

Impact of pre-operative serum 25-hydroxyvitamin D on post-operative serum calcium in patients undergoing total thyroidectomy for benign goitre: retrospective study of 246 patients

M ERLEM, N KLOPP-DUTOTE, A BIET-HORNSTEIN, V STRUNSKI, C PAGE

Department of ENT and Head and Neck Surgery, University Hospital, Amiens, France

Abstract

Objective: To determine whether pre-operative serum 25-hydroxyvitamin D has an impact on post-operative parathyroid hormone and serum calcium levels in patients undergoing total thyroidectomy for benign goitre.

Methods: This single-centre, retrospective study comprised 246 unselected surgical patients who had undergone total thyroidectomy for bilateral, benign, multinodular goitre. The correlation between pre-operative serum 25-hydroxyvitamin D and post-operative serum parathyroid hormone and serum calcium was studied to determine whether low pre-operative serum 25-hydroxyvitamin D was predictive of post-operative hypocalcaemia.

Results: Seventy-nine patients (32 per cent) had post-operative hypocalcaemia. Eighteen patients (7.32 per cent) experienced unintentional parathyroidectomy (1 parathyroid gland in 15 patients, 2 parathyroid glands in 3 patients). In univariate analysis, pre-operative serum 25-hydroxyvitamin D was not correlated with post-operative serum calcium ($p = 0.69$) or post-operative serum parathyroid hormone ($p = 0.5804$). Furthermore, in multivariate analysis, which took into account unintentional parathyroidectomy, no correlation was found ($p = 0.33$). Bilateral unintentional parathyroidectomy was statistically associated with post-operative hypocalcaemia ($p = 0.032$).

Conclusion: Pre-operative serum 25-hydroxyvitamin D did not appear to have any impact on post-operative serum calcium in patients undergoing total thyroidectomy for benign goitre.

Key words: Thyroidectomy; Hypocalcemia; Hypoparathyroidism; Vitamin D; Parathyroid Hormone

Introduction

Total thyroidectomy is a common surgical procedure, mainly performed for benign diseases. Although recurrent laryngeal nerve palsy is considered to be the main post-operative complication of total thyroidectomy (because it can induce significant voice disorders, swallowing difficulties, respiratory disorders and serious social problems especially when bilateral), hypocalcaemia is the most frequent complication of total thyroidectomy. It can be transient or permanent (permanent hypoparathyroidism), and is sometimes difficult to manage.¹ According to the medical literature, the incidence of transient and permanent hypocalcaemia ranges from 3 to 52 per cent and 0.4 to 13 per cent, respectively.²

Early post-operative hypocalcaemia is the main cause of prolonged post-operative hospital stay after total thyroidectomy, although the current trend is to decrease the length of hospital stay after thyroid surgery, especially by performing out-patient surgery in selected patients.^{3,4}

Although post-thyroidectomy hypocalcaemia is a common complication, its causes and mechanisms

remain unclear. Many risk factors for an increased risk of post-operative hypocalcaemia have been identified, including: old age, Graves' disease, surgical techniques, concurrent neck dissection, large surgical volumes (cervicothoracic goitre) or surgeon inexperience.⁵ However, some studies have implicated the role of 25-hydroxycholecalciferol (vitamin D3) deficiency in the pathogenesis of post-thyroidectomy hypocalcaemia.^{6–11}

This study was designed to determine whether pre-operative serum 25-hydroxyvitamin D has an impact on post-operative parathyroid hormone (PTH) and serum calcium levels in patients undergoing total thyroidectomy for benign goitre.

Materials and methods

This retrospective single-centre study was based on a four-year period from January 2010 to January 2014.

Ethical considerations

This study was approved by the Amiens University Medical Centre's Institutional Review Board, France.

The study was conducted in accordance with French law concerning ethical procedures in medical research.

Population

During the study period, 547 patients underwent total thyroidectomy for benign thyroid disease in the ENT and Head and Neck Surgery Department of Amiens University Hospital, France.

Method

Inclusion criteria were: patients of all ages and either gender; patients who underwent total thyroidectomy for multinodular benign goitre; patients for whom pre-operative serum 25-hydroxyvitamin D data from at least 2 weeks before surgery were available; patients with 6-hour post-operative PTH assay data; and patients with at least day 1 and day 2 post-operative serum calcium assay data.

Exclusion criteria were: patients undergoing unilateral thyroid lobectomy; patients with thyroid cancer, thyroiditis or Graves' disease; patients for whom no pre-operative serum 25-hydroxyvitamin D assay data were available; patients who had pre-operative vitamin D oral supplementation; patients for whom no post-operative serum calcium assay data were available; and patients with a history of external beam radiotherapy to the neck.

Total serum calcium was assayed during the first 2 post-operative days, on the 10–15th post-operative day, and thereafter as justified by the previous assay results. All post-operative serum calcium levels were corrected using the following formulae: corrected serum calcium (mmol/l) = measured serum calcium (mmol/l) – 0.025 × (serum albumin (g/l) – 40), or measured serum calcium (mmol/l) / (0.55 + serum protein (g/l) / 160).

Hypocalcaemia was defined as a serum calcium concentration of less than 2 mmol/l on two occasions (post-operative day 1 and day 2), while a serum calcium concentration of less than 1.85 mmol/l was considered to reflect severe hypocalcaemia. The lowest serum calcium level was used to define the presence of hypocalcaemia (absolute value for calculations).

Patients with symptomatic hypocalcaemia and serum calcium level greater than 1.85 mmol/l were treated by an oral calcium supplement (3 g per day). Patients with hypocalcaemia and serum calcium level of less than 1.85 mmol/l were almost always symptomatic, and were treated with oral vitamin D (alfacalcidol 0.25 µg three times daily or 1 µg once daily) and calcium (3 g daily) supplements.

Hypovitaminosis D was defined as pre-operative serum 25-hydroxyvitamin D level of less than 30 ng/ml.

All statistical analyses were performed with XLSTAT 2014 software, version 5.03 (Addinsoft, Paris, France) for Windows (Microsoft, Redmond, Washington, USA). The primary outcome was post-operative hypocalcaemia. Pre-operative serum 25-hydroxyvitamin D was compared to post-operative

serum calcium using Pearson product-moment correlation coefficient. Multivariate analysis, taking into account unintentional parathyroidectomy, was performed using analysis of covariance. Five subgroups based on pre-operative serum 25-hydroxyvitamin D levels (30 ng/ml or higher, 20–29 ng/ml, 15–19 ng/ml, 10–14 ng/ml and less than 10 ng/ml) were also studied by analysis of covariance.

Results

Patients

A total of 246 patients (176 females and 70 males), with a mean age of 55 years (range, 18–83 years), were included in the study. A total of 301 patients were excluded from the study because of the absence of pre-operative serum 25-hydroxyvitamin D assay data and/or oral vitamin D supplementation before surgery ($n = 238$), or the absence of post-operative serum calcium assay data ($n = 63$).

Surgery

All patients underwent total thyroidectomy via a small neck incision under general anaesthesia. This was performed by three senior surgeons (AB, VS and CP) using the same technique and materials. Thyroid lobectomies were performed in a caudocranial direction by capsular dissection, after first identifying the recurrent laryngeal nerve. Sternotomy and lymph node dissection along the recurrent laryngeal nerve were never performed.

Histological data

All patients had benign multinodular goitre on final histological examination. Unilateral unintentional parathyroidectomy was observed on final histological examination in 15 patients (6.1 per cent), and bilateral unintentional parathyroidectomy was observed in 3 patients (1.22 per cent).

Serum assays

The mean pre-operative serum 25-hydroxyvitamin D level was 18.6 ng/ml (standard deviation (SD) = 12.3; range, 3.7–71.6 ng/ml). The mean pre-operative serum calcium level was 2.33 mmol/l (SD = 0.13; range, 1.94–2.71 mmol/l).

The mean post-operative serum calcium level was 2.07 mmol/l (SD = 0.21; range, 1.47–2.45 mmol/l). Seventy-nine of the 246 patients (32 per cent) had a post-operative serum calcium level of less than 2 mmol/l.

Statistics

On univariate analysis ($p = 0.69$) and multivariate analysis ($p = 0.335$), pre-operative serum 25-hydroxyvitamin D was not correlated with post-operative serum calcium. On univariate analysis, pre-operative serum 25-hydroxyvitamin D was not correlated with 6-hour post-operative serum PTH ($p = 0.5804$). Subgroup

analysis showed no correlation between pre-operative serum 25-hydroxyvitamin D and post-operative serum calcium ($p = 0.24$). However, bilateral unintentional parathyroidectomy was correlated with post-operative hypocalcaemia ($p = 0.032$).

Discussion

The impact of pre-operative serum 25-hydroxyvitamin D on post-operative serum calcium is still debated in the literature and remains controversial.

Impact on post-operative calcium

Like other studies,^{12–18} this study showed no correlation between pre-operative serum 25-hydroxyvitamin D and post-operative serum calcium in patients who underwent total thyroidectomy (notably for benign goitre).

Other studies showed that a low pre-operative serum 25-hydroxyvitamin D level was predictive of post-operative hypocalcaemia.^{6–11} However, all of these studies (like the present study) were mainly retrospective, comprising relatively few patients. Several other studies have also involved patients (more or less selected) who received oral vitamin D supplementation (with or without oral calcium) before and/or after surgery, which seemed to lower the incidence of post-operative hypocalcaemia.^{19–21} This hinders interpretation of the results, as it has been clearly demonstrated that patients receiving routine oral calcium or vitamin D supplementation after total thyroidectomy have a significantly lower rate of post-operative hypocalcaemia.^{22,23}

Bias of previous studies

All of these conflicting results are therefore not really surprising and can be explained by several biases.

For instance, a standardised definition for post-operative hypocalcaemia after thyroidectomy has not yet been established, and no standardised definition for hypocalcaemia has been used in studies investigating techniques for the prediction of post-thyroidectomy hypocalcaemia.²⁴ So, how should hypocalcaemia be defined? By symptoms and signs? By symptoms alone? By absolute serum calcium (usually serum calcium levels of less than 2 mmol/l)? Or by the use of total, corrected or ionised calcium measurements?²⁴

Similarly, there is no standardised definition for vitamin D deficiency. How should vitamin D deficiency be defined? By serum 25-hydroxyvitamin D level (usually less than 30 ng/ml) alone? Or by low serum 25-hydroxyvitamin D levels associated with symptoms?

Globally, most authors consider that a serum calcium level of less than 2 mmol/l defines hypocalcaemia and a serum 25-hydroxyvitamin D level of less than 30 ng/ml defines hypovitaminosis D.^{25–28} It has been demonstrated that a serum 25-hydroxyvitamin D level of less than 30 ng/ml might increase the risk of bone fractures.²⁶ A serum 25-hydroxyvitamin

D level of less than 18 ng/ml might increase the risk of stroke.²⁷ In addition, a serum 25-hydroxyvitamin D level of more than 30 ng/ml is necessary to avoid secondary hyperparathyroidism.²⁸ However, the large Copenhagen Vitamin D ('CopD') study (an observational cohort study of 247 574 patients) showed a reverse J-shaped relationship between serum 25-hydroxyvitamin D and all-cause mortality, with a lowest overall mortality risk at 50–60 nmol/l (i.e. 19–23 ng/ml)²⁹ and a lowest cardiovascular disease risk at 70 nmol/l (i.e. 27 mg/ml).³⁰ True hypovitaminosis D can therefore be considered when the serum 25-hydroxyvitamin D level is less than 27 ng/ml (or 23 mg/ml).

Post-operative hypocalcaemia is multifactorial

Post-operative hypocalcaemia after total thyroidectomy must be considered to be multifactorial. Numerous factors, probably sometimes associated, might be responsible for post-operative hypocalcaemia. These factors include: haemodilution secondary to peri-operative intravenous fluid administration; increased urinary calcium excretion secondary to surgical stress; calcitonin release after thyroid gland manipulation during thyroid surgery; 'hungry bone syndrome' in patients with metabolic bone disease; and, of course, direct injury, removal or devascularisation of parathyroid glands during surgery.²⁴ All of these factors can introduce a bias in studies on post-operative hypocalcaemia.

Concept and results of study

This study was designed to reduce bias, particularly by matching the patient population in terms of disease (only benign lesions requiring conventional total thyroidectomy, with only limited dissection of the parathyroid gland region), the management of vitamin D status and post-operative hypocalcaemia (no pre-operative supplementation, and post-operative supplementation starting on post-operative day 2 based on the results of the second serum calcium assay), in order to precisely determine the role of the patient's pre-operative vitamin D status.

The majority of patients in this study (224 patients; 82 per cent) were considered to have hypovitaminosis D, and 160 patients (58.6 per cent) had 'severe' hypovitaminosis D (serum 25-hydroxyvitamin D level of less than 20 ng/ml). This is consistent with other studies which found that a low pre-operative serum 25-hydroxyvitamin D level was predictive of post-operative hypocalcaemia.^{8–10} However, this study showed no correlation between pre-operative serum 25-hydroxyvitamin D and post-operative hypocalcaemia, even in the case of 'severe' hypovitaminosis D.

This study also failed to demonstrate any correlation between pre-operative serum 25-hydroxyvitamin D and 6-hour post-operative serum PTH. Nevertheless, as reported by Sam *et al.* (in a relatively small series of 74 patients),³¹ it must be remembered that serum

PTH does not accurately predict hypocalcaemia development in vitamin D deficient patients. This seems to be an important finding in view of the high prevalence of vitamin D deficiency in patients undergoing total thyroidectomy.

- Hypocalcaemia is the most frequent complication of total thyroidectomy
- It is also the main cause of prolonged post-operative hospital stay after total thyroidectomy
- Pre-operative 25-hydroxycholecalciferol (vitamin D3) deficiency is a suspected risk factor for hypocalcaemia after total thyroidectomy
- In this study, pre-operative serum 25-hydroxyvitamin D did not influence post-operative serum calcium in patients undergoing total thyroidectomy for benign goitre
- Post-operative hypocalcaemia after total thyroidectomy is probably multifactorial and can be difficult to interpret

Role of parathyroid injury

In patients with secondary hypoparathyroidism associated with hypovitaminosis D, a correlation was observed between pre-operative serum 25-hydroxyvitamin D and post-operative hypocalcaemia. These patients appear to be more reactive to minor parathyroid gland injury during thyroid surgery.^{8–10,28,32,33} In particular, Lang *et al.*³² and especially Kirkby-Bott *et al.*⁸ showed that patients with a pre-operative serum 25-hydroxyvitamin D level of less than 30 ng/ml had more asymmetrical hyperplasia, corresponding to parathyroid ‘incidentalomas’; that is, parathyroid hyperplasia with normal serum calcium (but increased serum PTH level). These are at greater risk during thyroid surgery and more frequently result in post-traumatic post-operative hypocalcaemia after thyroid surgery. These authors suggest that such patients should receive pre-operative vitamin D supplementation to achieve a serum 25-hydroxyvitamin D level higher than 14 ng/ml prior to surgery, in order to significantly decrease the risk of post-operative hypocalcaemia due to direct surgical trauma of the parathyroid glands.^{8,32}

Conclusion

Post-operative hypocalcaemia after total thyroidectomy is multifactorial and can be difficult to interpret. This study showed that pre-operative serum vitamin D is not predictive of hypocalcaemia after total thyroidectomy for benign multinodular goitre. Routine pre-operative screening for vitamin D therefore does not appear to be useful and should not be systematically recommended.

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Address for correspondence:

Dr Cyril Page,
Service d'ORL et de chirurgie de la face et du cou,
Centre Hospitalier Sud,
80054 Amiens Cedex, France

E-mail: cyril_page@yahoo.fr

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