Concentration of serum calcium is not correlated with symptoms or severity of primary hyperparathyroidism: An examination of 20,081 consecutive adults

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Background. *Guidelines for operative treatment of primary hyperparathyroidism include calcium levels >1 mg/dL above normal. We sought to determine whether greater calcium concentrations were associated with increased symptoms or disease severity.*
Methods. *A retrospective review of a prospectively maintained database of adults undergoing parathyroidectomy for primary hyperparathyroidism, grouped according to greatest preoperative calcium level: those patients with calcium concentrations between 10.0 and 11.0 mg/dL and those with >11.0 mg/dL. We compared subjective symptoms and objective measures of disease severity.*
Results. *The review included 20,081 adults who were split nearly evenly between calcium concentrations between 10.0 and 11.0 (10,430, 51.9%) and those with >11.0 mg/dL (9,651, 48.1%). In both groups, an absence of symptoms related to primary hyperparathyroidism was uncommon (<5%). All subjective and objective measures of disease severity were nearly identical with no significant differences (percentages for calcium concentrations between 10.0 and 11.0 and those with >11.0 mg/dL, respectively), including fatigue (72% for both groups), heartburn (37% vs 34%), bone pain (50% vs 48%), sleep disturbances (68% vs 65%), osteoporosis (40% in both groups), kidney stones (21% vs 22%), chronic kidney disease with glomerular filtration rate <60 (29% vs 32%), and hypertension (50% vs 53%).*
Conclusion. *Serum calcium concentrations of greater than or less than 11 mg/dL are unrelated to symptoms and disease severity in primary hyperparathyroidism. There is no evidence to support a serum calcium threshold in parathyroidectomy guidelines. (Surgery 2017;161:98-106.)*

From the Norman Parathyroid Center, Tampa, FL

THERE IS UNIVERSAL AGREEMENT that symptomatic primary hyperparathyroidism (pHPT) should be treated by parathyroidectomy (PTX). In contrast, asymptomatic or mildly symptomatic pHPT allows great latitude in its management, with some arguing for a proactive approach[1] while others advocate for operative referral only when some triggering event has occurred, such as the development of kidney stones or a worsening biochemical profile.[2]

If long-term monitoring is the chosen route, it has been taught that the development of greater serum calcium levels also would trigger operative referral. The assumption has been that greater calcium levels are associated with greater rates of complications, signs, and symptoms. The recommendations of the 1990 National Institutes of Health (NIH) Consensus Conference on the treatment of asymptomatic pHPT stated that "conscientious surveillance may be justified in patients

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whose calcium levels are only mildly elevated and whose renal and bone status are close to normal."[3] Unfortunately, symptomatic disease was defined rather narrowly.[4] Conditions defining symptomatic disease included kidney stones, substantial loss of bone density, chronic kidney disease, clinically relevant neuromuscular derangements, and gastrointestinal manifestations. The more common, nonspecific symptoms of fatigue, general malaise, and body aches, which could be attributed to other common ailments, were excluded. If a stricter definition of symptoms is adhered to, most patients with pHPT will be considered asymptomatic.[5,6]

These guidelines have since been updated 3 times at the International Workshops on the Management of Asymptomatic PHPT,[7,8] most recently in 2014,[2] with refinements to their recommendations for following "asymptomatic" patients who are monitored long term to evaluate for kidney and bone disease. Using the assumption that greater serum calcium concentrations indicate greater disease severity, the guidelines always have recommended PTX when the calcium reached a certain threshold. For the past several decades, this trigger for operative referral was a serum calcium level >1.0 mg/dL above normal, with normal defined by the reporting laboratory.[2]

Although we now have evidence from high-quality studies on the deleterious effects of untreated pHPT,[6,9] there are no studies to show that greater serum calcium concentrations lead to or equate with greater disease severity.[10] The relationship between serum calcium concentrations and pHPT severity is established only in cases of hypercalcemic crisis, a very uncommon presentation of pHPT.[11] Many authors seem to make the assumption that the degree of increase in serum calcium concentration is an approximation of disease duration, a hypothesis that never has been confirmed and has even been refuted in some long-term studies.[12]

Despite a lack of evidence, the supposition that "mild hypercalcemia" equates to mild hyperparathyroidism is common in the literature and in clinical practice. But in treating many patients with pHPT annually, we have noticed that those with classic pHPT symptoms often have rather unimpressive biochemical profiles. It has long been our hypothesis that the degree of increase in serum calcium concentration does not predict disease severity; that a patient with a greater serum calcium concentration is not necessarily "sicker" than one with mild hypercalcemia. In this study, we sought to test this hypothesis by comparing the symptoms and end-organ effects in patients with "mild" hypercalcemia (≤11 mg/dL) to those with greater levels (>11 mg/dL).

METHODS

We performed a retrospective review of a single-institution, prospective database of patients who were operated on for pHPT during 13 consecutive years ending in January 2016. All patients signed consent for review of their clinical data which were collected in a nonidentifiable fashion. This study was approved by our Institutional Review Board. For this review, we included only adults ≥21 years old with pHPT; patients with secondary and tertiary HPT were excluded. In addition, patients with greatest serum calcium levels <10.0 mg/dL (ie, those with normocalcemic pHPT) were excluded from this analysis for 2 reasons. First, these patients are usually diagnosed only after they have developed severe, end-organ disease (eg, osteoporotic fracture) because most physicians do not check parathyroid hormone (PTH) levels in the setting of normal calcium levels. Second, our experience with normocalcemic pHPT has led us to use stricter criteria for operating on patients with calcium levels <10.0 mg/dL; we usually require these patients to have objective evidence of end-organ damage or symptoms that cannot be attributed to other causes. Our approach to these patients would necessarily skew any comparisons on symptoms, and thus we excluded this group. In all, 20,081 consecutive adults undergoing PTX for classic hypercalcemic pHPT were studied.

Collection of patient data. In our practice, all patients complete a preoperative questionnaire specific to HPT, which is combined with laboratory values, test results, comorbidities, and operative findings to establish a robust database that includes up to 70 parameters per patient. In addition to the standard questions addressing medical, operative, and medication history, our intake questionnaire includes detailed questions on the common symptoms of HPT, known causes of pHPT such as lithium use, family medical history, and known end-organ manifestations of HPT, including cardiac arrhythmias, chronic kidney disease or stones, hypertension, gastroesophageal reflux disease, and bone loss (Appendix A, online version only). Patient medical records are obtained, with a focus on obtaining all recorded calcium, ionized calcium, and PTH levels, results of any recent bone density/dual-energy X-ray absorptiometry (DEXA) scan results, creatinine and glomerular filtration rate (GFR) results, imaging or physician documentation of kidney stones, as

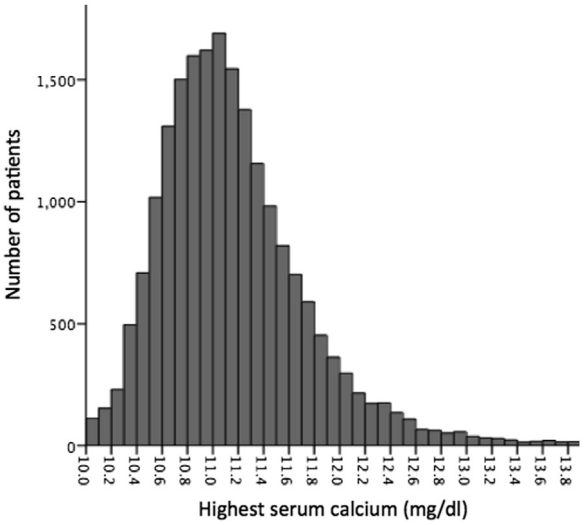

Fig 1. Distribution of patients with primary hyperparathyroidism, according to their greatest preoperative serum calcium levels. Patients with calcium levels between 10.0 and 11.0 mg/dL comprised 51.9% of the study population, while 48.1% had calcium levels of ≥11.1. Mean calcium = 11.1 ± 1.2 mg/dL; mode = 11.0; median = 11.0. All values above 14.0 mg/dL are shown with that group.

well as physician records to confirm other end-organ effects of HPT.

Statistical analysis. Patients were grouped by the greatest recorded preoperative serum calcium concentration. The first group consisted of those with serum calcium levels ≥10.0 mg/dL and ≤11.0 mg/dL (Ca ≤11). The second group consisted of those with highest calcium levels >11.0 mg/dL (Ca >11). These 2 groups were compared using independent samples *t* tests for mean values and χ^2 analysis for proportions. Receiver operating characteristic (ROC) curves were used to assess the predictive value of serum calcium concentrations on disease severity. Data are presented as mean plus or minus the standard deviation.

RESULTS

The greatest recorded serum calcium concentrations documented for each patient are shown in Fig 1. Patients were split nearly evenly between those with their greatest serum calcium levels between 10.0 and 11.0 mg/dL (inclusive) and those >11.0 mg/dL: 10,430 (51.9%) and 9,651 (48.1%), respectively. Demographic and biochemical data for both groups are detailed in Table. Patient age was nearly identical: 61.4 ± 11.6 years for Ca ≤11 and 60.8 ± 12.7 years for Ca >11 ($P = .4$). Women made up a greater percentage of patients with Ca ≤11 compared with those with Ca >11, 80% vs 74% respectively ($P < .001$). Preoperative vitamin D-25-OH levels were available for 9,674 patients, with vitamin D level being similar for both groups: 26 ± 16 ng/mL for Ca ≤11 vs 24 ± 13 ng/mL for Ca >11 ($P = .2$). Ionized calcium concentrations were recorded for 9,529 patients; the mean ionized calcium level for all patients was 5.8 ± 0.5 mg/dL. As expected, those with greater total serum calcium concentrations had greater ionized calcium concentrations (6.1 ± 0.5 vs 5.6 ± 0.4 mg/dL; $P < .001$). Preoperative 24 hour urine calcium excretion data were available for 7,126 patients; the mean urine calcium excretion was slightly greater in the Ca >11 group, 310 ± 213 vs 270 ± 160 mg/24 h ($P < .001$).

Table. Demographic and biochemical data for patients with greatest serum calcium levels between 10.0–11.0 mg/dL (Ca ≤11) and those with their greatest calcium levels >11.0 mg/dL (Ca >11)

	Calcium 10–11	*Calcium >11*	P *value*
No.	10,430	9,651	
Age (y)*	61.4 ± 11.6	60.8 ± 12.7	.4
Female (*n*, %)	8,328, 80%	7,137, 74%	<.001
Male (*n*, %)	2,102, 20%	2,514, 26%	
Greatest serum PTH (pg/mL)*	102 ± 57	130 ± 99	<.001
Median PTH (pg/mL)	92	107	
Mode PTH (pg/mL)	76	78	
Ionized calcium (mg/dL)*	5.6 ± 0.4	6.1 ± 0.5	<.001
Vitamin D (ng/mL)*	26 ± 16	23 ± 13	.2
Urine calcium (mg/24 h)*	270 ± 160	310 ± 213	<.001

*Mean ± standard deviation.

Mean values for the greatest recorded preoperative serum PTH levels were greater in patients with Ca >11 (130 ± 99 pg/mL) than for Ca ≤11 (103 ± 57 pg/mL; $P < 001$), but the mode PTH was nearly identical (76 vs 78 pg/mL, respectively). In both groups, greatest PTH levels were <30 pg/mL in <1% of patients. PTH levels were <60 pg/mL in 14% of patients with Ca ≤11 and 10% of patients with Ca >11. Elevated PTH levels >100 pg/mL were more common in those with Ca >11 than Ca ≤11, 55% vs 40%, respectively.

Comparison of disease severity. *Subjective and nonspecific symptoms.* The rates of various symptoms and end-organ effects of HPT are shown in Fig 2. Most patients reported the classic, nonspecific

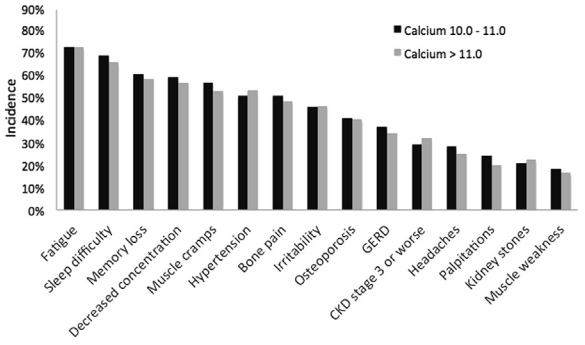

Fig 2. Frequency of common symptoms and complications of pHPT, comparing patients with their greatest serum calcium level between 10.0 and 11.0 mg/dL, and those with calcium levels >11.0 mg/dL. No differences between calcium level groups are statistically significant.

symptoms of HPT. Fatigue was the most common symptom, with <70% of patients reporting excessive tiredness and low energy preoperatively. This was true for all calcium levels, with no difference between Ca ≤11 and Ca >11 (72.1% vs 71.8%; $P = .2$). Sleep disturbances and insomnia occurred almost as frequently, again with no difference between groups (68% vs 65%; $P = .1$). Neurocognitive symptoms, including memory loss and decreased concentration, also occurred often. Memory loss was reported in 60% and 58%, respectively ($P = .1$). Decreased mental concentration ability was similar (58% vs 56%; $P = .2$). Heartburn and the use of medications for gastroesophageal reflux were reported by more than a third of patients in both groups (37% and 34%; $P = .1$). Headaches occurred in more than a quarter of patients (28% vs 25%; $P = .3$).

Bone and muscle involvement. Bone density loss, a classic and objective manifestation of HPT, occurred at the same rate in both groups. Preoperative DEXA scan results were available for 12,652 patients. In our analysis we used the lowest T-score reported, regardless of body site. The mean values for the lowest obtained T-scores for the Ca ≤11 and Ca >11 groups were −2.1 ± 1.2 and. −2.1 ± 1.1, respectively ($P = .7$). The prevalence of osteoporosis, defined as a T-score of −2.5 or lower, was 40% in both groups ($P = .7$). Bone pain was reported by 50% and 48% ($P = .5$). Neuromuscular involvement also was similar between groups. Just more than half of all patients in both groups reported muscle cramps. Subjective muscle weakness, although less common, also did not differ between groups (18% vs 17%; $P = .2$).

Renal disease. Kidney stones and chronic kidney disease occurred with equal frequency in those with mild hypercalcemia and those with more severe hypercalcemia (Fig 2). Kidney stones occurred in 4,317 patients, who were split evenly between groups (2,166 vs 2,151), equating to 21% of all adults with Ca ≤11 and 22% of adults with Ca >11 ($P = .6$). Mean preoperative creatinine levels were similar for both groups (0.9 ± 2.6 mg/dL vs 1.0 ± 2.4 mg/dL; $P = .8$). Chronic kidney disease stage 3 or 4, defined by a GFR <60, also was similar (29% vs 32%; $P = .06$). About half of all patients in both groups presented with a history of hypertension ($P = .09$).

Rates of symptomatic disease. Overall, fewer than 5% of all patients had no signs or symptoms of HPT, if nonspecific and subjective symptoms, such as fatigue and concentration difficulties, were included. If a stricter definition of "symptomatic HPT" was used, including only those patients with objective evidence of chronic kidney disease (stage 3 or greater), kidney stones, or osteoporosis, then just 43.5% of our patients were symptomatic, a percentage nearly identical for both groups (43.4% vs 43.6%; $P = .5$). Breaking the calcium levels down further in a follow-up analysis, we found that those with the greatest calcium levels on the lower end, between 10.0 and 10.5 mg/dL, had the same rate of these objective disease manifestations as those with calcium levels on the highest end, >11.5 mg/dL. In Fig 3, patients were divided into 4 groups to compare very mild calcium increases in serum calcium level (≥10.0 and ≤10.5 mg/dL), slightly greater levels (>10.5 and ≤11.0 mg/dL), moderate hypercalcemia (>11.0 and ≤11.5), and more pronounced hypercalcemia (>11.5 mg/dL). For each measure of these criteria for symptomatic disease according to International Workshop standards, there were no significant differences between these 4 groups.

PTH and disease severity. Although not the main focus of this study, serum PTH levels were also evaluated; the effect of increases in PTH levels on disease severity was mixed. For subjective symptoms, greater PTH levels did not predict the presence of symptoms. For some objective measurements, PTH >100 pg/mL was associated with slightly increased rates of disease. The rate of osteoporosis was slightly greater in those with PTH >100 pg/mL, both in patients with Ca ≤11 (44% vs 38%, $P < .001$) and Ca >11 (43% vs 37%, $P < .001$). Rates of kidney stones were not associated with PTH level, but chronic kidney disease (CKD) stage 3 or worse was more common in those with PTH levels >100 pg/mL (33% vs 26%; $P < .001$).

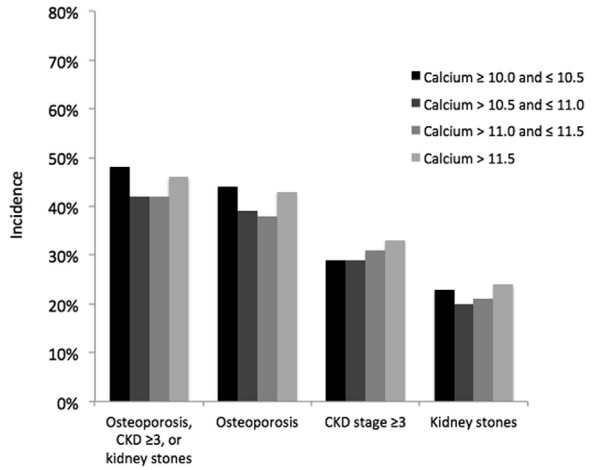

Fig 3. Frequency of established objective complications of pHPT to focus on the criteria for symptomatic disease used by the International Workshops (osteoporosis, CKD, and kidney stones). Patients were divided into 4 groups based on their greatest recorded preoperative calcium level: ≥10.0 and ≤10.5 mg/dL, >10.5 and ≤11.0 mg/dL, >11.0 and ≤11.5 mg/dL, and >11.5 mg/dL. No differences between calcium level groups were statistically significant.

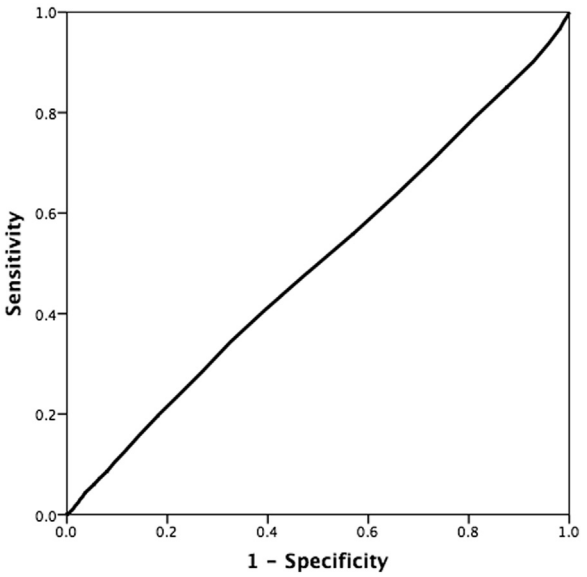

Fig 4. ROC curve for serum calcium concentration as a predictor of objective disease severity (including CKD, kidney stones, or osteoporosis). The area under the curve is 0.5, indicating that the serum calcium concentration is not an accurate predictor of disease severity. There is no threshold calcium level that would adequately predict worse disease.

Sex and disease severity. Although women accounted for a greater proportion of patients with Ca ≤11 and the rate of presenting symptoms varied somewhat by sex, overall the rate of symptomatic disease (either using nonspecific symptom criteria or by Consensus Conference standards) was similar between sexes. The main differences were in rates of osteoporosis and kidney stones. Women had greater rates of osteoporosis (41% vs 34%; $P < .001$) and men had greater rates of kidney stones (33% vs 18%; $P < .001$), but this did not have any influence on the comparisons between Ca ≤11 and Ca >11. If only female patients were considered, the rate of kidney stones was similar in both groups (17% vs 18%; $P = .6$). For males, the rate of kidney stones was identical (34% vs 33%; $P = .7$). The results for osteoporosis were similar: for women, the rate of osteoporosis was 42% for both groups, while for men, the rate of osteoporosis was 33% and 34% ($P = .7$).

Calcium thresholds. ROC curve analysis was used to assess the predictive value of serum calcium concentration on each subjective and objective measure of disease severity. These curves show that serum calcium concentration is a poor method for determining disease severity and that there is no threshold serum calcium concentration that would improve accuracy. The ROC curve for serum calcium concentration and objective symptomatic disease (kidney stones, osteoporosis, or CKD) is shown in Fig 4. ROC curves for subjective symptoms and for individual objective measures are nearly identical, with values of area under the curve of 0.5.

DISCUSSION

Internists and surgeons alike have long thought that mild hypercalcemia implied mild hyperparathyroidism and severe hypercalcemia inferred severe hyperparathyroidism. Despite a lack of high-level evidence to support this contention, the assumption that a greater serum calcium concentration equates to more severe disease has gone unquestioned for decades. It became an accepted norm when a calcium level threshold was incorporated into the original guidelines of the 1990 NIH Consensus Conference and all subsequent International Workshop guidelines on the treatment of asymptomatic primary hyperparathyroidism.[3] By stating that a greater serum calcium level (ie, 1 mg/dL above normal) was singularly an indicator for operative referral, the authors helped assure that physicians continued to estimate the severity of a patient's pHPT based on the degree of hypercalcemia. Although extreme increases in serum calcium concentrations leading to hypercalcemic crisis certainly represents a severe form of pHPT requiring urgent treatment, such a

presentation is rare and was seen in only a handful of the >20,000 patients contained in our database.

Our data show clearly that greater calcium levels, in the levels most commonly seen in practice, ie, between 10.0–13.0 mg/dL,[13] do not equate to greater disease severity. We have recognized for many years that subjective complaints and objective complications of pHPT occur at all calcium levels, even when the serum calcium concentration is only mildly increased, and our data confirm this observation. Our database was designed to allow examination of many parameters of HPT, and the inclusion of such high numbers of patients in this study helps alleviate any risk of type II error. Our study design also was excluded patients with secondary or tertiary HPT, or patients with normocalcemic HPT, because these 3 groups of patients have very different biochemical profiles and clinical presentations. Unfortunately, we do not have data on multiple endocrine neoplasia, but given the rarity of multiple endocrine neoplasia in our practice (<0.1%), the inclusion of a small number of these patients likely had minimal effect on our results.

It is important to note that 43.5% of this large cohort of patients had classic symptomatic pHPT as defined by the International Workshops, which requires objective evidence of chronic kidney disease (stage 3 or greater), kidney stones, or osteoporosis.[2,3,7,8] In contrast, fewer than 5% of all patients had no signs or symptoms of HPT if the so-called "nonspecific" subjective symptoms, such as fatigue and concentration difficulties, are included, and that rate was constant even as the calcium levels increased. Thus, the often-touted belief that patients with mild or modest elevations in serum calcium cannot have chronic fatigue, muscle aches, insomnia, and heart palpitations often seen in classic pHPT is not supported by the data.

The findings of this study are important, because most patients are labeled "asymptomatic" and assumed to have mild disease, based on mild increases in serum calcium concentrations and an absence of severe bone loss or kidney disease. Although fatigue, sleep difficulties, gastroesophageal reflux disease, and other nonspecific symptoms are relatively common complaints in any population, they occur with much greater frequency in patients with pHPT[14,15] and have been shown repeatedly and convincingly to improve after PTX.[16-20] Our study demonstrates that patients with "mild" hypercalcemia often experience the same symptoms as their counterparts with greater increases in serum calcium concentrations. Unfortunately, their less impressive biochemical profiles often lead their physicians to recommend nonoperative management. It is assumed that the patient can be monitored long-term and if the disease worsens—as evidenced by a greater increase in their serum calcium level—then the patient could be referred for PTX. Unfortunately, the majority of patients do not develop progressively greater serum calcium concentrations with time, often going indefinitely with mild to moderate hypercalcemia,[6] something we also have noticed in our patients. Thus, despite much evidence that PTX would improve quality of life,[21] these patients are observed simply because of their degree of hypercalcemia.

In surveys of physicians who treat parathyroid disease regularly, it is apparent that many have become much more liberal in recommending PTX than official guidelines would suggest.[22] We typically see patients from multiple different endocrinologists annually, many of whom do not follow the International Workshop guidelines, thinking that the guidelines are too restrictive. As PTX has become safer and faster during the past few decades,[23] the benefits of it seem to far outweigh the minimal risks. A better approach, one that would benefit the majority of patients with nonspecific symptoms and only "mild" hypercalcemia, is to assume that all patients will be offered PTX, with restrictions reserved for cases of diagnostic uncertainty or other compounding circumstances. Rather than waiting for complications and secondary health problems to develop, future guidelines should focus on preventing the known, long-term complications of parathyroid disease in patients who have been diagnosed with this progressive disease.

Our study does have some limitations. First, the absolute serum calcium concentrations were not corrected for serum albumin levels, but we would expect these patients to have normal serum albumin levels. Second, we evaluated the effect of total, rather than ionized, serum calcium concentration, although we would expect similar results given that greater total concentrations were associated with greater ionized concentrations. We focused on total calcium concentration as this is the measurement quoted most frequently in PTX guidelines. Third, our evaluations of the "nonspecific" symptoms (bone pain, fatigue, etc) treated these as binary values (yes/no); we did not attempt to quantitate the degree of symptomatology.

In conclusion, although serum calcium concentrations provide clinicians with a very quick ostensible indicator for the assessment of the severity of

pHPT, no studies support this dogma. Patients with only mild hypercalcemia have the same rates of every measure of disease severity. These patients should not be denied curative PTX because their serum calcium concentrations do not reach an arbitrary threshold. We hope that future guidelines will address this and no longer include the absolute increase in serum calcium concentration as a factor in determining candidacy for PTX.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2016.09.012.

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DISCUSSION

Dr Cord Sturgeon (Chicago, IL): I appreciate the size of this single-institution database and the richness of the data fields that you have.

I would like you to comment a little bit about that symptom graph that you showed. I did not catch what the tool was. Is it a survey that you could share with us? Is it a validated survey? Is it something that we can reproduce at our centers and compare?

Dr Deva Boone: For all of these subjective symptoms, we have a standard form that everyone fills out. It is not one of the published forms. It is one that we have created based on our population. It is all parathyroid specific. We can show it to you, if you would like, but it is what all patients have to fill out before they become our patients. That is for kind of the subjective things. For the objective

ones, we always collect creatinine. We always collect DEXA scores, and all of that goes in there.

Dr Cord Sturgeon (Chicago, IL): I think for the manuscript, it will be important to have that so that we can see what questions are asked and with what frequency they return positive, and perhaps there are questions that we did not see that are negative more often or something. It would be good to have a validated measure for this.

Dr Douglas L. Fraker (Philadelphia, PA): Just to follow up on that, my typical preoperative discussion is those symptoms, like your highest 5, are subjective, as you pointed out. And as a sidebar comment, the world is in the biggest state of disarray it has been in my 60 years on the planet, and I always say that just watching CNN will lead to most of these symptoms.

So my question is, what is not as important is if they are equal, but what is the delta? In other words, if you go from a calcium of 10.1–9.6, does your sleep disturbance, irritability, fatigue, and just feeling crummy, is that different than if you go from 12.1–9.6? Do you have the follow-up data?

Dr Deva Boone: That I do not have. That is interesting to see whether you have a better symptom resolution with a higher calcium. In our experience, no, but I do not have that data here.

Dr Sally E. Carty (Pittsburgh, PA): A couple of points. One is very minor. You do not mean height; you mean elevation. Elevation refers to a biochemical result.

Two, I do not think you looked—well, you certainly cannot be accused of type 2 error. You have got a huge series, but you do not look at disease severity. You looked at symptom severity, symptom severity differentiated by 2 different calcium elevation ranges. And disease severity in hyperparathyroidism, which I understand poorly compared to endocrinologists, is not a measure of symptom. Symptom is certainly part of it, and that is certainly something that we as surgeons want to pay attention to and fix with our knife. But disease severity is completely different than symptom severity. So you made conclusions that are unsupported by your data.

Dr Deva Boone: Well, I think chronic kidney disease and osteoporosis are not really symptoms, and that represents disease severity. So, yes, we are including things that are objective measures. And if you look at chronic kidney disease, GFR <60, the rate was exactly the same. Osteoporosis 40% in both groups. Those are pretty good measures of disease severity.

Dr Nancy D Perrier (Houston, TX): Thank you, Deva, for a presentation of a large cohort of patients. You all have done a great job of reiterating what I think Malcolm Wheeler wrote in the '80s about serum calcium not correlating with disease severity. And I think following that along with the ideas that size does not predict function, we talked through this, and you reiterate that today that the word "asymptomatic" is a medical misnomer, and that truly if you dig into these patients, these are subjective symptoms that are probably the most difficult to quantify. And by using objective measures, we might be better off for describing the actual symptoms.

Congratulations on those osteoporosis and those kidney stones that you talked about. And I think that is our marker of what we have heard here today earlier and what we heard from the UCLA group and the Mayo group in the past years, that bone disease itself gets better and is a great marker regardless of the disease severity. So even with mild, biochemical disease, bones get better. And I think that is something very objective and very important for our referring doctors and for the population as a whole.

So I ask you and invite you, with this tremendous amount of data, have you looked at the objectiveness of the bone symptoms, for instance, that take away all the subjectiveness, objective disease, and then look at it afterwards, and follow these patients up? We would love to know in 10,000 and 20,000 patients what the bone symptoms are at a year and at several years, because we talked about that earlier today. It seems to get better.

Can you answer that? Are you doing it? And if you are not, can I invite you on behalf of us to do that for us?

Dr Deva Boone: We can use your help, too. It is something that we are working on, but it is a big task to follow all those patients. But, yes, that is what we need.

Dr Nancy D. Perrier (Houston, TX): And repeat those same bone mineral densities at the same markers in the same institution. We invite you to do that, and we will take the objectiveness and use that as a caliber and get rid of the subjectiveness. Thank you.

Dr Deva Boone: Just a comment. Unfortunately, a lot of our patients when we do their DEXA scan scores, they are not calibrated to our hospital. Our patients come from all over, and we do not repeat their DEXA scan when they enter our hospital. We go by what their doctor did. So we are going by scans from all over the country, but it is a good point. Regardless, it will be good to follow.

Dr Nancy D. Perrier (Houston, TX): You have a great opportunity to make real science out of that and really help the population. Thank you.

Dr Richard A. Prinz (Evanston, IL): Very nice presentation. I congratulate you on using such a rich database to come up with what I think everyone in the room believes in, is that there is no such thing as asymptomatic primary hyperparathyroidism. I think it would be more convincing, though, if you looked at your data in a little different manner because you showed us the bell curve, and the vast majority of the patients fall right around that 11 number. So I wonder if you would want to go ahead and look at a group with real mild hypercalcemia, 10–10.5 and something above 11.5 or 12, so you have groups that really you can say are disparate.

Dr Deva Boone: When you do that, actually, you still do not see any difference. It seems like no matter what the calcium level is, patients have about the same rate of symptoms. I chose that cut-off because that is what the NIH guidelines are. And if we are going to go forward making our own guidelines, this is something that we need to re-evaluate.