

## ONLINE FIRST

# Parathyroidectomy, Elevated Depression Scores, and Suicidal Ideation in Patients With Primary Hyperparathyroidism

## Results of a Prospective Multicenter Study

Theresia Weber, MD; Julia Eberle, MD; Ursula Messelhäuser, MD; Leif Schiffmann, MD; Christoph Nies, MD; Jochen Schabram, MD; Andreas Zielke, MD; Katharina Holzer, MD; Edit Rottler; Doris Henne-Bruns, MD; Monika Keller, MD; Jörn von Wietersheim, MD

**Objective:** To assess anxiety and depression symptoms, suicidal ideation, and health-related quality of life (HRQOL) in a large series of consecutive patients with primary hyperparathyroidism (pHPT) before and after parathyroidectomy.

**Design:** This prospective multicenter study investigated preoperative and postoperative depression, anxiety, suicidal ideation, and HRQOL in patients with pHPT and compared these variables with a control group with nontoxic thyroid nodules.

**Patients:** The study included 194 patients with pHPT and 186 control subjects.

**Main Outcome Measures:** Depression was evaluated with the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire–9, which also assessed suicidal ideation. Anxiety was evaluated with the HADS. Health-related quality of life was measured with the 36-Item Short Form survey.

**Results:** Parathyroidectomy achieved a 98% cure rate. Preoperatively, severe depression (HADS score  $\geq 11$ ) was seen in 20% of the pHPT group and 9% of the control

group. The Patient Health Questionnaire–9 detected moderate to severe depression in 17% of the patients with pHPT and 7% of the control subjects. Patients with pHPT had higher HADS anxiety scores (mean, 7.7) than control subjects ( $P < .01$ ) or the German normative sample ( $P < .001$ ). Compared with control subjects, patients with pHPT had significantly lower 36-Item Short Form survey preoperative physical and mental health summary scores (42.7 vs 49.5 and 41.2 vs 46.8, respectively;  $P = .001$  for both comparisons). At 12 months follow-up, depression and anxiety decreased significantly in patients with pHPT; the prevalence of suicidal ideation was more than halved from the baseline (10.7% vs 22%;  $P = .008$ ). Both physical and mental health scores (45.7 and 47.7, respectively) improved in patients with pHPT ( $P < .001$  each) but not in control subjects.

**Conclusions:** Depression, anxiety, and decreased HRQOL appear to be related to pHPT. Successful parathyroidectomy seems to reduce psychopathologic symptoms and improve HRQOL in this setting.

*JAMA Surg.* 2013;148(2):109-115. Published online October 15, 2012. doi:10.1001/2013.jamasurg.316

**P**RIMARY HYPERPARATHYROIDISM (pHPT) is diagnosed by elevated serum calcium and parathyroid hormone (PTH) levels. In about 90% of cases, it is caused by a single parathyroid adenoma and less often by parathyroid hyperplasia due to multiglandular disease. Parathyroid adenoma induces increased secretion of PTH, leading to elevated serum calcium levels. Hypercalcemia may cause kidney stones, nephrocalcinosis, arteriosclerosis and hypertension, cardiovascular disease, gastrointestinal symptoms, and osteoporosis. In 1987, Palmer et al<sup>1</sup> found shorter survival time in 172

persons with mild to moderate hypercalcemia than in a normocalcemic control group. The incidence of pHPT is about 21 cases per 100 000 person-years.<sup>2</sup>

### See Invited Critique at end of article

Currently, pHPT often is diagnosed in asymptomatic patients as a result of routine calcium measurement during laboratory examinations. However, the term asymptomatic hyperparathyroidism is controversial because clinical symptoms of hypercalcemia are not very specific.<sup>3</sup>

Author Affiliations are listed at the end of this article.

Symptoms of severe depression caused by pHPT were first reported by Reinfrank<sup>4</sup> in an anecdotal publication in 1961. The wife of a 38-year-old man noted a “marked and rapid change in his personality.” The patient “became withdrawn and seclusive, and appeared sad and depressed. He lost interest in his family, friends, and work. Despite 12 to 14 hours of sleep a night, he was fatigued and listless. Frequent crying spells occurred, and he voiced recurrent thoughts of suicide.”

Since the 1990s, an increasing number of studies<sup>5-11</sup> have addressed psychologic or neurocognitive sequelae of pHPT. However, to our knowledge, only a few studies have used validated psychologic instruments and compared their study population with a control group. Despite this recognition in the literature, symptoms such as depression, anxiety, mood swings, fatigue, cognitive dysfunctions, or lack of concentration are often not evaluated during routine clinical practice.

Performed mainly via a unilateral approach to remove parathyroid adenoma, surgery is currently the only cure for pHPT. Intriguingly, the case reported by Reinfrank<sup>4</sup> suggested that surgery could alleviate depressive symptoms of pHPT; only 1 month after a 1-cm parathyroid adenoma was removed from the left side of the neck and before submission to electroshock therapy recommended in a psychiatric consultation, his patient “felt well, was mentally alert, and had regained his interest in his family and friends.”

Spurred by the loss of an 83-year-old female patient with pHPT to suicide the day before surgery, we conducted this prospective multicenter study to assess with validated instruments anxiety and depression symptoms, suicidal ideation, and health-related quality of life (HRQOL) in a large series of consecutive patients with pHPT before and after parathyroidectomy. We also compared these results with those of a control group undergoing surgical procedures for benign thyroid nodules and of the normative German population. In so doing, we sought to characterize the magnitude and impact of psychologic symptoms in patients with pHPT as well as the effect of parathyroidectomy on these symptoms and HRQOL.

## METHODS

### STUDY POPULATION AND ETHICS

All adults with pHPT referred for parathyroidectomy to 9 participating German hospitals between June 2006 and April 2010 were asked to participate in the study. Diagnosis of pHPT was established by elevated serum calcium and PTH levels. Blood tests for thyroid hormones (free triiodothyronine, free thyroxine, and thyroid-stimulating hormone) and serum creatinine were performed to exclude hyperthyroidism and renal hyperparathyroidism. A control group undergoing surgery for benign euthyroid nodular goiter at the same institutions was also recruited. For both groups, exclusion criteria were intraoperative or postoperative diagnosis of thyroid cancer, severe psychiatric or neurocognitive disorders, and inability to understand the German language. The study protocol was approved by the ethics committees of the Universities of Heidelberg, Ulm, and Frankfurt, Germany. All participants gave written informed consent.

## SURGERY, FOLLOW-UP, AND STUDY ASSESSMENTS

All patients underwent surgery under general anesthesia. Of the patients with pHPT, 68% had a unilateral focused approach; 60% of them underwent minimally invasive parathyroidectomy. In 32%, a bilateral neck exploration was performed. The control subjects with nontoxic goiter underwent (near) total thyroidectomy (57%) or lobectomy (43%).

Postoperative follow-up lasted 12 months. Clinical data collection included demographic information, clinical symptoms, psychiatric medication, surgical techniques, histopathologic reports, and postoperative results. Patients and control subjects underwent study assessments the day before surgery and at 2 weeks, 6 months, and 12 months, postoperatively. Because the study was anonymized, patients were not referred to psychiatrists for clinical or medical treatment based on the responses to the used psychologic instruments, although 1 female patient with pHPT who spoke of suicide on postoperative day 1 was admitted to the psychiatric ward.

For all study assessments, patients completed the instruments without assistance from health care professionals. For each postoperative assessment, study instruments were mailed to participants; if no answer was received after 2 weeks, the questionnaires were resent with a reminder 1 time.

### STUDY INSTRUMENTS

The 14-item Hospital Anxiety and Depression Scale (HADS) screens for clinically relevant anxiety and depression in patients attending medical clinics.<sup>12-14</sup> For each condition, there is a scale containing 7 items scored in a 4-point range from 0 to 3, with higher scores indicating more symptoms. The defined cutoffs were 8 or greater for mild to moderate symptoms and 11 or greater for severe symptoms of anxiety or depression. Advantages of the HADS include its reliability and validity in assessing medical and psychiatric patients, its ability to discriminate among groups with different intensities of depression and anxiety, and its ability to allow longitudinal assessments with repeated testing.<sup>7</sup> Another important aspect of the HADS is its ability to reflect any changes in the criterion variable, which occur during psychologic or, as in our study, surgical intervention (so-called treatment validation). In medical patients, HADS scores seem to be more normally distributed than, for example, those of the State-Trait Anxiety Inventory or the Beck Depression Inventory.<sup>13</sup>

The Patient Health Questionnaire-9 (PHQ-9) evaluates depressive symptoms via 9 items, each scorable from 0 (not at all) to 3 (nearly every day). Therefore, the total score ranges from 0 to 27, with higher values indicating more depressive symptoms. The advantages of the PHQ-9 are its brevity to identify and measure depression severity and its sensitivity to change over time, precisely measuring improving or worsening depression.<sup>15,16</sup> Item 9 of the PHQ-9 assesses suicidal ideation, querying about “thoughts that you would be better off dead or hurting yourself in some way.”

The HRQOL 36-Item Short Form (SF-36) survey<sup>17,18</sup> determines 8 subscales of health status, 4 of each pertaining to physical and mental health. The physical component summary scale assesses physical function, physical role limitations, bodily pain, and general health perception. The mental component summary scale describes vitality, social function, emotional role limitations, and mental health. The 36-Item Short Form scores were computed with the test manual software and transformed into *z* scores and *t* scores, with a population mean of 50 and a standard deviation of 10.

**Table. Demographics and Clinical Characteristics of Patients**

Characteristic	pHPT Group (n = 194)	Control Group, Nodular Goiter (n = 186)
Age, mean (range), y	58.5 (20-89)	51.1 (21-84)
Sex, %		
Female	79	72
Male	21	28
Osteoporosis, %	28.9	1.1
Nephrolithiasis/nephrocalcinosis, %	19.1	1.6
Antipsychotic drugs, %	6.7	2.7
Mean serum calcium, mg/dL (mmol/L)	11.36 (2.84)	9.32 (2.33)
Operation time, mean (range), min	94 (20-330) <sup>a</sup>	114 (30-246)

Abbreviation: pHPT, primary hyperparathyroidism.

<sup>a</sup>Including intraoperative parathyroid hormone measurement.

## STATISTICAL ANALYSIS

Because the dependent variables did not follow a normal distribution, nonparametric statistical methods were used. The Mann-Whitney *U* test was applied to compare 2 independent groups and the Wilcoxon test to compare 2 dependent groups. Correlations were computed with the Pearson correlation coefficient. SPSS software version 18 (SPSS Inc) was used for the analyses.

## RESULTS

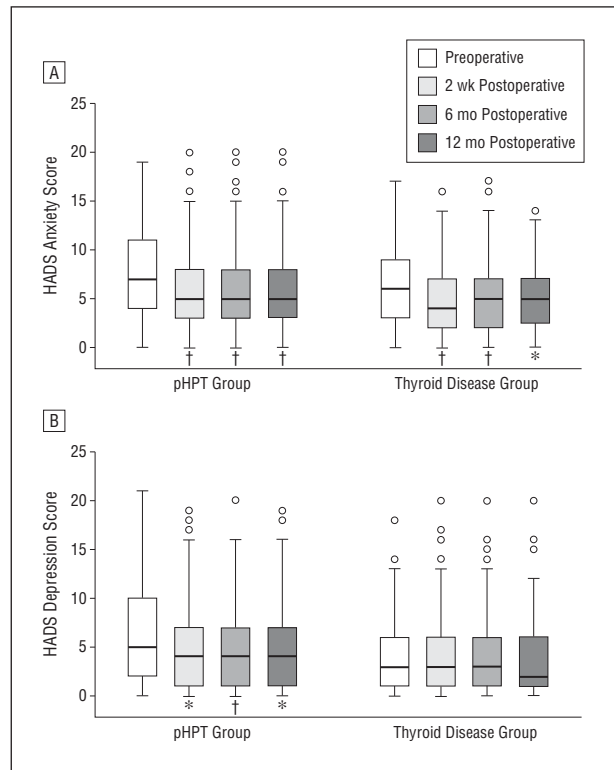
In total, 400 consenting patients were enrolled into the pHPT and nontoxic thyroid disease (control) groups. Six patients with pHPT and 14 control subjects were excluded because of intraoperative or postoperative diagnosis of thyroid cancer or metastases in the thyroid gland. The mean (SD) age was 58.5 (14.4) years for the patients with pHPT and 51.1 (14.6) years for control subjects (**Table**). Only 58% of the patients with pHPT met the National Institutes of Health 1990 Consensus Conference criteria for parathyroidectomy.<sup>18</sup>

The cure rate for pHPT was 98%, as assessed by postoperative serum calcium and PTH normalization. High study instrument completion rates of 78% for the pHPT group and 77% for the control group were noted at 12 months follow-up.

## HADS

Preoperatively, patients with pHPT showed elevated mean HADS anxiety scores (mean [SD], 7.71 [4.64]) compared with the control group (mean [SD], 6.44 [4.31];  $P < .01$ ) and the healthy German population (mean [SD], 5.8 [3.2];  $P < .001$ ).<sup>14</sup> In the pHPT group but not in the control group, women's preoperative anxiety scores exceeded those of men ( $P = .05$ ).

In the pHPT group, mean (SD) postoperative anxiety scores declined steadily to 5.94 (4.25) at 2 weeks, 5.89 (4.14) at 6 months, and 5.61 (4.18) at 12 months ( $P < .001$  for each value vs baseline). In the control group, such scores dropped to 4.86 [3.65] at 2 weeks ( $P < .001$ ) and showed no significant difference at 6 months and 12 months follow-up (**Figure 1A**).



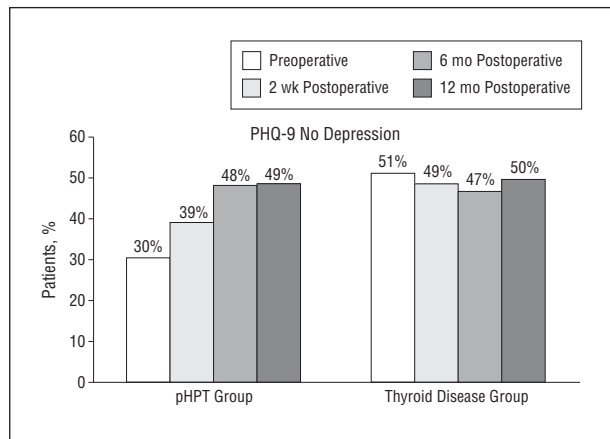
**Figure 1.** Anxiety and depression scale scores. A, Hospital Anxiety and Depression Scale (HADS) scores of preoperative and postoperative symptoms of anxiety among patients with primary hyperparathyroidism (pHPT) and thyroid disease (control group). B, HADS preoperative and postoperative symptoms of depression scores among patients with pHPT and thyroid disease (control group). \*  $P < .01$ ; †  $P < .001$ ; comparisons were made between admission and assessment point (Wilcoxon test).

Preoperatively, 49.0% of patients with pHPT scored higher than the 8 or greater anxiety threshold and 28.4% scored higher than the 11 or greater anxiety threshold. In the control group, 37.1% had anxiety scores of 8 or greater and 18.3% scored 11 or greater.

Preoperatively, mean HADS depression scores were highest in the pHPT group, significantly exceeding those of control subjects and the healthy German population (mean [SD], 6.19 [4.90] vs 4.21 [3.96] vs 3.40 [2.60], respectively;  $P < .001$  for both comparisons). Postoperatively, these scores declined significantly in patients with pHPT to 5.10 [4.49] at 2 weeks ( $P < .01$ ), 4.75 [4.20] at 6 months ( $P < .001$ ), and 4.70 [4.27] at 12 months ( $P < .01$ ). Compared with preoperative scores, mean depression levels remained unchanged among control subjects (Figure 1B).

According to the HADS, preoperatively, 33% of patients with pHPT scored 8 or greater, denoting mild to moderate symptoms, and 19.6% scored 11 or greater, denoting severe symptoms. By contrast, 17.7% of patients with benign goiters scored 8 or greater and only 9.1% scored 11 or greater. At 12 months follow-up, 22.4% of patients with pHPT scored 8 or greater and 12.5% scored 11 or greater in the depression subscale.

In patients with pHPT, serum calcium levels correlated significantly with preoperative depression scores ( $r = 0.17$ ,  $P = .02$ ), while PTH levels showed no significant correlation ( $r = -0.07$ ,  $P = .36$ ). No correlation was seen between both parameters and anxiety.



**Figure 2.** Graph showing the increasing percentage of patients with no depression in the group with primary hyperparathyroidism (pHPT) vs no difference in the group with thyroid disease, according to the Patient Health Questionnaire–9 (PHQ-9) scores.

### PHQ-9

Mean preoperative PHQ-9 depression scores in the pHPT group also significantly exceeded those of the control group (mean [SD], 8.52 [6.13] vs 5.64 [4.68];  $P < .001$ ). In patients with pHPT, mean (SD) postoperative scores dropped steadily to 6.40 [4.82] at 2 weeks, 6.11 [5.04] at 6 months, and 6.05 [4.85] at 12 months follow-up ( $P < .001$  for all 3 values vs baseline). In patients with thyroid diseases, mean PHQ-9 scores remained unchanged from preoperative levels.

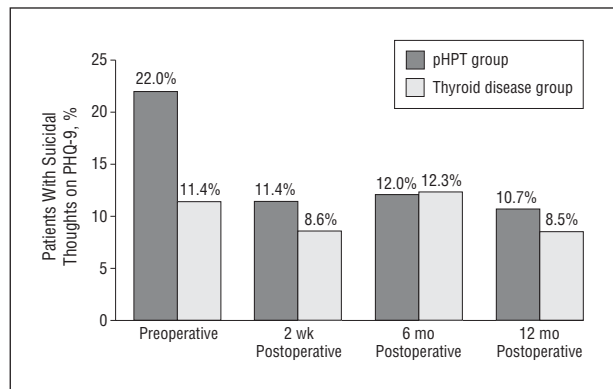
Before surgery, moderately severe or severe depression was observed in 16.7% of the pHPT group vs 6.5% of the control subjects. One year postoperatively, the proportion of patients exhibiting moderate or severe levels of depression declined to 6.6% in the pHPT group and 3.5% in the control group (**Figure 2**).

Before surgery, thoughts of death and suicide (item 9) were reported by 22.0% of patients with pHPT compared with 11.4% of patients with thyroid disease. Suicidal ideation disappeared in more than half of the patients with pHPT, remaining present in 10.7% of patients 1 year after surgery ( $P = .008$ ). The percentage of control subjects with suicidal thoughts declined from 11.4% preoperatively to 8.5% at 12 months follow-up (**Figure 3**).

In the pHPT group, but not in the control group, patients aged younger than 50 years showed more severe symptoms of preoperative depression ( $P < .01$ ). In patients with pHPT, serum calcium levels correlated significantly with preoperative PHQ-9 scores ( $r = 0.15$ ,  $P = .044$ ). There was also a significant, if small, correlation between serum calcium concentration and degree of suicidal ideation ( $r = 0.22$ ,  $P = .003$ ). Again, no correlation was seen for PTH ( $r = -0.09$ ,  $P = .23$ ).

### SF-36

Among patients with pHPT, preoperative HRQOL, as reflected by mean SF-36 physical and mental health summary scores, was significantly lower than in the control group (mean [SD], 42.66 [11.30] vs 49.49 [9.87] and 41.21 [13.48] vs 46.77 [11.61], respectively;  $P = .001$  for



**Figure 3.** Preoperative and postoperative responses to item 9 of the Patient Health Questionnaire–9 (PHQ-9): “thoughts that you would be better off dead or hurting yourself in some way.” pHPT indicates primary hyperparathyroidism.

both comparisons). At baseline, the mean physical and mental health scores of patients with pHPT also were significantly lower ( $P < .001$ ) than those of the healthy German population (mean [SD], 50.21 [10.24] and 51.54 [8.14], respectively).<sup>17</sup> The control group differed from the German normative sample only in having a significantly lower mental health summary score ( $P < .001$ ).

Mean (SD) physical health scores among patients with pHPT increased significantly from baseline to 44.91 (12.29) at 6 months and 45.74 (11.48) at 12 months follow-up ( $P < .01$  and  $P < .001$ , respectively). In the group with nodular goiter, a significant improvement was seen only at 6 months postoperatively (mean [SD], 50.20 [9.57];  $P < .05$ ) but not at 12 months (**Figure 4A**).

Among patients with pHPT, mental component scores improved significantly from baseline ( $P < .001$ ) at all postoperative measurement points (mean [SD], 2 weeks: 46.63 [11.54]; 6 months: 48.46 [10.68]; 12 months: 47.65 [11.65]). Patients with goiter showed mental health improvement only at 2 weeks postoperatively (mean [SD], 44.08 [9.35]) but not at 6 months or 12 months follow-up (Figure 4B).

### COMMENT

This multicenter study prospectively investigated the impact of surgery on depression, anxiety, suicidal ideation, and HRQOL in 194 patients with pHPT and compared them with 186 control subjects with nontoxic thyroid disease. The groups appeared not to differ according to age, sex, preoperative stress, or intraoperative trauma. To our knowledge, this is the first prospective multicenter study using validated instruments to assess depression, suicidal ideation, and anxiety, and the second largest study to measure HRQOL in patients with pHPT preoperatively and for 12 months postoperatively as well as to compare such observations with those in control subjects.

Our study had 3 main findings. First, preoperative depression, anxiety, and physical and mental HRQOL were on average significantly worse in patients with pHPT than in patients undergoing surgery for benign goiter. Second, more severe forms of depression and anxiety as well

as suicidal ideation were more prevalent preoperatively in patients with pHPT than in control subjects. Third, parathyroidectomy appears to have led to steady and significant decreases in the severity of depression and anxiety; decreased prevalence of pathologic levels of depression, anxiety, and suicidal ideation; and significantly improved mental and physical HRQOL over the first postoperative year.

Until now, multicenter studies analyzing HRQOL in pHPT were published by only 3 other groups.<sup>7,19,20</sup> In 1998, Pasiaka and Parsons<sup>6</sup> developed the Parathyroidectomy Assessment of Symptoms score, which was used to compare 203 patients with pHPT from different surgical centers with a control group of only 59 patients with thyroid disease.<sup>11</sup> Postoperatively, the Parathyroidectomy Assessment of Symptoms score decreased at 3 months follow-up, but it failed to show a relevant difference at 12 months postoperatively.

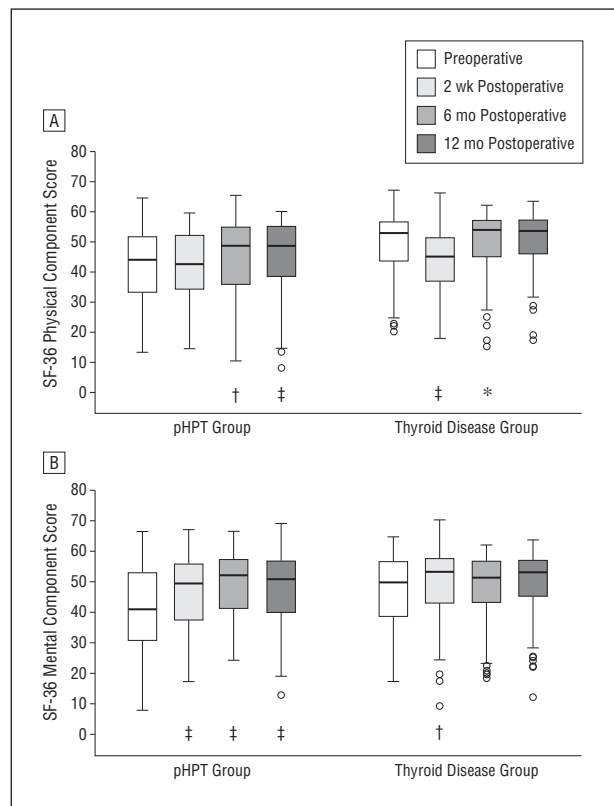
A 6-center French study<sup>19</sup> also used the SF-36 and found significantly improved physical and mental component scores in 100 patients with pHPT followed for 12 months postparathyroidectomy. A potential limitation of this study was that no control group was included. Bollerslev et al<sup>20</sup> found in a randomized multicenter trial performed in Norway, Sweden, and Denmark that even so-called asymptomatic patients with pHPT had a decreased SF-36 mental component score compared with the general population.

The present study found that preoperatively, both the SF-36 physical and mental health summary scores were significantly reduced in patients with pHPT compared with patients with benign thyroid disease or with the normative German population. During the postoperative follow-up, we observed that these scores improved significantly in patients with pHPT at 6 months and 12 months, whereas in the control group, the physical component scores improved only at 6 months after surgery.

During recent years, to our knowledge, only a few studies systematically evaluated the psychologic and neurocognitive symptoms in pHPT. In 1989, Joborn et al<sup>5</sup> studied 30 patients with pHPT and found that preoperatively, depression, anxiety, and cognitive disturbances were more prevalent and severe in pHPT compared with a control group. Six months postsurgically, patients with pHPT showed a clear improvement in mental health.<sup>5</sup>

To our knowledge, the largest prospective cohort study (n = 212) on psychologic and cognitive functioning in patients undergoing parathyroidectomy for pHPT was performed by Roman et al<sup>10</sup> almost simultaneously with the present study. The psychologic instruments that were administered were the Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory, and the Brief Symptom Inventory-18. On average, patients with pHPT had evidence of mild depression and anxiety at the preoperative visit, which significantly improved with successful parathyroidectomy. Possible limitations of the study were its 6-month participation rate of only 48% of the patients and lack of a control group.

For this study, we chose to apply the HADS,<sup>7</sup> which is a reliable and valid instrument for assessing anxiety and depression not only in psychiatric patients but also in medical patients. Our study showed that 194 patients



**Figure 4.** Physical and mental component scores. A, Preoperative and postoperative health-related quality of life measured with the 36-Item Short Form (SF-36) physical component score for patients with primary hyperparathyroidism (pHPT) and thyroid disease (control group). B, Preoperative and postoperative health-related quality of life measured with the SF-36 mental component score for patients with pHPT and thyroid disease (control group). \*  $P < .05$ ; †  $P < .01$ ; ‡  $P < .001$ ; comparisons were made between admission and assessment point (Wilcoxon test).

with pHPT had significantly higher preoperative scores for depression and anxiety compared with 186 control subjects with thyroid diseases and the normative sample. After parathyroidectomy, mean scores for depression and anxiety declined significantly. In the groups of mild to moderate and severe depression, 32% and 36%, respectively, improved significantly 1 year after surgery. The percentage of patients with no depressive symptoms improved from 66% preoperatively to 87.5% postoperatively. In the control group, no significant decrease in depressive symptoms was noted at any postoperative assessment time.

Depression severity was measured with the PHQ-9. According to this instrument, patients with pHPT had significantly more severe depressive symptoms than did control subjects, preoperatively. After successful parathyroidectomy, total PHQ-9 scores declined significantly among patients with pHPT, whereas no difference was noticed in control subjects. In 2011, Espiritu et al<sup>11</sup> published the PHQ-9 scores of 81 patients undergoing surgery for pHPT, 88 patients under watchful waiting, and 85 patients with benign thyroid disease. In analogy to our results and our previously published single-center study,<sup>9</sup> those authors reported that patients with pHPT had more depressive symptoms than did control subjects based on significantly higher PHQ-9 scores.

A special aim of our study was to determine the prevalence of suicidal ideation among our patients. Preoperatively, a relevant percentage (22.0%) of our pHPT cohort experienced thoughts of death and suicide; by contrast, our control subjects had an 11.4% prevalence, while Rief et al<sup>21</sup> found suicidal ideation in 10% of a representative sample of the German population. This suicidal ideation disappeared 1 year after parathyroidectomy in more than half of the patients with pHPT (51%). In contrast to our findings, the Espiritu et al<sup>11</sup> study, which also used the PHQ-9, found that only 6.8% of patients undergoing parathyroidectomy and 3.5% of a control group with thyroid diseases indicated suicidal thoughts.

The ultimate cause for a higher percentage of mood disorders and decreased cognitive function in patients with pHPT remains unclear. One possible explanation could be biochemical abnormalities associated with the disease. In the Rotterdam study on cognitive function in 3994 individuals between ages 55 and 90 years, high serum calcium was significantly associated with worse global cognitive function during a median follow-up of 11 years.<sup>22</sup> In the present study, high calcium levels in patients with pHPT correlated significantly with higher HADS depression scores, more severe depressive symptoms, and suicidal ideation on the PHQ-9, as well as reduced SF-36 mental health scores. No such correlation was seen in the control group. A positive link between serum calcium levels and depressive symptoms was demonstrated in 3 previous studies on pHPT,<sup>5,9,11</sup> while others found no such correlation.<sup>8,10</sup>

Cerebral blood flow may also be an explanatory factor. Mjåland et al<sup>23</sup> showed with single-photon emission computerized tomography that cerebral blood flow was pathologically reduced in 14 of 16 females with pHPT preoperatively and normalized after parathyroidectomy in almost all cases (13/14).

The current study had several strengths relative to previous published work including a large sample size, a multicenter approach, a control group with comparable operative trauma, and 77% of the control subjects and 78% of patients with pHPT participating at 12 months follow-up. One potential limitation was the lack of sample size calculation, which was owing to the study instruments having never previously been used in patients with pHPT vs control subjects with benign thyroid disease. Potential limitations also included the restriction of both groups to patients referred for surgery who therefore may have had more severe pHPT or nodular goiter. Additionally, preoperative questionnaires were answered the day before surgery, which might have led to the bias of higher HADS anxiety scores because one might presume that patients worry most shortly before undergoing operative procedures.

In conclusion, this study showed that preoperatively, patients with pHPT suffered more from depression, suicidal ideation, and anxiety, and they had reduced HRQOL, compared with a control group with nontoxic thyroid diseases and the general population. After parathyroidectomy, symptoms of depression and anxiety declined, and HRQOL significantly improved in the first year. Parathyroidectomy also was associated with a 51% reduced prevalence of suicidal ideation. These findings suggest that successful parathyroidectomy not only

cures pHPT physical symptoms but reduces patients' psychological distress and improves their HRQOL. Patients with suicidal ideation should be offered a corresponding psychosomatic evaluation.

**Accepted for Publication:** July 16, 2012.

**Published Online:** October 15, 2012. doi:10.1001/2013.jamasurg.316

**Author Affiliations:** Departments of Surgery (Drs Weber, Eberle, Messelhäuser, and Henne-Bruns) and Psychosomatic Medicine and Psychotherapy (Ms Rottler and Dr von Wietersheim), University Hospital, Ulm; Department of Surgery, University Hospital, Rostock (Dr Schiffmann); Department of Surgery, Marienhospital, Osnabrück (Dr Nies); Department of Surgery, St Josefs Krankenhaus, Gießen (Dr Schabram); Department of Surgery, Städtisches Klinikum, Offenbach (Dr Zielke); Department of Surgery, University Hospital, Frankfurt (Dr Holzer); and Department of General and Psychosomatic Medicine, University Hospital, Heidelberg (Dr Keller), Germany.

**Correspondence:** Theresia Weber, MD, Department of Surgery, University Hospital Ulm, Albert-Einstein-Allee 23, 89081 Ulm, Germany (theresia.weber@uniklinik-ulm.de).

**Author Contributions:** *Study concept and design:* Weber, Nies, Henne-Bruns, and Keller. *Acquisition of data:* Weber, Eberle, Messelhäuser, Schiffmann, Nies, Schabram, Zielke, and Holzer. *Analysis and interpretation of data:* Weber, Messelhäuser, Schiffmann, Zielke, Holzer, Rottler, Keller, and Wietersheim. *Drafting of the manuscript:* Weber, Messelhäuser, Schiffmann, and Rottler. *Critical revision of the manuscript for important intellectual content:* Weber, Eberle, Schiffmann, Nies, Schabram, Zielke, Holzer, Rottler, Henne-Bruns, Keller, and Wietersheim. *Statistical analysis:* Weber, Messelhäuser, Rottler, and Wietersheim. *Obtained funding:* Weber. *Administrative, technical, and material support:* Weber, Eberle, Schabram, and Henne-Bruns. *Study supervision:* Zielke, Holzer, Henne-Bruns, and Keller.

**Members of the Prospective Multicenter Study:** Theresia Weber, MD, Julia Eberle, MD, Ursula Messelhäuser, MD, Doris Henne-Bruns, MD, University of Ulm; Leif Schiffmann, MD, and Ernst Klar, MD, University of Rostock; Christoph Nies, MD, Marienhospital Osnabrück; Akan Gül, MD, and Jochen Schabram, MD, St. Josefskrankenhaus Gießen; Beate Knauer, MD, and Andreas Zielke, MD, Städtisches Klinikum, Offenbach; Katharina Holzer, MD, University Hospital Frankfurt; Nadja Lehwald, MD, University Hospital Düsseldorf; Dietmar Simon, MD, Evangelisches Krankenhaus Bethesda, Duisburg; Monika Keller, MD, University Hospital Heidelberg; Edit Rottler and Joern von Wietersheim, MD, University Hospital Ulm.

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** This study was funded by B. Braun-Stiftung, Germany.

**Previous Presentation:** This study was presented in part at the meeting of the German Surgical Society; April 24, 2012; Berlin, Germany.

**Additional Contributions:** We thank Robert J. Marlowe for carefully editing the manuscript. Our special thanks

go to our patients who participated in the study and helped us learn about psychologic symptoms in primary hyperparathyroidism.

## REFERENCES

1. Palmer M, Adami HO, Bergström R, Jakobsson S, Akerström G, Ljunghall S. Survival and renal function in untreated hypercalcaemia: population-based cohort study with 14 years of follow-up. *Lancet*. 1987;1(8524):59-62.
2. Wermers RA, Khosla S, Atkinson EJ, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res*. 2006;21(1):171-177.
3. National Institutes of Health. NIH conference: diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. *Ann Intern Med*. 1991;114(7):593-597.
4. Reinfrank RF. Primary hyperparathyroidism with depression. *Arch Intern Med*. 1961;108:606-610.
5. Joborn C, Hetta J, Lind L, Rastad J, Akerström G, Ljunghall S. Self-rated psychiatric symptoms in patients operated on because of primary hyperparathyroidism and in patients with long-standing mild hypercalcemia. *Surgery*. 1989; 105(1):72-78.
6. Pasiaka JL, Parsons LL. Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. *World J Surg*. 1998;22(6):513-518, discussion 518-519.
7. Pasiaka JL, Parsons LL, Demeure MJ, et al. Patient-based surgical outcome tool demonstrating alleviation of symptoms following parathyroidectomy in patients with primary hyperparathyroidism. *World J Surg*. 2002;26(8):942-949.
8. Dotzenrath CME, Kaetsch AK, Pflingsten H, et al. Neuropsychiatric and cognitive changes after surgery for primary hyperparathyroidism. *World J Surg*. 2006; 30(5):680-685.
9. Weber T, Keller M, Hense I, et al. Effect of parathyroidectomy on quality of life and neuropsychological symptoms in primary hyperparathyroidism. *World J Surg*. 2007;31(6):1202-1209.
10. Roman SA, Sosa JA, Pietrzak RH, et al. The effects of serum calcium and parathyroid hormone changes on psychological and cognitive function in patients undergoing parathyroidectomy for primary hyperparathyroidism. *Ann Surg*. 2011; 253(1):131-137.
11. Espiritu RP, Kearns AE, Vickers KS, Grant C, Ryu E, Wermers RA. Depression in primary hyperparathyroidism: prevalence and benefit of surgery. *J Clin Endocrinol Metab*. 2011;96(11):E1737-E1745.
12. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.
13. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale: a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17-41.
14. Herrmann-Lingen C, Buss U, Snaith RP. *HADS-D: Hospital Anxiety and Depression Scale, Deutsche Version: Ein Fragebogen zur Erfassung von Angst und Depressivität in der somatischen Medizin* [in German]. Bern, Switzerland: Hans Huber Verlag; 1995.
15. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
16. Walker J, Hansen CH, Hodges L, et al. Screening for suicidality in cancer patients using item 9 of the nine-item patient health questionnaire: does the item score predict who requires further assessment? *Gen Hosp Psychiatry*. 2010; 32(2):218-220.
17. Ware JE, Sherbourne CD. The MOS 35-item short-form health survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30:942-949.
18. Bullinger M, Kirchberger I. *SF-36 Fragebogen zum Gesundheitszustand, Deutsche Version des SF-36 Short Form Health Survey* [in German]. Göttingen, Germany: Hogrefe Verlag; 1998.
19. Caillard C, Sebag F, Mathonnet M, et al. Prospective evaluation of quality of life (SF-36v2) and nonspecific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up). *Surgery*. 2007;141(2):153-159, discussion 159-160.
20. Bollerslev J, Jansson S, Mollerup CL, et al. Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. *J Clin Endocrinol Metab*. 2007;92(5):1687-1692.
21. Rief W, Nanke A, Klaiberg A, Braehler E. Base rates for panic and depression according to the Brief Patient Health Questionnaire: a population-based study. *J Affect Disord*. 2004;82(2):271-276.
22. Schram MT, Trompet S, Kamper AM, et al. Serum calcium and cognitive function in old age. *J Am Geriatr Soc*. 2007;55(11):1786-1792.
23. Mjåland O, Normann E, Halvorsen E, Rynning S, Egeland T. Regional cerebral blood flow in patients with primary hyperparathyroidism before and after successful parathyroidectomy. *Br J Surg*. 2003;90(6):732-737.

## INVITED CRITIQUE

### ONLINE FIRST

# The Time Has Come to Redefine the Classic Symptoms of Primary Hyperparathyroidism

The diagnosis of primary hyperparathyroidism (pHPT) for clinicians in the 1920s through 1950s was a clinical diagnosis. Long before the ability to measure parathyroid hormone and before automated serum calcium measurements, patients were suspected of having pHPT when they presented with nephrolithiasis, osteitis fibrosis cystica, myopathy, and significant neuropsychiatric symptoms. Yet, much has changed since the first parathyroidectomy in 1925.

Hyperparathyroidism today is a biochemical diagnosis and diagnosed much earlier, with less than 20% of patients displaying these classic symptoms. This has led many authors to use the term asymptomatic pHPT for the remaining 80%. Yet, in the last decade, surgeons have contested that very few patients are truly asymptomatic and many benefit from surgery. At first, it was retrospective reflection by patients, claiming how much better they

felt following surgery. Then came the patient-based questionnaires and generic quality of life instruments. However, plagued by small series, lack of control groups, and conflicting data from the 3 randomized trials in this field, widespread acceptance of the existence of vague neuropsychologic symptoms in pHPT and their reversibility with surgery has not been forthcoming.<sup>1</sup>

Weber et al<sup>2</sup> have added to the growing body of surgical literature attempting to better quantify the preoperative neuropsychologic manifestations of pHPT and the impact of surgery. They used a battery of validated neuropsychiatric tools, an appropriate control group, and reasonable follow-up. Weber and colleagues' findings, along with those recently published by Roman et al,<sup>3</sup> should put to rest the debate of the positive impact that parathyroidectomy has on the neurocognitive dysfunction associated with pHPT. The time has come to recognize these