AMERICAN ACADEMY OF OTOLARYNGOLOGY– HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–
Head and Neck Surgery
2024, Vol. 170(2) 359–372

DOI: 10.1002/ohn.594
http://otojournal.org
WILEY

Management of Postthyroidectomy Hypoparathyroidism and Its Effect on Hypocalcemia-Related Complications: A Meta-Analysis

Sam P. J. van Dijk, BSc[1], M. H. Elise van Driel, BSc[1], Caroline M. J. van Kinschot, MD[2,3], Maarten F. M. Engel, PhD[4], Gaston J. H. Franssen, MD[1], Charlotte van Noord, MD, PhD[2], W. Edward Visser, MD, PhD[3], Cornelis Verhoef, MD, PhD[1], Robin P. Peeters, MD, PhD[3], and Tessa M. van Ginhoven, MD, PhD[1]

Abstract

Objective. The aim of this Meta-analysis is to evaluate the impact of different treatment strategies for early postoperative hypoparathyroidism on hypocalcemia-related complications and long-term hypoparathyroidism.

Data Sources. Embase.com, MEDLINE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and the top 100 references of Google Scholar were searched to September 20, 2022.

Review Methods. Articles reporting on adult patients who underwent total thyroidectomy which specified a treatment strategy for postthyroidectomy hypoparathyroidism were included. Random effect models were applied to obtain pooled proportions and 95% confidence intervals. Primary outcome was the occurrence of major hypocalcemia-related complications. Secondary outcome was long-term hypoparathyroidism.

Results. Sixty-six studies comprising 67 treatment protocols and 51,096 patients were included in this Meta-analysis. In 8 protocols (3806 patients), routine calcium and/or active vitamin D medication was given to all patients directly after thyroidectomy. In 49 protocols (44,012 patients), calcium and/or active vitamin D medication was only given to patients with biochemically proven postthyroidectomy hypoparathyroidism. In 10 protocols (3278 patients), calcium and/or active vitamin D supplementation was only initiated in case of clinical symptoms of hypocalcemia. No patient had a major complication due to postoperative hypocalcemia. The pooled proportion of long-term hypoparathyroidism was 2.4% (95% confidence interval, 1.9-3.0). There was no significant difference in the incidence of long-term hypoparathyroidism between the 3 supplementation groups.

Conclusions. All treatment strategies for postoperative hypocalcemia prevent major complications of hypocalcemia. The early postoperative treatment protocol for postthyroidectomy hypoparathyroidism does not seem to influence recovery of parathyroid function in the long term.

Keywords

hypoparathyroidism, postoperative management, parathyroid failure

Received August 16, 2023; accepted November 4, 2023.

Hypoparathyroidism is a common complication after total thyroidectomy. It leads to hypocalcemia and treatment consists of supplementation with calcium and/or active vitamin D. Postoperative hypoparathyroidism is usually diagnosed within 24 to 48 hours after surgery. Based on the time to recovery of parathyroid function the following definitions can be applied: short-term hypoparathyroidism (restored function within <30 days after thyroidectomy), protracted hypoparathyroidism (restored function within 1-6 months

[1]Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands
[2]Department of Internal Medicine, Maasstad Hospital Rotterdam, Rotterdam, The Netherlands
[3]Department of Internal Medicine and Thyroid Diseases, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[4]Medical Library, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Corresponding Author:
Sam P. J. van Dijk, BSc, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Department of Surgical Oncology and Gastrointestinal Surgery, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Email: s.p.j.vandijk@erasmusmc.nl

after thyroidectomy), and long-term hypoparathyroidism (persisting parathyroid failure for at least 6-12 months after thyroidectomy, with occasional long-term recovery of parathyroid function).[1] The estimated incidence of short-term hypoparathyroidism ranges from 20% to 40%[2] and the incidence of long-term hypoparathyroidism ranges from 1% to 15%.[3-5] Patients with long-term hypoparathyroidism have an impaired quality of life and long-term hypoparathyroidism is associated with an increased risk of death.[6,7]

The worldwide approaches for treating postthyroidectomy hypoparathyroidism can be categorized into 3 different strategies. One strategy encompasses routine calcium and/or active vitamin D supplementation in all patients undergoing thyroidectomy, which is regarded as a practical approach to facilitate early discharge after thyroid surgery and to limit the occurrence of symptomatic hypocalcemia.[8,9] However, routine supplementation results in overtreatment of patients who do not require supplementation. Another strategy involves calcium and/or vitamin D supplementation only in the presence of clinical symptoms, which aims to reduce overtreatment but studies on the safety of this strategy are scarce.[10] The third, most commonly used, strategy starts supplementation based on calcium or parathyroid hormone (PTH) levels.[11] A recent European expert consensus report emphasized, however, that there is no consensus or guideline on when to initiate calcium and/or active vitamin D supplementation in patients with early postoperative hypoparathyroidism.[12] Although not frequently reproduced, some studies state that aggressive supplementation in all patients with postoperative hypoparathyroidism induces metabolic rest of the injured parathyroid gland (concept of parathyroid splinting) and could have a beneficial impact on long-term parathyroid function.[1,13,14]

The goal of this systematic review is to summarize all available evidence of different treatment strategies for early postoperative hypoparathyroidism and their impact on hypocalcemia-related complications and long-term hypoparathyroidism.

Methods

Literature Search and Study Selection

The study protocol was registered in the PROSPERO database (CRD-42022378225). The methods in this systematic review and Meta-analysis are described based on the PRISMA Checklist[15] and the PRISMA-S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews.[16] An exhaustive search strategy was developed by an experienced information specialist (M.F.M.E.). The search was developed in Embase.com, optimized for sensitivity, and then translated to other databases following the method as described by Bramer et al.[17] The search was carried out in the databases Embase.com, Medline ALL via Ovid, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials via Wiley. Additionally, a search was performed in Google Scholar from which the 200 top-ranked references were downloaded using the software Publish or Perish.[18] The search was performed on September 20, 2022. The full search strategies of all databases are available in Supplemental 1, available online.

Two reviewers (S.P.J.v.D. and M.H.E.v.D.) independently screened titles and abstracts of articles in EndNote using the method as described by Bramer et al.[19] In case of disagreement in the selection of articles, a third reviewer (T.M.v.G.) was consulted to make the final decision. We aimed to identify other eligible studies by searching the reference lists of all included studies. This systematic review of scientific literature was conducted following the Meta-analysis of Observational Studies in Epidemiology reporting guideline[20] and we used the Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) as a guide in all steps of the Meta-analysis.[21] Studies were included if (1) they involved patients who underwent total, near-total, or completion thyroidectomy; (2) a treatment strategy for early postoperative hypoparathyroidism was specified; and (3) long-term hypoparathyroidism was an outcome of the study. There were no language restrictions applied. Exclusion criteria were case reports, case series including less than 5 patients, letters, (systematic) reviews, Meta-analyses, guidelines, study protocols, abstracts, statements, and studies on nonsurgical hypoparathyroidism.

Data Extraction and Outcomes

The following data were extracted: author names and affiliations, year of publication, type of study, study period, the total number of patients, the total number of surgeries, patient age, patient sex, the treatment protocol for postoperative hypoparathyroidism (eg, treatment initiation trigger, incidence, and duration of postoperative calcium and/or active vitamin D supplementation), follow-up data (eg, calcium or active vitamin D supplementation after 6 and 12 months), complications, health-related quality of life and mortality data. Patients receiving prophylactic supplementation postthyroidectomy, irrespective of their discharge medication regimen, were classified within the "routine supplementation" group. Long-term hypoparathyroidism was defined as "biochemical" when the definition of hypoparathyroidism comprised calcium and/or PTH levels. Long-term hypoparathyroidism was defined as "clinical" when the definition of hypoparathyroidism was based on the need for calcium and/or vitamin D supplementation. Postoperative seizures, laryngospasms, bronchospasms, and cardiac arrhythmias due to hypocalcemia were considered major complications. The primary outcome of this study was the incidence of major complications due to postoperative hypocalcemia. The secondary outcome was the incidence of long-term hypoparathyroidism.

Statistical Analysis

For most outcomes, proportions were used as the summary measure. Sample means with standard deviations were estimated from the median, sample size, interquartile range (IQR), and total range using Wan's method.[22] Results were pooled using random effects Meta-analysis. Studies without events for a specific outcome were excluded from the Meta-analysis as per COSMOS-E recommendations.[21] Two studies were excluded from all Meta-analyses as these studies only included patients with postoperative hypoparathyroidism.[23,24] We analyzed data for subgroup effects by supplementation strategy (routine vs biochemically based vs symptom-based supplementation), age (<50 vs ≥50 years), geographical location (America vs Asia vs Europe), the time of diagnosing long-term hypoparathyroidism (6 vs 12 months) and definition of long-term hypoparathyroidism (biochemical vs clinical). Studies assessing long-term hypoparathyroidism varied with respect to the time to onset of tapering off medication. We, therefore, analyzed the effect of duration of supplementation on the size of the associations by random-effects univariate meta-regressions, using restricted maximum likelihood which we present as mean effects with 95% confidence intervals (CIs). To assess publication bias, we used sample size-based funnel plots instead of the conventional standard error-based funnel plots, as these often show inaccurate findings in Meta-analyses of proportion studies.[25,26] Meta-analysis was performed using R version 4.1.2.

Results

Systematic Literature Search

A total of 1743 articles were screened (**Figure 1**) and 237 full-text articles were assessed for eligibility. After careful selection of the articles, 66 studies were eligible for the final synthesis and were included in this review.[10,14,23,24,27-88]

Study Characteristics and Quality Appraisal

Sixty studies were observational cohort studies and 6 studies were randomized controlled trials (RCTS) (**Table 1**). Sixty-one of the included studies were single-institution studies. Only 1 trial randomized patients into different treatment protocols and compared long-term hypoparathyroidism rates (outcome) between a biochemically based and a symptom-based treatment protocol (exposure).[23] All other 65 studies had no within-study comparison of early treatment strategies for hypoparathyroidism and were considered as case series, which generally have a high risk of bias and low certainty.[89,90]

Clinical Characteristics

In total, 51,096 patients were included in the final data synthesis. The median number of patients per study was 264 (range 57-19,662). Among all studies with data, the median patient age was 50 years (range, 34-57) and the

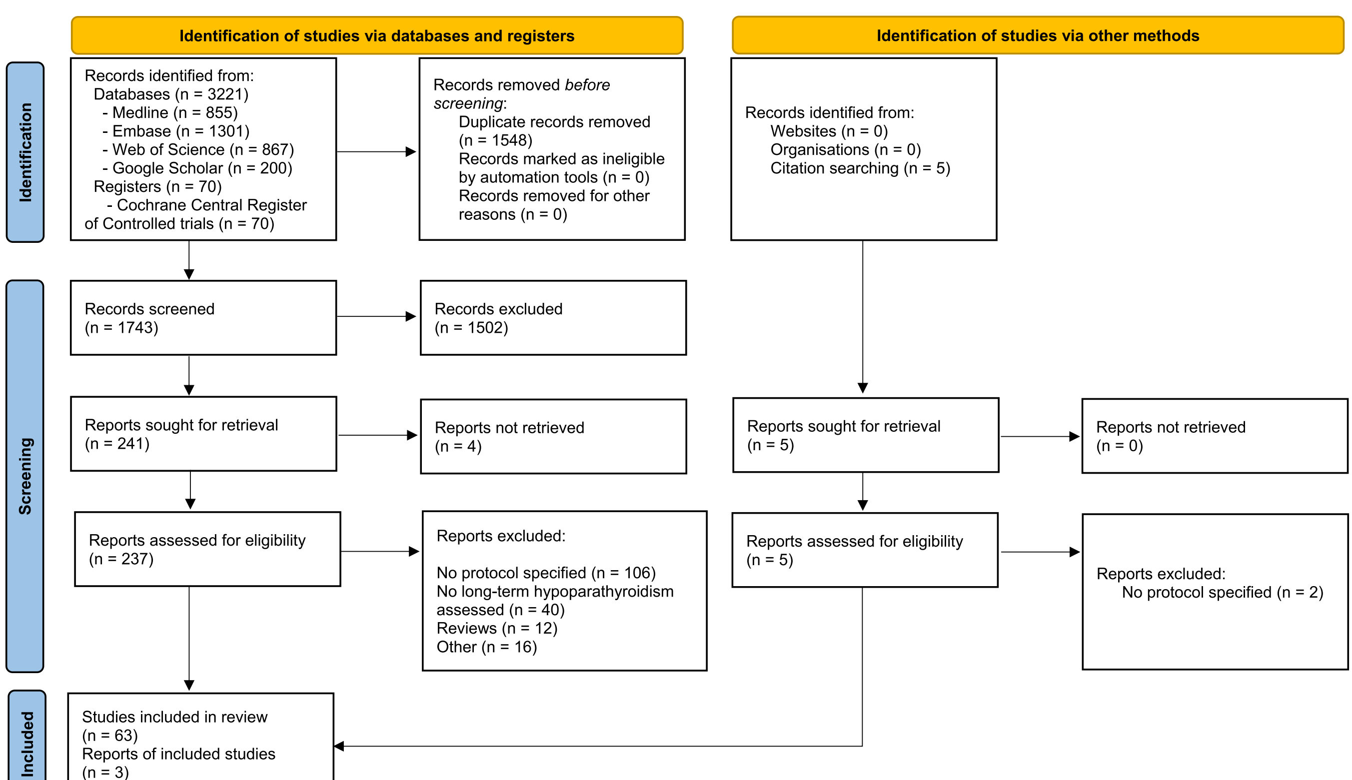

Figure 1. PRISMA 2020 flow diagram of identified studies.

Table 1. Characteristics of Included Studies (n = 66)

References	Number of patients	Study design	Surgical procedure	Treatment protocol
Abboud et al[27]	252	Retrospective cohort study	Total thyroidectomy (n = 93, 36.9%), near total thyroidectomy (n = 159, 63.1%)	Routine
Cocchiara et al[35]	126	Prospective RCT	Total thyroidectomy (n = 126, 100%)	Biochemical
Karamanakos et al[46]	2043	Retrospective cohort study	Total thyroidectomy (n = 1149, 56.2%), near total thyroidectomy (n = 777, 38.0%), subtotal thyroidectomy (n = 117, 5.7%)	Biochemical
Shindo and Stern[73]	256	Retrospective cohort study	Total thyroidectomy (n = 256, 100%)	Biochemical
Sitges-Serra et al[14]	442	Retrospective cohort study	Total thyroidectomy (n = 442, 100%)	Biochemical
Youngwirth et al[87]	271	Retrospective cohort study	Total thyroidectomy (n = 271, 100%)	Routine
Houlton et al[44]	180	Retrospective cohort study	Total thyroidectomy (n = 139, 77.2%), completion thyroidectomy (n = 41, 22.7%)	Biochemical
Sands et al[69]	270	Retrospective cohort study	Total thyroidectomy (n = 270, 100%)	Biochemical
Testini et al[76]	19662	Retrospective cohort study	Total thyroidectomy (n = 19,662, 100%)	Biochemical
Raffaelli et al[66]	186	Prospective cohort study	Total thyroidectomy (n = 186, 100%)	Biochemical
Sousa et al[74]	333	Retrospective cohort study	Total thyroidectomy (n = 160, 48.0%), subtotal thyroidectomy (n = 144, 43.2%), completion thyroidectomy (n = 29, 8.7%)	Symptom
Yano et al[83]	296	Retrospective cohort study	Total thyroidectomy (n = 296, 100%)	Biochemical
Dionigi et al[38]	199	Prospective RCT	Total thyroidectomy (n = 183, 92.0%), subtotal thyroidectomy (n = 16, 8.0%)	Biochemical
Julián et al[45]	70	Prospective cohort study	Total thyroidectomy (n = 70, 100%)	Biochemical
Pisanu et al[60]	112	Prospective cohort study	Total thyroidectomy (n = 112, 100%)	Symptom
Sheahan et al[71]	126	Prospective cohort study	Total thyroidectomy (n = 126, 100%)	Symptom
Shinall et al[72]	165	Retrospective cohort study	Total thyroidectomy (n = 165 patients underwent total thyroidectomy	Routine
Finel et al[41]	240	Prospective cohort study	Total thyroidectomy (n = 240, 100%)	Biochemical
Noureldine et al[57]	304	Retrospective cohort study	Total thyroidectomy (n = 304, 100%)	Biochemical
Puzziello et al[64]	2631	Prospective cohort study	Total thyroidectomy (n = 2364, 89.6%), near-total thyroidectomy (n = 185, 7.0%), completion thyroidectomy (n = 85, 3.2%)	Biochemical
Lorente-Poch et al[51]	657	Retrospective cohort study	Total thyroidectomy (n = 657, 100%)	Biochemical
Pasquale et al[36]	995	Prospective cohort study	Total thyroidectomy (n = 995, 100%)	Biochemical
Praženica et al[62]	788	Retrospective cohort study	Total thyroidectomy (n = 788, 100%)	Biochemical
Selberherr et al[70]	237	Prospective cohort study	Total thyroidectomy (n = 237, 100%)	Biochemical
Gupta et al[42]	90	Prospective cohort study	Total thyroidectomy (n = 90, 100%)	Biochemical
Cho et al[34]	1030	Retrospective cohort study	Total thyroidectomy (n = 1030, 100%)	Symptom
Järhult and Landerholm[10]	640	Prospective cohort study	Subtotal thyroidectomy (n = 190, 29.7%), Dunhill procedure (n = 123, 19.2%), total thyroidectomy (n = 327, 51.1%)	Symptom
Oran et al[58]	543	Retrospective cohort study	Total thyroidectomy (n = 455, 83.8%), subtotal thyroidectomy (n = 88, 16.2%)	Biochemical
Sung et al[75]	237	Retrospective cohort study	Total thyroidectomy (n = 237, 100%)	Symptom

Table 1. (continued)

References	Number of patients	Study design	Surgical procedure	Treatment protocol
Wang et al[81]	221	Retrospective cohort study	Total thyroidectomy (n = 164, 74.2%), completion thyroidectomy (n = 57, 25.8%)	Biochemical
Sitges-Serra[13]	145	Prospective cohort study	Total thyroidectomy (n = 145, 100%)	Biochemical
Wang et al[80]	487	Retrospective cohort study	Total thyroidectomy (n = 487, 100%)	Symptom
Aydın et al[31]	182	Retrospective cohort study	Total thyroidectomy (n = 182, 100%)	Biochemical
Falch et al[40]	702	Retrospective cohort study	Total thyroidectomy (n = 702, 100%)	Biochemical
Mazotas et al[53]	591	Retrospective cohort study	Total thyroidectomy (n = 568, 96.0%), completion thyroidectomy (n = 23, 4%) underwent completion thyroidectomy	Biochemical
Vasileiadis et al[78]	2556	Retrospective cohort study	Total thyroidectomy (n = 2556, 100%)	Biochemical
Dip et al[39]	170	Prospective RCT	Total thyroidectomy (n = 170, 100%)	Biochemical
Manzini et al[52]	361	Prospective cohort study	Total thyroidectomy (n = 288, 79.8%), Dunhill procedure (n = 71, 19.7%)	Biochemical
Ponce de león-Ballesteros et al[61]	956	Retrospective cohort study	Total thyroidectomy (n = 956, 100%)	Biochemical
Xue et al[82]	93	Retrospective cohort study	Total thyroidectomy (n = 93, 100%)	Biochemical
Dedhia et al[37]	811	Retrospective cohort study	Total thyroidectomy (n = 678, 83.6%), completion thyroidectomy (n = 133, 13.0%)	Biochemical
Hou et al[43]	197	Retrospective cohort study	Total thyroidectomy (n = 197, 100%)	Routine
Liu et al[50]	840	Prospective cohort study	Total thyroidectomy (n = 840, 100%)	Routine
Mehta et al[54]	265	Prospective cohort study	Total thyroidectomy (n = 265, 100%)	Biochemical
Mo et al[55]	176	Prospective cohort study	Total thyroidectomy (n = 176, 100%)	Biochemical
Peker et al[59]	57	Prospective cohort study	Total thyroidectomy (n = 57, 100%)	Biochemical
Villarroya et al[79]	811	Prospective cohort study	Total thyroidectomy (n = 811, 100%)	Biochemical
Zheng et al[88]	546	Retrospective cohort study	Total thyroidectomy (n = 546, 100%)	Biochemical
Celik et al[33]	144	Prospective cohort study	Total thyroidectomy (n = 144, 100%)	Symptom
Karunakaran et al[47]	328	Prospective cohort study	Total thyroidectomy (n = 328, 100%)	Biochemical
Kim et al[48]	542	Retrospective cohort study	Total thyroidectomy (n = 542, 100%)	Biochemical
Kim et al[49]	200	Prospective RCT	Total thyroidectomy (n = 200, 100%)	Symptom
Privitera et al[63]	187	Retrospective cohort study	Total thyroidectomy (n = 187, 96.8%), subtotal thyroidectomy (n = 6, 3.2%)	Biochemical
Qiu et al[65]	1749	Retrospective cohort study	Total thyroidectomy (n = 1749, 100%)	Routine
Van Slycke et al[77]	1043	Prospective cohort study	Total thyroidectomy (n = 1043, 100%)	Biochemical
Yao et al[84]	183	Retrospective cohort study	Total thyroidectomy (n = 183, 100%)	Routine
Ru et al.[68]	537	Retrospective cohort study	Total thyroidectomy (n = 537, 100%)	Biochemical
Abdelrahim et al[28]	90	Prospective cohort study	Total thyroidectomy (n = 90, 100%)	Biochemical
Arshad et al[29]	911	Retrospective cohort study	Total thyroidectomy (n = 911, 100%)	Biochemical
Avgeri et al[30]	116	Retrospective cohort study	Total thyroidectomy (n = 116, 100%)	Biochemical
Canu et al[32]	426	Retrospective cohort study	Total thyroidectomy (n = 426, 100%)	Biochemical

(continued)

Table 1. (continued)

References	Number of patients	Study design	Surgical procedure	Treatment protocol
Li et al[23]	203	Prospective RCT	Total thyroidectomy (n = 203, 100%)	Biochemical and Symptom
Moreno-Llorente et al[56]	120	Prospective cohort study	Total thyroidectomy (n = 120, 100%)	Biochemical
Riordan et al[67]	570	Retrospective cohort study	Total thyroidectomy (n = 521, 91.4%), completion thyroidectomy (n = 49, 8.6%)	Biochemical
Yin et al[85]	149	Retrospective cohort study	Total thyroidectomy (n = 149, 100%)	Routine
Yin et al[86]	180	Prospective RCT	Total thyroidectomy (n = 180, 100%)	Biochemical

Data are expressed as numbers with percentage.
Abbreviations: Biochemical, routine calcium and/or vitamin D medication was only given to patients with biochemically proven postthyroidectomy hypoparathyroidism; RCT, randomized controlled trial; Routine, routine calcium and/or vitamin D medication was given to all patients undergoing thyroidectomy; Symptom, calcium and/or vitamin D supplementation in case of clinical symptoms of hypocalcemia.

proportion of female patients was 73.4% (n = 35,515). Total thyroidectomy was performed in 48,891 patients (95.7%), near-total thyroidectomy in 1788 patients (3.5%), and completion thyroidectomy in 417 patients (0.8%). In all studies reporting on lymph node dissections and pathology results, central neck lymph node dissection was performed in 19.4% of patients (n = 9647) and malignancy was found in pathologic examination in 31.9% of all patients (n = 15,796). Further characteristics of included studies are shown in Supplemental 2, available online.

Treatment Protocols

In total, 67 protocols for early postoperative hypoparathyroidism were specified and all protocols included oral calcium with or without active vitamin D supplementation. In 8 protocols, routine calcium and/or active vitamin D supplementation was given to all patients directly after thyroidectomy (Group "routine," n = 3806). In 49 protocols, calcium and/or active vitamin D supplementation was only given to patients with biochemically proven post-thyroidectomy hypoparathyroidism (Group "biochemical," n = 44,012). In 10 protocols, calcium and/or active vitamin D supplementation was only initiated in case of clinical symptoms of hypocalcemia (Group "symptom," n = 3278).

Hypocalcemia-Related Symptoms, Supplementation, and Complications

The pooled proportion of symptomatic hypocalcemia was 9.4% (95% CI, 6.8-12.3), with high heterogeneity between the studies ($\tau^2 = 0.0143$, $I^2 = 97\%$; $P < .001$) (**Table 2**, Supplemental 3, available online). There was no significant difference in symptomatic hypocalcemia proportions between the 3 supplementation groups (Group "routine," n = 174, 5.2% [95% CI, 1.9-10.0]; Group "biochemical," n = 1041; 8.8% [95% CI, 5.6-12.7]; Group "symptom," n = 241, 13.5% [95% CI, 7.2-21.2], $P = 0.11$ for subgroup difference). The pooled proportion of calcium and/or active vitamin D supplementation at discharge was 48.6% (95% CI, 33.6-63.7), with high heterogeneity between the studies ($\tau^2 = 0.1739$, $I^2 = 100\%$; $P < .001$) (Supplemental 4, available online). The pooled proportion of calcium and/or active vitamin D supplementation at discharge was significantly lower in studies applying symptom-based supplementation (Group "symptom," 14.0%, n = 247; [95% CI, 7.4-22.1]) than in studies with biochemically based supplementation (Group "biochemical," 35.5%, n = 2551; [95% CI, 27.5-43.9]) and routine supplementation (Group "routine," 98.4%, n = 2077; [95% CI, 91.1-100], $P < .01$ for subgroup difference). The length of hospital stay was reported in 14 studies including 6028 patients and the median length of stay was 3.9 days (range, 2.0-7.0) and did not significantly differ between the supplementation groups. In 6 studies reporting on major hypocalcemia-related

Table 2. Summarized Clinical Outcome Measures of Included Studies

Characteristic	Number of studies	Number of patients	Pooled outcome measure	95% CI
Symptomatic hypocalcemia	30	15,332	9.4%	6.8-12.3
Long-term hypoparathyroidism	66	51,096	2.4%	1.9-3.0
Hospitalization time (d)	14	6028	3.4	2.5-4.4
Supplementation at discharge	31	11,047	48.6%	33.6-63.7
Major complications	6	1714	0	Na
Readmissions	5	1998	0.4%	(0-1.5)

Data are expressed as pooled proportion or pooled mean with 95% CIs.
Abbreviations: CI, confidence interval; Na, not applicable.

complications (1714 patients), no major complication occurred. Five studies (four biochemically based studies and 1 symptom-based study) comprising 1998 patients provided the number of hypocalcemia-related readmissions after hospital discharge. The pooled proportion of patients readmitted due to hypocalcemia was 0.4% (95% CI, 0-1.5), with high heterogeneity between studies ($\tau^2 = 0.0023$, $I^2 = 80\%$; $P < .01$). No studies reported on health-related quality of life and cost-effectiveness. Clinical outcomes of all individual studies can be seen in Supplemental 5, available online.

Long-Term Hypoparathyroidism

The incidence of long-term hypoparathyroidism ranged between 0% and 24.1%. The pooled proportion of long-term hypoparathyroidism was 2.4% (95% CI, 1.9-3.0), with high heterogeneity between the studies ($\tau^2 = 0.0041$, $I^2 = 92\%$; $P < .01$). Evidence of publication bias was detected in studies with small sample sizes (Supplemental 6, available online). Subgroup analysis showed that there was no significant difference in long-term hypoparathyroidism rates between the 3 supplementation groups (Group "routine," n = 82, 1.1% [95% CI, 0.2-2.7]; Group "biochemical," n = 1045; 2.9% [95% CI, 2.2-3.6]; Group "symptom," n = 72, 1.5% [95% CI, 0.6-2.8], $P = .054$ for subgroup difference) (**Figure 2**). The pooled proportion of long-term hypoparathyroidism of studies with a mean age >50 years was 3.6% (95% CI, 2.5-4.8) compared with 1.8% (95% CI: 1.0-2.8) for studies with a mean age <50 years ($P = .02$, **Table 3**). Studies performed in America showed a pooled proportion of 1.4% (95% CI, 0.7-2.3), compared with 2.5% (95% CI, 1.4-3.9) for Asian and 3.0% (95% CI, 2.2-4.0) for European studies ($P = .03$).

In 37 studies (n = 39,826), long-term hypoparathyroidism was defined as a condition persisting beyond 6 months, while in 20 studies (n = 11,270), it was defined as a condition persisting beyond 12 months. The proportion of long-term hypoparathyroidism did not significantly differ between the time points of diagnosis ($P = .40$). Long-term hypoparathyroidism was defined based on biochemical values (PTH and/or calcium) in 24 studies (n = 11,400), whereas the need for calcium and/or vitamin D supplementation was used as the definition of long-term hypoparathyroidism in 37 studies (n = 37,480). The incidence of long-term hypoparathyroidism did not differ between studies applying either the biochemical definition or the need for supplementation ($P = .46$).

Studies differed regarding the time to onset of weaning patients off supplementation. Among all studies with data, the median time to the first day of weaning off supplementation was 28 days (IQR, 14-28). By meta-regression, the proportion of long-term hypoparathyroidism did not significantly change with increasing time to weaning off supplementation (0.002 change per day, 95% CI −0.001 to 0.004; $P = .16$, Supplemental 7A, available online). A higher incidence of postoperative biochemical hypoparathyroidism and a more recent publication year were associated with a higher incidence of long-term hypoparathyroidism (0.253 change per 10% increase in postoperative biochemical hypoparathyroidism incidence, 95% CI, 0.142-0.365; $P < .01$, Supplemental 7B, available online) and (0.004 change per more recent year of publication, 95% CI, 0.000-0.008; $P = .04$, Supplemental 7C, available online), respectively.

Discussion

This Meta-analysis including 51,096 patients shows that all 3 treatment strategies for early postoperative hypoparathyroidism (routine vs biochemical-based vs symptom-based supplementation) prevent major hypocalcemia-related complications and did not show significant differences in hypoparathyroidism incidence in the long-term.

Patients undergoing thyroidectomy are at risk for postoperative hypoparathyroidism resulting in hypocalcemia. When left untreated, severe postoperative hypocalcemia can be lethal and increases the risk of various serious adverse events such as seizures, cardiac arrhythmias, and laryngospasms.[91] Therefore, there has been a rationale to prevent the potential dangers of hypocalcemia by providing calcium and/or vitamin D supplementation in patients with biochemical hypocalcemia or even in all patients who undergo total thyroidectomy.[92] Furthermore, routine calcium supplementation has demonstrated both cost-effectiveness and enhanced patient utility when compared to selective calcium supplementation.[93,94] However, this strategy possibly

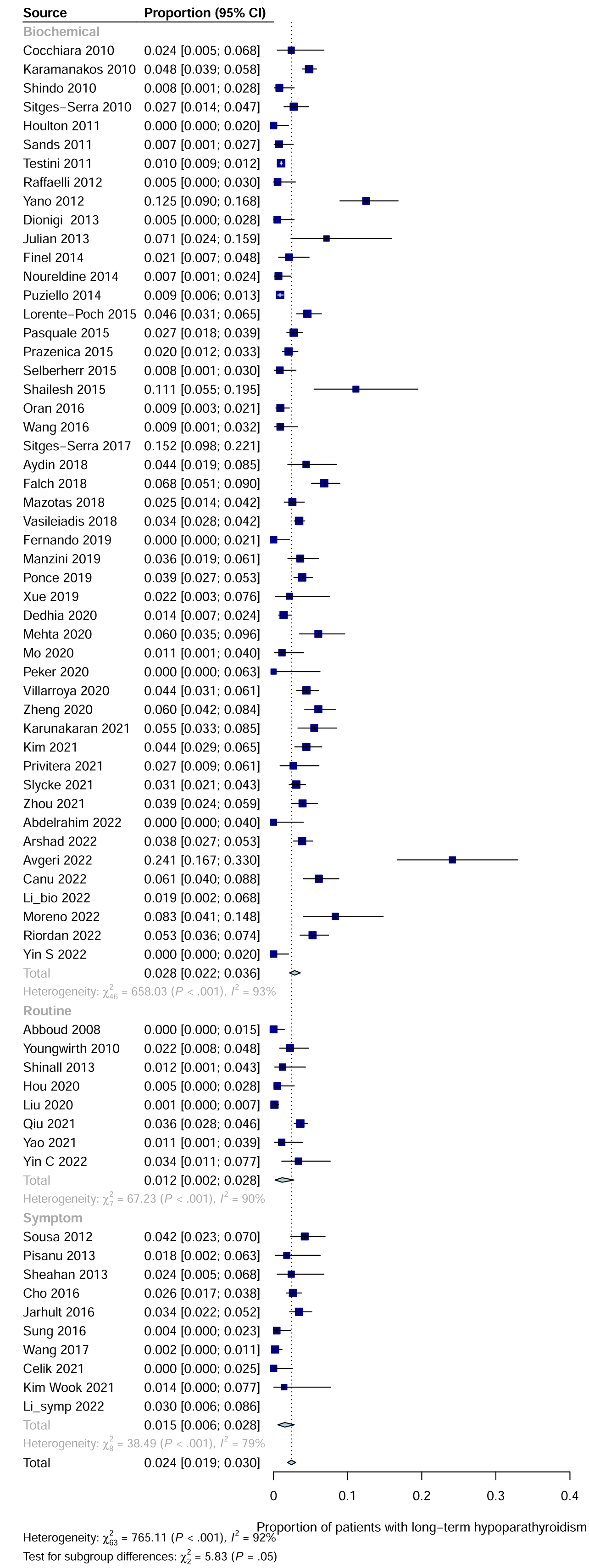

Figure 2. Forest plot of the incidence of long-term hypoparathyroidism. Biochemical, subgroup of patients who received calcium and/or active vitamin D supplementation in case of biochemical postthyroidectomy hypoparathyroidism; CI, confidence interval; Routine, subgroup of patients who received routine calcium and/or active vitamin D supplementation after thyroidectomy; Symptom, subgroup of patients who received calcium and/or active vitamin D supplementation after thyroidectomy only in case of clinical symptoms of hypocalcemia.

induces overtreatment in patients who do not appropriately wean off supplementation.[95] Jarhult et al showed that only providing supplementation in patients with symptoms of hypocalcemia avoids unnecessary treatment in most patients and could be a safe treatment option as the readmission rate after discharge was low (1%) and no major complications related to hypocalcemia occurred.[10] The current study showed that 14% of patients who were subjected to a symptom-based supplementation protocol received supplementation at discharge, whereas this percentage was 36% in the biochemical-based group and 98% in the routine supplementation group. Eight out of 10 included studies with symptom-based supplementation did not report on readmission rates or major complications. To evaluate the true potential of symptom-based supplementation in patients undergoing total thyroidectomy, high-quality data on adverse events, readmission rates, hospitalization time, and emergency department visits are needed. In addition, clinical and biochemical predictors for short- and long-term hypoparathyroidism such as PTH decreases could refine existing treatment protocols to provide tailor-made postoperative patient care.[11]

The pooled rate of long-term hypoparathyroidism in this study was 2.4%, which is substantially lower than the rates in recent nationwide studies from the Scandinavian and West-European countries.[5,7] This finding is emphasized by the presence of publication bias demonstrated in Supplemental 6, available online. The present study also shows that the incidence of long-term hypoparathyroidism significantly increased with a more recent year of article publication. A possible explanation for the higher incidence of long-term hypoparathyroidism in recent years could be the transparent reporting of nationwide studies wherein loss to follow-up is limited.[5,96] The burden of long-term hypoparathyroidism is therefore most likely a more prominent problem than the rates presented in this systematic review suggest. The definition of long-term hypoparathyroidism differed among included studies, which has been shown to influence the rate of long-term hypoparathyroidism.[97,98] However, we did not find evidence that there were differences in long-term hypoparathyroidism rates for different definitions in subgroup analyses, which substantiates the findings of a review from Harslof et al.[99]

Long-term hypoparathyroidism rates did not significantly differ between studies with symptom-based, biochemically based, or routine calcium and/or vitamin D supplementation. This substantiates findings from a recent trial comparing routine supplementation and symptom-based supplementation in a randomized,

Table 3. Subgroup Analysis of Long-Term Hypoparathyroidism Prevalence Studies

Variable	Number of studies	Proportion %	95% CI	*P* value
Age, y				
<50	22	1.8	1.0-2.8	.02
>50	26	3.6	2.5-4.8	
Geographical location				
America	11	1.4	0.7-2.3	.03
Asia	22	2.5	1.4-3.9	
Europe	31	3.0	2.2-4.0	
Supplementation protocol				
Routine	9	1.1	0.2-2.7	.05
Biochemical	47	2.9	2.2-3.6	
Symptom	10	1.5	0.6-2.8	
Time of diagnosis, mo				
6	37	2.3	1.6-3.1	.40
12	20	2.9	2.1-3.9	
Definition long-term hypoparathyroidism				.46
Biochemical	24	2.3	1.4-3.5	
Need for supplementation	37	2.9	2.1-3.7	

Abbreviations: Biochemical, routine calcium and/or vitamin D medication was only given to patients with biochemically proven post-thyroidectomy parathyroid failure; CI, confidence interval; Routine, routine calcium and/or vitamin D medication was given to all patients undergoing thyroidectomy; Symptom, calcium and/or vitamin D supplementation in case of clinical symptoms of hypocalcemia.

controlled setting.[23] Although the rate of symptomatic hypocalcemia in that study was more prevalent in patients relying solely on symptom-driven supplementation compared to those who received prophylactic supplementation, that study did not show any notable differences between the groups in long-term parathyroid function. This contradicts the theory of parathyroid splinting, which involves the belief that aggressive medical therapy in every patient with postthyroidectomy biochemical hypoparathyroidism enhances the restoration of the parathyroid function and improves long-term parathyroid function.[13] Little is known about the physiological mechanisms within the parathyroid when applying different postoperative treatment strategies. To provide any evidence that the treatment strategy for postoperative hypoparathyroidism affects long-term parathyroid function after iatrogenic damage, experiments in a controlled environment using organoids and/or animal models should be conducted. Methods to standardize a physiological hypoparathyroidism animal model are described and can be used for future studies on long-term parathyroid function under different supplementation regimens.[100]

This study has several limitations. Important data such as readmissions, hospitalization times, time to weaning off medication, and overall adherence to the supplementation protocols were frequently missing in included studies, limiting the sample size of these analyses. Our findings substantiate a review protocol from Edafe et al which noted this gap in current literature due to a lack of high-quality evidence in the management of temporary and long-term hypoparathyroidism after thyroid surgery.[101] In that study, no eligible studies (RCTs) were identified that investigated the effects of calcium, vitamin D, or recombinant PTH in individuals experiencing temporary and long-term postthyroidectomy hypoparathyroidism. An important limitation of the current study arises from the fact that, with the exception of 1 study, all included studies were noncomparative studies with differences in treatment schedules. These studies have a higher risk of bias and low certainty.[89,90] Although we made efforts to explain between-study heterogeneity through subgroup and meta-regression analyses, it is important to recognize that the certainty of evidence derived from this Meta-analysis is dependent on the design of included studies and their risk of bias,[102] which was high. Therefore, it is prudent to exercise a certain degree of caution when considering its findings. The recognition of disease process variability among patients in the included studies is acknowledged as a limitation of this study. A small subset of patients (0.8%) in this study underwent completion thyroidectomy, which carries a distinct risk profile for postoperative hypocalcemia.[103] While it is unlikely that their inclusion would substantially affect the study's findings, we recognize the potential for this subgroup to introduce cohort heterogeneity in this study. A systematic review and Meta-analysis from 2013 investigated various treatment approaches for postoperative hypocalcemia, revealing a reduced incidence of hypocalcemia-related symptoms in the group receiving routine calcium and vitamin D supplementation.[104] However, that study did not explore variations in major complications or the development of long-term hypoparathyroidism between the groups. Therefore, the current study contributes novel insights into the effects of the early supplementation protocol on long-term hypoparathyroidism, an aspect that has not been previously examined in the literature.

Conclusion

All treatment strategies (routine vs biochemically based vs symptom-based) for postoperative hypocalcemia prevent major complications of hypocalcemia. The early treatment protocol for postthyroidectomy hypoparathyroidism does not seem to influence recovery of parathyroid function in the long term. High-quality data regarding hospital stay, readmissions, and quality of life of these different treatment strategies for postthyroidectomy hypoparathyroidism are lacking. Therefore, no preference for a certain protocol can be defined.

Author Contributions

Sam P. J. van Dijk, led the conception and design of the study, analyzed the data, was a major contributor in interpreting the data analysis, and wrote the manuscript and revised the manuscript for important intellectual content. He had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; **M. H. Elise van Driel**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Caroline M. J. van Kinschot**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Maarten F. M. Engel**, was responsible for the search strategy, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Gaston J. H. Franssen**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Charlotte van Noord**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **W. Edward Visser**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Cornelis Verhoef**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Robin P. Peeters**, was a major contributor in interpreting the data analysis and revised the manuscript for important intellectual content; **Tessa M. van Ginhoven**, led the conception and design of the study, was a major contributor in interpreting the data analysis, and wrote the manuscript and revised the manuscript for important intellectual content.

Disclosures

Competing interests: All authors have no conflicts of interest to declare.

Funding source: None.

Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Additional supporting information is available in the online version of the article.

ORCID iD

Sam P. J. van Dijk http://orcid.org/0000-0002-4745-7978

References

1. Sitges-Serra A. Etiology and diagnosis of permanent hypoparathyroidism after total thyroidectomy. *J Clin Med*. 2021;10(3):543.
2. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and Meta-analysis of predictors of post-thyroidectomy hypocalcaemia. *Br J Surg*. 2014;101(4): 307-320.
3. Asari R. Hypoparathyroidism after total thyroidectomy: a prospective study. *Arch Surg*. 2008;143(2):132-137.
4. Díez JJ, Anda E, Sastre J, et al. Prevalence and risk factors for hypoparathyroidism following total thyroidectomy in Spain: a multicentric and nation-wide retrospective analysis. *Endocrine*. 2019;66(2):405-415.
5. Loncar I, Noltes ME, Dickhoff C, et al. Persistent postthyroidectomy hypoparathyroidism in the Netherlands. *JAMA Otolaryngol Head Neck Surg*. 2021;147(11):959-965.
6. McIntyre C, Di Marco A, Cox J, Robinson S, Palazzo F, Tolley N. The impact of permanent hypoparathyroidism on quality of life. *Eur J Surg Oncol*. 2017;43(12):2397.
7. Almquist M, Ivarsson K, Nordenström E, Bergenfelz A. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. *Br J Surg*. 2018;105(10):1313-1318.
8. Terris DJ, Snyder S, Carneiro-Pla D, et al. American Thyroid Association Statement on outpatient thyroidectomy. *Thyroid*. 2013;23(10):1193-1202.
9. Sanabria A, Rojas A, Arevalo J. Meta-analysis of routine calcium/vitamin D3 supplementation versus serum calcium level-based strategy to prevent postoperative hypocalcaemia after thyroidectomy. *Br J Surg*. 2019;106(9):1126-1137.
10. Järhult J, Landerholm K. Outcome of hypocalcaemia after thyroidectomy treated only in symptomatic patients. *Br J Surg*. 2016;103(6):676-683.
11. Orloff LA, Wiseman SM, Bernet VJ, et al. American Thyroid Association Statement on postoperative hypoparathyroidism: diagnosis, prevention, and management in adults. *Thyroid*. 2018;28(7):830-841.
12. Bollerslev J, Rejnmark L, Zahn A, et al. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2021). *Eur J Endocrinol*. 2022;186(2):R33-R63.
13. Sitges-Serra A. The PGRIS and parathyroid splinting concepts for the analysis and prognosis of protracted hypoparathyroidism. *Gland Surg*. 2017;6(suppl 1):S86-S93.
14. Sitges-Serra A, Ruiz S, Girvent M, Manjón H, Dueñas JP, Sancho JJ. Outcome of protracted hypoparathyroidism

after total thyroidectomy. *Br J Surg*. 2010;97(11): 1687-1695.

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178-189.
16. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev*. 2021;10(1):39.
17. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: an efficient and complete method to develop literature searches. *J Med Libr Assoc*. 2018;106(4):531-541.
18. Harzing.com. Publish or Perish, 2022. November 2022. Accessed October 12, 2023. https://harzing.com/resources/publish-or-perish
19. Bramer WM, Milic J, Mast F. Reviewing retrieved references for inclusion in systematic reviews using endNote. *J Med Libr Assoc*. 2017;105(1):84-87.
20. Stroup DF. Meta-analysis of observational studies in epidemiologya proposal for reporting. *JAMA*. 2000;283(15): 2008-2012.
21. Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. COSMOS-E: guidance on conducting systematic reviews and Meta-analyses of observational studies of etiology. *PLoS Med*. 2019;16(2): e1002742.
22. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135.
23. Li Z, Fei Y, Li Z, Wei T, Zhu J, Su A. Outcome of parathyroid function after total thyroidectomy when calcium supplementation is administered routinely versus exclusively to symptomatic patients: a prospective randomized clinical trial. *Endocrine*. 2022;75(2): 583-592.
24. Sitges-Serra A, Gómez J, Barczynski M, Lorente-Poch L, Iacobone M, Sancho J. A nomogram to predict the likelihood of permanent hypoparathyroidism after total thyroidectomy based on delayed serum calcium and iPTH measurements. *Gland Surg*. 2017;6(suppl 1):S11-S19.
25. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In Meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol*. 2014;67(8): 897-903.
26. Lin L. Graphical augmentations to sample-size-based funnel plot in Meta-analysis. *Res Synth Methods*. 2019; 10(3):376-388.
27. Abboud B, Sleilaty G, Zeineddine S, et al. Is therapy with calcium and vitamin D and parathyroid autotransplantation useful in total thyroidectomy for preventing hypocalcemia? *Head Neck*. 2008;30(9):1148-1154; discussion 1154-1145.
28. Abdelrahim HS, Amer AF, Mikhael Nageeb R. Indocyanine green angiography of parathyroid glands versus intraoperative parathyroid hormone assay as a reliable predictor for post thyroidectomy transient hypocalcemia. *J Invest Surg*. 2022;35(7):1484-1491.
29. Arshad MF, Dhami A, Quarrell G, Balasubramanian SP. Parathyroid hormone of ≥1.6 pmol/L at 6 months is associated with recovery in 'long-term' post-surgical hypoparathyroidism. *Eur Thyroid J*. 2022;11:3.
30. Avgeri TC, Sideris G, Maragoudakis P, Papadopoulos I, Nikolopoulos T, Delides A. The long-term need for calcium supplementation after incidental parathyroidectomy. *J Taibah Univ Med Sci*. 2022;17(2):214-219.
31. Aydın HO, Soy EHA, Moray G. Risk factors of hypoparathyroidism after bilateral total thyroidectomy. *Ann Clin Anal Med*. 2019;10(6):728-731.
32. Canu GL, Medas F, Cappellacci F, et al. Intact parathyroid hormone value on the first postoperative day following total thyroidectomy as a predictor of permanent hypoparathyroidism: a retrospective analysis on 426 consecutive patients. *Endokrynol Pol*. 2022;73(1):48-55.
33. Celik SU, Konca C, Genc V. A cohort study assessing the association between body composition parameters and symptomatic hypocalcemia after total thyroidectomy. *Am Surg*. 2021;87(8):1305-1312.
34. Cho JN, Park WS, Min SY. Predictors and risk factors of hypoparathyroidism after total thyroidectomy. *Int J Surg*. 2016;34:47-52.
35. Cocchiara G, Cajozzo M, Amato G, Mularo A, Agrusa A, Romano G. Terminal ligature of inferior thyroid artery branches during total thyroidectomy for multinodular goiter is associated with higher postoperative calcium and PTH levels. *J Visc Surg*. 2010;147(5):e329-e332.
36. De Pasquale L, Sartori PV, Vicentini L, et al. Necessity of therapy for post-thyroidectomy hypocalcaemia: a multi-centre experience. *Langenbecks Arch Surg*. 2015; 400(3):319-324.
37. Dedhia PH, Stoeckl EM, McDow AD, et al. Outcomes after completion thyroidectomy versus total thyroidectomy for differentiated thyroid cancer: a single-center experience. *J Surg Oncol*. 2020;122(4):660-664.
38. Dionigi G, Van Slycke S, Rausei S, Boni L, Dionigi R. Parathyroid function after open thyroidectomy: a prospective randomized study for ligasure precise versus harmonic FOCUS. *Head Neck*. 2013;35(4):562-567.
39. Dip F, Falco J, Verna S, et al. Randomized controlled trial comparing white light with near-infrared autofluorescence for parathyroid gland identification during total thyroidectomy. *J Am Coll Surg*. 2019;228(5):744-751.
40. Falch C, Hornig J, Senne M, et al. Factors predicting hypocalcemia after total thyroidectomy—a retrospective cohort analysis. *Int J Surg*. 2018;55:46-50.
41. Finel JB, Mucci S, Branger F, et al. Thyroidectomy in patients with a high BMI: a safe surgery? *Eur J Endocrinol*. 2014;171(1):99-105.
42. Gupta S, Chaudhary P, Durga CK, Naskar D. Validation of intra-operative parathyroid hormone and its decline as early predictors of hypoparathyroidism after total thyroidectomy: a prospective cohort study. *Int J Surg*. 2015;18:150-153.

43. Hou D, Xu H, Yuan B, et al. Effects of active localization and vascular preservation of inferior parathyroid glands in central neck dissection for papillary thyroid carcinoma. *World J Surg Oncol*. 2020;18:95.
44. Houlton JJ, Pechter W, Steward DL. PACU PTH facilitates safe outpatient total thyroidectomy. *Otolaryngol Head Neck Surg*. 2011;144(1):43-47.
45. Julián MT, Balibrea JM, Granada ML, et al. Intact parathyroid hormone measurement at 24 hours after thyroid surgery as predictor of parathyroid function at long term. *Am J Surg*. 2013;206(5):783-789.
46. Karamanakos SN, Markou KB, Panagopoulos K, et al. Complications and risk factors related to the extent of surgery in thyroidectomy. Results from 2,043 procedures. *Hormones (Athens)*. 2010;9(4):318-325.
47. Karunakaran P, Abraham DT, Devadas G, Ramalingam S, Balu S, Hussain Z. The impact of operative duration and intraoperative fluid dynamics on postoperative hypocalcemia after total thyroidectomy: a prospective non-randomized study. *Langenbecks Arch Surg*. 2021; 406(4):1211-1221.
48. Kim DH, Kim SW, Kang P, et al. Near-infrared autofluorescence imaging may reduce temporary hypoparathyroidism in patients undergoing total thyroidectomy and central neck dissection. *Thyroid*. 2021;31(9):1400-1408.
49. Kim WW, Cho J, Jeon YS, et al. Prospective, randomized, comparative, multicenter study of the hybrid ultrasonic advanced bipolar device and the ultrasonic coagulating shears in open thyroidectomy. *Surg Innov*. 2021;28(1): 41-47.
50. Liu X, Bian X, Li C, et al. Comparison of iPTH and calcium levels between total thyroidectomy and lobectomy: a prospective study of 840 thyroid cancers with three years of follow-up. *Ann Transl Med*. 2020;8:1243.
51. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. *Br J Surg*. 2015;102(4): 359-367.
52. Manzini G, Malhofer F, Weber T. Can preoperative vitamin D deficiency predict postoperative hypoparathyroidism following thyroid surgery? *Langenbecks Arch Surg*. 2019;404(1):55-61.
53. Mazotas IG, Yen TWF, Park J, et al. A postoperative parathyroid hormone-based algorithm to reduce symptomatic hypocalcemia following completion/total thyroidectomy: a retrospective analysis of 591 patients. *Surgery*. 2018;164(4):746-753.
54. Mehta S, Dhiwakar M, Swaminathan K. Outcomes of parathyroid gland identification and autotransplantation during total thyroidectomy. *Eur Arch Otrhinolaryngol*. 2020;277(8):2319-2324.
55. Mo K, Shang J, Wang K, et al. Parathyroid hormone reduction predicts transient hypocalcemia after total thyroidectomy: a single-center prospective study. *Int J Endocrinol*. 2020;2020:1-9.
56. Moreno-Llorente P, Garcia-Barrasa A, Pascua-Sole M, Videla S, Otero A, Munoz-de Nova JL. Usefulness of ICG angiography-guided thyroidectomy for preserving parathyroid function. *World J Surg*. 2023;47(2):421-428.
57. Noureldine SI, Genther DJ, Lopez M, Agrawal N, Tufano RP. Early predictors of hypocalcemia after total thyroidectomy: an analysis of 304 patients using a short-stay monitoring protocol. *JAMA Otolaryngol Head Neck Surg*. 2014;140(11):1006-1013.
58. Oran E, Yetkin G, Mihmanli M, et al. The risk of hypocalcemia in patients with parathyroid autotransplantation during thyroidectomy. *Turk J Surg*. 2016;32(1):6-10.
59. Peker Y, Cin N, Kar H, Tatar F, Kahya MC, Baran NG. Prospective evaluation of perioperative biochemical tests to predict hypocalcemia after total thyroidectomy. *Indian J Surg*. 2020;82(2):187-190.
60. Pisanu A, Saba A, Coghe F, Uccheddu A. Early prediction of hypocalcemia following total thyroidectomy using combined intact parathyroid hormone and serum calcium measurement. *Langenbecks Arch Surg*. 2013;398(3):423-430.
61. Ponce de león-Ballesteros G, Velázquez-Fernández D, Hernández-Calderón FJ, et al. Hypoparathyroidism after total thyroidectomy: importance of the intraoperative management of the parathyroid glands. *World J Surg*. 2019;43(7):1728-1735.
62. Praženica P, O'Keeffe L, Holý R. Dissection and identification of parathyroid glands during thyroidectomy: association with hypocalcemia. *Head Neck*. 2015;37(3): 393-399.
63. Privitera F, Gioco R, Fazio I, et al. Risk factors for low levels of parathyroid hormone after surgery for thyroid cancer: a single center study. *J Clin Med*. 2021;10(18): 4113.
64. Puzziello A, Rosato L, Innaro N, et al. Hypocalcemia following thyroid surgery: incidence and risk factors. A longitudinal multicenter study comprising 2,631 patients. *Endocrine*. 2014;47(2):537-542.
65. Qiu Y, Xing Z, Fei Y, Qian Y, Luo Y, Su A. Role of the 2018 American Thyroid Association statement on postoperative hypoparathyroidism: a 5-year retrospective study. *BMC Surg*. 2021;21(1):334.
66. Raffaelli M, De Crea C, Sessa L, et al. Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma. *Surgery*. 2012; 152(6):957-964.
67. Riordan F, Brophy C, Murphy MS, Sheahan P. Predictive value of postoperative day 1 parathyroid hormone levels for early and late hypocalcaemia after thyroidectomy. *Langenbecks Arch Surg*. 2022;407(4):1653-1658.
68. Ru Z, Mingliang W, Maofei W, Qiaofeng C, Jianming Y. Analysis of risk factors for hypoparathyroidism after total thyroidectomy. *Front Surg*. 2021;8:668498.
69. Sands NB, Payne RJ, Côté V, Hier MP, Black MJ, Tamilia M. Female gender as a risk factor for transient post-thyroidectomy hypocalcemia. *Otolaryngol Head Neck Surg*. 2011;145(4):561-564.
70. Selberherr A, Scheuba C, Riss P, Niederle B. Postoperative hypoparathyroidism after thyroidectomy: efficient and

cost-effective diagnosis and treatment. *Surgery*. 2015; 157(2):349-353.

71. Sheahan P, Mehanna R, Basheeth N, Murphy MS. Is systematic identification of all four parathyroid glands necessary during total thyroidectomy?: a prospective study. *Laryngoscope*. 2013;123(9):2324-2328.
72. Shinall Jr. MC, Broome JT, Nookala R. Total thyroidectomy for Graves' disease: Compliance with American Thyroid Association guidelines may not always be necessary. *Surgery*. 2013;154(5):1009-1015.
73. Shindo M, Stern A. Total thyroidectomy with and without selective central compartment dissection: a comparison of complication rates. *Arch Otolaryngol Head Neck Surg*. 2010;136(6):584-587.
74. Sousa AA, Salles JMP, Soares JMA, Moraes GM, Carvalho JR, Savassi-Rocha PR. Fatores preditores para hipocalcemia pós-tireoidectomia. *Rev Col Bras Cir*. 2012;39(6):476-482.
75. Sung TY, Lee Y, Yoon JH, Chung KW, Hong SJ. Importance of the intraoperative appearance of preserved parathyroid glands after total thyroidectomy. *Surg Today*. 2016;46(3):356-362.
76. Testini M, Gurrado A, Avenia N, et al. Does mediastinal extension of the goiter increase morbidity of total thyroidectomy? a multicenter study of 19,662 patients. *Ann Surg Oncol*. 2011;18(8):2251-2259.
77. Van Slycke S, Van den Heede K, Bruggeman N, Vermeersch H, Brusselaers N. Risk factors for postoperative morbidity after thyroid surgery in a PROSPECTIVE cohort of 1500 patients. *Int J Surg*. 2021;88:105922.
78. Vasileiadis I, Charitoudis G, Vasileiadis D, Kykalos S, Karatzas T. Clinicopathological characteristics of incidental parathyroidectomy after total thyroidectomy: the effect on hypocalcemia. a retrospective cohort study. *Int J Surg*. 2018;55:167-174.
79. Villarroya-Marquina I, Lorente-Poch L, Sancho J, Sitges-Serra A. Influence of gender and women's age on the prevalence of parathyroid failure after total thyroidectomy for multinodular goiter. *Gland Surg*. 2020;9(2):245-251.
80. Wang JB, Wu K, Shi LH, Sun YY, Li FB, Xie L. In situ preservation of the inferior parathyroid gland during central neck dissection for papillary thyroid carcinoma. *Br J Surg*. 2017;104(11):1514-1522.
81. Wang X, Xing T, Wei T, Zhu J. Completion thyroidectomy and total thyroidectomy for differentiated thyroid cancer: comparison and prediction of postoperative hypoparathyroidism. *J Surg Oncol*. 2016;113(5):522-525.
82. Xue SH, Li ZY, Wu WZ. Risk factors and prediction of postoperative hypoparathyroidism among patients with papillary thyroid carcinoma. *Transl Cancer Res*. 2019; 8(2):422-428.
83. Yano Y, Masaki C, Sugino K, et al. Serum intact parathyroid hormone level after total thyroidectomy or total thyroidectomy plus lymph node dissection for thyroid nodules: report from 296 surgical cases. *Int J Endocrinol Metab*. 2012;10(4):594-598.
84. Yao XY, Zhou Y, Chen SJ, et al. Is there a regular pattern in the recovery of parathyroid function after thyroid cancer surgery? *Cancer Manag Res*. 2021;13:6891-6899.
85. Yin C, Song B, Zheng W, Li X, Zhao H, Wang X. In situ preservation of parathyroid gland with vasculature for papillary thyroid carcinoma is associated with higher PTH levels after total thyroidectomy. *Ear Nose Throat J*. 2022; 101(2):95-104.
86. Yin S, Pan B, Yang Z, et al. Combined use of autofluorescence and indocyanine green fluorescence imaging in the identification and evaluation of parathyroid glands during total thyroidectomy: a randomized controlled trial. *Front Endocrinol*. 2022;13:13.
87. Youngwirth L, Benavidez J, Sippel R, Chen H. Parathyroid hormone deficiency after total thyroidectomy: incidence and time. *J Surg Res*. 2010;163(1):69-71.
88. Zheng J, Cai S, Song H, et al. Measurement of serum intact parathyroid hormone concentration 1 day after total thyroidectomy to assess risk of permanent hypoparathyroidism. *J Int Med Res*. 2020;48(6):0300060520927199.
89. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. *J Clin Epidemiol*. 2011;64(4):407-415.
90. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med*. 2018;23(2):60-63.
91. Duval M, Bach-Ngohou K, Masson D, Guimard C, Le Conte P, Trewick D. Is severe hypocalcemia immediately life-threatening? *Endocr Connect*. 2018;7(10):1067-1074.
92. Bellantone R, Lombardi CP, Raffaelli M, et al. Is routine supplementation therapy (calcium and vitamin D) useful after total thyroidectomy? *Surgery*. 2002;132(6): 1109-1113.
93. Wang TS, Cheung K, Roman SA, Sosa JA. To supplement or not to supplement: a cost-utility analysis of calcium and vitamin D repletion in patients after thyroidectomy. *Ann Surg Oncol*. 2011;18(5):1293-1299.
94. Singer MC, Bhakta D, Seybt MW, Terris DJ. Calcium management after thyroidectomy: a simple and cost-effective method. *Otolaryngol Head Neck Surg*. 2012; 146(3):362-365.
95. Huang S-M. Do we overtreat post-thyroidectomy hypocalcemia? *World J Surg*. 2012;36(7):1503-1508.
96. Annebäck M, Hedberg J, Almquist M, Stålberg P, Norlén O. Risk of permanent hypoparathyroidism after total thyroidectomy for benign disease: a nationwide population-based cohort study from Sweden. *Ann Surg*. 2021;274(6):e1202-e1208.
97. Lončar I, van Kinschot CMJ, van Dijk SPJ, et al. Persistent post-thyroidectomy hypoparathyroidism: a multicenter retrospective cohort study. *Scand J Surg*. 2022; 111(2):14574969221107282.
98. Mehanna HM, Jain A, Randeva H, Watkinson J, Shaha A. Postoperative hypocalcemia—the difference a definition makes. *Head Neck*. 2010;32:279-283.
99. Harsløf T, Rolighed L, Rejnmark L. Huge variations in definition and reported incidence of postsurgical

hypoparathyroidism: a systematic review. *Endocrine*. 2019;64: 176-183.
100. Jung SY, Kim HY, Park HS, Yin XY, Chung SM, Kim HS. Standardization of a physiologic hypoparathyroidism animal model. *PLoS One*. 2016;11(10):e0163911.
101. Edafe O, Mech CE, Balasubramanian SP. Calcium, vitamin D or recombinant parathyroid hormone for managing post-thyroidectomy hypoparathyroidism. *Cochrane Database Syst Rev*. 2019;2019(5):CD012845. doi:10.1002/14651858.CD012845.pub2
102. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. *Evid Based Med*. 2016;21(4):125-127.
103. Merchavy S, Marom T, Forest V-I, et al. Comparison of the incidence of postoperative hypocalcemia following total thyroidectomy vs completion thyroidectomy. *Otolaryngol Head Neck Surg*. 2015;152(1):53-56.
104. Alhefdhi A, Mazeh H, Chen H. Role of postoperative vitamin D and/or calcium routine supplementation in preventing hypocalcemia after thyroidectomy: a systematic review and Meta-analysis. *Oncologist*. 2013;18(5):533-542.