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ORIGINAL ARTICLE

Vitamin D level is not a predictor of hypocalcemia after total thyroidectomy

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Abstract
Purpose As the incidence of thyroid cancer has increased, hypocalcemia, a common complication of thyroid surgery, has become a serious problem. However, no definite predictor of postoperative hypocalcemia is known. In this study, our purpose was to investigate the potential role of vitamin D as a predictor of postoperative hypocalcemia.
Methods A prospective observational study was performed on patients who underwent total thyroidectomy for thyroid cancer performed by a single experienced surgeon between October 2013 and September 2014.
Measurements Their serum 25-OH vitamin D levels were measured preoperatively. On the day after surgery, serum calcium and intact parathyroid hormone levels were measured, and symptoms of hypocalcemia were recorded.
Results Of the 134 patients, laboratory and symptomatic hypocalcemia developed in 52 patients (39 %) and 25 patients (19 %), on the day after surgery. The preoperative vitamin D level was 16.5±9.2 ng/mL, and this value did not differ according to laboratory or symptomatic hypocalcemia (p=0.94). The incidence of laboratory or symptomatic hypocalcemia did not differ according to vitamin D deficiency. Only incidental parathyroidectomy was associated with symptomatic hypocalcemia (p=0.03).
Conclusions Vitamin D level is not a predictor of hypocalcemia after total thyroidectomy for thyroid cancer. Thus, routine preoperative screening for vitamin D is not recommended.

Keywords Hypocalcemia · Thyroid cancer · Thyroidectomy · Vitamin D

Introduction

As the incidence of thyroid cancer has increased, the number of thyroid surgeries performed has also increased [1]. The most common complications of thyroid surgery are hypoparathyroidism and recurrent laryngeal nerve injury. The incidence of postoperative hypocalcemia has been reported to range from 1 to 50 % [2–4]. Hypocalcemia can be asymptomatic but cause perioral or distal acral paresthesia, severe cramps, tetany, and convulsion. Although most patients with hypocalcemia recover within a few months [3], symptomatic hypocalcemia is of concern because it leads to prolonged hospitalization or readmission.

Several studies have tried to identify a risk factor for hypocalcemia after thyroid surgery. Some studies reported an association with early postoperative calcium level [5–7] or intraoperative parathyroid hormone (PTH) level (<10 pg/mL) [8], but they did not provide a definitive prediction of hypocalcemia. Some researchers propose routine oral calcium supplements with or without vitamin

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D to prevent postoperative hypocalcemia [9–13]. This may reduce symptomatic hypocalcemia and shorten hospital stay.

Recently, vitamin D has been suggested as a risk factor for postoperative hypocalcemia [14–16]. Vitamin D deficiency can decrease intestinal calcium absorption and stimulate PTH synthesis and secretion to maintain normal calcium levels [17]. Vitamin D deficiency is also reported to be associated with hyperparathyroidism [18, 19]. It has been hypothesized that temporary hypoparathyroidism after thyroid surgery may fail to compensate vitamin D deficiency and lead to postoperative hypocalcemia. Some studies showed the association between vitamin D deficiency and postoperative hypocalcemia or a longer hospital stay [14–16]; however, some did not [20–23], and Nhan et al. reported that vitamin D deficiency even had a tendency to decrease a risk of postoperative hypocalcemia [23].

Controversies remain regarding vitamin D deficiency as a predictor of postoperative hypocalcemia. Therefore, in this study, we investigated the association between vitamin D and postoperative hypocalcemia prospectively in patients undergoing total thyroidectomy for thyroid cancer.

Material and methods

Patients who underwent total thyroidectomy for thyroid cancer by a single surgeon in the Korea Cancer Center Hospital between October 2013 and September 2014 were enrolled prospectively. In accordance with the American Thyroid Association guidelines, total thyroidectomy was performed if there were big, multiple, or bilateral thyroid cancers with or without extrathyroid extensions and lymph node metastases. Patients who had had previous thyroid surgery or irradiation, concomitant parathyroid disease, or took either calcium or vitamin D supplements were excluded. Patients with abnormal renal function (glomerular filtration rate (GFR) <60 mL/min/1.73 m^2) were also excluded. Informed consent was obtained from all eligible patients. During study period, 138 patients underwent total thyroidectomy for thyroid cancer, and four patients were excluded because of previous thyroid irradiation (n=1), concomitant hyperparathyroidism (n=1), consent withdrawal (n=1), or loss to follow-up (n=1). Finally, 134 patients were included and analyzed in this study. The study protocol was approved by the institutional review board of Korea Cancer Center Hospital (IRB No. K-1401-002-036).

All patients underwent preoperative ultrasonography and fine-needle aspiration. The results of cytology were papillary thyroid carcinoma (PTC), suspicious PTC, or medullary thyroid carcinoma (MTC). All patients underwent total thyroidectomy with central compartment neck dissection (level VI) with or without selective neck dissection (level IIa, III, IV, and Vb) performed by an experienced senior thyroid surgeon. For total thyroidectomy, a capsular dissection technique was used with routine identification and preservation of the recurrent laryngeal nerves and parathyroid glands. The parathyroid glands were identified and preserved on their vascular pedicle whenever possible. Incidentally removed or devascularized glands were autotransplanted in a standard fashion into the sternocleidomastoid muscle. The surgical specimens were carefully checked for parathyroid glands.

Serum 25-OH vitamin D level was measured preoperatively by using a radioimmunoassay (Diasorin, Stillwater, MN, USA). Serum calcium, ionized calcium, and intact PTH levels were measured preoperatively, 1 day after surgery and 3 weeks after surgery. Intact PTH level was measured using an autoanalyzer (the ADVIA Centaur immunoassay, NY, USA). The reference range of PTH is 14–72 pg/mL. Laboratory hypocalcemia was defined as total calcium concentration less than 8.0 mg/dL, and symptomatic hypocalcemia was defined as subjective or objective symptoms such as tingling, numbness, or carpopedal spasm with laboratory hypocalcemia. When symptomatic hypocalcemia developed during hospital stay, calcium and vitamin D were administered orally. If the symptoms continued to persist, calcium gluconate was administered intravenously. The length of hospital stay was recorded for all patients.

We divided all patients into three groups according to the laboratory or symptomatic hypocalcemia. Age, sex, body mass index (BMI), laboratory findings, and incidental parathyroidectomy were compared among groups. The data were also analyzed by dividing the patients into two groups depending on vitamin D deficiency. Vitamin D deficiency was defined as vitamin D level <10 or 20 ng/mL.

Sample size calculation and statistical analyses

Based on previous studies [15, 16], we hypothesized that hypocalcemia developed in 25 % of patients without vitamin D deficiency, and the sample size of the study was calculated to detect a difference of 15 % in hypocalcemia using Flemming's model with a type 1 error (α) of 0.05 and a power (β) of 80 %,

Table 1 Patient characteristics

Parameter	Mean±SD
Age (years)	50±11
Sex (men:women)	21:113
BMI (kg/m^2)	24.6±3.9
Creatinine (mg/dL)	0.7±0.1
GFR (mL/min/1.73 m^2)	98±16
Calcium (mg/dL)	9.3±0.4
PTH (pg/mL)	50±18
Vitamin D (ng/mL)	16.5±9.2

BMI body mass index, *GFR* glomerular filtration rate, *PTH* parathyroid hormone

Table 2 Comparisons between patients with or without hypocalcemia

	No hypocalcemia (n=82)	Laboratory hypocalcemia without symptom (n=27)	Symptomatic hypocalcemia (n=25)	p value
Age (years)	50±11	52±14	48±10	0.47
Sex (men:women)	15:67	4:23	2:23	0.22
BMI (kg/m^2)	24.8±3.9	24.4±4.1	24.1±3.5	0.68
Preoperative calcium (mg/dL)	9.3±0.4	9.3±0.4	9.3±0.4	0.94
Preoperative PTH (pg/mL)	49±16	55±25	50±15	0.31
Preoperative vitamin D (ng/mL)	16.6±8.9	15.9±9.0	16.5±10.6	0.94
Selective neck dissection	9 (11 %)	8 (30 %)	3 (12 %)	0.44
Incidental parathyroidectomy	11 (13 %)	4 (15 %)	8 (32 %)	0.04

BMI body mass index, *PTH* parathyroid hormone

resulting in 57 subjects in each group (group with vitamin D deficiency and group without vitamin D deficiency).

All data are expressed as mean±standard deviation. Categorical variables (sex, incidental parathyroidectomy, and the presence of hypocalcemia) were analyzed using the χ^2 test, and continuous variables (age, BMI, calcium, PTH, and vitamin D) were compared using the Student's t test or one-way ANOVA. To identify predictor of postoperative hypocalcemia, logistic regression analysis was performed. All analyses were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA), and a $p<0.05$ was considered statistically significant.

Results

A total of 134 patients were included in this analysis. The mean age at surgery was 50 years (range, 24–77 years), and there were 21 men and 113 women. The patient characteristics are summarized in Table 1.

All patients underwent a total thyroidectomy with central compartment neck dissection. Among them, 20 (15 %) patients underwent additional selective neck dissection. The final pathological diagnoses were PTC (n=132) and MTC (n=2). The mean size of the tumor was 1.2±0.9 cm, and lymph node metastasis was observed in 83 (62 %) patients. During surgery, surgeon tried to preserve parathyroid glands, and parathyroid gland autotransplantations were performed in 19 (14 %) patients. Nevertheless, regarding surgical specimens, one parathyroid gland was removed incidentally in 22 patients, and two parathyroid glands were removed in one patient. Additional selective neck dissection did not increase the risk of incidental parathyroidectomy (p=0.75).

The mean preoperative calcium and PTH levels were 9.3±0.4 mg/dL and 50±18 pg/mL, respectively. On the day after surgery, serum calcium and PTH levels were 8.1±0.5 mg/dL and 26±20 pg/mL, respectively. Laboratory hypocalcemia developed in 52 (39 %) patients. Symptomatic hypocalcemia developed in 25 (19 %) patients, and calcium and vitamin D supplements were started.

There was no difference in age, sex, BMI, preoperative calcium or PTH levels, or selective neck dissection between patients with or without laboratory or symptomatic hypocalcemia on the day after surgery (Table 2). The length of hospital stay also did not differ between patients with or without symptomatic hypocalcemia (7.5±1.9 days vs. 7.9±3.1 days,

Table 3 Predictor of postoperative hypocalcemia

	Laboratory hypocalcemia	Symptomatic hypocalcemia
Age	1.00 (0.97–1.04)	0.98 (0.95–1.02)
Sex (women)	1.72 (0.62–3.75)	2.43 (0.53–11.18)
BMI	0.96 (0.88–1.05)	0.96 (0.85–1.08)
Preoperative calcium	0.86 (0.36–2.04)	0.84 (0.28–2.47)
Preoperative PTH	1.01 (0.99–1.03)	1.00 (0.98–1.03)
Vitamin D (<20 ng/mL)	0.85 (0.40–1.80)	0.93 (0.36–2.35)
Vitamin D (<10 ng/mL)	1.82 (0.86–3.83)	1.68 (0.68–4.13)
Selective neck dissection	2.18 (0.83–5.69)	0.74 (0.20–2.74)
Incidental parathyroidectomy	1.94 (0.78–4.79)	2.95 (1.08–8.03)*

BMI body mass index, *PTH* parathyroid hormone

*$p<0.05$

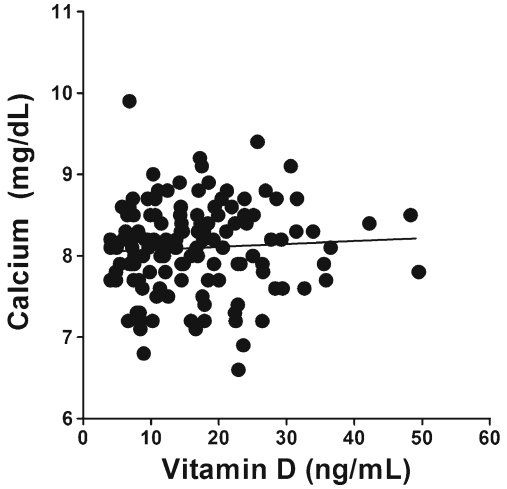

Fig. 1 The preoperative vitamin D level and postoperative calcium level

p=0.57). The mean preoperative vitamin D level was 16.5± 9.2 ng/mL and was not significantly different among groups. The parathyroid glands removed incidentally during surgery were more frequently found in patients with symptomatic hypocalcemia (p=0.04; Table 2). In logistic regression analysis, incidental parathyroidectomy was significantly associated with an increased risk of symptomatic hypocalcemia (p= 0.03; Table 3).

We examined the association between preoperative vitamin D level and postoperative calcium level. Postoperative calcium level did not correlate with preoperative vitamin D level (p=0.49; Fig. 1). Vitamin D deficiency is generally defined as a vitamin D level <20 ng/mL [24], and 90 (69 %) patients had vitamin D deficiency (<20 ng/mL). The incidence of laboratory hypocalcemia (38 vs. 42 %, p=0.70) or symptomatic hypocalcemia (18 vs. 20 %, p=1.00) was not different between patients with and without vitamin D deficiency. Next, we used a stricter cutoff value of 10 ng/mL. Vitamin D deficiency (<10 ng/mL) was found in 41 (31 %) patients. Postoperative calcium levels in patients with vitamin D deficiency were not different from those in patients without vitamin D deficiency (Table 4). The percentage of laboratory or symptomatic hypocalcemia did not differ according to vitamin D deficiency (Table 4).

At 3 weeks after surgery, laboratory and symptomatic hypocalcemia had developed in five additional patients. In all, laboratory hypocalcemia was noted in 57 (43 %) patients, while calcium and vitamin D supplements were administrated in 30 (22 %) patients. At the 6-month follow-up, calcium and vitamin D supplements were discontinued in 24 of the 30 patients and it was maintained in only six patients. Among them, five patients took below 500 mg of elemental calcium per day, and 1000 mg of elemental calcium per day was taken in one patient, which did not have vitamin D deficiency preoperatively.

Discussion

Vitamin D plays an important role in calcium homeostasis. Therefore, serum vitamin D level is expected to be associated with hypocalcemia after thyroidectomy. However, this hypothesis remains controversial [14–16, 20–22], and previous studies had some limitations such as retrospective design, differences in underlying disease, surgical extent, and surgeon. The surgical extent, surgeon's experience, and underlying disease such as hyperthyroidism affect the risk of hypocalcemia

Table 4 Comparisons between patients with or without vitamin D deficiency

	Vitamin D deficiency (<10 ng/mL)		p value
	No (n=93)	Yes (n=41)	
Vitamin D (ng/mL)	20.5±8.2	7.3±1.7	<0.01
Age (years)	49±11	50±11	0.67
Sex (men:women)	17:76	4:37	0.30
BMI (kg/m^2)	24.7±3.6	24.5±4.4	0.80
Preoperative calcium (mg/dL)	9.3±0.4	9.2±0.4	0.16
Preoperative PTH (pg/mL)	49±17	53±20	0.19
Selective neck dissection	16 (17 %)	7 (17 %)	1.00
Incidental parathyroidectomy	16 (17 %)	7 (17 %)	1.00
On the day after surgery			
Postoperative calcium (mg/dL)	8.1±0.5	8.0±0.5	0.16
Postoperative PTH (pg/mL)	24±16	30±27	0.12
Laboratory hypocalcemia	32 (34 %)	20 (49 %)	0.13
Symptomatic hypocalcemia	16 (17 %)	7 (17 %)	1.00

BMI body mass index, *PTH* parathyroid hormone

[25]. To cope with these limitations, we used a prospective design that included a similar population, a similar pathology, the same operation, and the same surgeon. In this study, preoperative serum vitamin D level was not associated with postoperative hypocalcemia. Only incidental parathyroidectomy showed an association with postoperative hypocalcemia. Because incidental parathyroidectomy significantly attributed to symptomatic hypocalcemia, we analyzed the group in which no parathyroid glands were removed incidentally (n=111). However, even excluding the patients whose parathyroid glands were removed incidentally, vitamin D level did not differ between patients with or without laboratory or symptomatic hypocalcemia (data not shown).

The causes of hypocalcemia and hypoparathyroidism are multifactorial and include hemodilution, surgical injury such as devascularization, and incidental resection of the parathyroid gland. The incidence of incidental parathyroidectomy ranges from 5 to 20 % even for experienced surgeons [25, 26]. Because a large number of parathyroid glands are located within the thyroid gland, incidental parathyroidectomy is difficult to avoid. However, the clinical relevance of incidental parathyroidectomy, i.e., whether it is associated with postoperative hypocalcemia, is unclear [3, 25–27]. The question of how many parathyroid glands must be preserved to avoid hypocalcemia remains unresolved. Some believe that a single intact parathyroid gland is enough, and others believe that at least three parathyroid glands are necessary [3]. In this study, incidental parathyroidectomy increased the risk of postoperative hypocalcemia, suggesting the importance of identifying and preserving as many parathyroid glands as possible during surgery.

Vitamin D deficiency is common in Korea, the USA, and Europe alike [28, 29]. In this study, the incidence of vitamin D deficiency was fairly high. However, vitamin D deficiency did not show an association with postoperative hypocalcemia. Currently, the role of vitamin D is being studied in several thyroid-related researches, in addition to its potential role in postoperative hypocalcemia. Vitamin D level has been reported to be associated with autoimmune thyroid disease or the stage of thyroid cancer [30, 31]. Therefore, there is a possibility that vitamin D level is not a predictor of postoperative hypocalcemia but a marker for disease severity, because for underlying disease with greater severities, a wider surgical extent is required, thus increasing the chances of hypocalcemia.

In this study, symptomatic hypocalcemia was finally noted in 22 % of all the patients although all operations were performed by an experienced surgeon. This result is in accordance with that of a previous report [4]. Since postoperative hypocalcemia is affected by the surgical procedure, it is difficult to predict. Moreover, hypocalcemia can develop a few days after thyroid surgery. Previous studies have reported that the time to reach the nadir of serum calcium level is generally 2 or 4 days after surgery [3, 32]. Unfortunately, we planned to measure serum calcium concentration only on 1 day after surgery, and serum calcium concentration on 2 or 3 days after surgery was measured only in 62 (46 %) patients. Among them, laboratory hypocalcemia on day 2 or 3 was newly developed in four patients. Some symptomatic hypocalcemia (17 %) also developed a few days after surgery. Therefore, if length of hospital stay is more than 4 days, the development of hypocalcemia can be observed without pre-medication. However, in case of outpatient-based thyroid surgery or early discharge after surgery, preoperative routine oral calcium and vitamin D supplementation can be considered [10, 13].

The method of vitamin D level measurement and the definition of vitamin D deficiency used here can be considered as the limitations of this study. High-performance liquid chromatography is the gold standard for vitamin D measurement, but we measured vitamin D level using a commercialized radioimmunoassay. The definition of vitamin D deficiency is controversial. We used two cutoff values of 10 and 20 ng/mL, and the incidence of postoperative hypocalcemia was not different between patients with and without vitamin D deficiency even if using any cutoff values. When patients were divided into quartiles according to the vitamin D level, there was no association between vitamin D level and postoperative hypocalcemia (data not shown). In addition, this study has a relatively small sample size. This study was terminated because an interim analysis revealed that the vitamin D deficiency group showed no tendency toward increased postoperative hypocalcemia.

Conclusion

In this study, we demonstrated that serum vitamin D level is not a predictor of hypocalcemia after total thyroidectomy for thyroid cancer. Thus, routine preoperative screening for vitamin D is not recommended.

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Conflicts of interest The authors declare that they have no conflict of interest.

Authors' contribution G. H. L. and M. J. K. contributed to the study conception and design, analysis and interpretation of data, and drafting of the manuscript. G. H. L. and M. L. collected the data. Y. H. K. and H. I. K. participated in the drafting and critical revision of the manuscript.

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