Risk Factors for Postoperative Hypocalcemia After Surgery for Primary Hyperparathyroidism

Johan Westerdahl, PhD; Pia Lindblom, MD; Stig Valdemarsson, PhD; Sten Tibblin, PhD; Anders Bergenfelz, PhD

Hypothesis: A variety of clinical and biochemical variables may be associated with hypocalcemia after surgery for parathyroid adenoma.

Design: A prospective study of patients who underwent surgery for solitary parathyroid adenoma.

Setting: A university hospital department of surgery.

Patients: Eighty-six consecutive patients who underwent surgery for solitary parathyroid adenoma.

Intervention: Parathyroidectomy according to the principles of unilateral neck exploration.

Main Outcome Measures: Clinical and biochemical risk factors for early (≤4 days after surgery) and late (1 year after surgery) postoperative symptomatic and biochemical hypocalcemia.

Results: Twenty-two patients developed early symptomatic hypocalcemia. The difference in total serum calcium levels between patients, with and without early symptomatic hypocalcemia, was evident on the third and fourth postoperative days. Serum level of osteocalcin greater than 6.0 µg/L, bilateral neck exploration, and history of cardiovascular disease were risk factors for symptomatic hypocalcemia (odds ratios [95% confidence intervals]: 4.4 [1.4-14.1], 3.8 [1.3-11.6], and 0.1 [0.02-0.60], respectively). Patients with up to 1 risk factor had a possibility of only 7% to develop early symptomatic hypocalcemia. One year after surgery, 16 patients had low levels of total serum calcium (late biochemical hypocalcemia) and were asymptomatic. Preoperative intermittent hypercalcemia was associated with an increased risk for late biochemical hypocalcemia (odds ratio, 3.9; 95% confidence interval, 1.0-16.3).

Conclusions: Clinical and biochemical risk factors for early and late postoperative hypocalcemia in patients who underwent surgery for solitary parathyroid adenoma were found. A clinically useful prognostic index for early symptomatic hypocalcemia was constructed using these risk factors.

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**P**rimary hyperparathyroidism (pHPT) is a common disease, especially in the elderly, and is associated with increased morbidity and mortality from cardiovascular disease. surgeon is the only beneficial treatment for patients with pHPT. A high proportion of patients undergoing operative treatment for pHPT are older and have cardiovascular disease, making them high-risk patients for surgery. Therefore, operative complications must be kept to a minimum to allow early ambulation of these patients.

See Invited Critique at end of article

Symptomatic hypocalcemia has long been recognized as a source of significant morbidity after surgery for pHPT. It also plays an important role in delaying hospital discharge. In a Scandinavian survey that included more than 600 operations, hypocalcemia occurred after surgery in 15% of patients. In response to the high rate of hypocalcemia, the surgical strategy of unilateral parathyroidectomy for solitary parathyroid adenoma in pHPT was adopted in the Department of Surgery, Lund University Hospital, Lund, Sweden, in 1977. The basic principle for the unilateral approach is to restrict neck exploration to the side with the solitary parathyroid adenoma, thereby minimizing the risk of postoperative surgical hypoparathyroidism. In a 5-year follow-up study of patients who underwent unilateral exploration, none had postoperative total calcium levels below 2.00 mmol/L (8.0 mg/dL). Furthermore, in a multicenter study, normocalcemia was observed in 96% and hypocalcemia in only 2% of patients who underwent unilateral exploration after an average of 8.7 years. Similar results were published recently by Worsey et al.

Although surgical damage to healthy parathyroid glands is probably of major importance, the cause of hypocalcemia after surgery for pHPT is likely to be multifactorial.
PATIENTS, MATERIALS, AND METHODS

PATIENTS

The study included 86 patients (22 men and 64 women) with the clinical and biochemical diagnosis of PHPT who subsequently underwent surgery for solitary parathyroid adenoma at the Department of Surgery, Lund University Hospital. None of the included patients had had previous neck surgery. Mean ± SD age of patients was 64 ± 13 years, and mean ± SD serum level of calcium was 2.77 ± 0.22 mmol/L (11.1 ± 0.9 mg/dL). Median weight of the excised parathyroid adenomas was 0.70 g (range, 0.10-10.10 g). Ten patients had slightly increased serum levels of creatinine before surgery.

SURGERY

All patients underwent surgery according to the principles of unilateral neck exploration by 3 surgeons with experience in endocrine surgery. Briefly, if the adenoma is found on the side explored first, it is excised along with the ipsilateral parathyroid gland. If the adenoma is not found on the side explored first, or if the results of frozen section or intraoperative plasma levels of parathyroid hormone (PTH) are inconclusive (see the next paragraph), comprehensive bilateral exploration is performed. In the present cohort, 52 patients underwent unilateral exploration and 34 underwent bilateral exploration. The skewed distribution of numbers between the 2 groups is due to a variety of localization procedures that were investigated during the study.

ADENOMA DIAGNOSIS

The diagnosis of parathyroid adenoma was made by the finding of an enlarged gland with histological features of adenoma (ie, a rim of healthy parathyroid tissue, chief cells with nuclear pleomorphism, and decreased cytoplasmic fat content) and signs of suppression in a normal-sized gland (chief cells with increased cytoplasmic fat content). The decline in the serum level of intact PTH was also determined during surgery when feasible (n = 74). In all but 3 patients, the decline 15 minutes after parathyroid gland excision was 60% or more below baseline, highly suggestive of solitary parathyroid adenoma, with a mean ± SD PTH concentration decline of 84% ± 10%. In 3 patients, PTH concentration declined by 40%, 54%, and 55%, suggesting that these patients did not have a solitary adenoma. However, these patients had a histological diagnosis of parathyroid adenoma, and their serum levels of calcium were normalized 1 year after surgery (2.31 [9.2], 2.23 [8.9], and 2.21 mmol/L [8.8 mg/dL], respectively).

BONE DENSITOMETRY

Bone density was evaluated using single photon absorption.

BIOCHEMICAL ANALYSES

All blood samples were collected after an overnight fast by patients. Preoperative data were obtained from blood samples collected the day before surgery. Serum levels of intact PTH were measured using the N-tact PTH-assy (Incstar, Stillwater, Minn). The sensitivity of this assay is 0.1 pmol/L.

Serum concentrations of osteocalcin (bone Gla protein) were measured with a commercially available kit (Osteocalcin125/RIA kit; Incstar). Levels of 25-Hydroxyvitamin D were measured using high-performance liquid chromatography. Levels of 1,25-Dihydroxyvitamin D were assessed using a radioimmunoassay (Incstar). Serum ionized calcium concentrations were analyzed using an ion-selective electrode (Radiometer, Copenhagen, Denmark).

Calcium, albumin, total alkaline phosphatase, serum urea nitrogen, and creatinine were assayed in a routine autoanalyzer (Ektachem 700XR-C, Eastman Kodak Co, Rochester, NY).

CLINICAL VARIABLES

The medical histories of all patients were recorded before surgery and included symptoms and signs, medications taken, and ongoing and previous diseases (Table 1). Symptomatic hypocalcemia included any of the following clinical manifestations: circumsoral tingling and numbness, tingling in the hands or feet, muscle cramps, Chvostek or Trousseau signs, or the need to take cholecalciferol analogues or oral calcium carbonate supplements to avoid these symptoms. Biochemical hypocalcemia denotes patients with serum levels of total calcium below the reference range. The diagnosis of PHPT was based on the presence of hypercalcemia and an inappropriately increased serum concentration of PTH (>5.0 pmol/L). Patients referred to as being preoperatively normocalcemic turned out to have total calcium levels within the reference range the day before surgery. These patients were therefore classified as having intermittent hypercalcemia.

Cardiovascular disease was based on the history of myocardial infarction, angina, heart failure, arrhythmia, stroke, and vascular disease, including thrombosis, embolus, and generalized atherosclerosis.

STATISTICS

Results are expressed as mean ± SD unless stated otherwise. For statistical evaluation of differences between groups, the Mann-Whitney test was used. For categorical data, statistical significance was analyzed using the χ² test and the Fisher exact test when expected frequencies were less than 5. In the multivariate analysis, stepwise logistic regression was used. The final model included independent variables that had initially showed a univariate association with the dependent variable. Furthermore, a prognostic index was constructed using the number of risk factors that were generated from multivariate analysis. P < .05 was considered significant, and 95% confidence intervals were used. Occasional missing values for some variables caused a slight variation in the number of patients used for each analysis.

In the present study, we analyzed clinical and biochemical risk factors for early and late postoperative symptomatic and biochemical hypocalcemia in patients who underwent surgery according to the principles of unilateral neck exploration for solitary parathyroid adenoma. We also investigated whether a prognostic index based on preoperative data could be constructed to differentiate between patients with higher and lower risk for early and late hypocalcemia.
In the early postoperative period (≤4 days after surgery), 22 patients developed symptomatic hypocalcemia with lower nadir of serum calcium levels than asymptomatic patients (1.96 ± 0.18 vs 2.10 ± 0.14 mmol/L [7.8 ± 0.7 and 8.4 ± 0.6 mg/dL], respectively) (P<.01). The 2 groups differed in their serum levels of calcium on the third and fourth postoperative days (Figure 1). Symptoms were mostly mild, and most patients required oral calcium substitution. However, 2 patients required cholecalciferol therapy.

Patients with symptomatic hypocalcemia had higher serum levels of osteocalcin and phosphate before surgery, and underwent bilateral exploration more often than did patients without symptomatic hypocalcemia (Table 2). Moreover, a history of cardiovascular disease was less common among symptomatic patients (Table 1).

As a group, patients who underwent bilateral neck exploration had lower nadir of total serum calcium levels (2.01 ± 0.17 mmol/L [8.0 ± 0.7 mg/dL]) compared with those who underwent unilateral exploration (2.10 ± 0.14 mmol/L [8.4 ± 0.6 mg/dL]) (P<.02). Furthermore, the former had lower levels of total serum calcium on the third and fourth postoperative days (Figure 2).

Serum concentrations of osteocalcin and phosphate, history of cardiovascular disease, and type of surgical neck exploration were included in a stepwise logistic regression analysis, and osteocalcin level, history of cardiovascular disease, and type of neck exploration were independent risk factors for the development of early symptomatic hypocalcemia (Table 3). Furthermore, a prognostic index was constructed (Table 4). None of the patients without any risk factors (index 0) and only 3 (7%) of 44 with up to 1 risk factor (indices 0 and 1) developed early symptomatic hypocalcemia.

Patients with early symptomatic hypocalcemia had lower serum levels of calcium 8 weeks after surgery compared with asymptomatic patients (2.25 ± 0.11 vs 2.32 ± 0.11 mmol/L [9.0 ± 0.4 vs 9.3 ± 0.4 mg/dL]) (P<.02). One year after surgery, there were no differences in serum levels of calcium between the 2 groups (2.25 ± 0.15 vs 2.28 ± 0.10 mmol/L [9.0 ± 0.6 vs 9.1 ± 0.4 mg/dL]) (P = .17). Patients who underwent bilateral vs unilateral exploration did not differ with regard to total serum calcium level 8 weeks after surgery (2.31 ± 0.11 vs 2.29 ± 0.12 mmol/L [9.2 ± 0.4 vs 9.1 ± 0.5 mg/dL]) (P = .61) or 1 year after surgery (2.28 ± 0.14 vs 2.27 ± 0.10 mmol/L [9.1 ± 0.6 vs 9.1 ± 0.4 mg/dL]) (P = .53).

Six patients were unavailable for 1-year follow-up: 5 had died and 1 had moved abroad. Level of total calcium for the remaining patients (n = 80) was 2.27 ± 0.11 mmol/L (9.1 ± 0.4 mg/dL). Sixteen patients had low levels of total serum calcium (late biochemical hypocalcemia), only 1 of whom (with bilateral neck exploration) had low levels of ionized calcium. However, all 16 patients were asymptomatic, and no patient received treatment with cholecalciferol analogues.

The same variables used in the univariate analyses of early symptomatic hypocalcemia (Tables 1 and 2) were included in analyses of late biochemical hypocalcemia (nonsignificant data not shown). Patients with low serum levels of total calcium at 1-year follow-up (n = 16) had preoperatively lower serum levels of total calcium,
higher urinary calcium levels, and lower serum levels of triglycerides compared with patients with normal serum concentrations of total calcium 1 year after surgery (Table 5). A higher proportion of these patients were normocalcemic before surgery, ie, they had intermittent hypercalcemia. They also had smaller adenomas.

When all variables with a univariate association with late biochemical hypocalcemia were included in a stepwise multiple regression analysis, preoperative normocalcemia was the only variable that was significantly associated with late biochemical hypocalcemia (odds ratio, 3.9; 95% confidence interval, 1.0-16.3).

Analyses using albumin-corrected calcium instead of total serum calcium levels gave essentially the same results (data not shown).

**COMMENT**

In the present investigation, early symptomatic hypocalcemia (≤4 days after surgery) was found in 22 (26%) of 86 patients who underwent surgery for solitary parathyroid adenoma using the unilateral approach. Except in 2 patients who were treated with cholecalciferol analogues, the symptoms were mostly mild.

High serum levels of osteocalcin and bilateral neck exploration were associated with increased risk of early symptomatic hypocalcemia. Thus, high bone turnover and surgical trauma might be important mechanisms for generating hypocalcemic symptoms.

On the other hand, a history of cardiovascular disease was related to a decreased risk of early symptomatic hypocalcemia. This finding is of great clinical interest because it indicates that these otherwise high-risk patients are not prone to develop hypocalcemia after surgery for PHPT. Our data did not provide any explanation for this association, even after further analyses on the relation between cardiovascular disease and the other clinical and biochemical variables (data not shown). However, our data on cardiovascular disease were based on a history of myocardial infarction, angina, heart failure, arrhythmia, stroke, and vascular disease, including thrombosis, embolus, and generalized atherosclerosis, and therefore provided us with relatively inexact information on cardiovascular disease. This might have, to some degree, introduced nondifferential misclassification of cardiovascular disease, but the effect of this error would rather lead to an underestimation of a true relationship. We do not believe that the data on cardiovascular disease differ between patients with and without early symptomatic hypocalcemia because the medical history was recorded before the operation. Whether this finding is due to chance, because of the multiple testing in our study, or represents a true finding needs to be further investigated.

The difference in total calcium levels between patients, with and without early symptomatic hypocalcemia, was evi-
dent on the third and fourth postoperative days. If patients are discharged early from the hospital, they should be informed that hypocalcemic symptoms could appear after a few days, even if the initial course was uneventful. Furthermore, using the suggested prognostic index, it is possible to select patients with minimal risk of postoperative symptomatic hypocalcemia and who are then, in this sense, suited for early ambulation. This is of major importance in times of increasing awareness of cost-containment because early hospital discharge will reduce the total cost of treatment. In the present study, the group with a prognostic index of 0 or 1, ie, a patient without any or with only 1 risk factor, constituted nearly half of the total group of patients. In this group, less than 10% had postoperative hypocalcemia.

Today, many patients with pHPT have mild or only intermittent hypercalcemia. Recently, the finding of incidental parathyroid adenomas during thyroid surgery and in patients with normocalcemic pHPT have been described. In our investigation, the patient with low serum levels of total calcium 1 year after surgery (late biochemical hypocalcemia) also had lower levels of total calcium before surgery. Preoperative normocalcemia was an independent risk factor for late biochemical hypocalcemia. Thus, patients with preoperatively intermittent hypercalcemia have an increased risk for postoperatively decreased serum levels of total calcium. Although only 1 of 16 patients with low serum levels of total calcium at 1-year follow-up also had low serum levels of ionized calcium, our findings suggest that expansion of the surgical indications should be cautioned.

Our study focused specifically on the risk of hypocalcemia after surgery for solitary parathyroid adenoma using the unilateral approach. It does not address the

### Table 3. Odds Ratios and 95% Confidence Intervals (CIs) for Developing Early (≤4 Days After Surgery) Symptomatic Hypocalcemia

<table>
<thead>
<tr>
<th>Factor Category</th>
<th>Yes (n = 22)</th>
<th>No (n = 64)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum osteocalcin level, µg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6.0</td>
<td>9</td>
<td>43</td>
<td>1.0† 1.0†</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>13</td>
<td>21</td>
<td>3.0 (1.1-8.0) 4.4 (1.4-14.1)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>43</td>
<td>1.0† 1.0†</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>21</td>
<td>0.2 (0.04-0.90) 0.1 (0.02-0.60)</td>
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<tr>
<td>Type of neck exploration</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>8</td>
<td>44</td>
<td>1.0† 1.0†</td>
</tr>
<tr>
<td>Bilateral</td>
<td>14</td>
<td>20</td>
<td>3.8 (1.4-10.6) 3.8 (1.3-11.6)</td>
</tr>
</tbody>
</table>

*Adjusted odds ratios are from a logistic regression model using all factors shown.
†Reference category.

### Table 4. Prognostic Index

<table>
<thead>
<tr>
<th>Index*</th>
<th>No (n = 64)</th>
<th>Yes (n = 22)</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>0</td>
<td>8</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>3</td>
<td>1.00</td>
<td>0.12</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>13</td>
<td>0.86</td>
<td>0.62</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>6</td>
<td>0.27</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Number of risk factors (serum osteocalcin level, type of neck exploration, and a medical history without cardiovascular disease).

### Table 5. Clinical and Biochemical Data on Patients Who Underwent Surgery for Solitary Parathyroid Adenoma With and Without Biochemical Hypocalcemia 1 Year After Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Late Biochemical Hypocalcemia</th>
<th>Total (N = 80)</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 16)</td>
<td>No (n = 64)</td>
<td></td>
</tr>
<tr>
<td>Glandular weight, mg</td>
<td>616 ± 670</td>
<td>1167 ± 1506†</td>
<td>1050 ± 1386</td>
</tr>
<tr>
<td>Total serum calcium level, mmol/L</td>
<td>2.67 ± 0.17</td>
<td>2.80 ± 0.22§</td>
<td>2.78 ± 0.22</td>
</tr>
<tr>
<td>Fasting serum triglyceride level, mmol/L</td>
<td>1.0 ± 0.4</td>
<td>1.3 ± 0.7§</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>Urinary calcium level, mmol/L†</td>
<td>6.4 ± 1.8</td>
<td>5.2 ± 3.2§</td>
<td>5.4 ± 3.1</td>
</tr>
<tr>
<td>Normocalcemic[/hypercalcemic before surgery, No.</td>
<td>6/10</td>
<td>10/54§</td>
<td>16/64</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD unless otherwise indicated. Biochemical hypocalcemia is defined as low serum levels of total calcium.
†P<.01 vs biochemical hypocalcemia.
‡To convert calcium from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.25.
§P<.05 vs biochemical hypocalcemia.
||To convert triglyceride from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.01129.
||Normocalcemic denotes patients with normal serum levels of total calcium the day before surgery.
Surgical Approach to Primary Hyperparathyroidism


Invited Critique

Symptomatic hypocalcemia occurs unpredictably in a few patients undergoing neck exploration for primary hyperparathyroidism. Conventional wisdom has attributed the likelihood of postoperative hypocalcemia to a variety of risk factors, including severity of the disease itself, e.g., a patient with a high preoperative calcium level or a large abnormal gland; the extent or activity of bone disease, sometimes referred to as “hungry bone” syndrome; and intraoperative injury to remaining glands, particularly when it is a reoperative case. The study by Westerdahl et al confirms conventional wisdom in 2 respects. First, intraoperative trauma is a risk factor. Second, hungry bones are also a risk factor if high osteocalcin levels can be used as an indicator of the activity of bone turnover. The study’s finding that cardiovascular disease, thought to be one of the sequelae of long-standing primary hyperparathyroidism, might protect against symptomatic hypocalcemia is, on the other hand, counterintuitive and puzzling.

Westerdahl et al offer a prognostic index based on these factors. They do not seem to have tested this index prospectively on a validation sample of new patients, however, and therefore, one cannot be certain of its utility. In this era of minimal hospitalization, almost all of our patients are given calcium (and sometimes cholecalciferol) immediately after surgery, and are discharged from the hospital within 24 to 36 hours.

The finding that patients with “intermittent” hypercalcemia are apparently more likely to have serum calcium levels below the reference range 1 year after surgery is interesting and raises several questions. Was long-standing hypercalcemia a stimulus to the development of primary hyperparathyroidism? Are they being treated with calcium, cholecalciferol, or both? What is the functional health status of these patients? Are they better off functionally and symptomatically than before surgery? These and many more questions remain to be answered about the effects of this fascinating disease and its treatment on the patients who have it.

Richard E. Burney, MD
Ann Arbor, Mich

References


