Creation of a "Wisconsin Index" Nomogram to Predict the Likelihood of Additional Hyperfunctioning Parathyroid Glands During Parathyroidectomy

Haggi Mazeh, MD, Herbert Chen, MD, FACS, Glen Leverson, PhD, and Rebecca S. Sippel, MD, FACS

Objective: The aim of our study was to create a preoperative "index" that could predict the likelihood of additional hyperfunctioning parathyroid glands and let the surgeon determine whether to wait for the intraoperative parathyroid hormone (ioPTH) or to explore further.

Background: During parathyroidectomy for primary hyperparathyroidism (PHPT), discovering a minimally "enlarged" parathyroid gland creates a dilemma for the surgeon regarding the need for further exploration. Although ioPTH testing can potentially solve this problem after a 20- to 30-minute period, several surgeons recognize that further operative exploration may be more effective.

Methods: We analyzed a prospective database of 1235 consecutive patients who underwent parathyroidectomy for PHPT at our institution between March 2001 and August 2010. The *Wisconsin Index* (*WIN*) was defined as the multiplication of preoperative serum calcium by preoperative parathyroid hormone (PTH). Patients were divided into 3 WIN categories: low (<800), medium (801–1600), and high (>1600). The utility of the WIN was then validated on a subsequent cohort of 216 patients.

Results: The median age of the patients was 61 years (range, 10–91), and 77% of the patients were female. The mean preoperative calcium and PTH levels were 11.0 ± 0 mg/dL and 127 ± 3 pg/mL, respectively. The mean WIN for the entire cohort was 1461 ± 38 and highly correlated with gland weight ($P < 0.000001$). A single adenoma was identified in 1000 patients (81%), double adenoma in 100 patients (8%), and hyperplasia in 135 patients (11%). The mean gland weights for the 3 WIN catagories were low = 370 ± 33 mg, medium = 532 ± 39 mg, and high = 985 ± 28 mg, respectively ($P < 0.000001$). A WIN nomogram, consisting of the combination of WIN and parathyroid gland weight, accurately predicted the likelihood of additional hyperfunctioning parathyroid glands. For example, for a WIN of less than 800 and a gland weight of 500 mg, there is a 9% chance for additional hyperfunctioning parathyroid glands based on the WIN nomogram. In contrast, for the same gland weight, if the WIN is 801 to 1600, these chances increase to 28%, and if the WIN is more than 1600, the chance of multigland disease is 61%. Comparison between the predicted chances for another gland with the actual chance in the validation cohort identified an R^2 value of 0.96.

Conclusions: The WIN nomogram predicts the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. This simple intraoperative tool may be used to guide the decision of whether to wait for ioPTH results or to proceed with further neck exploration.

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Over the past 2 decades, parathyroid surgery for primary hyperparathyroidism (PHPT) has evolved tremendously. The traditional bilateral neck exploration has been commonly replaced by a minimally invasive, localization guided parathyroidectomy.[1,2] The minimally invasive approach offers multiple advantages over a bilateral exploration, including a smaller scar, shorter operative time, fewer complications, and similar cure rates.[3–9] The minimally invasive parathyroidectomy relies on accurate preoperative localization and intraoperative adjuncts that assist the surgeon with decision-making. The most important and widely used adjunct is the intraoperative parathyroid hormone (ioPTH) testing. Dr George Irvin at the University of Miami measured ioPTH levels and confirmed removal of hypersecreting parathyroid glands for the first time in 1990.[10–12] The ability to confirm complete removal of all hypersecreting glands and predict operative success has minimized operative time, diminished the need for bilateral neck exploration, and improved cure rates.

Despite all the different utilities of the ioPTH, the main role of this adjunct is to assist the surgeon with decision-making while performing minimally invasive parathyroidectomy. Today, most protocols require establishing at least a 50% drop in parathyroid hormone (PTH) levels, as compared with preoperative or preincision values, to confirm cure and alleviate the need for further neck exploration.[13–18] This test often takes up to 30 minutes, which prolongs the operating time, especially in cases in which the level does not fall. Many surgeons get frustrated because they could have already performed a bilateral exploration during the time it took to get the PTH level back down. Operating room time is expensive, and surgeons want to optimize the use of their Operating room (OR) time by minimizing the number of patients in which the PTH level does not fall, requiring reopening of the neck with a significant increase in operative time.

The finding of a very small parathyroid gland or a very large parathyroid adenoma results in straightforward decision-making. A small, normal appearing parathyroid gland requires further neck exploration. In contrast, the finding of a very large parathyroid adenoma that is consistent with preoperative localization studies allows the surgeon to halt further exploration and await PTH results, with a small likelihood of needing to reopen. In certain cases, discovering a minimally "enlarged" parathyroid gland creates a dilemma for the surgeon regarding the need for further exploration. Although ioPTH can potentially solve this problem after a 20- to 30-minute period, several surgeons recognize that further operative exploration is more time efficient. It is in these cases that preoperative laboratory values may assist the surgeon to make an educated decision regarding the likelihood of additional hyperfunctioning glands. The aim of our study was to create a preoperative "index" that could predict the likelihood of additional hyperfunctioning parathyroid glands and let the surgeon determine whether to wait for the ioPTH or to explore further for additional abnormal parathyroid glands.

METHODS

A review of a prospective database was performed on all patients with hyperparathyroidism, using the University of Wisconsin Parathyroid Surgery Database. Data on demographics, surgical history, smoking history, location of parathyroid adenoma, and other

From the Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison.

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Reprints: Rebecca S. Sippel, MD, FACS, Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, K3/704 Clinical Science Center, 600 Highland Ave, Madison, WI 53792. E-mail: sippel@surgery.wisc.edu.

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histological and pathological features of the adenoma were collected prospectively. Laboratory studies, including serum calcium and PTH levels, were recorded before and after the operation. All parathyroidectomies were performed by 1 of 2 endocrine surgeons in the Department of Surgery at the University of Wisconsin.

From March 2001 to August 2010, a total of 1428 patients with hyperparathyroidism underwent parathyroidectomy at the University of Wisconsin. We included all patients with PHPT (N = 1309) regardless of imaging findings. Patients with secondary or tertiary hyperparathyroidism were excluded. The patients were divided into 2 groups on the basis of their surgical findings—patients with a single adenoma versus patients with multigland disease (double adenomas or multigland hyperplasia). The gland weight was documented for each patient. For patients with multigland disease, the largest gland weight was considered for all calculations. Surgery was terminated after a 50% fall in ioPTH levels was achieved, and a cure was defined as eucalcemia at 6 months after surgery.

The *Wisconsin Index* (*WIN*) was defined as the multiplication of preoperative serum calcium by preoperative PTH levels. Correlation studies were performed between the gland weight and the WIN. Patients were divided into 3 WIN categories: low (<800), medium (801–1600), and high (>1600). A WIN nomogram was created, consisting of the combination of WIN and parathyroid gland weight. The likelihood of additional hyperfunctioning parathyroid glands was calculated for any given gland weight according to the 3 WIN categories. Because not all patients had a bilateral exploration, we regarded a 50% drop in the ioPTH level as the gold standard for confirmation that no other additional hyperfunctioning glands were present. If the ioPTH levels did not fall by more than 50%, we took it to mean that additional hyperfunctioning glands were present.

To identify differences between the single and multigland groups, univariate analyses with the χ^2 or *t* test were used. Statistical calculations were completed using statistical software SPSS Version 11.5 (SPSS, Inc, Chicago, IL) and a *P* value of less than 0.05 was considered to represent statistical significance for all comparisons.

VALIDATION

After the establishment of the WIN, a cohort of 216 patients who underwent parathyroidectomy between September 2010 and April 2011 was included as a validation cohort. Positive preoperative imaging, extent of surgery, and a finding of single versus multigland disease were documented. As with the study cohort, surgery was terminated after a 50% fall in ioPTH levels was achieved and a cure was defined as eucalcemia at 6 months after surgery. These patients were not operated on using the WIN but were retrospectively evaluated for validation, had the WIN been used. The actual chance for another gland in the validation cohort was compared with the predicted one as determined by the study cohort. Pearson correlation coefficients were used to describe the association between the predicted and actual chance for another abnormal gland.

RESULTS

Of the 1428 patients who underwent parathyroidectomy during the study period, 1309 patients were operated on for PHPT. Sixty-seven patients were excluded because of missing pertinent data, such as gland weight due to cryopreservation (n = 47), or missing laboratory values (n = 20). Seven patients had parathyroid cancer and were also excluded from the comparison analysis. Of the remaining 1235 patients, 1000 patients (81%) were found to have a single adenoma, 100 patients (8%) had a double adenoma, and 135 patients (11%) had 4-gland hyperplasia. The later 2 groups were combined as the multigland disease group and compared with the single gland group (Fig. 1).

At our institution, we routinely perform preoperative imaging; however, we do not consider negative localization studies as a contraindication for surgery, and 203 patients (16%) had negative preoperative imaging of any modality. The rate of single adenomas identified in this group was significantly smaller than the entire cohort (64% vs 80%, $P = 0.03$); nevertheless, this did not translate to significant differences in cure or recurrence rates (97% vs 97%, $P = 0.89$; and 2% vs 3%; $P = 0.74$, respectively).

Minimally invasive parathyroidectomy was performed in 920 patients (74%), and bilateral exploration was required in 315 patients (26%). Patients in the single gland group were older (61 ± 0.4 vs 58 ± 0.3 years; $P = 0.02$) with comparable gender distribution (77% vs 79% females; $P = 0.5$). Cure and recurrence rates were also similar (98% vs 95%, $P = 0.28$; 2% vs 4%, $P = 0.33$).

For the entire cohort, the median age was 61 ± 0 years and 77% were females. The mean preoperative calcium and PTH levels were 11.0 ± 0 mg/dL and 127 ± 3 pg/mL, respectively. The mean WIN was 1461 ± 38, and the mean gland weight was 769 ± 28 mg. Preoperative calcium levels were categorized as normal (<10.2 mg/dL), mildly elevated, and high (>11.2 mg/dL). Figure 2 demonstrates the correlation of calcium levels with gland weight ($P = 0.003$). Preoperative PTH levels were categorized as normal (<72 pg/mL) and 2, 3, and more than 3 times the normal range. Figure 3 demonstrates the correlation of PTH levels with gland weight ($P = 0.001$). The WIN was categorized as low (<800), medium (800–1600), and high (>1600).

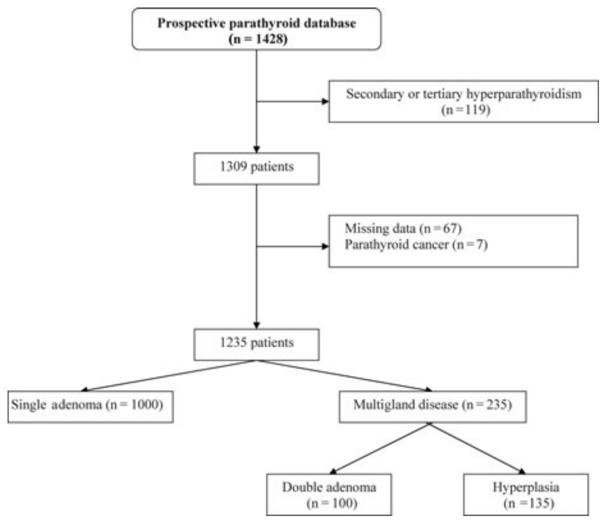

FIGURE 1. Study flow chart.

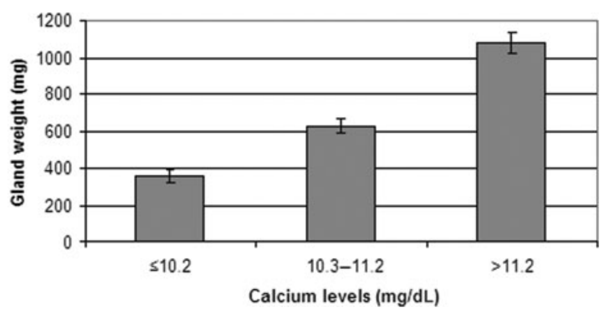

FIGURE 2. Correlation between calcium levels and gland weight ($P = 0.003$).

This resulted in highly significant correlation to gland weight ($P < 0.000001$). Patients with multigland disease had significantly lower WIN levels (1138 ± 59 vs 1481 ± 37; $P < 0.000001$) and this correlated to a significantly lower weight gland (393 ± 27 vs 768 ± 32 mg; $P < 0.00001$) (Fig. 4).

A WIN nomogram, consisting of the combination of WIN and parathyroid gland weight, was created. The nomogram accurately predicted the likelihood of additional hyperfunctioning parathyroid glands for each WIN category. The chances of finding another enlarged gland for a WIN of less than 800 and a gland weight of 100 to 1000 mg ranged from 83% to 0%, respectively. The chances of finding another enlarged gland for a WIN of 800 to 1600 and a gland weight of 100 to 1000 mg was 94% to 2%, respectively. Finally, the chances of finding another enlarged gland for a WIN of more than 1600 and a gland weight of 100 to 1000 mg was 97% to 19%, respectively. This is graphically presented in Figure 5.

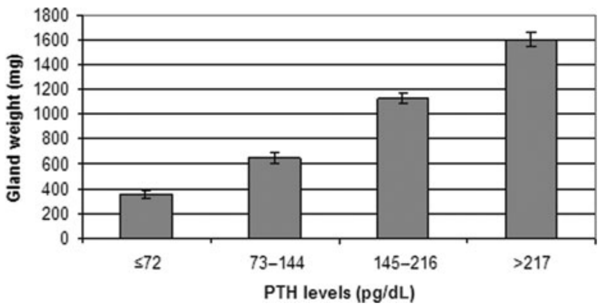

FIGURE 3. Correlation between PTH levels and gland weight ($P = 0.001$).

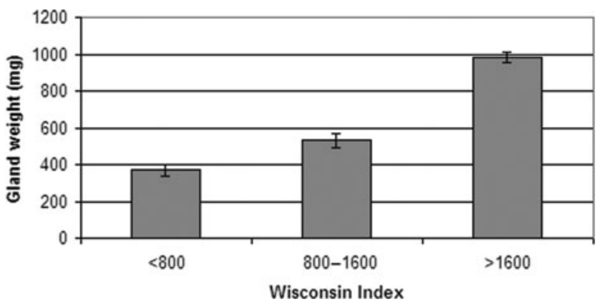

FIGURE 4. Correlation between WIN and gland weight ($P < 0.000001$).

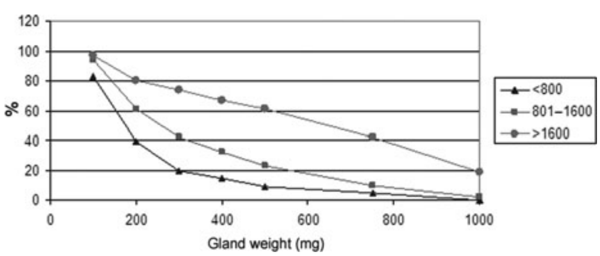

FIGURE 5. Nomogram of the chances for another enlarged parathyroid gland in relation to the index gland found and the different WIN categories.

To validate our findings, we retrospectively examined an additional 216 patients and used them as a validation cohort. A positive preoperative technetium-99m sestamibi scan was identified in 146 patients (68%), and a positive ultrasound result was documented in 110 patients (51%). Single adenoma was identified in 151 patients (70%), and multigland disease in 65 patients (30%). Minimally invasive parathyroidectomy was performed in 135 patients (63%) and bilateral neck exploration in 81 patients (37%). Pearson correlation coefficient identified an association of $R^2 = 0.96$ between the predicted and actual chances for finding another hyperfunctioning gland. An R^2 association of 0.96 was identified for a WIN of less than 800, 0.98 for a WIN of 800 to 1600, and 0.90 for a WIN of more than 1600.

DISCUSSION

Minimally invasive parathyroidectomy is based on preoperative localization and intraoperative adjuncts that all contribute to the confidence level of the surgeon in avoiding the need for a bilateral exploration. Obviously, when a large parathyroid gland is found at a location that corresponds with the preoperative imaging studies, the level of confidence increases. The ioPTH level serves as an important adjunct to establish a cure, but results may take up to 30 minutes. On the basis of our results, we suggest another intraoperative adjunct that may assist in the decision process.

In this study, we identified a strong correlation between preoperative calcium and PTH levels and gland weight ($P = 0.003$ and $P = 0.001$, respectively). We chose to enhance the correlation by multiplying the 2 and creating the WIN. This resulted in a very high correlation between the WIN and the gland weight ($P < 0.000001$). When we compared the single adenoma group with the multigland group, significantly higher WIN levels ($P < 0.000001$) and corresponding higher gland weight ($P < 0.00001$) were identified. The nomogram created (Fig. 5) identifies the risk for another hypersecreting parathyroid gland for each WIN category. We further validated the nomogram by comparing the predictive chance for another gland with the actual chance in a cohort of 216 patients and found that our nomogram was accurate at predicting the chance of multigland disease.

Earlier studies based on limited numbers of patients with mixed causes of disease reported a direct correlation between serum Ca^{2+} and gland weight. Some have shown a variable, and clinically unreliable, relation between abnormal gland size or weight and preoperative Ca^{2+}.[19–21] In 2002, Mozes et al[22] studied the predictive values of preoperative laboratory findings in 166 patients with PHPT. They concluded that laboratory studies do not differentiate adenoma from hyperplasia, nor do they pinpoint the size of abnormal glands with moderate-range PTH values. It was only for the extreme values of PTH that gland weight could potentially affect decision-making. Preoperative calcium levels showed only a modest correlation with the gland weight. Correlation between preoperative calcium levels, PTH levels, and gland weight has also been established by Moretz et al[23] on a small cohort of 30 patients.

In 2006, Kebebew et al[24] developed a predicting scoring model to distinguish between single gland and multigland disease. It was based on preoperative calcium levels and PTH levels and ultrasound and technetium -99m sestamibi scan results. This predicting model was highly accurate for patients with very elevated preoperative laboratory levels and concordant imaging studies. Nevertheless, the model was not as accurate for patients with milder disease or poor localization and did not include gland weight in the calculations.

This study differs from the previous studies in several aspects. First, this study includes a substantially higher number of patients (n = 1235). Second, and similar to the findings of Moretz et al,[23] we did identify a highly significant correlation of both calcium levels and

PTH levels with the gland weight. Finally, we used this correlation to create the WIN that capitalizes on this correlation to assist with intraoperative decision-making. The nomogram reflects this correlation and provides the likelihood of another hyperfunctioning gland for every gland weight identified on initial exploration. We intentionally wanted the nomogram to be simple. We did not include vitamin D levels or preoperative imaging results, as this would complicate the nomogram and rely on parameters that are not always available (vitamin D) or that are subjective to interpretation and not reproducible (imaging). We wanted to emphasize that the nomogram should be used by surgeons debating whether to further explore the neck or to await ioPTH results.

The nomogram provides a statistically based chance for another hyperfunctioning gland. For example, a probability of 80% on the nomogram for another functioning gland suggests that there is a 20% risk of negative contralateral exploration. It is not our intention to determine a cutoff for which we would recommend further exploration, as we believe that this decision should be tailored to the surgeon's level of confidence in each patient. It may be of specific use to surgeons who perform minimally invasive parathyroidectomy where ioPTH is not available. The nomogram does not predict a cure; for that, we have to rely on ioPTH testing. What the nomogram does is give you an estimate of the likelihood that there is another hyperfunctioning gland present so that you can decide if it is worthwhile to close and wait for the PTH levels or to just proceed immediately to a bilateral exploration. This nomogram can help maximize efficiency in the operating room and help the surgeon to minimize the number of cases in which the PTH level does not fall and the patient ends up needing further exploration.

This is a retrospective observational study, and as such, it has several inherent disadvantages including selection bias. We have tried to overcome and minimize this bias by including all patients with PHPT. As expected, most of the patients were found to have a single adenoma (81%) and thus the number of patients with multigland is smaller; nevertheless, our results were highly statistically significant. We also attempted to overcome this selection bias by validating our results with an additional cohort of 216 patients who were not included in the creation of the nomogram. The optimal validation would be a prospective one at a different institution; however, the statistical nature of the nomogram requires a relatively large cohort. We also acknowledge that the rate of multigland disease was higher in the validation group than in the study cohort, and we are not confident of the etiology of this difference. A larger validation group would likely be more evenly distributed. We did not correct the calcium levels for patients with low vitamin D, and we did not correct the WIN for patients with low albumin levels. Doing so would have complicated the calculation of what is intended to be a simple index and would probably only have affected a small number of patients.

We conclude that preoperative laboratory values, and more specifically the WIN, in relation to the gland weight may serve as an important adjunct to minimally invasive parathyroidectomy. The WIN nomogram predicts the likelihood of additional hyperpfunctioning parathyroid glands during parathyroidectomy. This simple intraoperative tool may be used to guide the decision of whether to wait for ioPTH results or to proceed with further neck exploration. This can be translated to an increased operating room efficiency and the optimization of the use of PTH testing during minimally invasive parathyroidectomy.

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