Normocalcemic parathormone elevation after successful parathyroidectomy: Long-term analysis of parathormone variations over 10 years

Melanie Goldfarb, MD,a Stephen Gondek, MD, MPH,b George L. Irvin III, MD, FACS,a and John I. Lew, MD, FACS,a Miami, FL, and Boston, MA

Background. The long-term significance of normocalcemic parathormone elevation (NPE) after successful parathyroidectomy for sporadic primary hyperparathyroidism remains unclear.

Method. Of 239 consecutive patients who underwent targeted parathyroidectomy with intraoperative parathormone monitoring, 96 were followed for ≥ 10 years. NPE was defined as a normal serum calcium level and parathormone (PTH) above the normal reference range 6 months after successful parathyroidectomy. Recurrence was defined as elevated serum calcium and PTH levels ≥6 months after parathyroidectomy. Risk factors for NPE, patterns of postoperative PTH variation, and 10-year outcomes were analyzed.

Results. Of 96 patients followed ≥ 10 years, 42 had postoperative NPE. Only male gender (P = .008) was a risk factor for NPE, and NPE did not predict recurrence. Three patterns of postoperative NPE were identified in patients with ≥ 3 PTH measurements over this 10-year period. Group 1 (n = 11): 1 to 2 consecutive PTH elevations; none recurred, and most were explained by physiologic variation. Group 2 (n = 23): multiple PTH fluctuations; 3 recurred, and almost all had physiologic variations. Group 3 (n = 4): PTH always elevated; 2 recurred.

Conclusion. Postoperative NPE may be a dynamic, reversible, and transient clinical entity that does not predict recurrence. Nevertheless, patients with postoperative NPE should be monitored and an attempt made to correct any obvious potential causes of PTH elevation. (Surgery 2011;150:1076-84.)

From the Division of Endocrine Surgery,a University of Miami Health System, University of Miami Leonard M. Miller School of Medicine, Miami, FL; and the Department of Surgery,b Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Normocalcemic parathormone elevation (NPE) is a known biochemical phenomenon that occurs after successful parathyroidectomy for sporadic primary hyperparathyroidism (SPHPT). Postoperative NPE is documented when parathormone (PTH) levels above normal reference range in the setting of serum calcium levels within normal reference range are measured. In short-term studies as long as 2 years after parathyroidectomy, the incidence of NPE varied from 8% to 43%.1-11 It is not surprising that this biochemical finding after successful parathyroid surgery is disturbing to referring physicians and treating surgeons, who are worried about the possibility of recurrent disease in these patients.

The pathogenesis and clinical significance of postoperative NPE is not well understood. Some authors assert that NPE is a mild form of hyperparathyroidism due to renal or vitamin D insufficiency, a condition at the molecular level in which there is decreased peripheral PTH sensitivity or a demonstration of normal physiologic variation in which PTH elevation is an adaptive compensatory mechanism to restore calcium homeostasis after successful parathyroidectomy.6,9,12,13

With the exception of 1 known study with a postoperative follow-up beyond 2 years after parathyroidectomy, all other previous reports have
examined postoperative calcium and PTH levels at only 1 or 2 static time points beyond 6 months after parathyroidectomy. To our knowledge, no previous studies have examined the dynamic PTH variations over the long term in patients after successful parathyroidectomy. The purpose of this study, therefore, was to examine PTH variations in patients with postoperative NPE over a 10-year period and discern its clinical significance, if any, in predicting recurrent disease.

**METHODS**

Of 239 consecutive patients with SPHPT who underwent initial targeted parathyroidectomy with intraoperative parathormone monitoring (IPM) at the University of Miami Health System between September 1993 and July 2000, 96 patients were followed for more than 10 years (average follow-up, 143 months). All patients had secure biochemical diagnoses of SPHPT (ie, elevated serum calcium and PTH levels) and underwent sestamibi scans to localize abnormal parathyroid glands preoperatively. Prospectively collected data for all patients, including operative indication, preoperative laboratory values and imaging, IPM dynamics and postoperative laboratory values, including serum calcium, PTH, and creatinine at 2, 6, and 12 months and yearly thereafter, when available, were retrospectively reviewed. Vitamin D levels were not routinely prospectively collected until later in this long-term period. Furthermore, patients with low vitamin D levels did not routinely receive vitamin D supplements. Patients with multiple endocrine neoplasia; secondary, tertiary, or familial hyperparathyroidism; or parathyroid cancer were excluded from this study.

Indications for parathyroidectomy followed National Institutes of Health guidelines or a previous report from this institution. Targeted parathyroidectomy with IPM was the initial approach performed in all patients. The intraoperative PTH criterion used for predicting successful parathyroidectomy was defined by a decrease of intact PTH levels of more than 50% from the highest preincision or preexCISION hormone level in a peripheral blood sample obtained 10 minutes after removal of all abnormal parathyroid tissue. If the 10-minute sample did not meet the criterion, a delayed sample at 20 minutes was usually measured. Further neck exploration was continued until all hypersecreting glands were removed and levels confirmed >50% drop from the highest preexciSion sample.

Operative success was defined as continuous normocalcemia for 6 months or longer after parathyroidectomy. Operative failure was defined as elevated serum calcium and PTH levels above normal reference range within 6 months after parathyroid surgery. Recurrent hyperparathyroidism was defined as elevated serum calcium and PTH levels above normal reference range more than 6 months after successful parathyroidectomy. Multiglandular disease (MGD) was defined by the known involvement of more than 1 gland at the time of initial operation as determined by persistently elevated PTH levels despite removal of 1 hypersecreting gland or when removal of a single parathyroid gland resulted in operative failure.

Postoperative NPE was defined as a serum calcium level of ≤10.2 mg/dL and a PTH level above normal reference range for more than 6 months and for at least 1 instance during a 10-year period after successful parathyroidectomy. The normal reference ranges for PTH and serum calcium varied for each laboratory facility during the 10-year postoperative follow-up period. Study patients from this time period were divided into 2 groups: patients in group A (n = 54) had PTH and calcium levels within the normal reference range for their entire postoperative course or until recurrence; and patients in group B (n = 42) had postoperative NPE over the same time period. In all patients identified with postoperative NPE, all individual PTH values were verified using the original laboratory-result documents to confirm the normal reference range of the respective laboratory facilities performing the biochemical test during any particular time period.

Clinical and laboratory values prospectively collected from patients in group A and group B were compared for predictors of NPE and overall outcome, including recurrence rate. Postoperative PTH variations were further examined only in group B patients with NPE and ≥3 PTH measurements over this 10-year period. Physiologic variation was defined as a transient PTH elevation above the normal reference range with an associated decrease in serum calcium that later returned to normal range with a responsive elevation in calcium during the 10-year period. Vitamin D insufficiency was defined as a 25-hydroxy-D level <30 mg/dL. Renal insufficiency was defined as a serum creatinine level ≥1.5 mg/dL.

All patients’ charts and information were prospectively collected and retrospectively reviewed in accordance with Institutional Review Board guidelines at the University of Miami Health System. Statistical analyses of prospectively collected data were performed using SPSS 18.0 (IBM Co., Somers, NY). Univariate analysis was performed using the
Student t test for continuous data and chi-squared or Pearson-squared analysis for categorical data, followed by multivariate regression analysis. A P value of < .05 was considered statistically significant.

RESULTS

Of the entire group of 239 patients, 222 patients were followed for more than 6 months, and there was an average follow-up of 85.4 months. Operative success was 98.2%, and the overall recurrence rate was 3.3%. Of the 239 patients who initially underwent targeted parathyroidectomy with IPM, 25 (10%) were converted to bilateral neck explorations. The majority (97%) of these 239 patients had single-gland disease, whereas 3% had MGD. Of the 222 patients, 48 patients died and 78 patients were lost to follow-up during this long-term period, leaving 96 patients with at least 10 years of follow-up after successful parathyroidectomy. In this subset of 96 patients who were followed ≥119.5 months, the overall recurrence rate was 6.2%. In group A patients (n = 54) with postoperative PTH and calcium levels within the normal reference range, the recurrence rate was 1.1%; in group B patients (n = 42) with postoperative NPE, the recurrence rate was 5.1%. When both groups were compared, postoperative NPE was not a statistically significant risk factor for recurrent disease (P = .09).

In patients in groups A and B, univariate analysis demonstrated that male gender (P = .041) and higher preoperative PTH levels (P = .048) were predictors of postoperative NPE (Table I). Multivariate analysis was performed with all significant and nearly significant variables (Table II). Only male gender (P = .008) reached statistical significance for predicting postoperative NPE.

Patients in group B who had postoperative PTH levels above the normal reference range in the setting of normal serum calcium levels and ≥3 PTH measurements (n = 38), 3 main patterns of PTH variation were identified during the 10-year study period.

Group 1 consisted of 11 patients who had 1 or 2 consecutive PTH elevations above normal reference range over the 10-year postoperative period. An example of a study patient’s PTH variations over time is depicted in Fig 2, which also shows superimposed serum calcium levels. Of these 12 patients, 3 developed recurrent hyperparathyroidism at 99, 108, and 120 months. All but 1 of the 23 patients showed physiologic variation of PTH and calcium levels, and 7 patients demonstrated NPE only at last follow-up. Additionally, 5 patients had vitamin D insufficiency and 3 patients demonstrated renal insufficiency.

Group 2 consisted of 23 patients who had multiple fluctuations in PTH levels above the normal reference range over the 10-year postoperative period. An example of a study patient’s PTH variations over time is depicted in Fig 2, which also shows superimposed serum calcium levels. Of these 12 patients, 3 developed recurrent hyperparathyroidism at 24 and 151 months. Of the 2 remaining patients, 1 had vitamin D insufficiency, but there was no explanation for the persistent PTH elevation in the other patient.

DISCUSSION

Postoperative NPE is not an uncommon finding in patients after successful parathyroidectomy for SPHPT. Such elevated postoperative PTH values are of concern for recurrent hyperparathyroidism. At this time, no definitive explanation for this postoperative phenomenon exists to alleviate both patients’ and clinicians’ concerns about PTH levels above the normal reference range after parathyroidectomy. As previous studies have reported, the majority of patients reveal normalization of PTH levels on subsequent blood draws, and only a very small percentage actually develop recurrent disease many years after successful operation. This current study demonstrates a recurrence rate of 5.1% in patients who exhibited postoperative NPE for more than 10 years; this rate is not statistically significant when compared to the rates in the patients whose PTH remained in the normal range for the entire postoperative period or until recurrence.

Three distinct patterns of postoperative PTH variation in patients with 3 or more PTH measurements over a 10-year period were observed in this series: (1) 1 or 2 consecutive PTH elevations above the normal reference range; (2) multiple fluctuations of PTH levels above the normal reference range; or (3) PTH levels that were constantly above the normal reference range. In a Swedish study of 73 patients who underwent successful parathyroidectomy for SPHPT, yearly laboratory values over a 5-year period were obtained. Three groups of
PTH variation over the 5 years (aside from those with constantly normal PTH levels) were identified and were similar to our findings: (1) early elevated PTH levels at 8 weeks postoperatively that later normalized; (2) fluctuating PTH levels; or (3) constantly elevated PTH levels throughout the 5-year postoperative period. In agreement with this study, the Swedish study concluded that such postoperative PTH variations are not static and do not signify recurrent disease.

One explanation for NPE is the concept of physiologic variation in which PTH elevation is an adaptive response to dynamic changes in serum calcium levels. Total serum calcium is known to vary over time in an individual. A decrease in serum ionized calcium triggers the calcium receptor of the parathyroid cell, inducing it to secrete more PTH. This known association between the extracellular ionized calcium concentration and PTH secretion has been described as an inverse sigmoidal curve.

Studies have shown that elevated PTH levels respond to oral calcium loading. Postoperative patients who were given oral calcium loads at 8 weeks after parathyroidectomy demonstrated decreased PTH levels not caused by decreased calcium sensitivity. Mild unsubstituted hypocalcemia has been shown generally to be associated with

---

**Table I. Univariate analysis for predictors of postoperative normocalcemic PTH elevation**

<table>
<thead>
<tr>
<th>Pre-op variables</th>
<th>Normal calcium and PTH throughout (%)</th>
<th>Normocalcemic PTH elevation NPE (%)</th>
<th>P value (chi-square [C] or Fisher exact [F])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (28.5)</td>
<td>10 (71.4)</td>
<td>.041 (F)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (60.0)</td>
<td>32 (40.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27 (52.9)</td>
<td>24 (47.1)</td>
<td>.936 (C)</td>
</tr>
<tr>
<td>Black</td>
<td>15 (55.6)</td>
<td>12 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (58.3)</td>
<td>5 (41.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58.3 ± 2.9</td>
<td>59.7 ± 4.3</td>
<td>.581</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.7 ± .2</td>
<td>11.7 ± .3</td>
<td>.861</td>
<td></td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>145.8 ± 15.0</td>
<td>187.9 ± 41.8</td>
<td>.048</td>
</tr>
</tbody>
</table>

| Symptoms         |                                        |                                      |                                          |
| Bone pain        | 17 (63.0)                              | 10 (37.0)                            | .407 (C)                                 |
| Stones           | 12 (63.2)                              | 7 (36.8)                             | .498 (C)                                 |
| Mental           | 1 (50.0)                               | 1 (50.0)                             | 1.00 (F)                                 |
| Fatigue          | 3 (60.0)                               | 2 (40.0)                             | 1.00 (F)                                 |
| Asymptomatic     | 11 (47.8)                              | 12 (52.2)                            | .350 (C)                                 |
| Crisis           | 0 (0)                                  | 1 (100)                              | .437 (F)                                 |
| Calcium >11.2    | 33 (57.9)                              | 24 (42.1)                            | .696 (C)                                 |
| Age <40          | 12 (57.1)                              | 9 (42.9)                             | .926 (C)                                 |
| High urinary Ca  | 3 (37.5)                               | 5 (62.5)                             | .292 (F)                                 |
| Cr ≥1.5          | 1 (33.3)                               | 2 (66.7)                             | .585 (F)                                 |

| Intraop variables|                                         |                                      |                                          |
| Correct preop localization* | 43 (52.4) | 39 (47.6) | .215 (F) |
| BNE               | 7 (50)                                      | 7 (50)                              | .773 (F) |
| MGD               | 0 (0)                                       | 3 (100)                             | .086 (F) |
| % IPM drop        | 77.6 ± 2.7                                 | 77.0 ± 3.1                          | .774 |
| >50% PTH drop to normal range at 10 min | 36 (63.2) | 21 (36.8) | .058 (C) |
| >50% PTH drop from preincision at 10 min | 47 (57.3) | 35 (42.7) | .362 (F) |

| Postop variables |                                         |                                      |                                          |
| Immediate calcium level (within 7 days) | 9.15 ± .18 | 9.08 ± .20 | .546 |
| Elevated PTH in first 6 months | 6 (30.0) | 14 (70.0) | .050 (C) |

*According to sestamibi scan.
BNE, Bilateral neck exploration; IPM, intraoperative parathormone monitoring; MGD, multiglandular disease; NPE, normocalcemic parathormone elevation; PTH, parathormone.
slightly elevated PTH levels, and there is an inverse correlation with both the immediate postoperative period and with many years after successful parathyroidectomy.\textsuperscript{20} Other authors have proposed PTH resistance, reduction in number of PTH receptors, or dysfunction at the receptor level in patients with elevated PTH levels.\textsuperscript{12} Considered together, such studies suggest that NPE may be related to decreased calcium absorption at a given time and that it is a reversible and transient phenomenon. In this study, most patients with postoperative NPE and 3 or more PTH measurements over the 10-year period demonstrated PTH and calcium level variations after parathyroidectomy that fit this model of dynamic or physiologic variation.

There are several possible causes of hypocalcemia that could lead to a compensatory PTH elevation. Bone remineralization is known to cause hypocalcemia and a resultant increase of PTH levels in the first few years after parathyroidectomy, although there is a discrepancy in the duration of this increase in bone mineral content; it varies from 3 months to as long as 4 years.\textsuperscript{21,22} Dietary insufficiency or decreased gastrointestinal absorption could also result in hypocalcemia. Additional considerations include bisphosphonates, which have been shown to decrease calcium and cause compensatory increases in PTH, as well as elevations in PTH that are corrected by estrogen replacement therapy in postmenopausal women.\textsuperscript{23}

All postoperative NPE cannot be accounted for by physiologic variation, so other explanations must exist. One potential underlying cause is vitamin D insufficiency. In patients with normal calcium levels and PTH levels above the normal reference range within the first 6 months after parathyroidectomy, some authors have observed lower postoperative 25-hydroxy-D levels.\textsuperscript{2,8} Lower vitamin D levels preoperatively have also been reported in patients with SPHPT, and studies suggest that postoperative PTH elevation may be due to a decrease in 1-alpha hydroxylation of 25-hydroxy vitamin D3.\textsuperscript{3,6} Finally, because PTH resistance to low vitamin D levels can be treated with vitamin D compounds, the administration of preemptive vitamin D (calcitriol) supplementation to patients after parathyroidectomy has been shown to decrease postoperative NPE at 6 months compared to controls.\textsuperscript{24} This study demonstrated low 25-hydroxy-D levels in some patients with postoperative NPE; unfortunately, the vitamin D (25-hydroxy and 1,25-dihydroxy) data remain incomplete, so no meaningful conclusions can be made.

Renal insufficiency is a third possible explanation for postoperative NPE. Patients with uremia are known to have impaired peripheral sensitivity to the calcemic actions of PTH and resistance to serum PTH stimulation. In addition, patients with decreased renal function have been shown to

---

**Table II.** Multivariate analysis for predictors of postoperative normocalcemic PTH elevation

\begin{tabular}{|l|c|}
\hline
Predictor & P Value \\
\hline
>50% Intraop PTH drop to normal range at 10 min & .157 \\
Preoperative PTH level & .081 \\
Multiglandular disease & .113 \\
Male gender & .008 \\
\hline
\end{tabular}

**Fig 1.** Postoperative NPE patient with 1 or 2 consecutive PTH elevations above normal reference range.

**Fig 2.** Postoperative NPE patient with multiple fluctuations of PTH levels above normal reference range.

**Fig 3.** Postoperative NPE patient with always elevated PTH levels above normal reference range.
exhibit decreased production of the PTH receptor mRNA. These responses may present as secondary hyperparathyroidism, with elevated PTH in uremic patients, though the degree of PTH elevation and its clinical significance vary. Furthermore, some studies suggest impaired renal responsiveness to PTH as a cause for postoperative NPE, and many attribute this phenomenon to higher preoperative PTH levels and more severe disease. Indeed, most studies that have investigated PTH in the immediate postoperative period have been able to show a correlation between higher preoperative PTH concentrations and postoperative PTH elevations. However, this may not necessarily be relevant to what is happening physiologically years after successful parathyroidectomy.

Other risk factors for postoperative NPE have been the subject of a few previous investigations. Reported causes include higher preoperative calcium level, adenoma size, advanced age, ethnicity, osteoporosis, and MGD. Again, these studies primarily examined PTH levels within the first 6 months after parathyroidectomy. This current study demonstrated only male gender and preoperative PTH levels as predictors of NPE, and only male gender was significant according to multivariate analysis; the clinical significance of this is unknown.

This is the first published study, to our knowledge, that examines postoperative PTH variations with at least 3 successive PTH measurements over a long-term period of 10 years in patients surgically treated for SPHPT. Two other long-term Swedish studies in the literature consider only 1 end-term PTH level at a static time point and report on the recurrence and operative failures in their patient populations. Lungren and colleagues followed 410 patients for a mean of 14.2 years, reporting an 8.3% recurrence rate and an 11% incidence of NPE. Hedback and colleagues followed 785 patients for a mean of 10 years and reported a recurrence rate of 5%. Both studies were performed in an era before targeted parathyroidectomy and IPM, which allow surgeons to confirm removal of all hypersecreting parathyroid glands biochemically. In these Swedish studies, abnormality of parathyroid glands was determined by size and histopathologic diagnosis. Nonetheless, the recurrence rates reported in the Swedish studies are comparable to the recurrence rate of 6.2% we found in this study.

Furthermore, in this study, 45% of patients had PTH levels above the normal reference range at some point during the 10-year period after parathyroidectomy. Although this number may seem high, it is in accordance with the findings of Nordenstrom and colleagues, who reported 48% of patients with PTH levels above the normal reference range at least once during a 5-year period. Previous published studies that report NPE rates between 8% and 43% are limited by the fact that they consider only a single time point rather than several PTH and calcium measurements over a long period; therefore, their results cannot be compared to those of the 2 aforementioned studies. More important, neither our study nor that of Nordenstrom and colleagues gives any indication that postoperative NPE itself predicts recurrent hyperparathyroidism.

As a retrospective analysis, one major limitation to this study is the lack of complete data that would offer other possible causes of elevated PTH levels at each time point for each patient. Such causes might have included consumption of bisphosphonates, or vitamin D insufficiency. Another important limitation of this series is the uncertainty concerning the PTH and calcium variations that occurred between biochemical measurements in these postoperative patients over this long-term period. Another consideration, although it is unlikely to happen repeatedly, is that PTH is an intermittently secreted hormone, where some patients may have had their blood drawn during a transient spike in PTH secretion.

In conclusion, NPE can occur after successful parathyroidectomy for SPHPT, but this biochemical presentation does not in itself predict recurrent hyperparathyroidism. Postoperative NPE may be a dynamic, reversible, and transient clinical entity. As demonstrated by this study over a 10-year period, postoperative PTH levels may vary, and factors such as physiologic variation, renal and vitamin D insufficiency may be underlying causes of PTH elevation above the normal reference range. No postoperative patients with 1 or 2 consecutive PTH elevations over a long-term period ever develop recurrent disease. Nevertheless, patients with postoperative NPE should be monitored and an attempt made to correct any obvious potential causes of PTH elevation.

REFERENCES

DISCUSSION

Dr Eric Nordenstrom (Lund, Sweden): I am very happy that you have conducted this study. We did the same a couple of years ago, and I’m just wondering, have you done a multivariate analysis to predict which patients have fluctuation or elevated PTH levels?

Second, I know you have a lot of sun in Miami, more than we have in Sweden, but did you see any seasonal variation in these PTH levels? Was there a sun variation together with vitamin D?

Dr Melanie Goldfarb (Miami, FL): I’ll answer your second question first. I looked at your paper a lot while we were planning this paper. We did not look at seasonal variation for PTH. In terms of vitamin D, in Miami, we have only started collecting vitamin D levels routinely in the past 3 to 4 years. And while we did see some patients who had low vitamin D levels at a time when they had elevated PTH in the postoperative period, our data are not really complete enough to draw any definitive conclusions from them.

In answer to your first question, which was about a multivariate analysis, we did perform a multivariate analysis, looking for predictors of disease, similar to a few other papers by members in this room, which will be presented in our paper. But basically, the only thing we found on multivariate analysis that was predictive was male gender, and I’m not really sure how much clinical significance that has. But we did look at it.

Dr Janice Pasieka (Calgary, AB): Clearly, the vitamin D level is what we need to sort of hear.

My question is this: You have now shown us a group of patients, 42, who have the diagnosis of normocalcemic hyperparathyroidism. I am wondering if any of your preoperative patients had that diagnosis, and was there a difference? This a new phenomenon that’s coming into vogue.
Dr Melanie Goldfarb (Miami, FL): In this group of patients, again with the early using of IPM, only patients with both elevated calcium and elevated PTH were operated on. Obviously, since that time, as you said, the normocalcemic hyperparathyroidism has become a new phenomenon. As we go forward, we will have long-term data about those patients. But in this study, there were none of those patients.

Dr Martha A. Zeiger (Baltimore, MD): A question for you in follow-up to Dr. Pasieka’s question. Postoperatively there’s a difference between high-normal calcium and elevated PTH and normocalcemia that’s a low-normal calcium and high PTH. I wondered if you looked at the patients who had high-normal calcium and high PTH, and what the recurrence rate was in that group, because they would be likely to be patients who had persistent hyperparathyroidism.

Dr Melanie Goldfarb (Miami, FL): To try to standardize all our results, we chose a calcium level of 10.2 as our cutoff, so that the high-normal group that I am guessing would you define as 10.3 to 10.6 or 10.7, we defined as elevated calcium. So, all of our patients with normocalcemia and PTH elevation had calcium levels of 10.2 or lower. And there were no patients who had that high-normal calcium level.

Dr Christopher R. McHenry (Cleveland, OH): My question, first of all, is this: In the past, we have thought that patients with more severe hyperparathyroidism are more likely to develop postoperative PTH elevation with normal calcium levels. In your study, you demonstrated that these patients had higher preoperative PTH levels, if I am not mistaken. Did you look at other factors, for instance, that may predict severity of hyperparathyroidism, meaning their bone mineral density or alkaline phosphatase levels or the weight of the excised parathyroid gland?

My second question is this: When you looked at your total group, what percentage of your patients with normocalcemic levels and PTH elevation actually normalized their PTH levels?

Finally, although your recurrence rates were not statistically different, you had small numbers. Could this be just a function of small numbers in each of your groups?

Dr Melanie Goldfarb (Miami, FL): The last question, about recurrence rate: Yes, we did have a small number; but it was more than 96 patients, and there was no statistical significance. It wasn’t trending toward it. So, these are our data; that’s how we’re presenting them.

In terms of your first question, predictors of PTH elevation. As I mentioned before, we did do both a univariate and a multivariate analysis, and they are in our paper. It was a lot of stuff to present today. We did see, on univariate analysis, that a higher preoperative PTH level was predictive of having 1 instance of normocalcemic PTH elevation, but it did not pan out on multivariate analysis. We did not look at bone mineral density or alkaline phosphatase. It’s just not data that we generally can collect.

Dr Christopher R. McHenry (Cleveland, OH): What percentage of the total number of patients had normocalcemic PTH elevation or went on to normalize their PTH levels?

Dr Melanie Goldfarb (Miami, FL): We didn’t actually look at the data that way. That’s, I think, how both yourself and a few other people in this room have done similar studies, in which we look at PTH elevation early on and whether it normalizes.

We actually, for this study, didn’t look at PTH elevation within the first 6 months. That was 1 of the factors that we looked at to see if it predicted long term, and it didn’t. But we did not look at whether it normalized. Our definition was: Did the patient have one instance of PTH elevation?

Dr Sally E. Carty (Pittsburgh, PA): This is a great example of the meticulous outcomes research that endocrine surgeons are so notable for. It’s a very honest and comprehensive study. The last sentence of your abstract says, “Nevertheless, patients with postoperative NCHPT should be monitored.” Do you think that’s cost-effective?

Dr Melanie Goldfarb (Miami, FL): I think there are 2 parts to the answer to that question. One, as you said, clinical research is important. And it’s important to try to figure out all these answers that we don’t know. So, in terms of a clinical research standpoint: yes, it is cost-effective. The need to check PTH levels every 6 months for the rest of patients’ lives? No.

But we do advocate checking the levels. We do it yearly at Miami. I know other centers have different protocols. But I do think its important. As we have shown, we don’t quite know why these PTH elevations are occurring; but there are suggestions in some papers by AAES members that there are correctable causes of PTH elevation. And if we can find those patients and identify them and correct those levels, that may be helpful.

Dr Collin J. Weber (Atlanta, GA): We, too, see some patients whose postoperative PTH values remain elevated while their calcium levels normalize. And I think most of us in the room have seen this. Rob Udelsman, I think, is the most recent publisher of data showing that it’s basically vitamin D deficiency for most of these patients.

And the other elephant in the room is the concern about a missed second lesion, but the majority of them will be corrected with vitamin D. Many times, for our patients, it takes a long time. It takes months and months of vitamin D replacement.

Dr Herb Chen (Madison, WI): Just looking at your data, this seems to be a very highly selected group of patients, about 35 patients a year. And I know that Miami does many more parathyroidectomies than that. I was wondering, in the remaining patients: Who are probably more likely to have multigland disease? Who are not focused parathyroidectomies? Is elevated PTH a risk factor for recurrence? Because I would think it would be in the patients that you did not study.

Dr Melanie Goldfarb (Miami, FL): The initial group of patients that had the IPM at Miami had sporadic...
primary hyperparathyroidism and had a definite diagnosis of hyperparathyroidism. I guess if you want to call that selective, sure, it’s selective. But in the years to come, as you said, and as I’ve mentioned in my responses to some other questions, more patients are operated on with, let’s say, normocalcemic hyperparathyroidism or other things.

I don’t know and I can’t quite answer that question, but these are patients who had primary hyperparathyroidism. And using IPM in order to get our definition of multigland disease and of recurrent disease, I think that if you use the IPM criteria appropriately and you follow your patients, that this is what you are going to get.

**Dr James Norman** (Tampa, FL): Two very brief comments. I would suggest to all of you that taking a calcium level of 10.1 or 10.2 as normal is not correct. I think that we have plenty of data showing that adults live with calcium levels in the 9s, not the 10s. And similar to what Dr. Zeiger said a few minutes ago, you get patients who are living at 10.1, 10.0, 10.2, with elevated PTH levels—those people have a parathyroid tumor in the neck. If they are in the 9s, I’ll buy it, that’s persistent.

The second comment is, contrary to what Dr. Weber has just stated, vitamin D is a symptom, not a cause. Giving vitamin D to these patients will not affect their PTH levels postop. If you want to affect their PTH levels, give them calcium. They’re total body calcium–deficient; give them calcium. Vitamin D levels are symptoms, not causes.