Head & Neck

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Preoperative Vitamin D Supplementation to Reduce Hypocalcemia Following Total Thyroidectomy: Systematic Review and Meta-Analysis of Randomized Clinical Trials

Luca Canali[1,2] | Gian Marco Pace[1,2] | Marika D. Russell[3] | Francesca Gaino[1,2] | Luca Malvezzi[2] | Gherardo Mazziotti[1,4] | Andrea Lania[1,4] | Giuseppe Spriano[1,2] | Michael Mannstadt[5] | Gregory W. Randolph[3,6] | Giuseppe Mercante[1,2]

[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy | [2]Otorhinolaryngology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy | [3]Division of Thyroid and Parathyroid Endocrine Surgery, Department of Otolaryngology-Head and Neck Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, USA | [4]Endocrinology, Diabetology and Medical Andrology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy | [5]Harvard Medical School, Endocrine Unit, Massachusetts General Hospital, Boston, Massachusetts, USA | [6]Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Gian Marco Pace (gianmarco.pace1996@gmail.com)

Received: 3 January 2025 | **Revised:** 20 March 2025 | **Accepted:** 15 April 2025

Funding: The authors received no specific funding for this work.

Keywords: hypocalcemia | surgical complications | thyroid | total thyroidectomy | vitamin D

ABSTRACT

Objective: This study aims to determine whether preoperative supplementation of vitamin D reduces the incidence of hypocalcemia following total thyroidectomy.

Methods: Conducted in conformity with the PRISMA statement, a systematic review and meta-analysis of randomized clinical trials (RCT) was performed assessing postoperative hypocalcemia and postoperative symptomatic hypocalcemia.

Results: The search strategy yielded 3808 potentially relevant publications, with eight RCTs ultimately included. These eight trials included a total of 902 patients (22.73% male, $n = 205/902$), with a median age of 48.9 years (95% CI, 43.5–53.5). Four trials administered only vitamin D in the interventional arm, three trials administered both calcium and vitamin D in the interventional arm, and one trial administered vitamin D in the interventional arm and calcium in both arms. Pooled results from the eight included trials showed a reduced risk of postoperative hypocalcemia in the intervention arm (RR, 0.77; 95% CI, 0.62–0.96; $p = 0.02$). When excluding the studies that administered calcium supplements in addition to vitamin D, the pooled results showed a similar reduced risk of postoperative hypocalcemia (RR, 0.74; 95% CI, 0.57–0.96; $p = 0.03$). Analysis of six trials reporting the incidence of postoperative symptomatic hypocalcemia ($n = 564$) showed a reduced risk in the vitamin D arm, with or without calcium, compared to the control arm (RR, 0.56; 95% CI, 0.34–0.93; $p = 0.023$).

Conclusions: Our findings suggest that preoperative vitamin D administration, with or without calcium carbonate, significantly reduces the risk of postoperative hypocalcemia and symptomatic hypocalcemia in patients undergoing total thyroidectomy.

Level of Evidence: 1.

1 | Introduction

Performed at a rate of 60 operations per 100000 inhabitants per year, with more than 100000 surgeries performed annually in the United States alone, total thyroidectomy (TT) stands as one of the most frequently performed surgical procedures, addressing a broad spectrum of indications [1]. While generally regarded as a safe procedure, TT still bears the risk of surgical complications. The most frequent postoperative complication is hypocalcemia related to hypoparathyroidism, resulting from injury to the parathyroid glands or their blood supply. This is estimated to occur transiently in approximately 30% of cases of TT, with permanent hypocalcemia occurring in approximately 4% [2]. Standard surgical practice involves the identification and preservation of the parathyroid glands and their blood supply. However, the small size of these glands, their anatomical variability, and their proximity to the thyroid may render it difficult, even in experienced hands, to preserve them with their blood supply intact [3]. In this regard, new technologies have recently emerged to facilitate the preservation of parathyroid function during TT [4]. However, the implementation of these tools is still far from being widespread.

Hypocalcemia resulting from impaired function of the parathyroid glands often necessitates pharmacological therapy, can prolong postoperative hospitalization, and lead to a decrease in quality of life; moreover, postoperative hypocalcemia has been associated with an increase in healthcare expenses and has been linked to an increased risk of mortality [5–8]. Several risk factors for hypocalcemia following TT have been recognized, including advanced age, female sex, thyroid gland size, substernal goiter, Graves' disease, central compartment dissection, advanced thyroid tumors, and reoperation [9–11]. The contribution of preoperative vitamin D deficiency to hypocalcemia after TT remains an area of debate [12].

To mitigate the potential impact of vitamin D deficiency on postoperative hypocalcemia, a common strategy involves preoperative treatment with vitamin D and/or calcium. Some studies assessing preoperative administration of vitamin D have shown promising results in reducing the incidence of postoperative hypocalcemia [13]. Administering vitamin D prior to surgery may reduce both the rate of development and duration of hypocalcemia after TT [14]. The aim of this systematic review and meta-analysis of current published randomized clinical trials (RCT) is to examine the effects of preoperative vitamin D supplementation on reducing the risk of postoperative hypocalcemia after TT.

2 | Methods

The study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] statement. Neither ethics approval nor informed consent was required for this review of previously published studies. No study protocol was registered for this study.

2.1 | Data Sources and Eligibility Criteria

PubMed/MEDLINE, Scopus, and Cochrane Library databases were searched for relevant publications. In accordance with the requirements of each database, the search was conducted by combining the following search terms, along with their corresponding MeSH (Medical Subject Headings) terms, using Boolean AND/OR operators: "Thyroid," "Thyroidectomy," "Thyroidectomies," "Vitamin D," "Vitamin D3," "Calcitriol," "Cholecalciferol," "Colecalciferol," "Calcifediol," "Alfa-calcidol," "Calcidiol". The reference lists of all papers selected for full-text assessment, as well as those of all retrieved systematic and narrative reviews, were scrutinized for completeness of the search. The "cited by" function on Google Scholar was used to minimize the risk of missing relevant data. The last research was carried out on December 10, 2023.

All RCTs examining the impact of preoperative vitamin D supplementation (with either cholecalciferol or calcitriol), alone or in combination with calcium, on postoperative hypocalcemia outcomes in patients undergoing either TT or completion thyroidectomy were considered eligible for inclusion. Studies were excluded if they were not RCTs, were ongoing projects, involved the use of additional medications beyond vitamin D and calcium, included patients who underwent either hemithyroidectomy/lobectomy, enrolled patients with parathyroid diseases, did not report postoperative hypocalcemia outcomes, or if the full text in English was not available. Studies were also excluded if postoperative administration of calcium or vitamin D for hypocalcemia control differed between the two arms or was influenced by the trial itself.

2.2 | Data Extraction and Outcomes

The reference lists from the abovementioned databases were merged, and the duplicates removed using the reference management software EndNote (version 20.6). Subsequently, two authors (L.C. and G.M.P.) independently assessed the titles and abstracts for all identified articles. Then, a full-text review was performed to evaluate for the aforementioned inclusion and exclusion criteria. The relevant data from the included studies were systematically extracted in a prespecified form. The following data variables were documented in a customized Excel spreadsheet (Microsoft Corp, Seattle, Washington, USA): title and reference details (first author and year), study design and characteristics (recruitment centers, recruitment period, randomization, blinding), features of the interventional and control groups (type of drugs administered, timing, dosage, and whether a placebo was used or not), study inclusion and exclusion criteria, hypocalcemia definition, characteristics of the study population (total number of enrolled patients, number of patients in each arm, gender, and age), surgical indications, and postoperative outcomes (incidence of postoperative hypocalcemia and incidence of symptomatic hypocalcemia). When multiple measurements for postoperative hypocalcemia were reported, the measurement closest to the time of surgery was considered. The accuracy of the extracted data was verified by a third author (G.M.).

The primary outcome was postoperative hypocalcemia, as defined by each individual study, while the secondary outcome was postoperative symptomatic hypocalcemia.

2.3 | Quality Assessment

The quality of the studies included in this systematic review was assessed independently by two authors (L.C. and G.M.P.)

using the Cochrane Risk of Bias tool, version 2 (RoB2) [16]. Disagreements were resolved by consensus and arbitration by the senior review author (G.M.).

2.4 | Statistical Analysis

Quantitative synthesis of included studies was performed using RStudio (version 2023.09.1+494) and R (version 4.3.2, The R Foundation for Statistical Computing). For each outcome, a pairwise meta-analysis was performed utilizing the Mantel–Haenszel fixed effects model [17]. The Paule-Mandel estimator [18] was used to calculate the heterogeneity variance τ^2. Dichotomous variables were reported as counts and percentages, while continuous variables were reported as median and 95% confidence interval (CI), calculated using the method described by McGrath et al. [19] The pooled risk ratio (RR) with a 95% CI was calculated. A two-sided $p<0.05$ or a 95% CI excluding 1 was considered statistically significant. Cochran's Q method was used to assess between studies heterogeneity [20]. The I^2 statistic, along with its corresponding p value, was computed as an indicator of heterogeneity [21] (low, 0%–40%; moderate, 30%–60%; substantial, 50%–90%; and considerable, 75%–100%). A random-effects model was adopted in cases where I^2 was substantial or considerable and the Cochran's Q test indicated significant heterogeneity. The results were presented with forest plot graphs. Publication bias analysis was conducted through visual inspection of the funnel plot and by calculating Egger's regression intercept, which statistically assesses funnel plot asymmetry [22]. Additionally, a meta-regression was performed to assess the potential impact of the different types of vitamin D formulations on the outcome. Furthermore, a sensitivity test was carried out through a meta-analysis including only the studies rated as having low risk of bias (ROB), allowing examination of changes in the effect size estimates as studies with high or unclear ROB were removed. Moreover, because preoperative calcium supplementation could potentially influence the analyzed outcomes, an additional post hoc sensitivity test was conducted by excluding trials that involved varied preoperative calcium administration between the two arms.

3 | Results

3.1 | Characteristics of Included Studies

The initial literature search yielded a total of 3808 records. After removing duplicates, 2030 were screened based on their titles and abstracts, and 38 articles underwent a full-text review. Following the exclusion of 11 studies due to their non-RCT design, 16 trials because they reported preestablished differences in postoperative treatment between the two study arms, two trials that were unrelated to the topic, and one trial that preoperatively administered an additional unrelated drug, a total of eight trials [13, 14, 23–28] were selected for inclusion in the meta-analysis (Figure 1). Characteristics of the included RCTs are presented in Table 1. Data from a total of 902 patients (22.73% male, $n=205/902$) with a median age of 48.9 years (95% CI, 43.5–53.5) were included in the analysis. The interventional arm consisted of 451 patients (25.28% male, $n=114/451$), while the control arm included the remaining 451 individuals (20.18% male, $n=91/451$). The number of participants in the included studies ranged from 47 to 246. Only four trials utilized a double-blinded placebo control approach ($n=399/902$, 44.24%), while the others were open label studies ($n=503/902$, 55.76%). In the study by Ramouz et al., only patients with vitamin D deficiency were included in both arms. Four trials preoperatively administered only vitamin D in the interventional arm, three trials administered both calcium and vitamin D in the interventional arm, and one trial administered vitamin D in the interventional arm and calcium in both arms. In three trials, vitamin D was given as calcitriol, with doses ranging from 0.5 mcg twice daily for 3 days to 1.0 mcg twice daily for 7 days before surgery. In the remaining five trials, cholecalciferol was used, with three studies administering a single high dose of 200 000 or 300 000 IU the day before surgery, and two following a protocol 50 000 or 60 000 IU once weekly for 4 or 6 weeks prior to surgery, respectively. The only patient who experienced hypercalcemia following the preoperative treatment was from the interventional arm in the Shonka et al. study (serum calcium 13 mg/dL). Details about the types of drugs, dosages, and timing of administration are presented in Table 1.

The definition of hypocalcemia differed between trials, with the serum calcium level threshold ranging from 8.0 to 8.5 mg/dL (2.0–2.1 mmol/L). In six trials, the occurrence of postoperative symptomatic hypocalcemia was reported ($n=564/902$, 62.53%).

Finally, regarding postoperative supplementation, four trials administered a standardized protocol to all patients, regardless of their assigned arms, while the other four included studies managed postoperative hypocalcemia based on each patient's clinical needs and the internal protocols of each center, independently from the patients' assigned arms. Details about the postoperative supplementation are presented in Table 1.

3.2 | Quality Assessment

The Cochrane ROB assessment for the included trials is summarized in Figure S1. The majority of studies ($n=6$, 75%) [13, 14, 24, 26–28] including 79.82% of patients ($n=720/902$), were considered to have a low ROB. Only one study [25] raised some concerns about the randomization process ($n=100/902$, 11.1%), since no information was provided about the allocation sequence concealment, while another trial [23] raised concerns about the effect of assignment to the intervention ($n=82/902$, 9.1%) because the intention-to-treat analysis was not reported.

3.3 | Primary Outcome: Postoperative Hypocalcemia

Pooled results from the fixed effects model of the eight included trials ($n=902/902$, 100%) showed that patients treated preoperatively with vitamin D had a statistically significant reduced risk of developing postoperative hypocalcemia (RR, 0.77; 95% CI, 0.62–0.96; $p=0.02$; Figure 2). Low heterogeneity between studies was observed ($I^2=28\%$; $p=0.21$). To assess publication bias, a funnel plot was generated and examined (Figure S2). Egger's test did not reveal any statistically significant funnel plot asymmetry

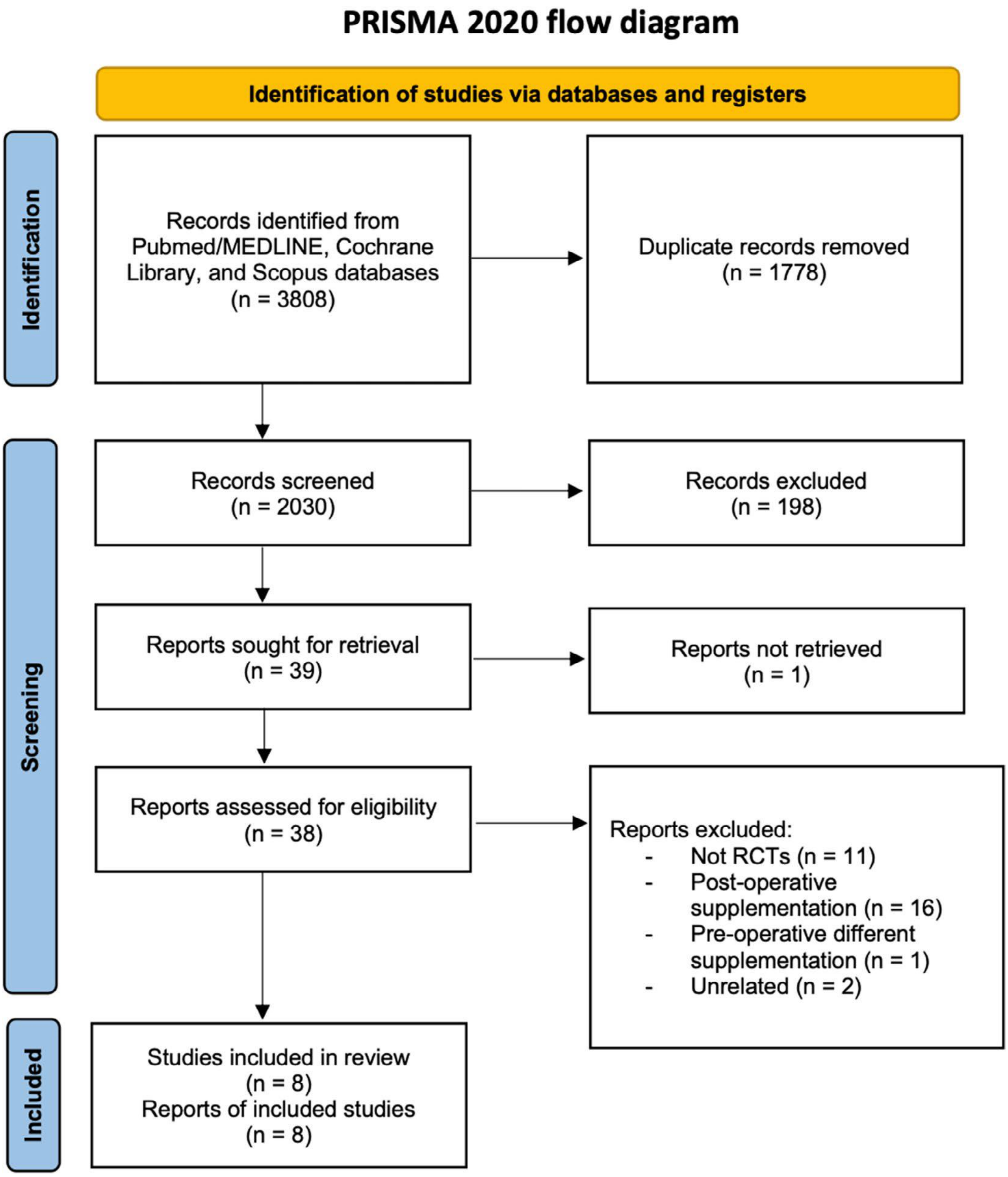

FIGURE 1 | PRISMA flow diagram. [Color figure can be viewed at wileyonlinelibrary.com]

(intercept = −1.46; 95% CI, −3.59 to 0.67; $p = 0.24$). Meta-regression showed no statistically significant impact of vitamin D type (cholecalciferol vs. calcitriol) on the effect sizes ($p = 0.498$). A sensitivity analysis was conducted including only the six studies rated as low risk at the ROB assessment ($n = 720/902$, 79.8%). The pooled results remained consistent, demonstrating a reduction in the risk of developing postoperative hypocalcemia even when studies with some concerns or high ROB were excluded (RR, 0.77; 95% CI, 0.61–0.97; $p = 0.03$; $I^2 = 49.4\%$, Figures S3 and S4). To better evaluate the utility of supplementation with vitamin D alone without calcium, a post hoc sensitivity analysis was conducted excluding the four studies that administered different calcium supplementation between the two arms. The pooled results indicate a statistically significant reduction in the risk of developing postoperative hypocalcemia in the group ($n = 645/902$, 71.5%) treated solely with vitamin D (RR, 0.74; 95% CI, 0.57–0.96; $p = 0.03$; $I^2 = 0\%$; Figure 3). Examination of the funnel plot and the Egger's test (intercept = −1.74; 95% CI, −3.06 to −0.42; $p = 0.12$; Figure S5) confirmed the absence of apparent publication bias among the studies in this subcategory.

3.4 | Secondary Outcome: Postoperative Symptomatic Hypocalcemia

An analysis of six trials reporting the incidence of postoperative symptomatic hypocalcemia in a total of 564 patients (16.84% male, $n = 95/564$) was conducted. The results showed a reduced risk of occurrence in the vitamin D arm compared with the control arm (RR, 0.56; 95% CI, 0.34–0.93; $p = 0.023$). A forest plot is provided in Figure 4. The observed heterogeneity between studies was low ($I^2 = 0\%$; $p = 0.72$) and the Egger's test (intercept = −0.86; 95% CI, −2.15 to 0.43; $p = 0.26$) along with the funnel plot did not show evident publication bias (Figure S6).

TABLE 1 | Characteristics of included trials.

Source (year)	Design; recruiting country	Recruiting period	Blinding	*N* participants (male)	Age (SD)	Indication (*N* benign/*N* malignant)	Preoperative treatment protocol	Definition of hypocalcemia	Postoperative hypocalcemia treatment protocol	*N* postoperative hypocalcemia (%)	*N* postoperative symptomatic hypocalcemia (%)	Overall risk of bias
Bhettani et al. (2019)	Single-center RCT; Pakistan	June 2016–July 2017	Double blinding	Treatment = 51 (6) Control = 51 (7)	Treatment = 38.9 (7.5) Control = 39.8 (6.5)	Treatment = 46/5 Control = 48/3	Treatment: D3 200000 UI, 1× Day 1 + CC 700 mg, 1× Day 1, 1× Day 2 Control: placebo + CC 700 mg, 1× Day 1, 1× Day 2	< 8.0 mg/dL or < 2 mEq/dL (POD 1)	In both arms: D3 800 UI, once/day + CC 1000 mg once/day	Treatment = 7 (13.7) Control = 12 (23.6)	Treatment = 1 (2.0) Control = 4 (7.8)	Low risk
Malik et al. (2019)	Single-center RCT; Pakistan	January 2017–July 2017	Open label	Treatment = 46 (22) Control = 46 (27)	Treatment = 38.7 (8.6) Control = 41.2 (9.5)	Treatment = 42/4 Control = 43/3	Treatment: D3 200000 UI, 1× Day 1 + CC 1000 mg, 1× Day 1 Control: nothing	< 8.5 mg/dL (within 1 month post-op)	In both arms: calcium ± calcitriol based on each patient's clinical needs	Treatment = 3 (6.5) Control = 12 (26.1)	N/A	Low risk
Ramouz et al. (2020)	Single-center RCT; Iran	August 2015–December 2016	Double blinding	Treatment = 50 (6) Control = 50 (3)	Treatment = 44.0 (1.4) Control = 41.5 (1.6)	Treatment = 36/14 Control = 33/17	Treatment: D3 50000 UI, 1× Week × 4 weeks preop Control: placebo	Not specified (12 h post-op)	In both arms: calcium ± calcitriol based on each patient's clinical needs	Treatment = 12 (24.0) Control = 17 (34.0)	Treatment = 2 (4.0) Control = 8 (16.0)	Some concerns
Sonnenberg et al. (2021)	Multicenter RCT; Germany	July 2014–March 2015	Open label	Treatment = 130 (35) Control = 116 (26)	Treatment = 48.5 (N/A) Control = 48.9 (N/A)	Treatment = 130/0 Control = 116/0	Treatment: calcitriol 0.5 µg bid × 3 days preop Control: nothing	< 2.1 mmol/L (during hospitalization)	In both arms: calcium ± calcitriol based on each patient's clinical needs	Treatment = 38 (29.2) Control = 39 (33.6)	N/A	Low risk
Shonka et al. (2021)	Multicenter RCT; USA	June 2013–April 2016	Double blinding	Treatment = 23 (5) Control = 24 (2)	Treatment = 49.9 (14.5) Control = 46.0 (16.5)	Treatment = 7/16 Control = 12/12	Treatment: calcitriol 1 µg bid × 7 days preop Control: placebo	< 8.0 mg/dL (POD 1)	In both arms: CC 1000 mg tid + calcitriol 0.5 µg bid	Treatment = 0 (0%)[a] Control = 0 (0%)	Treatment = 1 (4.3) Control = 1 (4.2)	Low risk

(Continues)

TABLE 1 | (Continued)

Source (year)	Design; recruiting country	Recruiting period	Blinding	N participants (male)	Age (SD)	Indication (N benign/N malignant)	Preoperative treatment protocol	Definition of hypocalcemia	Postoperative hypocalcemia treatment protocol	N postoperative hypocalcemia (%)	N postoperative symptomatic hypocalcemia (%)	Overall risk of bias
Sasi et al. (2022)	Single-center RCT; India	April 2018–July 2019	Open label	Treatment = 41 (6) Control = 42 (1)	Treatment = 39.7 (12.8) Control = 43.4 (13.9)	Treatment = 41/0 Control = 38/4	Treatment: D3 60 000 UI, 1× Week × 6 weeks preop + CC 1000 mg bid × 6 weeks preop Control: nothing	< 8.2 mg/dL (POD 1)	In both arms: calcium ± calcitriol based on each patient's clinical needs	Treatment = 21 (51.2) Control = 18 (42.9)	Treatment = 7 (17.1) Control = 11 (26.2)	Low risk
Rowe et al. (2019)	Single-center RCT; Australia	August 2014–December 2017	Double blinding	Treatment = 72 (19) Control = 78 (17)	Treatment = 49.0 (15.0) Control = 55.0 (17.0)	Treatment = 57/15 Control = 63/15	Treatment: D3 300 000 UI, 1× Day 7 Control: placebo	< 2.1 mmol/L (within 48 h post-op)	In both arms: if calcium < 2.2 mmol/L or symptoms, CC 1200 mg tid; if calcium < 2.0 mmol/L, also calcitriol 0.5 μg bid	Treatment = 16 (22.2) Control = 27 (34.6)	Treatment = 9 (12.5) Control = 12 (15.4)	Low risk
Donahue et al. (2021)	Single-center RCT; USA	September 2017–April 2019	Not specified	Treatment = 38 (15) Control = 44 (8)	Treatment = 59.3 (15.7) Control = 52.5 (13.3)	Treatment = 24/14 Control = 34/10	Treatment: calcitriol 0.25 μg bid × 5 days preop + CC 1500 mg tid × 5 days preop Control: nothing	< 8.5 mg/dL (during hospitalization)	In both arms: calcitriol 0.25 μg bid + CC 1500 mg tid	Treatment = 4 (10.5) Control = 4 (9.1)	Treatment = 1 (2.6) Control = 3 (6.8)	Some concerns

Abbreviations: CC, calcium carbonate; D3, cholecalciferol; POD, postoperative day; RCT, randomized clinical trial; SD, standard deviation.
[a]One patient (4.4%) suffered from severe hypercalcemia (calcium 13 mg/dL).

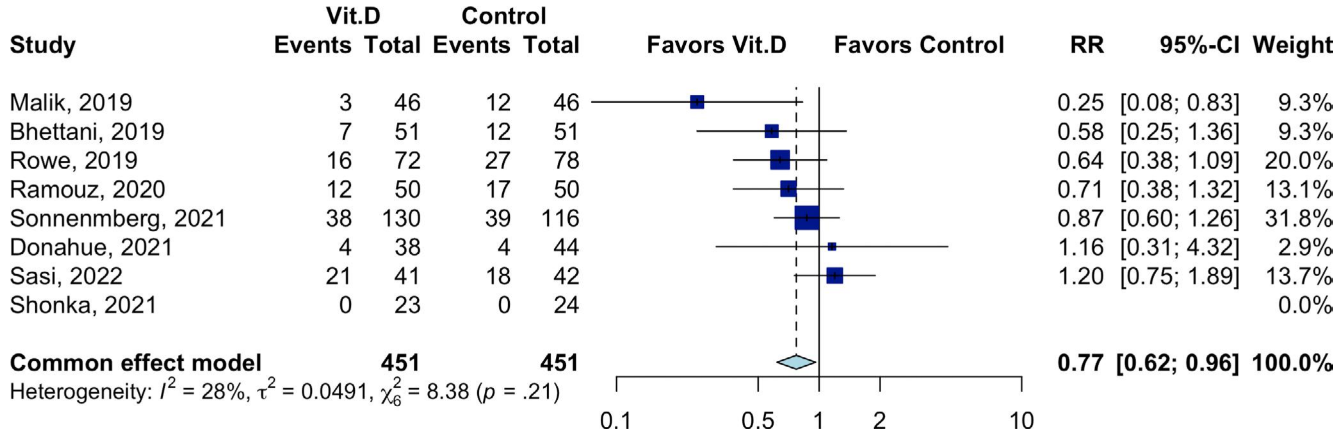

FIGURE 2 | Risk of developing postoperative hypocalcemia. Forest plot showing the pooled risk ratio (RR) of postoperative hypocalcemia. Different sizes of squares indicate the different weights used for pooled analysis. The dotted line represents the average effect of all studies when pooled together. [Color figure can be viewed at wileyonlinelibrary.com]

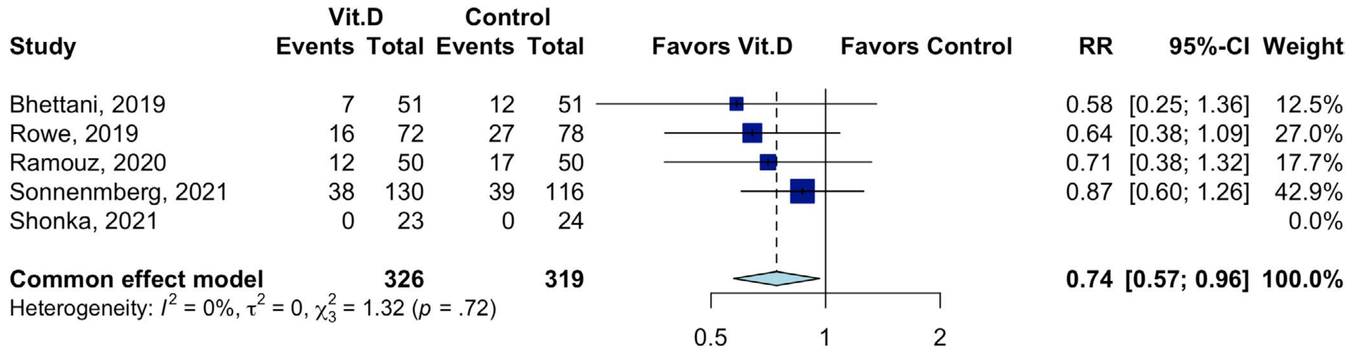

FIGURE 3 | Risk of developing postoperative hypocalcemia, with only preoperative vitamin D. Forest plot showing the results of the post hoc analysis in which were included only the studies that evaluated the effect of an exclusive preoperative administration of vitamin D. Different sizes of squares indicate the different weights used for pooled analysis. The dotted line represents the average effect of all studies when pooled together. [Color figure can be viewed at wileyonlinelibrary.com]

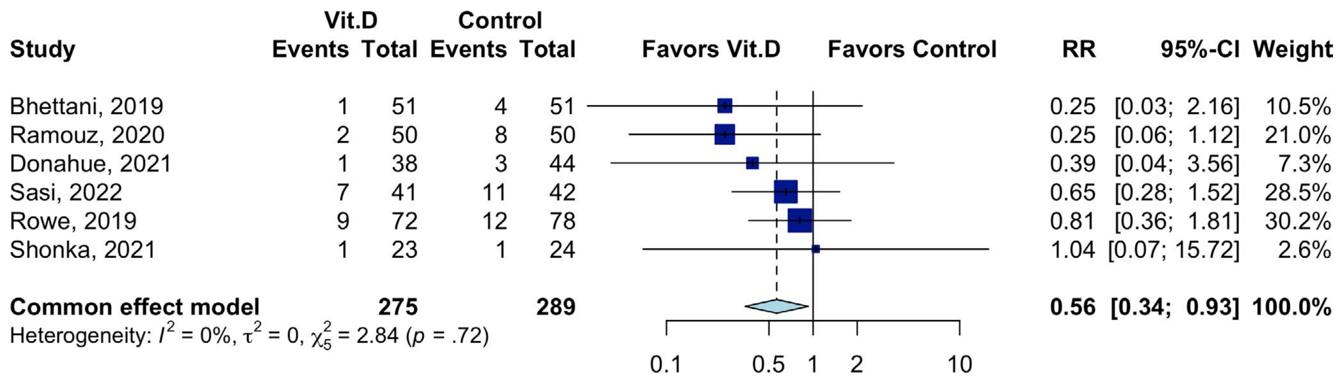

FIGURE 4 | Risk of developing postoperative symptomatic hypocalcemia. Forest plot showing the pooled risk ratio (RR) of postoperative symptomatic hypocalcemia. Different sizes of squares indicate the different weights used for pooled analysis. The dotted line represents the average effect of all studies when pooled together. [Color figure can be viewed at wileyonlinelibrary.com]

4 | Discussion

In this meta-analysis comprising eight RCTs with 902 individuals undergoing TT or completion thyroidectomy, we found that preoperative vitamin D (with or without calcium) supplementation is associated with a 23% reduction in the risk of postoperative hypocalcemia and a 44% reduction in the risk of symptomatic hypocalcemia. The statistically significant reduction in the risk of postoperative hypocalcemia persisted when excluding studies with concomitant supplementation of calcium, suggesting that vitamin D has value as a stand-alone preoperative prophylaxis. To our knowledge, this is the first systematic review and meta-analysis of RCTs demonstrating the impact of preoperative vitamin D supplementation alone on the prevention of post-thyroidectomy hypocalcemia.

Hypocalcemia is the most common complication following TT [29, 30]. Its incidence varies significantly across studies, with temporary hypocalcemia reported in 19%–38% of cases and permanent hypocalcemia in 0.2%–10% [6, 31]. Clinically, hypocalcemia can present with symptoms such as peri-oral and peripheral paresthesia, muscle spasms, or tetany. In severe cases, it may lead to significant neurological or psychological symptoms including confusion, memory loss, delirium, depression, hallucinations, and seizures, and may also cause aberrations in cardiac rhythm. Postoperative hypocalcemia has significant negative implications for both quality of life and healthcare costs, and limiting its occurrence is of pressing importance.

One initial strategy implemented to mitigate postoperative hypocalcemia has been routine postoperative administration of calcium and/or vitamin D to all patients undergoing TT [32]. Mercante et al. aimed to evaluate the most effective postoperative treatment strategy and showed that the most cost-effective measure was universal use of calcium and vitamin D supplementation [33]. However, this strategy often necessitates postoperative hospitalization of varying lengths and results in overtreatment in approximately 60% of patients who would not have developed postoperative hypocalcemia. On the other hand, targeting select subgroups of patients anticipated to benefit most from routine treatment remains an area of study and debate.

Some authors have suggested that vitamin D deficiency predisposes patients to postoperative hypocalcemia, rendering vitamin D levels a potential predictor of this outcome [11]. Tripathie et al. proposed a correlation between preoperative serum levels of 25-hydroxyvitamin D (25(OH)D) and postoperative serum calcium levels, suggesting that patients with serum 25(OH)D levels below 20 ng/mL are more likely to experience early hypocalcemia post-thyroidectomy [34]. However, findings have been inconsistent, with other studies failing to establish any causal relationship between preoperative serum vitamin D and postoperative hypocalcemia [35, 36]. Still, given the high reported incidence of vitamin D deficiency and the fact that it is a potentially modifiable risk factor, vitamin D represents an attractive therapeutic target [37]. For this reason, several studies have attempted to evaluate whether supplementing patients with vitamin D preoperatively can reduce the incidence of postoperative hypocalcemia.

In our study, we included only RCTs that evaluated preoperative vitamin D supplementation in patients undergoing TT or completion thyroidectomy. In four studies, preoperative treatment consisted exclusively of vitamin D administration, while in three studies, vitamin D was combined with calcium carbonate. In the study by Betthani et al., preoperative treatment included vitamin D and calcium, but the calcium was administered preoperatively in both the treatment and control arms, allowing for selective assessment of the impact of preoperative vitamin D treatment.

When examining the results of individual trials, most of the included studies did not report a statistically significant difference in the incidence of postoperative hypocalcemia or hypocalcemia symptoms in the intervention arm. Notably, Shonka et al. reported no occurrences of postoperative hypocalcemia in either treatment arm, limiting the study's conclusions. However, it is important to note that one out of 23 patients in the treatment arm developed severe hypercalcemia (serum calcium 13 mg/dL), likely as a result of the remarkably high preoperative dose of calcitriol (1 mcg twice daily for 7 days, followed by 0.5 mcg twice daily postoperatively). Malik et al. was the only trial that reported a statistically significant decrease in the rate of postoperative hypocalcemia in the treatment group. However, when pooling the results of the included eight studies, a statistically significant reduction in postoperative hypocalcemia and symptomatic hypocalcemia was observed with preoperative vitamin D administration, even when studies using calcium carbonate in addition to vitamin D were excluded from the analysis.

The results of our study align with those of the meta-analysis by Casey and Hopkins, which demonstrated a modest reduction in the rate of postoperative hypocalcemia, both laboratory-confirmed and symptomatic, in patients treated preoperatively with vitamin D and/or calcium [38]. Conversely, Alhakami et al. found slightly different results, observing a modest reduction in symptomatic hypocalcemia but not in laboratory-confirmed hypocalcemia [39]. However, both articles also included trials where postoperative supplementation differed between the interventional arm and the control arm as part of the trial protocol, raising the question as to whether postoperative treatment played a role in reducing the rate of postsurgical hypocalcemia, possibly impacting the results presented. In the network meta-analysis by Ren et al., preoperative treatments with teriparatide or vitamin D plus calcium were shown to reduce the rate of postoperative hypocalcemia in thyroidectomy patients [40]. However, in contrast to our findings, treatment with vitamin D alone did not result in a significant reduction in postoperative hypocalcemia. Again, this article included studies where postoperative supplementation differed between the intervention and control arms as part of the trial protocol itself. Additionally, many retrospective studies were included, potentially introducing a ROB.

While our sensitivity analysis and ROB analysis confirmed the significance of the data presented in this study, several limitations must be considered. First, there is a lack of uniformity in the definition of postoperative hypocalcemia across the included studies, both in terms of laboratory values and the time frame in which hypocalcemia was evaluated. Specifically, four studies defined hypocalcemia as a calcium level below 8.0 mg/dL (two of which reported this threshold as 2.0 mmol/L), two studies as below 8.5 mg/dL, one as below 8.2 mg/dL, while another did not denote a cut-off value. In five studies, postoperative hypocalcemia was evaluated 12–48 h postoperatively; in two studies, hypocalcemia was assessed during the postoperative hospitalization period, and in one study, the timeframe of assessment was 1 month postoperatively. Additionally, five studies used albumin-adjusted calcium to define hypocalcemia, while three relied on unadjusted serum calcium. Shonka et al. specifically noted that corrected calcium levels were unnecessary, as no patients had low serum albumin. Further significant heterogeneity arises from the varied formulations, dosages, and regimens of vitamin D administration in the preoperative period. Although calcitriol (i.e., active analogue of vitamin D) is always used for treatment of hypocalcemia related to postsurgical hypoparathyroidism, prophylactic administration before surgery is not standard, nor is its use supported by available evidence [6]. Based on results of studies included in the meta-analysis, the use of calcitriol did not provide any advantage over native vitamin D in preventing post-thyroidectomy hypocalcemia, at least outside the context of specific clinical conditions such as chronic renal insufficiency or malabsorption syndrome. Still, while the meta-regression analysis did not find a significant impact of different vitamin D formulations on the outcome, the variability in dosage and regimens may have contributed to the heterogeneity observed and highlights the challenge of drawing direct comparisons and conclusions across these studies. Considering these methodological differences, the impact of preoperative vitamin D supplementation on surgical outcomes must be interpreted with caution. An additional limitation is that all the included trials were conducted in referral centers, limiting the generalizability of the findings. This is particularly significant considering that thyroid surgery is predominantly performed in small- to medium-sized centers [41].

Despite these limitations, the strength of our study lies in the randomized control design of the included trials and the strict inclusion and exclusion criteria, which reduce confounding factors and ensure higher-quality evidence compared to network meta-analyses which include every available study. Given the substantial number of patients included in the analysis, the low risk of adverse events arising from supplementation of vitamin D, and the low cost of these medications, we believe the findings provide robust evidence supporting the use of preoperative vitamin D supplementation to reduce the risk of postoperative hypocalcemia following TT. Still, the potential for overtreatment and the cost-effectiveness of this intervention require further investigation, and future studies should address these issues. Moreover, while some conditions such as advanced thyroid cancer, Graves' disease, Hashimoto's thyroiditis, large-volume goiter, and recurrent goiter have been associated with an increased risk of postoperative hypocalcemia [10, 14, 42], there is no information regarding which patients might benefit most from the preoperative administration of vitamin D. Therefore, further studies should aim to identify patients who would derive the greatest benefit from preoperative vitamin D treatment, allowing for more accurate patient selection for preoperative prophylaxis. Finally, additional prospective multicentric trials investigating the optimal dosage and administration regimen of Vitamin D are warranted.

5 | Conclusions

We present a systematic review and meta-analysis of randomized controlled clinical trials examining the impact of preoperative vitamin D supplementation on reducing the risk of postoperative hypocalcemia. Our findings suggest that vitamin D administered preoperatively, with or without calcium carbonate, reduces the risk of postoperative hypocalcemia and symptomatic hypocalcemia in patients undergoing TT. Further work is needed to assess the cost-effectiveness of this approach, standardize the dosage and administration regimen, and identify which patients would benefit the most from supplementation.

Author Contributions

Luca Canali: conceptualization (lead), writing – original draft (supporting), formal analysis (lead). **Gian Marco Pace:** writing – original draft (lead), formal analysis (supporting). **Marika D. Russell, Luca Malvezzi, Andrea Lania, Giuseppe Spriano, and Gregory W. Randolph:** writing – review and editing (equal). **Francesca Gaino:** writing – original draft (supporting), formal analysis (supporting). **Gherardo Mazziotti:** conceptualization (supporting), formal analysis (lead). **Michael Mannstadt:** writing – review and editing (equal), formal analysis (supporting). **Giuseppe Mercante:** conceptualization (supporting), writing – original draft (supporting), writing – review and editing (lead).

Acknowledgments

The authors have nothing to report.

Disclosure

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

Gregory W. Randolph has received research grants from Eisai, Medtronic, and Fluoptics and consulting fees from Medtronic. Gregory W. Randolph is the program director of the Mass. Eye and Ear Infirmary Endocrine Surgery Clinical Fellowship, which receives partial funding from Medtronic. Gregory W. Randolph is the President of the International Thyroid Oncology Group (ITOG) and the World Congress on Thyroid Cancer (WCTC), is Chair of the Administrative Division of the American Head and Neck Society (AHNS), and is the American College of Surgeons (ACS) Otolaryngology Governor. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. J. A. Sosa, J. W. Hanna, K. A. Robinson, and R. B. Lanman, "Increases in Thyroid Nodule Fine-Needle Aspirations, Operations, and Diagnoses of Thyroid Cancer in the United States," *Surgery* 154, no. 6 (2013): 1420–1426, https://doi.org/10.1016/j.surg.2013.07.006.

2. G. D. Koimtzis, L. Stefanopoulos, K. Giannoulis, and T. S. Papavramidis, "What Are the Real Rates of Temporary Hypoparathyroidism Following Thyroidectomy? It Is a Matter of Definition: A Systematic Review," *Endocrine* 73, no. 1 (2021): 1–7, https://doi.org/10.1007/s12020-021-02663-8.

3. C. Meltzer, M. Hull, A. Sundang, and J. L. Adams, "Association Between Annual Surgeon Total Thyroidectomy Volume and Transient and Permanent Complications," *JAMA Otolaryngology. Head & Neck Surgery* 145, no. 9 (2019): 830–837, https://doi.org/10.1001/jamaoto.2019.1752.

4. L. Canali, M. D. Russell, A. Sistovaris, et al., "Camera-Based Near-Infrared Autofluorescence Versus Visual Identification in Total Thyroidectomy for Parathyroid Function Preservation: Systematic Review and Meta-Analysis of Randomized Clinical Trials," *Head & Neck* 47, no. 1 (2025): 225–234, https://doi.org/10.1002/hed.27900.

5. A. Bergenfelz, E. Nordenström, and M. Almquist, "Morbidity in Patients With Permanent Hypoparathyroidism After Total Thyroidectomy," *Surgery* 167, no. 1 (2020): 124–128, https://doi.org/10.1016/j.surg.2019.06.056.

6. L. A. Orloff, S. M. Wiseman, V. J. Bernet, et al., "American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults," *Thyroid* 28, no. 7 (2018): 830–841, https://doi.org/10.1089/thy.2017.0309.

7. F. Benmiloud, C. Le Bihan, S. Rebaudet, P. Marino, P. J. Bousquet, and E. Bouée-Benhamiche, "Hypoparathyroidism-Related Health Care Utilization and Expenditure During the First Postoperative Year After Total Thyroidectomy for Cancer: A Comprehensive National Cohort Study," *Frontiers in Endocrinology* 14 (2023): 1193290, https://doi.org/10.3389/fendo.2023.1193290.

8. M. Almquist, K. Ivarsson, E. Nordenström, and A. Bergenfelz, "Mortality in Patients With Permanent Hypoparathyroidism After Total Thyroidectomy," *British Journal of Surgery* 105, no. 10 (2018): 1313–1318, https://doi.org/10.1002/bjs.10843.

9. O. Thomusch, A. Machens, C. Sekulla, et al., "Multivariate Analysis of Risk Factors for Postoperative Complications in Benign Goiter Surgery: Prospective Multicenter Study in Germany," *World Journal of Surgery* 24, no. 11 (2000): 1335–1341, https://doi.org/10.1007/s002680010221.

10. A. E. L. McMurran, R. Blundell, and V. Kim, "Predictors of Post-Thyroidectomy Hypocalcaemia: A Systematic and Narrative Review," *Journal of Laryngology & Otology* 134, no. 6 (2020): 541–552, https://doi.org/10.1017/S0022215120001024.

11. O. Edafe, R. Antakia, N. Laskar, L. Uttley, and S. P. Balasubramanian, "Systematic Review and Meta-Analysis of Predictors of Post-Thyroidectomy Hypocalcaemia," *British Journal of Surgery* 101, no. 4 (2014): 307–320, https://doi.org/10.1002/bjs.9384.

12. W. W. Kim, S. H. Chung, E. J. Ban, et al., "Is Preoperative Vitamin D Deficiency a Risk Factor for Postoperative Symptomatic Hypocalcemia in Thyroid Cancer Patients Undergoing Total Thyroidectomy Plus Central Compartment Neck Dissection?," *Thyroid* 25, no. 8 (2015): 911–918, https://doi.org/10.1089/thy.2014.0522.

13. C. W. Rowe, S. Arthurs, C. J. O'Neill, et al., "High-Dose Preoperative Cholecalciferol to Prevent Post-Thyroidectomy Hypocalcaemia: A Randomized, Double-Blinded Placebo-Controlled Trial," *Clinical Endocrinology* 90, no. 2 (2019): 343–350, https://doi.org/10.1111/cen.13897.

14. M. Khan Bhettani, M. Rehman, M. Ahmed, H. N. Altaf, U. K. Choudry, and K. H. Khan, "Role of Pre-Operative Vitamin D Supplementation to Reduce Post-Thyroidectomy Hypocalcemia: Cohort Study," *International Journal of Surgery* 71 (2019): 85–90, https://doi.org/10.1016/j.ijsu.2019.08.035.

15. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* 372 (2021): n71, https://doi.org/10.1136/bmj.n71.

16. J. A. C. Sterne, J. Savović, M. J. Page, et al., "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials," *BMJ* 366 (2019): l4898, https://doi.org/10.1136/bmj.l4898.

17. N. Mantel and W. Haenszel, "Statistical Aspects of the Analysis of Data From Retrospective Studies of Disease," *Journal of the National Cancer Institute* 22, no. 4 (1959): 719–748.

18. R. C. Paule and J. Mandel, "Consensus Values and Weighting Factors," *Journal of Research of the National Bureau of Standards* 87, no. 5 (1982): 377–385, https://doi.org/10.6028/jres.087.022.

19. S. McGrath, X. Zhao, Z. Z. Qin, R. Steele, and A. Benedetti, "One-Sample Aggregate Data Meta-Analysis of Medians," *Statistics in Medicine* 38, no. 6 (2019): 969–984, https://doi.org/10.1002/sim.8013.

20. W. G. Cochran, "The Combination of Estimates From Different Experiments," *Biometrics* 10, no. 1 (1954): 101–129, https://doi.org/10.2307/3001666.

21. J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring Inconsistency in Meta-Analyses," *BMJ* 327, no. 7414 (2003): 557–560, https://doi.org/10.1136/bmj.327.7414.557.

22. M. Egger, G. Davey Smith, M. Schneider, and C. Minder, "Bias in Meta-Analysis Detected by a Simple, Graphical Test," *British Medical Journal* 315, no. 7109 (1997): 629–634, https://doi.org/10.1136/bmj.315.7109.629.

23. C. Donahue, H. J. Pantel, B. B. Yarlagadda, and D. Brams, "Does Preoperative Calcium and Calcitriol Decrease Rates of Post-Thyroidectomy Hypocalcemia? A Randomized Clinical Trial," *Journal of the American College of Surgeons* 232, no. 6 (2021): 848–854, https://doi.org/10.1016/j.jamcollsurg.2021.01.016.

24. M. Z. Malik, A. A. Mirza, S. A. Farooqi, N. A. Chaudhary, M. Waqar, and H. W. Bhatti, "Role of Preoperative Administration of Vitamin D and Calcium in Postoperative Transient Hypocalcemia After Total Thyroidectomy," *Cureus* 11, no. 4 (2019): e4579, https://doi.org/10.7759/cureus.4579.

25. A. Ramouz, M. Hosseini, S. S. Hosseinzadeh, and S. Z. Rasihashemi, "Preoperative Vitamin D Supplementation in Patients With Vitamin D Deficiency Undergoing Total Thyroidectomy," *American Journal of the Medical Sciences* 360, no. 2 (2020): 146–152, https://doi.org/10.1016/j.amjms.2020.04.036.

26. D. C. Shonka, A. K. Maxwell, G. R. Petroni, and M. J. Jameson, "Phase II Randomized Study of Preoperative Calcitriol to Prevent Hypocalcemia Following Thyroidectomy," *Head & Neck* 43, no. 10 (2021): 2935–2945, https://doi.org/10.1002/hed.26775.

27. S. Sonnenberg, M. Scheunchen, C. A. Smaxwil, et al., "Short-Term Hypocalcemia Prophylaxis With Calcitriol Before Thyroidectomy—A Multicenter Randomized Trial," *Deutsches Ärzteblatt International* 188, no. 47 (2021): 799, https://doi.org/10.3238/arztebl.m2021.0351.

28. M. Sasi, M. Shreyamsa, G. Surabhi, et al., "Role of Preoperative Calcium and Vitamin D Supplementation in Preventing Post-Total Thyroidectomy Hypocalcemia," *World Journal of Endocrine Surgery* 14, no. 1 (2022): 7–14, https://doi.org/10.5005/jp-journals-10002-1421.

29. D. R. Chadwick, "Hypocalcaemia and Permanent Hypoparathyroidism After Total/Bilateral Thyroidectomy in the BAETS Registry," *Gland Surgery* 6, no. 1 (2017): S69–S74, https://doi.org/10.21037/gs.2017.09.14.

30. L. Rosato, N. Avenia, P. Bernante, et al., "Complications of Thyroid Surgery: Analysis of a Multicentric Study on 14,934 Patients Operated on in Italy Over 5 Years," *World Journal of Surgery* 28, no. 3 (2004): 271–276, https://doi.org/10.1007/s00268-003-6903-1.

31. S. T. Seo, J. W. Chang, J. Jin, Y. C. Lim, K. S. Rha, and B. S. Koo, "Transient and Permanent Hypocalcemia After Total Thyroidectomy: Early Predictive Factors and Long-Term Follow-Up Results," *Surgery* 158, no. 6 (2015): 1492–1499, https://doi.org/10.1016/j.surg.2015.04.041.

32. A. Sanabria, L. C. Dominguez, V. Vega, C. Osorio, and D. Duarte, "Routine Postoperative Administration of Vitamin D and Calcium After Total Thyroidectomy: A Meta-Analysis," *International Journal of Surgery* 9, no. 1 (2011): 46–51, https://doi.org/10.1016/j.ijsu.2010.08.006.

33. G. Mercante, A. Anelli, D. Giannarelli, et al., "Cost-Effectiveness in Transient Hypocalcemia Post-Thyroidectomy," *Head & Neck* 41, no. 11 (2019): 3940–3947, https://doi.org/10.1002/hed.25934.

34. M. Tripathi, R. K. Karwasra, and S. Parshad, "Effect of Preoperative Vitamin D Deficiency on Postoperative Hypocalcemia After Thyroid Surgery," *Thyroid Research* 7 (2014): 8, https://doi.org/10.1186/1756-6614-7-8.

35. E. M. Salinger and J. T. Moore, "Perioperative Indicators of Hypocalcemia in Total Thyroidectomy: The Role of Vitamin D and Parathyroid Hormone," *American Journal of Surgery* 206, no. 6 (2013): 876–881, https://doi.org/10.1016/j.amjsurg.2013.08.020.

36. B. H. H. Lang, K. P. Wong, C. Y. Cheung, Y. K. Fong, D. K. K. Chan, and G. K. Y. Hung, "Does Preoperative 25-Hydroxyvitamin D Status Significantly Affect the Calcium Kinetics After Total Thyroidectomy?," *World Journal of Surgery* 37, no. 7 (2013): 1592–1598, https://doi.org/10.1007/s00268-013-2015-8.

37. R. M. Daly, C. Gagnon, Z. X. Lu, et al., "Prevalence of Vitamin D Deficiency and Its Determinants in Australian Adults Aged 25 Years and Older: A National, Population-Based Study," *Clinical Endocrinology* 77, no. 1 (2012): 26–35, https://doi.org/10.1111/j.1365-2265.2011.04320.x.

38. C. Casey and D. Hopkins, "The Role of Preoperative Vitamin D and Calcium in Preventing Post-Thyroidectomy Hypocalcaemia: A Systematic Review," *European Archives of Oto-Rhino-Laryngology* 280, no. 4 (2023): 1555–1563, https://doi.org/10.1007/s00405-022-07791-z.

39. M. Alhakami, G. B. Lajdam, A. A. Ghaddaf, et al., "Preoperative Vitamin D and Calcium Administration in Patients Undergoing Thyroidectomy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *OTO Open* 8, no. 1 (2024): e116, https://doi.org/10.1002/oto2.116.

40. S. Ren, Y. Zhu, Y. Dong, et al., "Relative Efficacy of Prophylactic Strategies for Postthyroidectomy Hypocalcemia: A Systematic Review and Network Meta-Analysis," *International Journal of Surgery* 109, no. 3 (2023): 429–437, https://doi.org/10.1097/JS9.0000000000000266.

41. B. R. Haugen, E. K. Alexander, K. C. Bible, et al., "2015 American Thyroid Association Management Guidelines for Adult Patients With Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer," *Thyroid* 26, no. 1 (2016): 1–133, https://doi.org/10.1089/thy.2015.0020.

42. R. Simó, L. Nixon, V. Vander Poorten, et al., "Surgical Management of Intrathoracic Goitres," *European Archives of Oto-Rhino-Laryngology* 276, no. 2 (2019): 305–314, https://doi.org/10.1007/s00405-018-5213-z.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.