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Running Title: Metabolic profiles of primary HPT.

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Abstract.

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

Methods: A single-center, prospectively conducted study of serum calcium, parathyroid hormone, and Vitamin D in 10,000 consecutive patients over a 7 year period with surgically proven PHPT. Over 210,000 calcium, PTH, and vitamin D values were evaluated.

Results: Both calcium and PTH levels demonstrate a Gaussian distribution with the average calcium being 10.9 ± 0.6 mg/dl and the average PTH being 105.8 ± 48 pg/ml. The average highest calcium and PTH was 11.4 ± 0.7 mg/dl and 115.3 ± 50 pg/ml, respectively. At least one calcium level of 11.0 mg/dl is seen in 87% of patients, but only 21% had one or more calcium levels above 11.5 mg/dl. Only 7% had a single serum calcium level reaching 12.0 mg/dl. Normocalcemic HPT was seen in 2.5% of patients who had identical findings at surgery. An average PTH less than 65 pg/ml was seen in 16.5% with 10.5% having zero high PTH values. The average vitamin D-25 was 22.4 ± 9 ng/ml, with levels decreasing as calcium levels increased ($p < 0.001$); 36% had vitamin D-25 levels below 20ng/ml.

Conclusion: Patients with PHPT present with a number of distinct biochemical profiles, but as a group present with a near-normal Gaussian distribution of both calcium and PTH.

Either serum calcium or PTH remained normal in 13% of patients yet the findings at surgery are similar to those with elevated calcium or PTH. Low vitamin D is an expected finding in patients with PHPT, decreasing as serum calcium levels increased.

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 non-suppressed) 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). 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 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 plays in calcium absorption, utilization, and excretion (2,6,7).

The knowledge of the variability of hypercalcemia associated with PHPT has come from many hundreds of studies which were typically undertaken with some other endpoint being 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 examined 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 individuals or less, 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, there has been no large-scale analysis of calcium levels in patients with PHPT presented alongside a detailed look at PTH and vitamin D levels. Normograms for these inter-related 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 his/her patient with presumed PHPT with respect to 10,000 others with surgically proven disease.

Methods.

A prospectively maintained database of calcium, PTH, 24-hour urine calcium, and Vitamin D-25 was established for 10,000 patients operated on at a single center for PHPT during a 7-year period ending June 2010. Patients with renal failure or renal transplantation were excluded. To be included in this analysis, patients were required to have laboratory data consistent with PHPT, and one or more parathyroid adenomas (or more uncommonly, 4 hyperplastic glands) had to be found at surgery. The diseased glands had to be overproducing hormone by at least 4-fold over normal—proven by intraoperative hormone assessments of individual gland activity as described previously (17-20), and established as a diseased gland(s) by histology. All removed tumors were photographed with photos becoming part of the permanent records. The laboratory values indicating the presence of PHPT must have been reversed and normal values re-established postoperatively for patients to be included in this analysis. Postoperative laboratory analysis was established immediately after the operation, at one month, and then required for a minimum of 3 months. All patients were put on our postoperative oral calcium protocol as described in detail recently (21). The average duration of followup is 3.7 years (range 3 months to 7 years). All data was collected in a non-identifiable fashion in accordance with the principles outlined in the Declaration of Helsinki (22) and as required for our institutional IRB approval. The average age in this study was 59.9 ± 13.0 years, range 13-105. Women comprised 75.1% while 24.9% were men.

An effort was made to obtain as many serum calcium, serum intact-PTH, and vitamin D levels on every patient as possible, obtaining labs from all doctors that the patient had seen in the past decade whenever feasible. In an effort to establish the duration of the disease,

lab values were obtained for at least 10 years prior to the date of surgery in 39% of patients, and at least 5 years in 86% of patients. A total of 116,337 calcium levels were included in this study (average 11.6 per patient, mode 9, range 2 to 41). A total of 40,882 PTH values were included (average 4.1 per patient, mode 3, range 1 to 15). Vitamin D-25 levels were available in 4758 patients which were obtained prior to the administration of vitamin D. Values obtained when the patient was taking 1000 IU vitamin D per week or more were excluded. None of the calcium, PTH, or vitamin D levels were obtained at our facility; all were obtained by referring physicians at standard labs throughout the nation.

If there was an obvious point in a patient's past where normal calcium levels were the norm 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 eliminate the calcium levels obtained prior to developing PHPT from being included in our analysis (21, 23-25). Over 22,000 normal calcium levels were thus excluded. 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 lead to a hospital emergency room visit. If so, that value was discarded. A total of 289 inappropriately high calcium levels were eliminated for this reason. 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. Less than 0.5% of patients were given an IV bisphosphonate for purposes of lowering serum calcium levels.

Eighty-nine percent of patients in this study were seen by one or more of 1328 different endocrinologists who assisted in establishing the diagnosis of PHPT. The other 11% were referred for surgery by a primary care physician. Patients came from all 50 states with 42% from Florida (all counties), and 58% coming from all other 49 states. The potential bias from regional differences in referral patterns was examined by sub-dividing the population into 3 groups according to the distance they (and their doctors) live from our center in Tampa, FL. Normograms and statistical analysis was compared for each group (less than 50 miles, 51 to 500 miles, and more than 500 miles).

Results.

Serum Calcium Levels in Primary Hyperparathyroidism: The distribution of average calcium levels in the population of 10,000 patients with PHPT is seen in Figure 1. 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: less than 25 years, between 26 and 50 years, and greater than 50 years. Calcium levels for the total PHPT patient population represented a Gaussian distribution with the mean level of each patient's average serum calcium being 10.9 mg/dl. The most frequent (mode) average calcium value seen was 10.8 mg/dl and the median calcium level was 10.9 mg/dl. Interestingly, 8534 (85%) of patients had average serum calcium levels below 11.5 mg/dl, the level that has often been quoted as being an indication for surgical referral (1,25,27-29). Furthermore, 69% of patients never had a single calcium level of 11.5 mg/dl or above (Figure 2). When teenagers are eliminated, 72% of adults never had a single calcium level reach 11.5 mg/dl. The number of patients having an average calcium level of 12.0 mg/dl or above was only 4%, with 93% of patients never having a single calcium level this high.

Figure 2 shows the *highest* serum calcium level seen within the population of PHPT patients and again, Table 1 shows the statistical analysis of the highest calcium levels according to age groups. The mean value of the highest serum calcium seen in PHPT patients was 11.4 mg/dl, 0.5 mg/dl higher than each patient's average calcium. Virtually all patients with PHPT had variable calcium levels that went up and down from one measurement to the next. Seventy-four percent of patients had one or more normal (below 10.0 mg/dl) calcium levels within the previous year, scattered among the other higher levels.

Patients with an average calcium level of 10.0 mg/dl or lower comprised 2.5% of the population. A more strict definition of normocalcemic HPTH where *every* measurement of an individual patient's serum calcium levels were below 10.0 mg/dl was seen in only 1.1% of patients. Each of these patients had high PTH levels, 78% had high urinary calcium levels (>250 mg/24 hours) and, as required to be in this study, all were found to have one or more parathyroid tumors at surgery with resolution of the preoperative high PTH. Kidney stones or osteoporosis resistant to medical therapy were overwhelmingly cited as the cause 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 to the findings of PHPT patients with higher calcium levels, however their tumor size and weight was, on average, less.

Patients under the age of 25 years with PHPT made up 1.4% in this study (n=144) and they typically presented with higher average calcium levels (11.6 mg/dl) than those over the age

of 25 (10.9 mg/dl) ($p < 0.001$) as seen in Table 1. The degree of calcium elevation associated with any particular PTH level was also higher in patients under age 25 than patients over 25 ($p < 0.001$). Similarly, the highest observed calcium associated with PHPT in patients under 25 (11.9 mg/dl) was higher ($p < 0.001$) than those over 25 (11.3 mg/dl) (Table 1). All age groups (regardless of breakdown) over the age of 25 had similar average and high calcium levels.

Serum calcium levels are more variable in patients with PHPT than they were in those same patients prior to the development of PHPT. Prior to the first calcium level over 10.2 mg/dl (prior to the development of hypercalcemic PHPT), patients showed little differences from one calcium measure 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 ($p < 0.001$). Calcium levels occasionally varied by more than 1mg/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 0.4mg/dl are rare ($p < 0.001$). Patients with normocalcemic PHPT are the exception to this rule which typically presents with very little variability in serum calcium levels, like their normal counterparts without parathyroid pathology.

24-hour urinary calcium testing showed tremendous variability at all levels of serum calcium and PTH. The average 24-hour urine calcium concentration was 297.7 ± 174 (SD). A detailed look at 24-hour urine calcium measurements will be a part of an upcoming report.

Serum PTH Levels in Primary Hyperparathyroidism: 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 individuals is shown in Figure 4, both representing a near Gaussian distribution. The mean PTH level was 105.8 pg/ml (SD 48.2), the median was 95 pg/ml, and the mode was 84 pg/ml. The average of the highest PTH seen in each of these patients was 115.3 pg/ml (SD 50.0) with a median of the highest PTH levels being 104 pg/ml and the mode for the highest PTH being 95 pg/ml.

Parathyroid hormone levels remained (on average) within the normal 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 under age 25 had significantly higher PTH levels than patients over the age of 25 ($p < 0.001$) (Table 2). In contrast to serum calcium levels, however, PTH values in patients over 80 years old were also higher than patients between 26 and 79 ($p < 0.001$) 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 compared to 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) ($p < 0.001$). 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 elevation of PTH was compared to the duration of hypercalcemia several observations were made. Adults (over age 25) with hypercalcemia due to PHPT for 6, 8, or even 10 years or more can occasionally have PTH levels which are only mildly elevated or even in the high normal range. The opposite (very high PTH in a patient with recent onset PHPT) is quite uncommon, however. When the PTH was over 150 the duration of hypercalcemia was over 6 years in 78% of adults. Similarly, 86% of those with PTH levels over 180 had hypercalcemia (>10.2 mg/dl) for 6 years or longer; 75% had hypercalcemia for 8 years or more.

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 for patients when the data was examined according to the distance the patient lives from our center, indicating no regional treatment differences and no discernable bias in the population of 10,000 patients due to our local community.

25 hydroxyvitamin D levels in primary hyperparathyroidism. The 25-hydroxyvitamin D (25 OHD) levels averaged 22.4 ng/ml (\pm 9.4) for the entire population (lower limit of normal = 20 ng/ml). Figure 6 shows the relationship between vitamin D levels and average serum calcium. 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 25 OHD levels decrease as average serum calcium increases ($p<0.001$). Of all patients undergoing surgery for PHPT, 76.8% had preoperative 25 OHD levels below 30 ng/ml, and 36.4% had levels 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 to allow a better understanding of the many ways a patient with a parathyroid tumor may present, providing physicians a means by which they can compare their patient to 10,000 others. By including only patients who had parathyroid tumor(s) surgically removed resulting in resolution of the biochemical profile of PHPT, we aim to provide an accurate picture and eliminate bias which could be included in patients who have not undergone surgery.

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

We found that PHPT patients less than 25 years of age presented with significantly higher average calcium and highest calcium levels than patients over the age of 25. This phenomenon has been reported previously by other authors (9-12). Thus a normogram of serum calcium levels in patients less than 25 years of age is different from any other age group, being shifted to the right 0.5mg/dl, with all other age groups having identical normograms. This lack of differences in calcium levels in adult patient populations is consistent with 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 will have average calcium levels which 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, regardless of the upper limit of normal (which can be as high as 10.6 mg/dl in some labs). Many of the previously reported patients with normocalcemic PHPT have been followed clinically and have not had their disease proven at surgery, yet in this study, the findings at surgery are identical to those patients with a classic presentation of PHPT with elevated calcium levels. It is likely that this area of the bell-shaped may actually be larger, as it is likely there are more patients with normocalcemic PHPT who were not referred for surgery and instead elected to be followed non-surgically, or their PHPT has gone undetected.

At the upper end of the bell shaped curve it is interesting to note is that only 7% of patients ever have a single calcium level above 12.0 mg/dl, with only 4% having average calcium levels this high. We still see on occasion 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 will ever reach this degree of hypercalcemia and that waiting for this to occur is not the practice norm 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 awaiting for higher calcium levels to develop must be re-thought. Fifty eight percent of patients with calcium levels above 12 mg/dl had PHPT for 5 years or less, while only 23% of patients with hypercalcemia for more than 10 years presented with even a single calcium level of 12 mg/dl. It is our strong opinion that the “severity” of PHPT is much more closely related to the duration of the disease or the associated signs and symptoms, rather than the degree of calcium elevation. Several upcoming articles from this large database (now over 13,000 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 the complications that arise from PHPT.

It is important to note that 8534 (85%) of patients had average serum calcium levels 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 NIH consensus statement regarding surgical treatment of asymptomatic PHPT (1, 25, 26-28). An upcoming study from our group will look at 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 level of 11.5 mg/dl or above. This is clear evidence that practicing endocrinologists take into account many variables when assessing a patient's need for surgical removal of the offending parathyroid tumor(s), and shows that the vast majority of the 1328 endocrinologists represented in this study favor surgical treatment of PHPT once the diagnosis is made regardless of the degree of elevation of a patient's serum calcium.

Our review of over 150,000 calcium levels revealed that the hypercalcemia associated with PHPT is typically variable for each patient from month to month, week to week, and even from day to day. Most patients with PHPT have one or more normal calcium levels (below 10.0 mg/dl) scattered among elevated levels. In contrast, prior to developing PHPT, these same patients had normal calcium levels which 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 make the diagnosis of 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) which is not responding to appropriate feedback. Normocalcemic PHPT is the exception to the rule, where less variability exists from one calcium measure to the next mimicking patients with normal parathyroid function where calcium levels show little change over time.

There is a great deal of individual variation between calcium levels observed at a particular PTH level (Figure 5), but as expected, there is a positive correlation between these two 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 seen in Figure 5 illustrates this well.

As seen with serum calcium, serum PTH levels in patients with PHPT represent a Gaussian distribution centered about 105 pg/ml for the average PTH and 115 for the highest PTH level observed. Several findings are important to note, such as the fact that 16.5% of patients have an average PTH level that is in the normal range, and 10.5% never have a single high PTH level (with a minimum of 3 measurements). This represents the classic “inappropriately normal” and “non-suppressed” PTH levels known to be associated with PHPT (4). We often see a delay in diagnosis of PHPT by physicians who wait for the PTH to be elevated at the same time as the calcium is elevated. The data here clearly shows 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 over 8 years can present with PTH levels that are only modestly elevated or very high. However, PTH levels above 180 are associated with hypercalcemia (and PHPT) for more than 8 years 84% of the time. Thus, not all patients get 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 levels of PTH at the extremes of life with patients less than 20 years old having the highest levels. This difference has been previously noted by our group (23) and others (9-11). Higher average PTH levels were also noted in the older population despite calcium levels that are not different from 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 level of calcium in patients without hyperparathyroidism (30,31).

Interestingly, this upward trend in PTH levels does not become apparent until the 7th decade of life and does not subside as age increases.

Low vitamin D has been reported to be present in patients with PHPT previously in smaller studies (6-7). This study is the first to show that 25 hydroxyvitamin D (25 OHD) decreases as average serum calcium levels rise (figure 6). We frequently see physicians attempt to assign a diagnosis of secondary HPT to patients with high serum calcium and high PTH when these findings are associated with low vitamin D. This phenomenon has been suggested by some authors (2,6,25,32), but it is our opinion that this mechanism occurs very rarely if ever. While it is possible for a low vitamin D level to cause a slight increase in PTH levels, these parathyroid glands do not become hyperplastic leading to autonomous PTH secretion which 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 ($p < 0.001$), while 25 OHD levels are decreasing to very low levels. An upcoming publication from our group looks at vitamin D levels (25 and 1-25) in great detail; however, the current study shows clearly that a low vitamin D-25 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 HPT is the diagnosis, and in our opinion, a low vitamin D level will rarely, if ever, cause an elevation in 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 our patients reside in other states, with all 50 states being represented. Eighty-nine percent of the referring endocrinologists ($n=1187$) practice outside of the state of Florida, with over 1000 being located more than 500 miles away. It was interesting to find, however, that patients who did not see an

endocrinologist but were referred by their primary care doctor or gynecologist had nearly identical biochemical profile with regards to 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 one calcium level above 11.0 mg/dl, but 12% have persistent calcium levels in the 10's, never reaching 11.0 mg/dl. Just over half of patients with PHPT have average serum calcium levels below 11 mg/dl illustrating that persistent calcium levels in the 10's in an adult is highly suggestive of a parathyroid tumor. A full 85% of PHPT patients will have average serum calcium levels below 11.5 mg/dl with nearly 70% never having a single level reaching 11.5 mg/dl. Calcium levels of 12 mg/dl or higher are uncommon and often represent larger tumors that have gone un-diagnosed or un-treated for many years. Teens and young adults present with higher serum calcium levels for a given PTH level compared to older patients, while patients over 25 with PHPT present with nearly identical calcium normograms through all decades of life. Although most patients will be 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 HPT) and another 10.5% who present with consistently normal PTH levels. Low vitamin D-25 is the rule and not the exception in patients with PHPT, with levels decreasing as calcium levels or the duration of the disease increases. The vast majority of

the more than 1300 endocrinologists representing the 10,000 patients in this study referred the patient for surgery based on many factors without regards to their degree of serum calcium elevation once the diagnosis of PHPT was made.

Figure 1

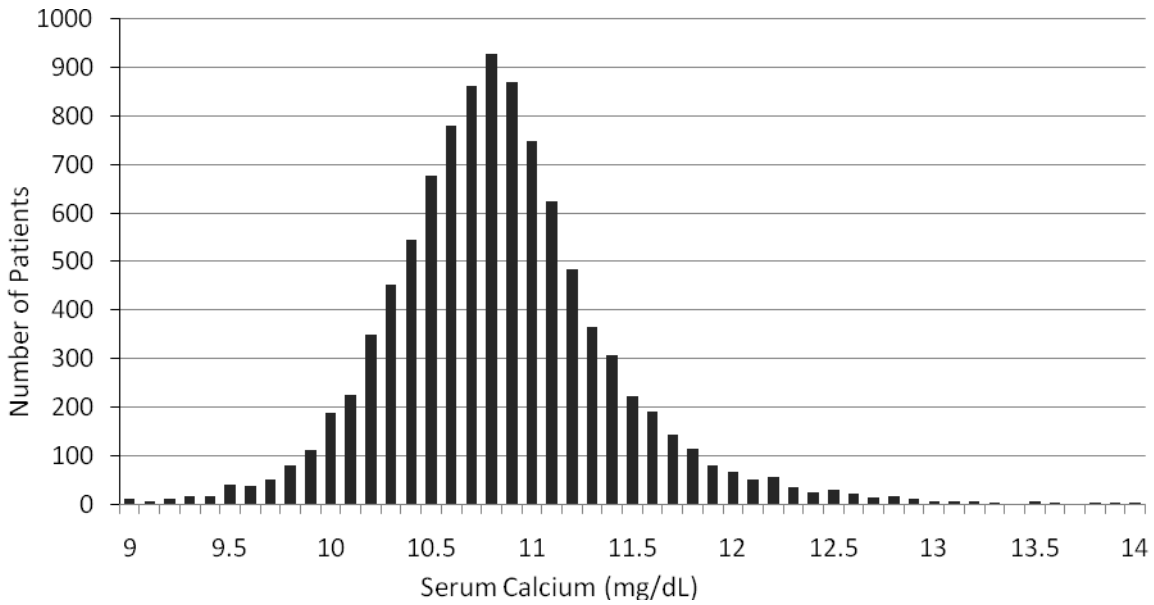


Figure 1. Normogram of average serum calcium (mg/dl) in 10,000 patients with primary hyperparathyroidism. Mean = 10.9 ± 0.6 , median = 10.9, mode = 10.8. Patients with an average calcium level of 10.0 mg/dl or lower comprised 2.5% of the population, while only 15% had average calcium levels above 11.5 mg/dl. Most patients with PHPT have average calcium levels below 11 mg/dl.

Figure 2.

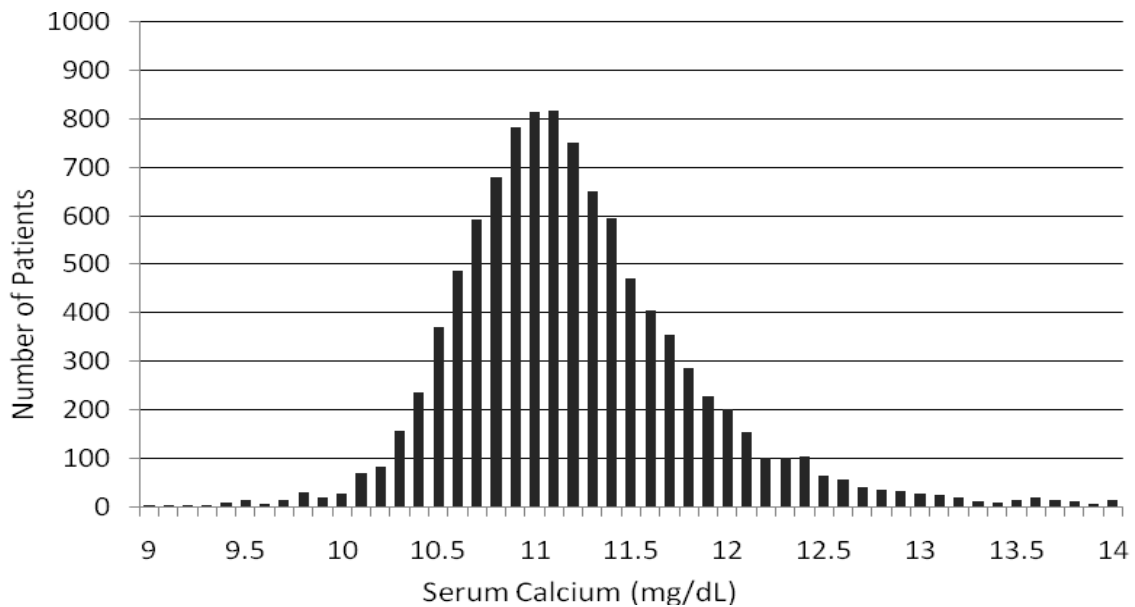


Figure 2. Normogram of the highest serum calcium (mg/dl) observed in 10,000 patients with primary hyperparathyroidism. Mean = 11.4 ± 0.7 , median = 11.2, mode = 11.2. Just over 1% of patients never had a single calcium level above 10.0 mg/dl, while two-thirds (69%) of patients never had a single calcium level of 11.5 mg/dl or above.

Figure 3.

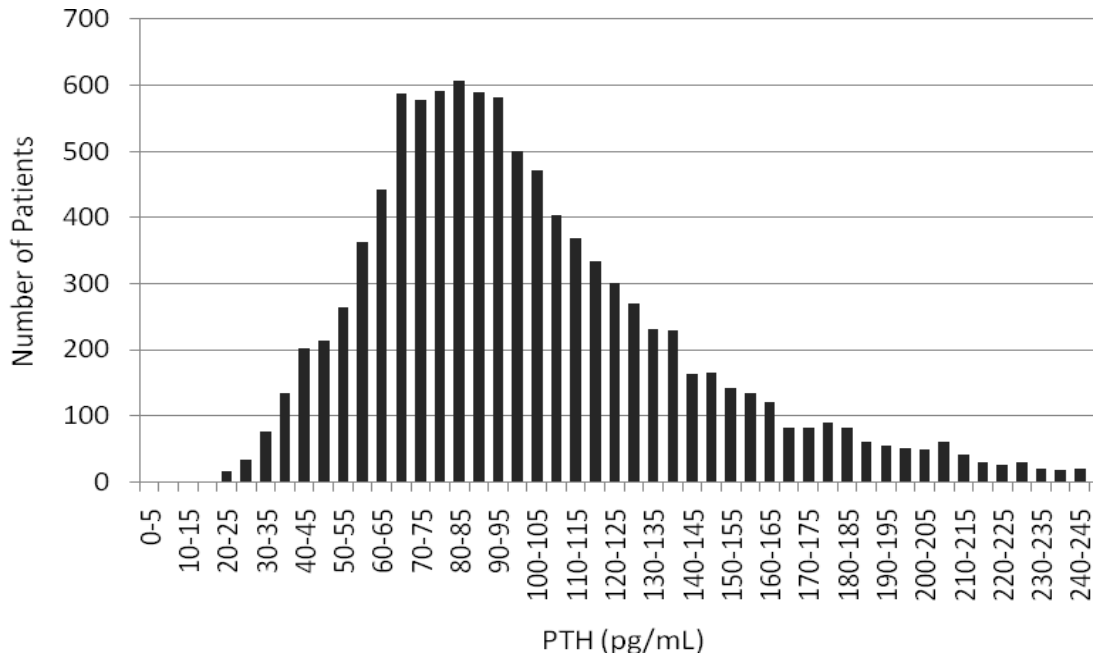


Figure 3. Normogram of average serum PTH (pg/ml) in 10,000 patients with primary hyperparathyroidism. Mean = 105 ± 48.2 , median = 95, mode = 84. Average PTH levels remained in the normal range (below 65 pg/ml) in 15% of patients.

Figure 4.

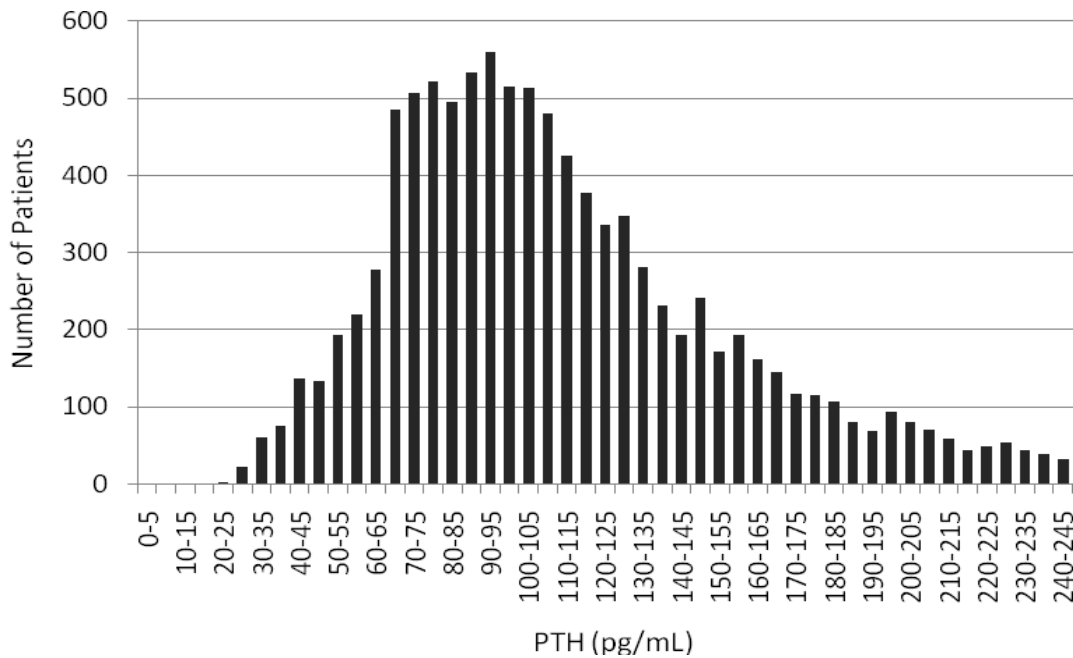


Figure 4. Normogram of the highest serum PTH (pg/ml) in 10,000 patients with primary hyperparathyroidism. Mean = 115.3 ± 50.0 , median = 104, mode = 95. 10.5% of patients had no PTH levels above 65 pg/ml.

Figure 5.

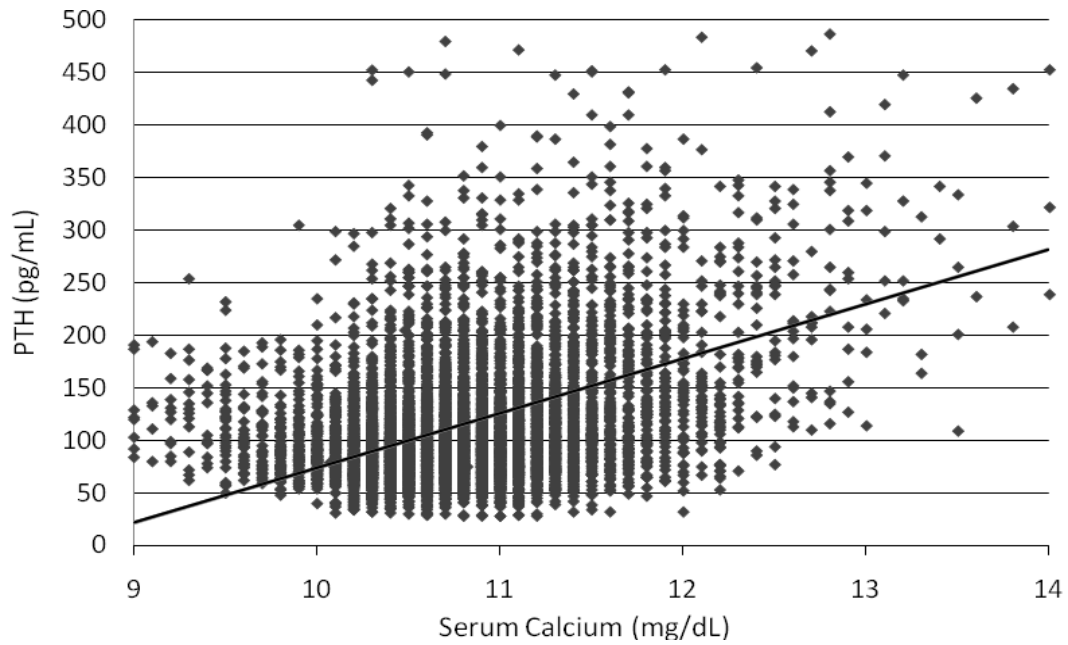


Figure 5. Average serum calcium vs. average PTH in patients with primary hyperparathyroidism. The relationship between serum PTH levels (pg/ml) and their corresponding serum calcium levels (mg/dl) is shown for 10,000 patients demonstrating a positive slope but a very poor correlation ($R^2=0.139$) signifying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

Figure 6.

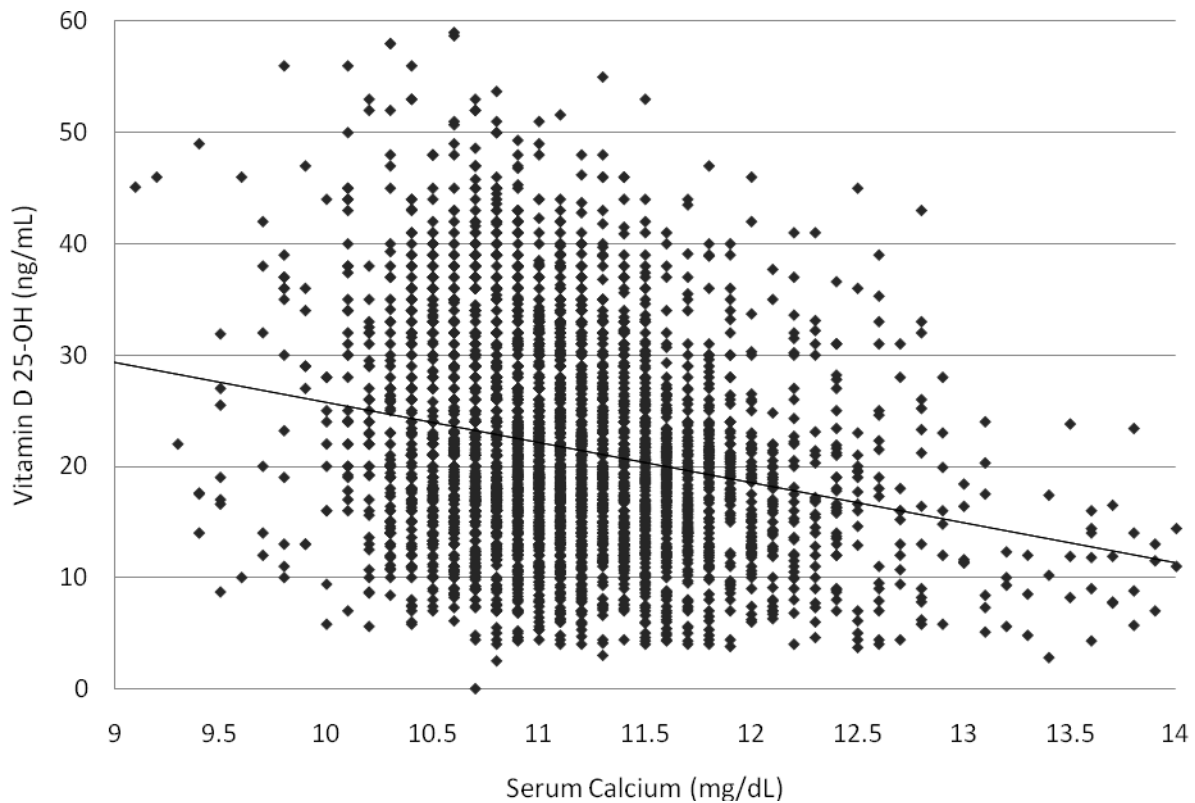


Figure 6. Vitamin D-25 levels according to average serum calcium in patients with primary hyperparathyroidism (PHPT). Values of vitamin D-25 (ng/ml) were obtained prior to administration of exogenous vitamin D in 4,758 patients subsequently operated on and cured of PHPT. Vitamin D levels decreased as calcium levels increased ($p < 0.001$) despite significant individual variation $R^2 = 0.066$.

Table 1

	Mean Serum Calcium (mg/dl;) (Std. Dev)	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)*	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)*	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

Table 1. Serum calcium levels (mg/dl) in 10,000 patients with surgically proven primary hyperparathyroidism according to age. The average and highest calcium levels for patients <25 years of age are higher than patients over age 25 years (*both $p < 0.001$). Patients over the age of 25 had identical average and highest calcium levels regardless of how this group was subdivided into smaller age groups. 85% of all patients had average calcium levels < 11.5 mg/dl, with 72% of adults never having a single calcium level of 11.5 mg/dl or higher.

Table 2

Age Group	Average PTH (pg/ml)(SD)
<25	148 (113)*
26-75	112 (73)
>76	133 (80)*

Table 2. Average serum PTH levels (pg/ml) in 10,000 patients with primary hyperparathyroidism according to age. Patients less than 25 and over 75 years of age present with significantly higher PTH levels than patients between these to age extremes. * denotes $p < 0.001$ compared to age 26-75.

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