Vitamin D and Risk of Postoperative Hypocalcemia After Total Thyroidectomy

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IMPORTANCE Transient hypocalcemia is a well-recognized occurrence after total thyroidectomy. It has been hypothesized that underlying vitamin D deficiency may increase the risk of this complication, although to date there are few data in the literature supporting this hypothesis.

OBJECTIVE To investigate whether perioperative vitamin D levels have any effect on postthyroidectomy hypocalcemia.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective review of a prospectively maintained database of thyroidectomies from November 1, 2009, through September 30, 2012, at an academic teaching hospital. The study included 121 patients with available vitamin D levels undergoing total or completion thyroidectomy. Patients with preexisting hypercalcemia or hyperparathyroidism were excluded.

INTERVENTIONS All patients underwent total removal of all thyroid tissue by a capsular dissection technique. Routine calcium or vitamin D supplementation was not administered. Biochemical hypocalcemia was defined as any single postoperative corrected calcium level less than 8.0 mg/dL (to convert to millimoles per liter, multiply by 0.25) and symptomatic hypocalcemia as any symptoms of hypocalcemia.

MAIN OUTCOMES AND MEASURES Outcome measures were incidence of postoperative hypocalcemia and association with vitamin D levels. A multivariate analysis was performed to study the effect of other variables, including performance of central neck dissection, incidental parathyroidectomy, and hyperthyroidism, on the incidence of postoperative hypocalcemia.

RESULTS The incidence of transient biochemical hypocalcemia was 24% (n = 29/121). There was no correlation between vitamin D levels and risk of postoperative hypocalcemia. On univariate analysis, performance of concomitant central compartment neck dissection revealed an increased risk of hypocalcemia (P = .06), but this finding was not significant on multivariate analysis.

CONCLUSIONS AND RELEVANCE Vitamin D levels do not appear to have a significant effect on the risk of postthyroidectomy hypocalcemia.
Transient hypocalcemia is a well-recognized occurrence after thyroid surgery. It is generally considered to be due to early postoperative hypoparathyroidism, which occurs secondary to intraoperative trauma to parathyroid glands or their blood supplies, or inadvertent parathyroid removal. This condition leads to reduced circulating levels of parathyroid hormone (PTH). Low PTH levels lead to reduced reabsorption of calcium in the kidney and decreased release of calcium from bones, which in turn leads to reductions in serum calcium levels.

Vitamin D is a fat-soluble vitamin that plays an important role in calcium homeostasis, including facilitating calcium absorption from the gastrointestinal tract. Vitamin D deficiency is common in many countries, including the United States and Ireland, owing to a combination of dietary deficiency and lack of exposure to natural sunlight. Vitamin D deficiency may lead to a compensatory hyperparathyroidism, with the increased PTH levels offsetting insufficient gastrointestinal calcium absorption by enhancing renal calcium reabsorption, thus maintaining normal calcium levels.

It has been hypothesized that patients who are vitamin D deficient and who experience temporary hypoparathyroidism after thyroid surgery are at increased risk of developing symptomatic hypocalcemia due to the loss of this compensatory role of PTH in maintaining eucalcemia. However, whether low or insufficient vitamin D levels affect the incidence of hypocalcemia after thyroid surgery is not clear. Only a small number of studies have investigated this, with mixed results.

At our institution (South Infirmary Victoria University Hospital), most patients undergoing thyroidectomy have undergone testing for vitamin D levels along with PTH measurement in the early postoperative period in an effort to predict the course of postoperative hypocalcemia and the requirement for vitamin D and calcium replacement. The purpose of this study was to investigate whether vitamin D levels at the time of thyroidectomy have any effect on the risk of postoperative hypocalcemia.

Methods

This study comprised a retrospective review of all thyroidectomy operations performed by one of us (P.S.) from November 1, 2009, through September 30, 2012. Cases of total thyroidectomy or completion thyroidectomy (defined as operations that involve removal of all remaining thyroid tissue in patients who had previously undergone a partial thyroidectomy) were included. Exclusion criteria were any case of less-than-total thyroidectomy or preoperative hypercalcemia or primary hyperparathyroidism. Cases were identified from a prospectively maintained database of all thyroid operations performed by the senior author (P.S.). The prospective database and case notes of patients were reviewed and data extracted, including age and sex; type of surgery performed; performance of concomitant central neck dissection; pathologic diagnosis of cancer; and postoperative calcium, albumin, PTH, and vitamin D levels. Data regarding symptoms of hypocalcemia in the postoperative period and use of calcium replacement had been prospectively recorded and were available from the prospective database.

Permission to perform the study was obtained from the Cork Clinical Research Ethics Committee. Because this was a retrospective study, informed consent was not required.

Thyroid surgery was performed using a capsular dissection technique. Care was taken to ensure that any parathyroid glands attached to the thyroid capsule were reflected down and preserved with their vasculature intact. In cases where parathyroid glands were not readily recognized, they were not systematically sought out but considered to have been most likely reflected off the thyroid during dissection and preserved. We have found that this does not lead to any increased risk of postoperative hypocalcemia. Recurrent laryngeal nerves were always identified. In all cases, surgery involved removal of all thyroid tissue. There were no cases of subtotal or near-total thyroidectomy.

None of the patients were administered prophylactic calcium before or after surgery, and routine preoperative blood testing was not performed. Postoperatively, all patients stayed in the hospital for 2 nights. Calcium levels were generally measured at 6 AM and 5 PM on the first postoperative day and at 6 AM on the second postoperative day. Patients with normal-corrected calcium levels were discharged home on the second postoperative day. Patients with below-normal calcium levels were kept in the hospital with daily calcium levels measured and were discharged home when calcium levels were considered stable. The decision to institute calcium and/or vitamin D supplementation was made on a case-by-case basis. In general, supplementation was administered to symptomatic patients or any patient with persistent biochemical hypocalcemia for 2 or 3 days.

Both PTH and vitamin D levels were measured at the same time as the first calcium measurement on postoperative day 1, which was usually between 12 and 18 hours after surgery. The PTH levels were measured using electrochemiluminescence immunoassay and the vitamin D levels using direct competitive chemiluminescence immunoassay. Vitamin D levels were categorized as sufficient (>30 ng/mL), insufficient (<30 ng/mL), deficient (<20 ng/mL), and severely deficient (<10 ng/mL) (to convert to nanomoles per liter, multiply by 2.496).

Postoperative hypocalcemia was defined as the occurrence of any single corrected calcium level less than 8.0 ng/mL (to convert to millimoles per liter, multiply by 0.25) in the postoperative period. Corrected calcium was calculated according to the following formula: corrected calcium = measured calcium + 0.02 × (40 − serum albumin). Symptomatic hypocalcemia was the presence of any paresthesia, numbness, muscle cramps, or other symptoms that could be attributable to hypocalcemia in the postoperative period. The presence of symptomatic hypocalcemia was recorded prospectively in all patients who had undergone thyroid surgery performed by the senior author. Persistent hypoparathyroidism was considered to be present in any patient taking any form of regular calcium and/or vitamin D supplementation at 6 months postoperatively.
Table 1. Incidence of Incidental Parathyroidectomy and Biochemical and Symptomatic Hypocalcemia According to Vitamin D Levels

<table>
<thead>
<tr>
<th>Vitamin D Level, ng/mL</th>
<th>Total No. of Patients</th>
<th>Incidental Parathyroidectomy</th>
<th>Biochemical Hypocalcemia</th>
<th>Symptomatic Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency (&lt;10)</td>
<td>37</td>
<td>5 (13.5)</td>
<td>7 (18.9)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Deficient (10-19)</td>
<td>54</td>
<td>7 (13.0)</td>
<td>14 (25.9)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Insufficient (20-29)</td>
<td>19</td>
<td>6 (31.6)</td>
<td>5 (26.3)</td>
<td>0</td>
</tr>
<tr>
<td>Sufficient (≥30)</td>
<td>11</td>
<td>2 (18.2)</td>
<td>3 (27.3)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

Table 2. Corrected Calcium Levels According to Vitamin D Levels

<table>
<thead>
<tr>
<th>Vitamin D Level, ng/mL</th>
<th>Total No. of Patients</th>
<th>Morning Calcium on Day 1</th>
<th>Evening Calcium on Day 1</th>
<th>Morning Calcium on Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency (&lt;10)</td>
<td>37</td>
<td>8.76 (0.52)</td>
<td>8.76 (0.56)</td>
<td>8.68 (0.68)</td>
</tr>
<tr>
<td>Deficient (10-19)</td>
<td>54</td>
<td>8.80 (0.52)</td>
<td>8.80 (0.60)</td>
<td>8.56 (0.64)</td>
</tr>
<tr>
<td>Insufficient (20-29)</td>
<td>19</td>
<td>8.88 (0.44)</td>
<td>8.84 (0.48)</td>
<td>8.68 (0.72)</td>
</tr>
<tr>
<td>Sufficient (≥30)</td>
<td>11</td>
<td>8.60 (8.80)</td>
<td>8.64 (0.60)</td>
<td>8.22 (0.80)</td>
</tr>
</tbody>
</table>

Results

During the study period, 245 patients underwent thyroid surgery, of whom 149 underwent either total or completion thyroidectomy. One hundred twenty-three (82.6%) of these had postoperative vitamin D levels measured. Two patients were excluded because of preoperative hyperparathyroidism. The final study population consisted of 121 patients (109 female), with a mean age of 51.6 years (range, 14-87 years).

One hundred ten patients underwent total thyroidectomy, and 11 underwent completion thyroidectomy. Sixteen underwent concomitant central compartment neck dissection. Forty-one had a final pathologic diagnosis of cancer (exclusive of 6 patients with a diagnosis of cancer who underwent completion thyroidectomy with no cancer in the completion specimen). Twenty patients had hyperthyroidism, which was due to Graves disease (n = 12), toxic multinodular goiter (n = 5), amiodarone-induced thyrotoxicosis (n = 2), or De Quervain thyroiditis (n = 1).

The median vitamin D level of the entire cohort was 12.4 ng/mL (interquartile range, 10.20 ng/mL). The mean vitamin D level was 15.8 ng/mL (interquartile range, 4-48 ng/dL). One hundred ten patients (90.9%) were categorized as having insufficient vitamin D levels (<30 ng/mL). Ninety-one (75.2%) had vitamin D deficiency (<20 ng/mL), and 37 (30.6%) had severe deficiency (<10 ng/mL).

Postoperatively, 29 patients developed hypocalcemia (24.0%). Fourteen (11.6%) had symptoms of hypocalcemia at some point. Nineteen patients were prescribed calcium supplementation.

The mean postoperative PTH level in patients developing hypocalcemia was 9.7 pg/mL vs a mean PTH level of 27.3 pg/mL (to convert to nanograms per milliliter, multiply by 2.496) in patients not developing hypocalcemia (P < 1 × 10^-8).

Mean vitamin D levels were 15.6 ng/mL among patients who developed postoperative hypocalcemia vs 15.8 ng/mL among patients who remained eucalcemic throughout the postoperative period. There was no significant difference (P = .91).

Table 1 presents the incidence of postoperative biochemical and symptomatic hypocalcemia according to vitamin D category. No significant difference was found in the incidence of biochemical hypocalcemia between patients with severe vitamin D deficiency (<10 ng/mL) and patients with vitamin D levels of 10 ng/mL or greater (7 of 37 vs 22 of 84, P = .49). Similarly, no significant difference was found in the incidence of symptomatic hypocalcemia between patients with and without severe vitamin D deficiency (4 of 37 vs 10 of 84, P > .99).

Using a vitamin D cutoff of 20 ng/mL, no difference was found between patients with vitamin D deficiency (<20 ng/mL) and patients with vitamin D levels of 20 ng/mL or higher in the incidence of either biochemical (21 of 91 vs 8 of 30, P = .81) or symptomatic hypocalcemia (12 of 91 vs 2 of 30, P = .51).

Finally, no significant difference was found in the incidence of biochemical (P = .72) or symptomatic (P = .61) hypocalcemia in patients with sufficient vs insufficient vitamin D levels, although there were only 11 patients in the vitamin D sufficient group.

We also compared patients with vitamin D levels greater than 20 ng/mL and those with vitamin D levels less than 10 ng/mL. Once again no difference was found in the incidence of hypocalcemia (26.7% vs 18.9%, P = .56).

Mean calcium levels on the first postoperative day (morning and evening) and on the morning of the second postoperative day according to vitamin D category are presented in Table 2.

Statistics analysis was performed using XLSTAT statistical software (Addinsoft). A 2-tailed t test was used to analyze for differences in normally distributed data. A Fisher exact test was used on 2 × 2 contingency tables. Multivariate analysis was performed using logistic regression analysis.
Vitamin D and Postthyroidectomy Hypocalcemia

Table 3. Univariate Analysis of the Effect of Variables Studied on the Risk of Postoperative Biochemical Hypocalcemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of Patients</th>
<th>No. (%) of Patients With Hypocalcemia</th>
<th>P Value (Fisher Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D &lt;10 ng/mL</td>
<td>37</td>
<td>7 (18.9)</td>
<td>.49</td>
</tr>
<tr>
<td>Vitamin D &lt;20 ng/mL</td>
<td>91</td>
<td>21 (23.1)</td>
<td>.51</td>
</tr>
<tr>
<td>Vitamin D &lt;30 ng/mL</td>
<td>110</td>
<td>26 (23.6)</td>
<td>.72</td>
</tr>
<tr>
<td>Total thyroidectomy vs completion thyroidectomy</td>
<td>110</td>
<td>28 (25.5)</td>
<td>.46</td>
</tr>
<tr>
<td>Central neck dissection</td>
<td>16</td>
<td>7 (43.8)</td>
<td>.06</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>41</td>
<td>13 (31.7)</td>
<td>.18</td>
</tr>
<tr>
<td>Hyperthyroidism, any cause</td>
<td>20</td>
<td>6 (30.0)</td>
<td>.57</td>
</tr>
<tr>
<td>Graves disease</td>
<td>12</td>
<td>4 (33.3)</td>
<td>.48</td>
</tr>
</tbody>
</table>

(P = .73, P = .78, and P = .53, respectively). Similarly, no significant differences were found at any of these times between patients with vitamin D deficiency and vitamin D levels of 20 ng/mL or higher (P = .89, P = .90, and P = .93, respectively) or between patients with vitamin D insufficiency and vitamin D sufficiency (P = .26, P = .43, and P = .46, respectively).

Final histologic analysis revealed incidental parathyroidectomy in 20 patients (16.5%). The incidence of hypocalcemia among these patients was 35% (7 of 20) vs 22% (22 of 101) in patients without incidental parathyroidectomy. This difference was not significant (P = .25) (Table 3).

Among the other variables analyzed that may affect postoperative hypocalcemia, performance of a central neck dissection revealed an increased risk of hypocalcemia, but this was just outside the 5% level of significance on univariate analysis (P = .06). None of the other variables was significant (Table 3).

A multivariate analysis of the studied risk variables, including vitamin D levels greater than the median, performance of central neck dissection, total thyroidectomy (vs completion thyroidectomy), histologic diagnosis of cancer, presence of hyperthyroidism, and incidental parathyroidectomy, was performed. None of the studied variables was found to have any significant effect on the risk of hypocalcemia (Table 4).

At 6 months postoperatively, all patients had normal calcium levels. Six (5.0%) were still taking some regular calcium and/or vitamin D supplementation. Three of these 6 patients (50.0%) had undergone total thyroidectomy with concomitant central compartment neck dissection. Mean vitamin D level at the time of thyroidectomy in patients with persistent hypoparathyroidism was 18.0 ng/mL vs 15.7 ng/mL in patients without hypoparathyroidism (P = .53). None of the patients with persistent hypoparathyroidism had severe vitamin D deficiency (<10 ng/mL) at the time of thyroidectomy. The only factor that was significant for persistent hypoparathyroidism 6 months postoperatively was performance of concomitant central compartment neck dissection (P = .03).

Discussion

Transient hypocalcemia is a common occurrence after total thyroidectomy. The reported incidence of this phenomenon is highly variable (0%-65%) and depends to a large extent on the definition of hypocalcemia used.27 The cause would appear to be postoperative hypoparathyroidism due to intraoperative trauma to parathyroid glands or their vasculature or inadvertent parathyroid removal. With increasing economic pressures to shorten the length of hospital stay in patients undergoing total thyroidectomy, there has been much recent interest in studying risk factors for the development of postoperative hypocalcemia.

Vitamin D plays an important role in calcium metabolism by increasing calcium absorption for the gastrointestinal tract. Patients with vitamin D deficiency thus have impaired gastrointestinal tract calcium absorption. These patients commonly have a secondary hyperparathyroidism, which restores calcium levels by increasing renal calcium reabsorption and increasing bone turnover. It has been suggested that preoperative secondary hyperparathyroidism in patients with medically treated Graves disease and vitamin D deficiency can render patients especially susceptible to postthyroidectomy tetany due to loss of a compensatory role of PTH in maintaining calcium levels concomitant with continued increased demand for bone restoration.10 Therefore, it would seem reasonable to hypothesize that low vitamin D levels in all patients undergoing thyroidectomy may predispose patients to increased risk of hypocalcemia.

A small number of studies have examined the role of vitamin D levels as a risk factor for hypocalcemia after total thyroidectomy. Lin et al14 reported that vitamin D levels did not predict hypocalcemia after thyroidectomy in a series of 152 patients undergoing near-total thyroidectomy. However, all patients in this study were routinely prescribed calcium carbonate and cholecalciferol (vitamin D) postoperatively. Chia et al11 reported no association between vitamin D levels and postoperative hypocalcemia among a series of 103 patients. However, this was a heterogenous group, including a large number of patients undergoing parathyroidectomy, with only 27 patients undergoing total thyroidectomy. In contrast to the above studies, Erbull et al24 reported vitamin D levels less than 15 ng/mL to be associated with a significantly higher rate of postthyroidectomy hypocalcemia among a series of 200 patients undergoing thyroidectomy in Turkey, whereas Kirkby-Bott et al15 reported that patients with vitamin D levels greater than 50 nmol/L had a significantly lower incidence of hypocalcemia after total thyroidectomy than patients with vita-
The incidence of hypocalcemia in the present study was found to be 87%. In contrast, all patients in our study undergoing total thyroidectomy underwent total thyroidectomy. The number of patients undergoing total thyroidectomy was 148, with 1 cm³ or less of thyroid tissue left around the Berry ligament, and a few (n = 52) undergoing total thyroidectomy. This finding was important because extent of thyroidectomy was found by these authors to be a significant factor for predicting hypocalcemia. The incidence of hypocalcemia in the total thyroidectomy group was 87%. In contrast, all patients in our study who underwent total thyroidectomy were found to be free of any evidence of postoperative hypocalcemia by Kirkby-Bott et al., with an incidence of zero.

One difference between our series and that of Erbil et al. was that in their series most patients (n = 110) underwent near-total thyroidectomy, with 1 cm³ or less of thyroid tissue left around the Berry ligament, and a few (n = 52) undergoing total thyroidectomy. This finding was important because extent of thyroidectomy was found by these authors to be a significant factor for predicting hypocalcemia. The incidence of hypocalcemia in the total thyroidectomy group was 87%. In contrast, all patients in our study who underwent total thyroidectomy were found to be free of any evidence of postoperative hypocalcemia by Kirkby-Bott et al., with an incidence of zero.

On univariate analysis, performance of concomitant central compartment neck dissection trended toward a higher incidence of postoperative hypocalcemia, although this finding was not significant on the multivariate analysis. Central compartment neck dissection may increase the risk of inadvertent parathyroid removal and/or disruption of parathyroid blood supply due to proximal ligation of the inferior thyroid arteries. The effect of central neck dissection on postoperative hypocalcemia is controversial. Several authors have reported that this significantly increases the risk of postoperative hypocalcemia. However, others have reported no difference.

Many factors should be considered in interpreting the findings of the present study. First, this was a retrospective study, with vitamin D levels not measured in more than one-sixth of patients operated on during the study period. Second, there was a high incidence of vitamin D insufficiency in our series, with less than 10% having vitamin D levels that would be considered sufficient. Even though we examined many different cutoff levels for vitamin D without finding any significant effect on postthyroidectomy hypocalcemia, because the number of patients with sufficient vitamin D levels was low, we cannot discount the possibility that there might be a difference in postthyroidectomy calcium levels in patients with sufficient as opposed to insufficient vitamin D levels. Third, this was a single-surgeon series of thyroid operations. Thus, it is possible that our findings may not be applicable to thyroidectomy performed by different techniques to those used by the senior author.

The strengths of this study include the use of a prospectively maintained database to extract much of the data, including symptoms of hypocalcemia, calcium replacement, and incidence of long-term hypoparathyroidism; the homogeneity of the surgical series, with inclusion of only patients undergoing total thyroidectomy or total completion thyroidectomy, without inclusion of any cases of subtotal thyroidectomy; the fact that patients were not routinely prescribed oral calcium or vitamin D in the perioperative period; and the inclusion of multiple variables with a putative effect on postoperative hypocalcemia along with vitamin D levels in multivariate analysis.

Conclusions

The findings of our study suggest that perioperative vitamin D levels do not have any significant effect on the incidence of postthyroidectomy hypocalcemia. However, this does not discount the possible importance of vitamin D levels in facilitating restoration of calcium levels in patients who do develop postoperative hypocalcemia. Confirmation of our findings by future multicenter studies is warranted, with possible stratification by surgeon volume and/or practice setting (academic vs community) to minimize bias.


