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Role of Postoperative Vitamin D and/or Calcium Routine Supplementation in Preventing Hypocalcemia After Thyroidectomy: A Systematic Review and Meta-Analysis

AMAL ALHEFDHI, HAGGI MAZEH, HERBERT CHEN

Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, Wisconsin, USA
Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Vitamin D • Calcium • Hypocalcemia • Post-thyroidectomy • Prevention

Learning Objectives

Discuss the role of routine early postoperative oral calcium and/or vitamin D supplementation in preventing symptomatic post-thyroidectomy hypocalcemia.

Describe the effect of treatment with a combination of oral calcium and vitamin D supplements on the risk of hypocalcemia in post-thyroidectomy patients and its potential to facilitate early discharge.

ABSTRACT

Background. Transient hypocalcemia is a frequent complication after total thyroidectomy. Routine postoperative administration of vitamin D and calcium can reduce the incidence of symptomatic postoperative hypocalcemia. We performed a systematic review to assess the effectiveness of this intervention. The primary aim was to evaluate the efficacy of routine postoperative oral calcium and vitamin D supplementation in preventing symptomatic post-thyroidectomy hypocalcemia. The second aim was to draw clear guidelines regarding prophylactic calcium and/or vitamin D therapy for patients after thyroidectomy.

Methods. We identified randomized controlled trials comparing the administration of vitamin D or its metabolites to calcium or no treatment in adult patients after thyroidectomy. The search was performed in PubMed, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Google Scholar, and Web of Knowledge databases. Patients with a history of previous neck surgery, calcium supplementation, or renal impairment were excluded.

Results. Nine studies with 2,285 patients were included: 22 in the vitamin D group, 580 in the calcium group, 792 in the vitamin D and calcium group, and 891 in the no intervention group, with symptomatic hypocalcemia incidences of 4.6%, 14%, 14%, and 20.5%, respectively. Subcomparisons demonstrated that the incidences of postoperative hypocalcemia were 10.1% versus 18.8% for calcium versus no intervention and 6.8% versus 25.9% for vitamin D and calcium versus no intervention. The studies showed a significant range of variability in patients' characteristics.

Conclusions. A significant decrease in postoperative hypocalcemia was identified in patients who received routine supplementation of oral calcium or vitamin D. The incidence decreased even more with the combined administration of both supplements. Based on this analysis, we recommend oral calcium for all patients following thyroidectomy, with the addition of vitamin D for high-risk individuals. *The Oncologist* 2013;18:533–542

Implications for Practice: Excision of the thyroid gland (thyroidectomy) is a common therapy for thyroid diseases. It is a safe procedure if performed by an expert surgeon. Temporary low serum calcium level (transient hypocalcaemia) is the most common complication of this surgery. This complication may occur in 10%–45% of the cases and may result in mild to severe symptoms. Postoperative treatment with calcium and vitamin D may prevent or minimize hypocalcemic symptoms; however, until now, clear guidelines for the optimal use of these supplements were not available. The aim of this review is to compare the outcomes of different supplementation protocols in an attempt to assist surgeons decrease the incidence of hypocalcemia after thyroid surgery.

INTRODUCTION

Thyroid surgery is one of the most frequently performed surgical procedures worldwide [1]. In fact, total thyroidectomy is now widely accepted as the gold standard for the management of thyroid carcinoma and benign bilateral thyroid disease due to suspi-

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cion of cancer, symptoms of local compression, and a patient's desire for rapid and definitive treatment [2]. Currently, total thyroidectomy is considered a safe procedure when performed by experienced surgeons. The main postoperative complications are recurrent laryngeal nerve palsy and hypocalcemia [1, 3].

By definition, transient hypocalcemia resolves within 6 months after total thyroidectomy; its reported incidence ranges from 0.3% to 49% [4]. Permanent hypocalcemia persists after 6 months, with an incidence ranging from 0% to 13% [4]. Therefore, hypocalcemia is one of the main outcomes for auditing and patient consent [5, 6]. Inpatient admission and close monitoring of postoperative serum calcium level has been proposed to prevent postoperative symptoms related to hypocalcemia [7]. However, this approach has been criticized mainly due to the fact that the lowest concentration of serum calcium is usually not reached until 48−72 hours after thyroidectomy; therefore, it has major implications for safe early discharge planning [8].

Transient post-thyroidectomy hypocalcemia is self-limiting, but it could potentially be life-threatening [9]. Hypocalcemia symptoms are uncommon unless serum calcium level is below 8.0 mg/dL (2.0 mmol/L) [10]. Symptoms depend on the degree and rapidity of hypocalcemia onset, ranging from mild paresthesia and tingling to more severe cramps, tetany, seizures, laryngospasm, congestive heart failure, and arrhythmias due to prolonged QT intervals [8, 11]. Hungry bone syndrome could also occur after total thyroidectomy for Graves' disease as the patient recovers from the disease's thyrotoxic effects on bone metabolism [12].

To manage postoperative hypocalcemia, most practitioners obtain serial serum calcium measurements and respond appropriately to low levels [13]. Oral supplementation is started with elemental calcium with or without calcitriol for immediate management of postsurgical hypoparathyroidism [12]. For patients whose symptoms persist despite oral replacement therapy, intravenous replacement and closer monitoring are indicated [8]. Moreover, some centers routinely supplement all patients to facilitate early discharge [14]. Parathyroid autotransplantation also has been used to prevent hypocalcemia. Wells et al. first reported its successful use in patients with multigland hyperplasia, but it has also been used for delayed transplantation with variable success rates [12].

Several studies suggested that low postoperative parathyroid hormone (PTH) levels can predict hypocalcemia; it can be used to tailor supplement treatment options and prevent transient hypocalcemia [8, 15–17]. Despite the different methods to evaluate and predict postoperative hypocalcemia, there is no consensus on the role of routine calcium and/or vitamin D following thyroid surgery. The objectives of this meta-analysis are to evaluate the potential role of routine calcium or vitamin D supplementation for the prevention of post-thyroidectomy hypocalcemia and to draw therapy guidelines that may prevent this common complication.

METHODS

The study population included adults who underwent thyroidectomy as presented in the international literature. Interventions included post-thyroidectomy treatment with vitamin D, calcium, or both. The following types of interventions were considered: vitamin D and/or calcium orally, vitamin D and/or calcium intravenously, and vitamin D and/ or calcium in any

combination. The control group was compared with one type of treatment or no intervention. Outcomes were the effects of treatment on the incidence of hypocalcemia.

Studies included only randomized controlled trials. There was no time limitation. The review was limited to English language studies of adult patients (>18 years old). Studies that were designed to have a crossover management, were conducted on animals, included a pediatric population, or were unpublished/dissertation data were excluded. Studies that included patients with renal failure or previous neck surgery were also excluded, as the latter group of patients is at an increased risk for hypocalcemia with multiple cofactors involved (and for the same reason was excluded by the majority of randomized controlled trials).

An extensive literature search was conducted. Several electronic databases (including PubMed, Cochrane, Cumulative Index to Nursing and Allied Health Literature, Google Scholar, Web of Knowledge, and Snowball) were searched to locate studies that examined prevention of hypocalcemia after thyroidectomy. References were explored to identify other articles. Titles and abstracts were searched. Articles meeting inclusion criteria were retrieved and reviewed by the first and the second authors.

Key words and MeSH terms included the following: (post-thyroidectomy) OR (after thyroidectomy) AND (hypocalcemia OR low calcium) AND (prevention OR prophylactic or role) AND (calcium or vitamin D, OR calcifirole, OR caltrat, OR 1, 25-dihydroxyvitamin D, OR calcitriol, OR 25-hydroxyvitamin D, OR calcidiol, OR calcifediol, OR calcitroic acid, OR cathelicidin, OR cholecalciferol 7-dehydrocholesterol, OR 22-dihydroergocalciferol, OR dihydrotachysterol, OR 1, 25-dihydroxycholecalciferol, OR ergocalciferol, OR ergosterol, OR lumisterol, OR paricalcitol, OR tacalcitol).

Only randomized controlled trials were included; they were evaluated for concealment of randomization, blinding, and intention-to-treat analysis. Any study that did not have a reference standard or control group was excluded. Study quality was assessed using the Strength of Recommendation Taxonomy (SORT) grading system [26]; the level of evidence was therefore rated as 1 or 2 only. Assessment was not blinded. Studies were weighted based on their level of evidence as well as the number of patients involved.

Statistical Analyses

For each prophylactic method, separated analyses had been conducted using the difference between the change in the incidence of hypocalcemia for each type of treatment and the change in the control to determine the best treatment. Comparison groups included vitamin D versus no intervention, calcium versus no intervention, calcium versus calcium + vitamin D, and calcium + vitamin D versus no intervention. Final conclusions on the use of calcium or/and vitamin D as a prophylactic therapy for post-thyroidectomy hypocalcemia were based on the analysis of these studies. Mantel-Haenszel methods and raw counts from each study were used in the meta-analysis.

The I^2 test and associated *p* values were used to assess the heterogeneity of the studies. The software used for analysis was R (R Foundation for Statistical Computing, Vienna, Austria). The package that was used within the software to perform meta-analysis (including the figures and funnel plot to

assess bias and heterogeneity) was Meta 2.1–1 (Guido Schwarzer, Freiburg, Germany). Two independent reviewers evaluated the studies' eligibility, assessed the quality, and assessed the extracted data, aiming for achieving a high level of correlation in quality and validity of the findings. Disagreements were resolved by consensus.

RESULTS

The search identified 1,180 studies focusing on post-thyroidectomy hypocalcemia. A total of 132 studies remained after eliminating those that were duplicated. Of these 132 studies, 88 studies were excluded because they did not investigate post-thyroidectomy hypocalcemia. Another 13 articles were excluded because they had indirect measurement of our inclusion outcomes. Twenty-one articles were excluded because they were not randomized controlled trials and 1 article was excluded because it had crossover management. Thus, nine studies met the inclusion criteria and were chosen for analysis (Fig. 1). Two of the included studies were conducted by the same author: Roh et al. in 2006 and 2009 [9, 18]. Risks of biases were evaluated for all studies (Table 1).

SUMMARY OF STUDY FINDINGS

Bellantone et al. showed that routine supplementation therapy with oral calcium or vitamin D effectively prevents symptomatic hypocalcemia after total thyroidectomy and may allow for a safe early discharge [19]. Tartaglia et al. demonstrated that oral administration of calcitriol and calcium salts after total thyroidectomy significantly decreases the risk of severe postoperative hypocalcemia [20].

Pisaniello et al. concluded that early and combined oral administration of both calcium and vitamin D seemed to have major efficacy in preventing and treating postoperative hypocalcemia, demonstrating mean serum calcium levels higher than those of patients who received only oral calcium administration [21]. Testa et al. observed that the administration of calcitriol plus hydrochlorothiazide was able to prevent transient post-thyroidectomy hypocalcemia and reduce hospital stay [22].

Uruno et al. mentioned that a prophylactic infusion of calcium solution after total thyroidectomy may be useful in reducing the development of symptomatic hypocalcemia and reducing a patient's risk of discomfort and anxiety due to hypocalcemia [23]. In 2006, Roh et al. showed that routine administration of a supplement containing oral calcium and vitamin D is effective in reducing the incidence and severity of hypocalcemia after total thyroidectomy [9]. In 2009, Roh et al. also showed that central lymph dissection significantly increased the rate of postoperative hypocalcemia compared with total thyroidectomy alone; this could be prevented by routine postoperative supplementation with oral calcium and vitamin D [18].

Kurukahvecioglu et al. showed that routine postoperative calcium and vitamin D supplementation therapy may be useful for the prevention of symptomatic hypocalcemia after total thyroidectomy and may allow for a safe and early discharge from the hospital [24]. Finally, Choe et al. confirmed that routine oral calcium and vitamin D supplements were beneficial after total thyroidectomy with central neck lymph node dissection, with no difference between cholecalciferol and cal-
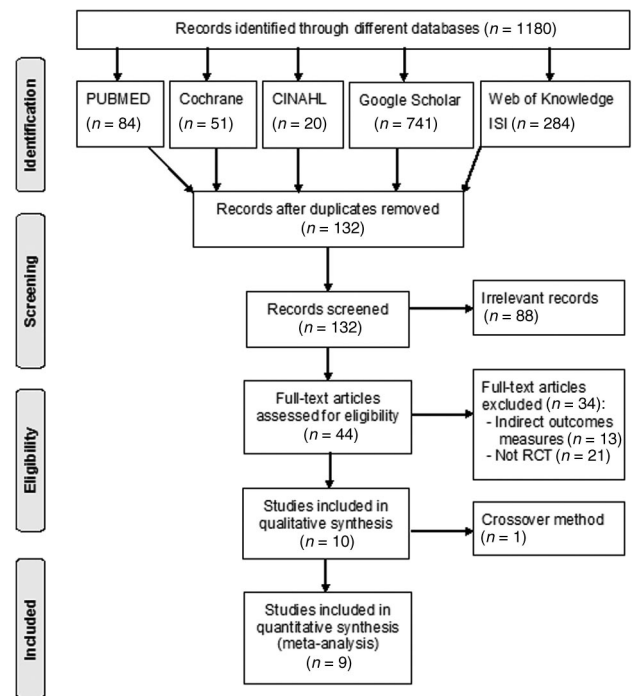
Figure 1. Flow of information through the different phases of the systematic review.
Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; RCT, randomized controlled trial.

citriol. If taken after the onset of hypocalcemia, however, calcitriol along with calcium carbonate seem to be more effective than cholecalciferol with calcium carbonate [25].

Overall Results of Meta-Analysis

Among the nine studies included, six were SORT class II and three were SORT class I. The combined studies recruited 2,285 patients, and the overall incidence of post-thyroidectomy hypocalcemia was 26.1% (Table 2). There was a significant range of variability in patient characteristics. A total of 394 males and 1,891 females were included, and the mean age was 50 ± 8 years. Among these patients, 1,183 had thyroid cancer and 904 patients had benign disease. Central lymph node dissection was performed for 845 patients (Table 3).

Four different groups were identified: vitamin D treatment ($n = 22$), calcium treatment ($n = 580$), vitamin D and calcium treatment ($n = 792$), and no intervention ($n = 891$). Accordingly, the rates of hypocalcemia amongst the different groups were 4.6%, 14%, 14%, and 20.5%, respectively. Thus, there were four comparisons: vitamin D and calcium versus no intervention, calcium versus vitamin D and calcium, calcium versus no intervention, and vitamin D versus no intervention. The incidences of postoperative hypocalcemia were 6.8% versus 25.9%, 22.6% versus 17.1%, 10.1% versus 18.8%, and 5% versus 50%, respectively (Table 4, Fig. 2). The meta-analysis showed a significant decrease in the rate of symptomatic postoperative hypocalcemia between the groups treated with vitamin D or its metabolites along with calcium compared with no prophylaxis or calcium alone. There was a high heterogeneity between the studies for vitamin D and calcium versus no intervention, as well as for calcium versus calcium and vitamin D. However, there was no significant heterogeneity for calcium versus no intervention. Two separate analyses were per-

Table 1. Risk of bias evaluation

Study	Sequence generation	Allocation concealment	Blind evaluation	Incomplete outcome	Intention-to-treat analyses	Statistical methods description	Intervention description
Bellantone et al. [19]	Yes	Unclear	Unclear	No	Yes	Yes	Yes
Tartaglia et al. [20]	No	Unclear	Unclear	No	Yes	Yes	Yes
Pisaniello et al. [21]	Yes	Unclear	Yes	No	Yes	Yes	Yes
Testa et al. [22]	Yes	Unclear	Yes	No	Yes	Yes	Yes
Uruno et al. [23]	Yes	Yes	Unclear	No	Yes	Yes	Yes
Roh et al. [9]	Yes	Unclear	Yes	No	Yes	Yes	Yes
Kurukahvecioglu et al. [24]	Yes	Unclear	Unclear	No	Yes	Yes	Yes
Roh et al. [18]	Yes	Yes	Yes	No	Yes	Yes	Yes
Choe et al. [25]	Yes	Unclear	Unclear	No	Yes	Yes	Yes

Table 2. Randomized controlled trials included in meta-analysis

Study	Location	No. of patients	No. of patients with hypocalcemia (%)	SORT class	Hypocalcemia definition
Bellantone et al. [19]	Italy	79	26 (36.7)	II	Ca <0.8 mg/dL
Tartaglia et al. [20]	Italy	417	94 (22.5)	II	Hypocalcemia symptoms and signs
Pisaniello et al. [21]	Italy	120	5 (4.2)	I	Ca <0.8 mg/dL
Testa et al. [22]	Italy	42	11 (26.2)	I	Ca <2.10 mmol/L
Uruno et al. [23]	Japan	547	250 (45.7)	II	
Roh et al. [9]	Korea	90	22 (24.4)	II	Ca <0.8 mg/dL or ionized calcium <1.0 mmol/L
Kurukahvecioglu et al. [24]	Turkey	487	21 (4.3)	II	Symptoms that required calcium supplementation
Roh et al. [18]	Korea	197	66 (33.5)	I	Ca <0.8 mg/dL
Choe et al. [25]	Korea	306	101 (33)	II	Ca <0.8 mmol/L or ionized calcium <1.0 mmol/L
Total		2,285	596 (26.1)	I (n = 3); II (n = 6)	

Table 3. Demographic data

Study	No. of patients	Age (yrs ± SD)	Sex (male/female)	No. of patients with malignancy (%)	No. of patients with benign disease (%)	No. of TT (%)	No. of TT + CND (%)	No. of TT + MRND (%)	No. of parathyroid autotransplantations (%)
Bellantone et al. [19]	79	49 ± 1	18/61	5 (6.3)	74 (93.7)	79 (100)	0 (0)	0 (0)	NA[a]
Tartaglia et al. [20]	417	51.5 ± 2	71/346	86 (20.6)	331 (79.4)	417 (100)	0 (0)	0 (0)	0 (0)
Pisaniello et al. [21]	120	. . . . data not available.							
Testa et al. [22]	42	56.2 ± 12	14/28	11 (26.2)	31 (73.8)	42 (100)	0 (0)	0 (0)	0 (0)
Uruno et al. [23]	547	51 ± 14	74/473	427 (78)	120 (22)	120 (22)	427 (78)	0 (0)	Yes, if needed
Roh et al. [9]	90	47 ± 2	17/73	75 (83.3)	15 (16.7)	71 (79)	0 (0)	19 (21)	19 (21)
Kurukahvecioglu et al. [24]	487	47.4 ± 12	86/401	76 (15.6)	411 (84.4)	487 (100)	0 (0)	0 (0)	
Roh et al. [18]	197	48.5 ± 12	38/159	197 (100)	0 (0)	49 (25)	112 (57)	36 (18)	16 (8)
Choe et al. [25]	306	48.5 ± 10	76/230	306 (100)	0 (0)	0 (0)	306 (100)	0 (0)	123 (40.2)
Total	2,285	50 ± 8	394/1,891	1,183 (51.8)	982 (43)	1,265 (55.4)	845 (37)	55 (2.4)	>158

[a]The number was not reported, but the mean number of parathyroid autotransplantations was 3.5 ± 0.7.

Abbreviations: CND, central neck dissection; MRND, modified radical neck dissection; NA, not available; TT, total thyroidectomy.

formed for the first and second comparisons, with and without the studies with high heterogeneity. The results were the same, but the confidence interval was narrower in the second analysis (Fig. 2).

Hypocalcemia Data

The definition of hypocalcemia varied between the studies. Five studies defined hypocalcemia as calcium levels <0.8 mmol/L [9, 18–19, 21, 25]. In comparison, Testa et al. used calcium levels <2.10 mmol/L as a cutoff [22]. Tartaglia et al. and Kurukahvecioglu et al. defined hypocalcemia as symptoms that required calcium supplementation [20, 24] (Table 2).

Serum calcium and PTH readings at 1 day, 2 days, 3 days, 1 week, and 1 month postoperatively were collected in all the studies (Table 5). A compression of the different treatments showed that there were significant statistical differences in

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Table 4. Hypocalcaemia incidence

	Intervention		No intervention		
Study	n	Hypocalcemia symptoms (%)	n	Hypocalcemia symptoms (%)	p value
Vitamin D and calcium vs. no intervention					
Bellantone et al. [19]	26	6 (23)	27	11 (24.4)	.24
Roh et al. [9]	45	6 (13.3)	45	16 (35.5)	.03
Kurukahvecioglu et al. [24]	243	10 (4.1)	244	11 (4.5)	1.0
Roh et al. [18]	49	4 (8.2)	99	44 (44.4)	.0001
Choe et al. [25]	154	36 (23.4)	152	65 (42.8)	.0004
Total	517	62 (12)	567	147 (25.9)	.0001
Calcium vs. vitamin D and calcium					
Bellantone et al. [19]	26	9 (34.6)	26	6 (23)	.54
Tartaglia et al. [20]	202	45 (22.3)	215	49 (22.8)	.91
Pisaniello et al. [21]	60	4 (6.6)	60	1 (1.6)	.36
Roh et al. [18]	49	18 (36.7)	49	4 (8.2)	.003
Total	337	76 (22.6)	350	60 (17.1)	.09
Calcium vs. no intervention					
Bellantone et al. [19]	26	9 (34.6)	27	11 (24.4)	.78
Uruno et al. [23]	243[a]	5 (2.1)	304	26 (8.6)	.001
Roh et al. [18]	49	18 (36.7)	99	44 (44.4)	.38
Total	318	32 (10.1)	430	81 (18.8)	.001
Vitamin D vs. no intervention					
Testa et al. [22]	22	1 (5)	20	10 (50)	.001

p values were calculated using Fisher's exact test.
[a]Intravenous calcium.

serum calcium level on the first and second days as well as 1 week after surgery. However, the only significant statistical difference for the serum PTH was at 1 month after surgery, even though all values were within normal limits (Table 6).

In the 2006 Roh et al. study [9], there were minimal hypocalcemic symptoms in the group who received both vitamin D and calcium but more severe symptoms in the group with no intervention, including carpopedal spasms in three patients. Intravenous calcium was administered to five patients in the group who received no intervention but not to any patients in the supplement group (p = .022). In the Choe et al. study [25], most hypocalcemic symptoms were mild, with moderate or severe symptoms occurring in only 13 (4.3%) patients. Intravenous calcium injections were necessary in 43 (14.1%) patients; 34 (11%) patients needed only one injection, whereas 3 (1%) patients required more than three injections.

In the 2009 Roh et al. study [18], hypocalcemic symptoms were minimal in the oral calcium and vitamin D group and in the noncentral neck dissection group, but they were more severe in the group who received no intervention. Intravenous calcium was administered to seven (7%) patients in the no intervention group, compared with no patients in the oral calcium and vitamin D group (p = .096). Kurukahvecioglu et al. [24] showed that minor symptoms occurred in 4 patients in the group who received no intervention and 10 patients in the treated group. Intravenous calcium administration was required for seven patients in the group who received no intervention, but in none of the patients in the treated group (p < .001). The mean hospital stay in the control group was 2.9 ±

0.9 days (range: 2–7 days) and 1.2 ± 0.4 days (range: 1–2 days) in the treated group (p < .001).

Bellantone et al. [19] showed that 11 patients (40.7%) in the group who received no intervention experienced symptoms of hypocalcemia and required oral calcium and vitamin D administration. Two patients (7.7%) in the oral calcium group required vitamin D administration because of persistent hypocalcemia. Two patients (7.4%) in the group who received no intervention had carpopedal spasms and nine patients (33.3%) had perioral numbness with positive Chvostek sign. Patients who were symptomatic in the oral calcium and vitamin D groups experienced minor symptoms (mild perioral tingling, with a positive Chvostek sign). No patients in the oral calcium and vitamin D groups and two patients (7.4%) in the group who received no intervention required intravenous calcium administration (p < .01).

Pisaniello et al. [21] demonstrated that four (6.6%) patients in the oral calcium group and one patient (1.6%) in the oral calcium and vitamin D group experienced symptomatic hypocalcemia that required intravenous calcium (p = .36). The patients experienced muscle cramps and tingling. Testa et al. [22] reported that symptomatic hypocalcemia (muscle cramps and tingling of the face and extremities) developed in four (20%) patients (7.4%) in the group who received no intervention but in no patients in the oral calcium and vitamin D group (p < .05).

DISCUSSION

Postoperative hypocalcemia is one of the most immediate and common surgical complications of total thyroidectomy [27]. To minimize the symptoms of postoperative hypocalce-

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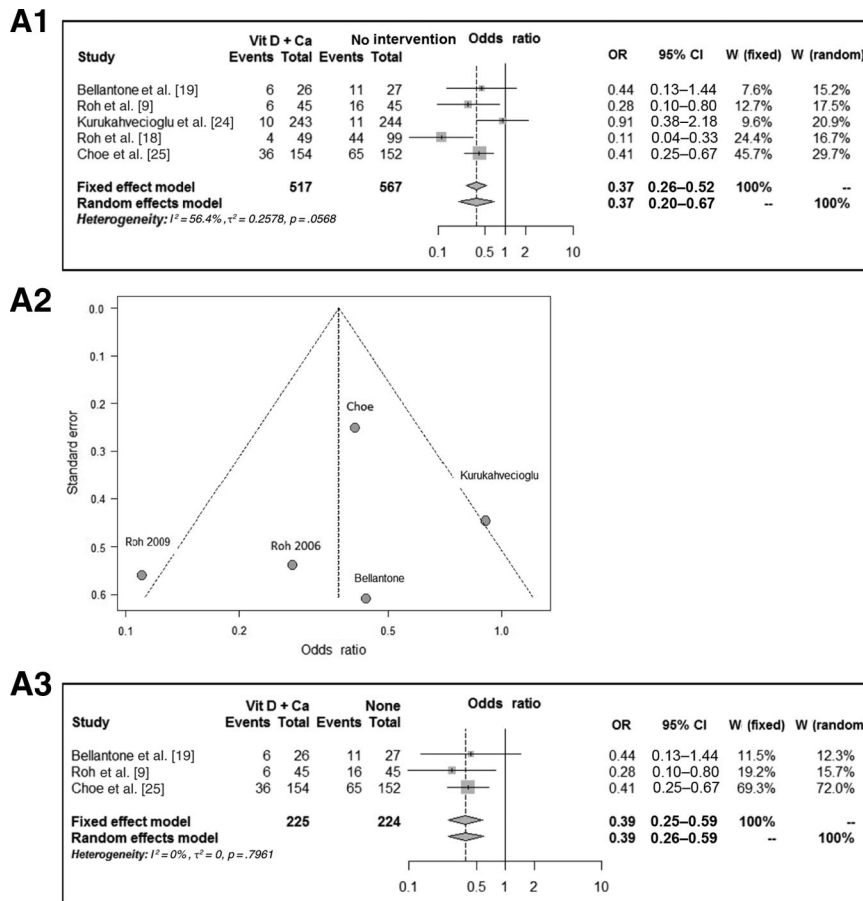
Figure 2. **(A1):** Vitamin D and calcium versus no intervention. **(A2):** Funnel plot for heterogeneity. **(A3):** Vitamin D and calcium versus no intervention, excluding the studies with high heterogeneity. **(B1):** Vitamin D and calcium versus calcium. **(B2):** Funnel plot for heterogeneity. **(B3):** Vitamin D and calcium versus calcium, excluding the studies with high heterogeneity. **(C1):** Calcium versus no intervention. **(C2):** Funnel plot for heterogeneity.

Abbreviations: Ca, calcium; CI, confidence interval; OR, odds ratio; Vit D, vitamin D.

mia, some surgeons prefer to give calcium treatment empirically, whereas others prefer to educate patients about symptoms so that they can return to the hospital if these symptoms arise [28]. Moreover, it has been reported that administration of post-thyroidectomy oral calcium with vitamin D did not appear to inhibit the function of normal parathyroid glands [29].

Several studies have investigated the role of postoperative PTH as a predictor of hypocalcemia. It has been suggested that calcium and/or vitamin D supplementation may be dictated by the postoperative PTH level [6]. Postoperative PTH levels were shown to have a high sensitivity and specificity for predicting hypocalcemia [16–17, 29–30]. In a meta-analysis of four Australian studies, Grodski et al. [31, 32] found that an undetectable PTH level 4 hours after surgery predicted hypocalcemia with a sensitivity of 48.4%, specificity of 96.7%, and positive predictive value of 83.8%, but that 16% of patients with an undetectable PTH level remained normocalcemic without treatment. Noordzij et al. analyzed the pooled data from 9 studies and found that the PTH level 6 hours after surgery had the highest accuracy for predicting hypocalcemia; in addition, a greater than 65% decline from the baseline serum PTH level 6 hours postoperatively predicted hypocalcemia with a sensitivity of 96.4% and a specificity of 91.4% [34].

Youngwirth et al. demonstrated that postoperative PTH may be used to decrease the incidence of hypocalcemia and emergency room visits [8]. Nevertheless, there is no consensus on the role and benefits of routine calcium and/or vitamin supplementation following thyroidectomy.

The meta-analysis conducted in this study showed a significant decrease in the rate of symptomatic postoperative hypocalcemia between the groups treated with vitamin D or its metabolites along with calcium as compared to no prophylaxis or calcium alone. The results showed that the combination vitamin D or metabolites with calcium is the most effective strategy. Our results are similar to the meta-analysis con-

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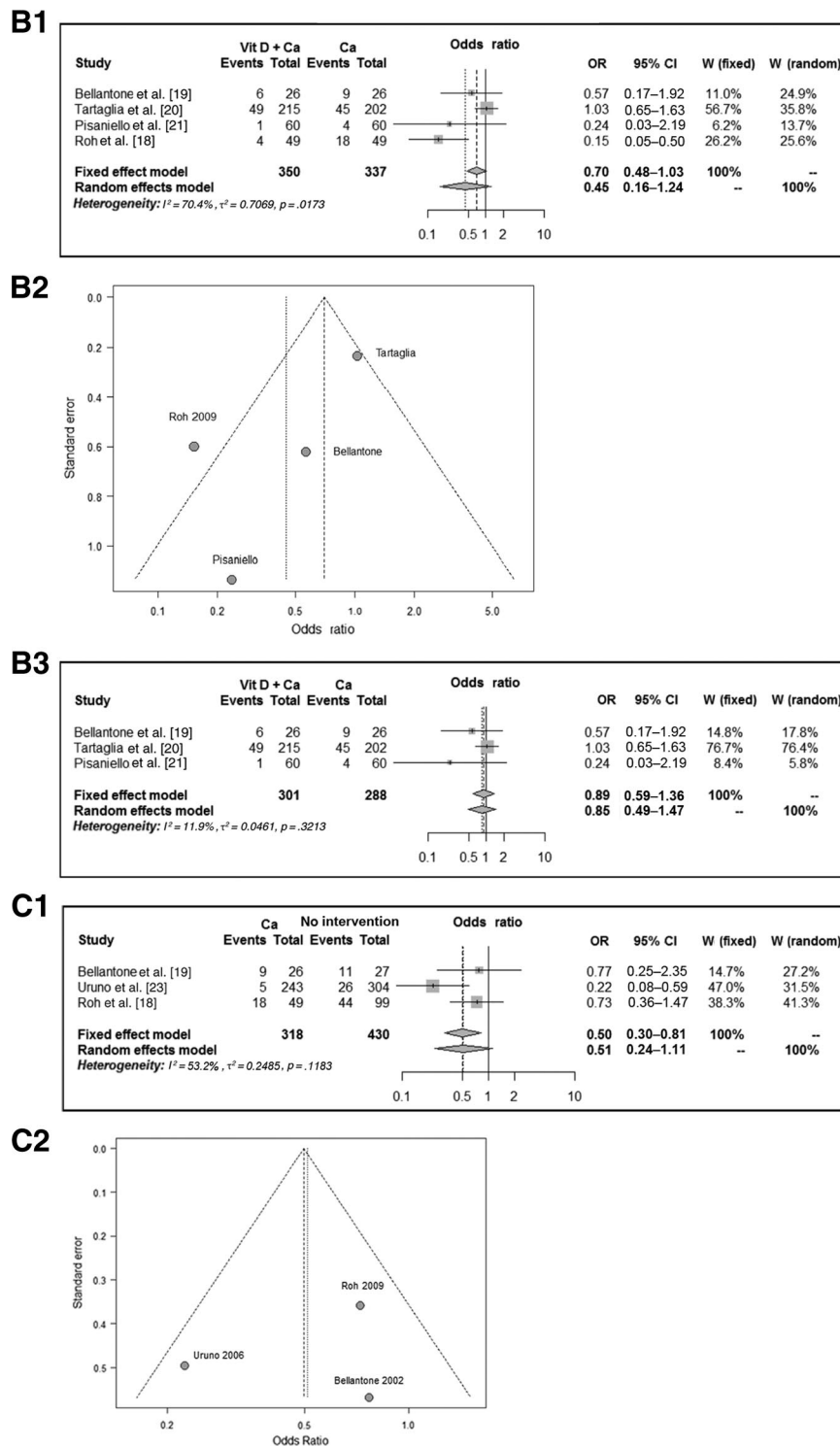
B1

Study	Vit D + Ca Events	Total	Ca Events	Total	Odds ratio	OR	95% CI	W (fixed)	W (random)
Bellantone et al. [19]	6	26	9	26		0.57	0.17–1.92	11.0%	24.9%
Tartaglia et al. [20]	49	215	45	202		1.03	0.65–1.63	56.7%	35.8%
Pisaniello et al. [21]	1	60	4	60		0.24	0.03–2.19	6.2%	13.7%
Roh et al. [18]	4	49	18	49		0.15	0.05–0.50	26.2%	25.6%
Fixed effect model		350		337		**0.70**	**0.48–1.03**	**100%**	**--**
Random effects model						**0.45**	**0.16–1.24**	**--**	**100%**
Heterogeneity: $I^2 = 70.4\%$, $\tau^2 = 0.7069$, $p = .0173$					0.1 0.5 1 2 10				

B2

B3

Study	Vit D + Ca Events	Total	Ca Events	Total	Odds ratio	OR	95% CI	W (fixed)	W (random)
Bellantone et al. [19]	6	26	9	26		0.57	0.17–1.92	14.8%	17.8%
Tartaglia et al. [20]	49	215	45	202		1.03	0.65–1.63	76.7%	76.4%
Pisaniello et al. [21]	1	60	4	60		0.24	0.03–2.19	8.4%	5.8%
Fixed effect model		301		288		**0.89**	**0.59–1.36**	**100%**	**--**
Random effects model						**0.85**	**0.49–1.47**	**--**	**100%**
Heterogeneity: $I^2 = 11.9\%$, $\tau^2 = 0.0461$, $p = .3213$					0.1 0.5 1 2 10				

C1

Study	Ca Events	Total	No intervention Events	Total	Odds ratio	OR	95% CI	W (fixed)	W (random)
Bellantone et al. [19]	9	26	11	27		0.77	0.25–2.35	14.7%	27.2%
Uruno et al. [23]	5	243	26	304		0.22	0.08–0.59	47.0%	31.5%
Roh et al. [18]	18	49	44	99		0.73	0.36–1.47	38.3%	41.3%
Fixed effect model		318		430		**0.50**	**0.30–0.81**	**100%**	**--**
Random effects model						**0.51**	**0.24–1.11**	**--**	**100%**
Heterogeneity: $I^2 = 53.2\%$, $\tau^2 = 0.2485$, $p = .1183$					0.1 0.5 1 2 10				

C2

Figure 2. Continued.

ducted by Sanabria et al., who evaluated the routine postoperative administration of vitamin D and calcium after total thyroidectomy in studies published from January 1980 to April 2008 [14]. In their analysis, four studies—Roh et al. [9], Bellantone et al. [19], Pisaniello et al. [21], and Tartaglia et al. [22]—were included with 706 patients. Calcitriol and calcium were compared to no treatment and only calcium treatment, with a decreased rate of hypocalcemia identified for both comparisons (odds ratio [OR] = 0.32, 95% confidence inter-

val [CI]: 0.13–0.79; and OR = 0.31, 95% CI: 0.14–0.70, respectively). Despite wide confidence intervals, the results are statistically significant. Our study, in comparison, included 9 studies of 2,285 patients, 4 groups, and 3 comparisons; the demonstrated OR was more significant with a narrower CI (Fig. 2).

The studies included in this study showed a wide range of variability in patient characteristics. For example, the malignancy rate varied from 8% to 100%. Similar variability is evi-

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Table 5. Postoperative serum calcium and parathyroid hormone readings

Study	1 day Ca (mg/dL)	1 day PTH (pg/mL)	2 days Ca (mg/dL)	2 days PTH (pg/mL)	3 days Ca (mg/dL)	3 days PTH (pg/mL)	1 week Ca (mg/dL)	1 week PTH (pg/mL)	1 month Ca (mg/dL)	1 month PTH (pg/mL)	Treatment
Vitamin D and calcium											
Bellantone et al. [19]	8.5 ± 0.6	28 ± 17	8.6 ± 0.5	25 ± 18	8.8 ± 0.7		9.3 ± 0.5	21 ± 13			Oral calcium 3 g/day + calcitriol 1 µg/day
Roh et al. [9]	8.3 ± 0.7	23.8 ± 26	8.5 ± 0.7		8.6 ± 0.7	22.5 ± 32	9.0 ± 0.7	20.5 ± 16.8	9.2 ± 1.3	33.4 ± 30.2	Oral calcium 3 g/day + vitamin D 1 g/day for 2 weeks
Kurukahvecioglu et al. [24]											Oral calcium 600 mg/day + vitamin D 400 IU
Roh et al. [18]	8.5 ± 0.5	17.1 ± 4.4	8.8 ± 0.6		9.0 ± 0.7	17.8 ± 4.1	9.2 ± 0.4	19.6 ± 5.0	8.9 ± 0.4	30.2 ± 10.6	Oral calcium 3 g/day + vitamin D 1 µg/day
Choe et al. [25]	7.88 ± 0.6	12.1 ± 8.5	8.14 ± 0.63				8.95 ± 0.6		10.8 ± 9.8		Oral calcium 3 g/day + calcitriol 0.5 µg/day or cholecalciferol 20 µg/day
Tartaglia et al. [20]											Oral calcium 1.5 g/day + calcitriol 1 µg or 2 µg/day
Pisaniello et al. [21]a	8.4		8.7		8.6						Oral calcium 3 g/day + cholecalciferol 400 IU/day
Average	8.3 ± 0.6	20.3 ± 14	8.6 ± 0.6	25 ± 18	8.8 ± 0.7	20.2 ± 18	9.2 ± 0.5	20.4 ± 11.6	9.0 ± 0.8	24.8 ± 18.9	
Calcium											
Bellantone et al. [19]	8.5 ± 0.5	24 ± 20	8.3 ± 0.5	24 ± 18	8.2 ± 0.7		9.1 ± 0.5	20 ± 12			Oral calcium 3 g/day
Tartaglia et al. [20]											Oral calcium 1.5 g/day
Pisaniello et al. [21]a	8.4		8.7		8.6						Oral calcium 300 mg/day
Uruno et al. [23]	7.91 ± 0.5	15.6 ± 13.9									3–8 hrs postoperatively, 78–156 mg of calcium (30–60 minutes of drip infusion)
Roh et al. [18]	8.5 ± 0.4	16.6 ± 6.1	8.6 ± 0.5		8.5 ± 0.7	17.5 ± 5.5	8.6 ± 0.6	22.9 ± 9.3	8.8 ± 0.6	31.5 ± 10.3	Oral calcium 3 g/day
Average	8.3 ± 0.5	18.7 ± 13.3	8.5 ± 0.5	24 ± 18	8.4 ± 0.7	17.5 ± 5.5	8.85 ± 0.55	21.5 ± 10.7	8.8 ± 0.6	31.5 ± 10.3	
No intervention											
Bellantone et al. [19]	8.4 ± 0.6	25 ± 19	8.2 ± 0.7	27 ± 23	8.5 ± 0.6		9.3 ± 0.7	26 ± 17			None
Roh et al. [9]	8.3 ± 0.7	25.8 ± 15.4	8.0 ± 0.7		7.9 ± 0.7	23.6 ± 26	8.4 ± 0.7	24.8 ± 19.5	8.9 ± 1.3	31.6 ± 32.2	None
Kurukahvecioglu et al. [24]											None
Uruno et al. [23]	7.65 ± 0.54	17.9 ± 15.7									None
Roh et al. [18]	8.2 ± 0.4	18.6 ± 6.7	8.1 ± 0.6		8.2 ± 0.7	19.2 ± 8.3	8.6 ± 0.6	22.5 ± 11	8.8 ± 0.6	29.5 ± 11	None
Choe et al. [25]	7.87 ± 0.5	12.7 ± 10.6	7.89 ± 0.6						8.87 ± 0.6	18.5 ± 11.4	None
Testa et al. [22]a	2.07 ± 0.08	2.3 ± 2.0	2.10 ± 0.1		2.12 ± 0.1		2.10 ± 0.1				Placebo (mineral integrates)
Average	8.08 ± 0.55	20 ± 13.5	8.05 ± 7	27 ± 23	8.2 ± 0.7	21.4 ± 17	8.76 ± 0.7	24.4 ± 15.8	8.86 ± 0.8	26.5 ± 18.2	
Vitamin D											
Testa et al. [22]a	2.21 ± 0.08	1.6 ± 1.5	2.20 ± 0.1		2.30 ± 0.1		2.30 ± 0.12				Oral 1.5 µg calcitriol + 25 mg hydrochlorothiazide

aStandard deviation was reported to be similar in all groups. The calcium reading was for the ionized calcium so it was not included in the compression.

Abbreviations: Ca, calcium; PTH, parathyroid hormone.

Table 6. Postoperative serum calcium and parathyroid hormone readings: Compression

Time of measurement	Vitamin D + calcium Ca (mg/dL)	Vitamin D + calcium PTH (pg/mL)	Calcium Ca (mg/dL)	Calcium PTH (pg/mL)	No intervention Ca (mg/dL)	No intervention PTH (pg/mL)	p value Ca (mg/dL)	p value PTH (pg/mL)
1 day	8.17 ± 0.6	16.37 ± 14	8.11 ± 0.5	16.44 ± 13.3	7.87 ± 0.6	17.62 ± 13.5	<.05	>.05
2 days	8.42 ± 0.6	25 ± 18	8.59 ± 0.5	24 ± 18	7.996 ± 0.7	27 ± 23	<.05	>.05
3 days	8.74 ± 0.7	20.05 ± 18	8.49 ± 0.7	17.5 ± 5.5	8.17 ± 0.7	20.58 ± 17	>.05	>.05
1 week	9.15 ± 0.5	20.24 ± 11.6	8.77 ± 0.6	21.9 ± 10.7	8.66 ± 0.7	23.66 ± 15.8	<.05	>.05
1 month	8.99 ± 0.8	24.8 ± 18.73	8.8 ± 0.6	31.5 ± 10.3	8.85 ± 0.8	24.17 ± 18.2	>.05	<.05

Abbreviations: Ca, calcium; PTH, parathyroid hormone.

dent by the inclusion of patients with radical neck dissection, Graves' disease, surgery type, parathyroid identification, and autotransplantation. However, randomization of the studies balanced these differences. Importantly, there were some weaknesses and limitations in some of the included studies. The blind evaluation of results and allocation concealment reporting were inadequate, which may have biased the results. The potential adverse events of the treatment of all patients were not adequately evaluated and could repre-

sent an increase in costs not considered in this analysis. None of the included studies reported or denied any conflict of interest, apart from Roh et al., who specifically reported none [18], and Testa et al., who mentioned a grant provided by the Ministero Della Pubblica Istruzione edella Ricerca Scientifica [22].

Multiple other specific limitations should be noted. Choe et al. did not investigate the effect of preoperative vitamin D deficiency on the postoperative hypocalcemia [24]. The study by

Tartaglia et al. was not blinded and did not evaluate the costs of calcitonin and ionized calcium measurement [20]. The 2006 Roh et al. study [9] did not observe for hypercalcemia or other side effects. The prevalence of hypocalcemia in the Testa et al. study is high because they used the "biochemical definition," and 70% of the patients presented predisposing factors for hypoparathyroidism (voluminous and/or toxic goiter) [22]. Their study has several other limitations such as small sample size, and their inclusion criteria may have introduced bias to it [22]. Pisaniello et al. did not report the point at which treatment was suspended [21]. The 2009 Roh et al. study [18] did not provide any information about the rate of permanent hypoparathyroidism. These study limitations should be noted but do not affect the validity of our meta-analysis results.

Although a cost analysis is beyond the scope of this study, it has been shown that routine oral calcium with or without vitamin D reduces patients' length of stay at the hospital. The economic profitability of thyroid surgery is improved when mean length of stay is reduced to 2 days through a fast-track protocol. Decreasing the duration of hospitalization was more effective than decreasing operative duration in controlling overall costs [34]. Moreover, routine oral calcium and calcitriol supplementation in patients after thyroidectomy seems to be less expensive and results in higher patient utility than selective supplementation [31]. Routine calcium supplementation would save $29,365 per quality-adjusted life year (QALY), with a savings of $62 per patient and an incremental benefit of 0.002 QALYs [36]. Singer et al. reported that the cost of a 3-week regimen of calcium carbonate is approximately $15, which is less expensive than either the cost of overnight admission or published laboratory protocols that are designed to predict the risk of hypocalcemia [37].

Overall Study Recommendations

The analysis of our results suggests several recommendations that may result in decreased incidence of hypocalcemia, hypocalcemic symptoms, and hospital length of stay. Although the serum calcium values were higher for the patients who received calcium and vitamin D than for those who received calcium only, all values were within normal limits. Based on these data, it is reasonable to recommend that calcium supplementation is enough to decrease the risk of post-thyroidectomy hypocalcemia. Vitamin D supplementation should be reserved for patients who have a higher risk of developing postoperative hypocalcemia, including patients who undergo central lymph node dissection, recurrent neck surgery, intraoperative parathyroid gland injury; patients who have intraoperative or postoperative low PTH; and patients who are known to have a vitamin D deficiency.

Postoperative oral calcium at a minimum dose of 3 g/day should be routinely given to all patients for 2 weeks following thyroid surgery. Patients who are at increased risk of postoperative hypocalcemia should be treated with the same cal-

> Postoperative oral calcium at a minimum dose of 3 g/day should be routinely given to all patients for 2 weeks following thyroid surgery. Patients who are at increased risk of postoperative hypocalcemia should be treated with the same calcium regimen, along with the addition of calcitriol at a dose of 1 μg/day.

cium regimen, along with the addition of calcitriol at a dose of 1 μg/day. This analysis does not support routine use of higher doses of calcium or vitamin D; however, no clear recommendations can be made against increasing the initial calcium dosage for patients who are at increased risk of postoperative hypocalcemia.

CONCLUSIONS

This meta-analysis demonstrated a decrease in postoperative hypocalcemia rates for patients who received calcium supplementation routinely. This rate decreased further with administration of vitamin D. The results of this study support a change in clinical practice and suggest that all patients undergoing thyroidectomy should be discharged with continued calcium and/or vitamin D supplementation for 1–2 weeks. Despite the significant results presented in this analysis, further investigation is needed to evaluate the exact dose and route of supplementation, as well as whether supplements should be given to patients preoperatively or postoperatively. Cost-effectiveness studies should also be considered.

AUTHOR CONTRIBUTIONS

Conception/Design: Amal Alhefdhi, Herbert Chen
Provision of study material or patients: Amal Alhefdhi, Haggi Mazeh, Herbert Chen
Collection and/or assembly of data: Amal Alhefdhi, Haggi Mazeh
Data analysis and interpretation: Amal Alhefdhi, Herbert Chen
Manuscript writing: Amal Alhefdhi, Haggi Mazeh
Final approval of manuscript: Amal Alhefdhi, Haggi Mazeh, Herbert Chen

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