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Thyroid Disease

Hypocalcemia prevention and management after thyroidectomy in children: A systematic review☆,☆☆,★

Ankitha Radakrishnan [a], Abhita T. Reddy [b], Prarthana Dalal [a], Jeffrey C Rastatter [b], Jami L. Josefson [c], Jill H. Samis [c], Molly Beestrum [d], Yao Tian [a], Mehul V. Raval [a,*]

[a] Division of Pediatric Surgery, Department of Surgery, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
[b] Department of Otorhinolaryngology-Head & Neck Surgery, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
[c] Division of Endocrinology, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
[d] Galter Health Sciences Library & Learning Center, Northwestern University Feinberg School of Medicine, Chicago, IL

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ABSTRACT

Introduction: Hypocalcemia is the most common complication following thyroidectomy in children. Guidelines to manage post-thyroidectomy hypocalcemia are available for adults, but not children. The objective of this review was to identify practices related to hypocalcemia prevention and management in pediatric patients.
Methods: We identified studies examining the prevention and management of hypocalcemia in pediatric patients post-thyroidectomy within PubMed, EMBASE, Web of Science and Cochrane databases. Three independent reviewers screened citations and reviewed full-text papers.
Results: A total of 15 studies were included, representing 1552 patients. The overall study quality was weak with lack of randomization and inconsistent outcome reporting. The pooled incidence of hypocalcemia from the 15 studies was 35.5% for transient hypocalcemia and 4.2% for permanent hypocalcemia. All studies discussed post-operative hypocalcemia treatment, with most patients requiring admission for intra-venous calcium therapy. One study described a protocol discharging asymptomatic patients on calcitriol and calcium. Three studies discussed preoperative calcium supplementation in patients at risk of hypocalcemia. No studies examined routine use of calcium and/or vitamin D supplementation to prevent post-operative hypocalcemia.
Conclusion: A significant number of children undergoing thyroidectomy develop hypocalcemia. Despite this high incidence, our systematic review demonstrates significant practice variation surrounding post-thyroidectomy hypocalcemia prevention and management in children.
Level of Evidence: III (systematic review of studies of which some were case–control studies (III) and some were case series (IV)).

Hypocalcemia is the most common endocrine-specific complication following thyroidectomy in both children and adults [1]. Hypocalcemia occurs secondary to hypoparathyroidism due to trauma or devascularization of the parathyroid glands during thyroidectomy [2]. Post-operative hypocalcemia can be asymptomatic if calcium levels are mildly reduced, but can also present with muscle spasms, paresthesias, and even neurological manifestations if not treated. Additionally, post-operative hypocalcemia requires therapy and monitoring that may prolong inpatient hospitalizations [3]. While less consistently reported, hypocalcemia rates after thyroidectomy are higher for pediatric populations compared to adults (ranging from less than 10% to over 60%) [4–6].

Management of post-operative hypocalcemia for adult populations ranges from treatment of low calcium or parathyroid hormone (PTH) levels [7,8] to more preemptive approaches [5,9]. In 2013, Alhefdi et al. [9] published a systematic review and meta-analysis of nine adult studies with 2285 patients and concluded that routine, prophylactic supplementation of oral calcium or vitamin D significantly decreases post-operative hypocalcemia. A similar 2019 review by Xing et al. [10] had similar conclusions, and found specifically that calcium and vitamin D administered prophylactically in the post-operative period is more effective than calcium alone in preventing immediate post-operative hypocalcemia.

There is no clearly defined consensus on calcium management in the pediatric population to manage or prevent post-operative hypocalcemia after thyroidectomy. Our aim was to conduct a systematic review to

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* Corresponding author at: Department of Surgery, Division of Pediatric Surgery, Northwestern University Feinberg School of Medicine, 633 North Saint Clair Street, 20th Floor, Chicago, Illinois 60611. Tel.: +1 312 227 4210.
E-mail address: mraval@luriechildrens.org (M.V. Raval).

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identify practices related to hypocalcemia management in pediatric patients, and evaluate the potential role of calcium or vitamin D supplementation for the prevention of post-operative hypocalcemia.

1. Methods

This review was comprised of studies that included children and adolescents with benign or malignant thyroid conditions who underwent thyroidectomy and reported calcium levels. Interventions included pre-operative or post-operative treatment with oral or intravenous (IV) vitamin D, calcium, or both. Outcomes included the incidence of hypocalcemia in the post-operative recovery period and length of inpatient hospitalization.

1.1. Data extraction

The review was limited to English language studies of pediatric patients (<21 years old). Animal studies, systematic reviews and meta-analyses, letters, commentaries, and editorials were excluded. An extensive literature search was initially conducted in November 2018 and repeated in June 2020. Multiple electronic databases (including PubMed, EMBASE, Scopus and Cochrane) were searched to identify studies that examined the management of hypocalcemia/hypoparathyroidism in pediatric patients after thyroidectomy. These studies did not distinguish between hypocalcemia and hypoparathyroidism, often utilizing these terms interchangeably. The initial query was developed in consultation with a library scientist and was refined to ensure that articles known be to relevant appeared in the search results. All databases were searched back to their inception and no date limits were applied. Titles and abstracts were searched using the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) methodology [11]. Covidence systematic review software was used to collect, organize, and manage titles (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Articles meeting inclusion criteria were retrieved and reviewed by the three authors (AR, PD, and ATR) with adjudication and clarification provided by a fourth author (MVR).

Key words and MeSH terms included the following: ((((((“child”[MeSH terms] OR “child”[all fields] OR “children”[all fields] OR “adolescent”[MeSH terms] OR “adolescent”[all fields] OR “adolescents”[all fields] OR “adolescence”[all fields] OR “teen”[all fields] OR “teens”[all fields] OR “teenagers”[all fields] OR “teenager”[all fields] OR “youth”[all fields] OR “youths”[all fields] OR “infant”[MeSH] OR “pediatrics”[all fields] OR “pediatrics”[MeSH terms] OR “pediatrics”[all fields])))) AND ((“thyroidectomy”[MeSH terms] OR “thyroidectomy”[all fields] OR “thyroidectomies”[all fields] OR “parathyroidectomy”[MeSH terms] OR “parathyroidectomy”[all fields] OR “parathyroidectomies”[all fields]) OR ((“thyroid gland”[MeSH terms] OR “thyroid”[all fields] OR “parathyroid glands”[MeSH terms] OR “parathyroid”[all fields]) AND (“surgical procedures, operative”[MeSH terms] OR “removal”[all fields] OR “surgery”[subheading] OR surgery[all fields] OR surgeries[all fields] OR surgical[all fields])))) AND ((“vitamin d”[MeSH terms] OR “vitamin d”[all fields] OR “ergocalciferols”[MeSH terms] OR “ergocalciferols”[all fields] OR “ergocalciferol”[all fields] OR “calcium”[MeSH terms] OR calcium*[all fields] OR factor IV*[all fields] OR “calcitriol”[MeSH terms] OR calcitriol*[all fields] OR “Rocaltrol”[all fields] OR “Silkis”[all fields] OR “Soltriol”[all fields]))) AND ((calcemia*[all fields] OR hypocalcaemia*[all fields] OR “hypocalcemia”[MeSH terms] OR hypocalcemia*[all fields] OR “hypoparathyroidism”[MeSH terms] OR “hypoparathyroidism”[all fields]))).

1.2. Quality assessment

Three independent reviewers (AR, PD, and ATR) assessed study quality and resolved discrepancies through discussion and mutual agreement and adjudication with a fourth team member (MVR). To assess study quality, we used the validated Quality Assessment Tool for Quantitative Studies (https://merst.ca/ephpp/) [12], as recommended by the Guidelines for Systematic Reviews in Health Promotion and Public Health Taskforce [13]. Our data extraction process was modeled on taskforce recommendations, including assessment of evidence for the intervention and implementation fidelity [13].

2. Results

2.1. Study selection

The search identified 1589 studies focusing on post-operative hypocalcemia in children and adolescents undergoing thyroidectomy. A total of 178 studies remained after title and abstract screening eliminated duplicates. Studies were further eliminated based on exclusion criteria outlined in the PRISMA flow diagram depicted in Fig. 1 resulting in 15 studies representing a total of 1552 patients.

2.2. Quality assessment

Overall, the study quality was weak. All studies lacked randomization, and there was inconsistent outcome reporting across studies. Most were single-center studies based on retrospective reviews. Due to the consistent lack of blinding and presence of confounders, there was a “weak” global rating across all studies included in this review. Because the pediatric literature on this topic is in its early stages compared to adult literature, all studies had weak to moderate study designs, and demonstrated moderate selection bias.

2.3. Definition and incidence of post-operative hypocalcemia

Characteristics of the included studies are shown in Table 1. The primary outcomes reported by the included studies were rates of transient and permanent hypocalcemia and/or hypoparathyroidism, the definitions of which varied between studies. The pooled incidence of hypocalcemia from the 15 studies was 35.5% for transient hypocalcemia (ranging from 24.7% to 47.9%) and 4.2% for permanent hypocalcemia (ranging from 1.9% to 9.1%).

Post-operative hypocalcemia was defined using a combination of laboratory values for calcium levels [5,14–26], symptoms and need for calcium supplementation during initial post-operative hospitalization or at discharge [5,15,17], and duration of symptoms (typically 6 months after surgery) to codify permanent hypocalcemia [5,14,16,17,19]. Others incorporated the need for calcitriol/active Vitamin D [14,18–21,23,24,26,27] or extended the definition of permanent hypocalcemia out to one year [24,25].

2.4. Treatment of post-operative hypocalcemia

All studies discussed treatment methods for post-operative hypocalcemia. The specific laboratory tests used, frequency of studies, and threshold for treatment of hypocalcemia varied tremendously between studies. While the majority of studies (9 of 15) noted patient admission for IV calcium gluconate therapy [5,14–16,19–21,24,26], there were several other treatment strategies including variable thresholds of using oral calcium supplementation [14,17,18,22,23,25] as well as the use of vitamin D [14,26,27] or calcitriol [18–21,23,24,26]. Most studies checked calcium levels [5,14–27] or PTH levels [17–19,22,23] immediately after surgery and several studies noted continued calcium level assessment at 4 to 8 h increments [5,17,18].

Several recent studies have shifted toward reliance on PTH levels. Overman et al. describe the implementation of a protocol that uses 4-h post-operative PTH levels [20]. If PTH was less than 10 pg/dL, patients were supplemented with calcium carbonate. Symptomatic patients also received calcitriol or, if severe, were started on IV calcium supplementation. Similarly, Patel et al. describe a protocol that utilizes intraoperative PTH levels collected 25 min after thyroidectomy. They used PTH

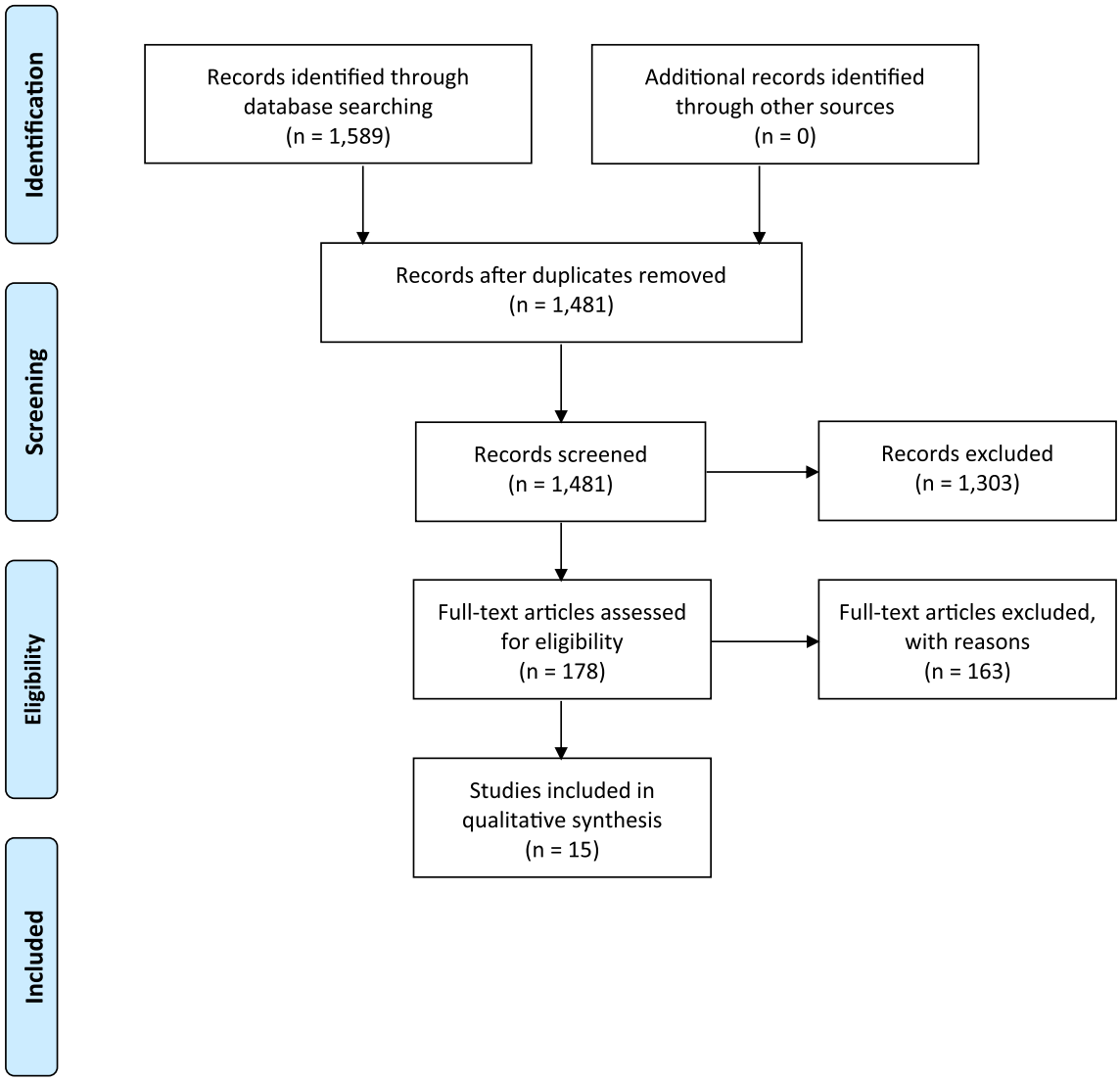

Fig. 1. PRISMA diagram. A total of 1589 studies were identified through our search, 15 of which included necessary data to be included in the qualitative synthesis.

levels to stratify patients to either high (PTH </= 16 pg/mL) or low risk (PTH > 16 pg/mL) of hypocalcemia [21]. High risk patients were immediately started on oral calcium carbonate and calcitriol for empiric treatment of hypocalcemia, within two hours of thyroidectomy. High risk patients with PTH </= 16 pg/mL were given first doses as IV calcium gluconate and IV calcitriol. Wu et al. checked calcium and PTH levels within 24 h after thyroidectomy [23]. Tsai et al. described a pre-operative assessment using serum 25-hydroxy vitamin D (25-OHD) and prescribed oral vitamin D3 if their 25-OHD was <20 ng/mL [26]. Patients who did not have 25-OHD levels available received a single dose of 50,000 U oral D3 1 week prior to surgery. They then used intraoperative PTH to further stratify patients into high-risk patients (intraoperative PTH <10 pg/mL), moderate-risk (intraoperative PTH >10 but <20 pg/mL), and low-risk (intraoperative PTH >/= 20 pg/mL). High-risk patients received a single 1mcg dose of IV calcitriol in the operating room or shortly after arrival in post-operative care unit, and were started on oral calcium and calcitriol. Moderate-risk patients were started on oral calcium with the addition of oral calcitriol supplementation based on post-op calcium and phosphorous levels, and low-risk patients were start on oral calcium or calcitriol only if post-op calcium and phosphorous levels were abnormal.

2.5. Preemptive calcium management

Three studies discussed pre-operative calcium supplementation. Breuer et al. report treating 20 of the 32 pediatric patients involved in the study with 0.5 mcg of calcitriol twice daily for 3 days prior to surgery [15]. Post-operatively, the calcitriol was weaned over 15 days. With the use of preemptive calcitriol, the number of patients that required IV calcium decreased from 50% to 16% ($p = 0.02$). Yu et al. describe that 45% of patients in their study received pre-operative oral calcium carbonate supplementation and oral calcitriol for 1 week prior to surgery [24]. Of the patients who received pre-operative calcium supplementation, 55% developed hypocalcemia, versus 45% of patients who did not receive pre-operative calcium supplementation. As noted, Tsai et al. used pre-operative 25-OHD to dictate preemptive supplementation [26].

2.6. Risk factors for hypocalcemia

Multiple studies identified risk factors for hypocalcemia (Table 2). The most common risk factors for hypocalcemia were Graves' disease [5,14,24], central compartment neck dissection [5,14,17–19,21,23–25], malignancy/thyroid tumors [5,14,23–25], total thyroidectomy [5,18,24], and younger age [14,24]. Several studies specifically described the impact

Table 1
Summaries of 158 studies included in this systematic review of hypocalcemia management among pediatric patients undergoing partial or total thyroidectomy.

Source	Study design	Pts, No.	Age (mean), years	Indication for surgery	Operation type	Timing of supplementation	Supplementation dosing and delivery	Main outcome measures	Definitions of transient and permanent hypocalcemia/hypoparathyroidism	Rates of transient and permanent hypocalcemia
Akkari et al., 2014	Retrospective Review	34	12.5	Suspicious nodule (32, 94.1%), Toxic multinodular goiter (8, 23.5%), Graves' Disease refractory to medical treatment (14, 41.2%), Family history of MTC with RET mutation (11, 32.4%)	Total thyroid (44.6%), Total thyroid w/ lymph node dissection (7.7%), lobectomy (38.5%), enucleation (9.2%)	Post-op only	Calcium, vitamin D	Postoperative hypocalcemia rate (transient and permanent), Recurrent laryngeal nerve complications, Histological results	Hypocalcemia: serum calcium <7.5 mg/dL Permanent hypocalcemia: persisting 6 months or longer post-op	Transient: 23.5% Permanent: 14.7%
Breuer et al., 2013	Retrospective Review	32	Children: 9.7 Adults: 44.9	Graves' Disease (32, 100%)	Total thyroid (100%)	Pre-op (20) Post-op for all pts	IV calcium gluconate	Postoperative hypocalcemia rate (transient), Hospital length of stay, Recurrent laryngeal nerve complications, Postoperative hematoma occurrence	Hypocalcemia: serum calcium levels (corrected for total protein) <8.0 mg/dL in the presence of symptoms (i.e. hand paresthesias, perioral numbness, muscle cramps, the presence of a Chvostek's sign) or <7.5 mg/dL without symptoms; did not distinguish between transient and permanent	Transient: 18%
Bussieres et al., 2019	Retrospective Review	98	11.8	Nodule (63, 64.3%), MEN2 Mutation Carrier (21, 21.4%), Hyperthyroidism (7, 7.1%), Goiter (7, 7.1%)	Total thyroid (38.1%), Hemithyroid (55.1%), LND w/o thyroid resection (2.5%), Other (4.2%)	Post-op only	IV or oral calcium	Postoperative hypocalcemia rate (transient and permanent), Recurrent laryngeal nerve injury, Histological results	Hypocalcemia: serum calcium concentration below the normal values established by lab. Transient hypocalcemia: hypocalcemia with calcium supplementation for 6 months or less Permanent: hypocalcemia requiring calcium supplementation for greater than 6 months	Transient: 13.6% Permanent: 1.7%
Chen et al., 2015	Retrospective Review	171	15.4	Nodule (128, 74.7%), Hyperthyroidism (21, 12.4%), Completion (14, 8.1%), MEN type 2, (8, 4.8%), Graves' Disease (20, 11.9%), Follicular adenoma (54, 31.4%), PTC (47, 27.4%) PTC, MTC (5, 2.7%), FTC (3, 1.6%)	Hemithyroid (48.8%), total thyroid (40.1%), enucleation (4.3%), completion thyroid (6.8%), lymph node dissection (17.9%)	Post-op only	IV or oral calcium	Postoperative hypocalcemia rate (transient and permanent)	Transient hypocalcemia: post-op serum calcium of less than 8.0 mg/dL and treatment with oral calcium supplementation or IV calcium during hospitalization Permanent hypocalcemia: taking oral calcium supplementation beyond 6 months post-op with a serum calcium <8.0 mg/dL or PTH <15 pg/mL	Transient: 12.9% Permanent: 0.9%
de Jong et al., 2019	Retrospective Review	106	12 (median)	Graves' Disease (52, 49.1%), Hereditary medullary thyroid carcinoma (36, 33.9%), Multinodular goiter (3, 2.8%), Thyroid carcinoma – follicular or papillary (15, 14.2%)	Total thyroid (100%)	Post-op only	Oral calcium, oral alfacalcidol	Postoperative hypocalcemia (transient), hypoparathyroidism (at discharge and 6 months), Hospital length of stay	Hypocalcemia: calcium level <2.15 mmol/L within 24 h of surgery, hypoparathyroidism on discharge, or supplementation requirement upon discharge Long-term hypoparathyroidism: supplementation still necessary at 6 months	Transient: 59.4% Permanent: 21.7%

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Table 1 *(continued)*

Source	Study design	Pts, No.	Age (mean), years	Indication for surgery	Operation type	Timing of supplementation	Supplementation dosing and delivery	Main outcome measures	Definitions of transient and permanent hypocalcemia/hypoparathyroidism	Rates of transient and permanent hypocalcemia
Jiang et al., 2019	Retrospective Review	38	14.3 (median)	Multinodular goiter (8, 21.1%), Graves' Disease (5, 13.2%), Medullary thyroid carcinoma (4, 10.5%), Well-differentiated thyroid carcinomas (21, 55.3%)	Total thyroid (84.2%), completion thyroid (15.8%)	Post-op only	Oral calcium, with or without calcitriol Subcutaneous teriparatide (recombinant N-terminal human PTH 1–34)	Postoperative hypocalcemia rate (transient), postoperative hypoparathyroidism (permanent) Postoperative PTH, Hospital length of stay, Risk factors for hypocalcemia	Hypocalcemia: total serum calcium level <8.5 mg/dL Permanent hypoparathyroidism: PTH <10 pg/mL at 3 and 7 year follow-ups	Transient: 63.2% Permanent: 5.3%
Morris et al., 2012	Retrospective Review	74	12.5 (median)	MEN2A/B (31, 41.9%), Suspicious nodule (2, 2.7%), Toxic multinodular goiter (1, 1.4%), Malignancy (40, 54.1%)	Total thyroid (37.8%), Total thyroid w/ lymph node dissection (62.2%)	Post-op only	Oral calcitriol, Oral calcium, IV calcium	Postoperative hypocalcemia rate (transient and permanent), Postoperative thyroid hormone regulation, Medication adherence, Postoperative psychological, behavioral, and physiologic problems	Temporary hypoparathyroidism: 1) PTH <2 pg/mL, 2) PTH <10 pg/mL and discharged receiving calcitriol, or 3) PTH not measured and patient discharged receiving calcitriol based on calcium levels Permanent hypoparathyroidism: PTH level <10 pg/mL lasting >6 months post-op and need for continued daily calcium supplementation (with or without calcitriol)	Transient: 30% Permanent: 8%
Nordenstrom et al., 2018	Retrospective Review	274	14.9	Graves' Disease (214, 78.1%), Other Benign Disease (27, 9.9%), Malignancy (33, 12.0%)	Total thyroid (86.1%), Total Thyroid w/ lymph node dissection (13.9%)	Post-op only	Oral Vitamin D	Postoperative hypocalcemia rate (transient and permanent), Risk factors for hypocalcemia	Permanent hypoparathyroidism: prescription of active vitamin D in the first 180 days after surgery and any time after 180 days after surgery	Transient: N/A Permanent: 7.3%
Overman et al., 2019	Retrospective Review	56	14 (median)	Malignancy (20, 35.7%) Graves' Disease (15, 26.8%), Hashimoto's thyroiditis (7, 12.5%), MEN syndrome (5, 8.9%), Follicular lesion of unknown significance (4, 7.1%), Multinodular goiter (3, 5.4%), Bilateral nodules (2, 3.6%)	Total thyroid, completion thyroid (unspecified)	Post-op only	Oral calcium carbonate, Oral calcitriol, IV Calcium	Postoperative hypocalcemia rate (transient and permanent), Hospital length of stay	Hypocalcemia: ionized calcium <1.12 mmol/L	Pre-implementation: 26.3% Post-implementation: 29.7% Permanent: N/A
Patel et al., 2018	Retrospective Review	53	15	Papillary Thyroid Cancer (34, 64.2%), Graves' Disease (7, 13.2%), C-Cell Hyperplasia (5, 9.4%), Follicular Adenoma (5, 9.4%), Multinodular Goiter (5, 9.4%), Follicular Carcinoma (3, 5.7%), Large B-Cell Lymphoma (1 1.9%)	Total thyroid (58.5%), Total Thyroid w/ lymph node dissection (41.5%)	Post-op only	Oral calcitriol, Oral Calcium, IV Calcium, IV Magnesium	Postoperative hypocalcemia rate (transient), Postoperative calcium draws, Hospital length of stay	Hypocalcemia: total serum calcium values <8.7 mg/dL; did not assess permanent hypoparathyroidism	Transient: 58.5%
Schneider et al., 2004	Retrospective Review	208	Unspecified	Advanced papillary thyroid carcinoma (208, 100%)	Total thyroid (100%)	Post-op only	Dihydrotachysterol (AT-10): 0.2–0.9 mg, Oral Calcium 500 mg tid-qid	Parathyroid function, whole-body bone mineral content (TBMC), projected "areal" bone mineral density (TBMD), total lean	Hypoparathyroidism: at least one instance of serum PTH <10 pg/mL and serum calcium <8 mg/dL; did not distinguish between transient and permanent	Boys: 68% Girls: 55% (did not distinguish)

								mass (TLM), total fat mass (TFM)		
Tsai et al., 2019	Retrospective Review	65	15.1	Graves' Disease (29, 44.6%), Thyroid Cancer (36, 55.4%)	Total thyroid (100%)	Pre-op for all pts. Intra-op Post-op	Pre-op: 50,000 U oral D3 1 week prior to surgery High-risk pts.: 1mcg IV calcitriol intra- or post-op Moderate- and low-risk pts.: Oral calcium, oral calcitriol	Intra-operative PTH (ioPTH), Time to recovery (TOR) of parathyroid function	Normalization of parathyroid gland function: normal serum calcium and phosphorus levels when off of supplemental calcium and calcitriol	Permanent: 0%
Wu et al., 2020	Retrospective Review	184	Unspecified	Papillary thyroid carcinoma (111, 60.3%), RET germline mutation (73, 39.7%)	Total thyroid (100%)	Post-op only	Oral calcium, Oral calcitriol	Postoperative hypoparathyroidism (transient and permanent), Median recovery time	Transient hypoparathyroidism: PTH level <10 pg/mL or symptoms resolving without requiring calcium/calcitriol supplementation. Permanent hypoparathyroidism: PTH <10 pg/mL with patients requiring continuous daily calcium and calcitriol supplementation at last follow-up	Transient: 33.1% Permanent: 3.3%
Yu et al., 2017	Retrospective Review	91	13.7	Malignancy (47, 51.6%), Graves' Disease (24, 26.4%), Hashimoto's thyroiditis (3, 3.3%), MEN 2A/2B (6, 6.6%), McCune Albright Syndrome (2, 2.2%), PTEN hamartoma syndrome (1, 1.1%), Enlarging goiter/mass (5, 5.5%), Refractory hyperthyroidism (3, 3.3%)	Total thyroid (66%), total thyroid w/ lymph node dissection (34%)	Pre-op (41) Post-op for all pts	Oral calcium, oral calcitriol, IV calcium; Oral calcium carbonate (750–1500 mg 3–4×/day) and oral calcitriol	Postoperative hypocalcemia rate (transient and permanent), Risk factors for hypocalcemia	Hypocalcemia: calcium <8.0 mg/dL or ionized calcium <1.0 mmol/L Permanent hypocalcemia: calcium <8.0 mg/dL requiring calcium supplementation >1 year and PTH <15 pg/mL without evidence of parathyroid recovery	Transient: 34% Permanent: 1%
Zobel et al., 2020	Retrospective Review	68	15	Graves' Disease (38, 55.9%), Goiter (5, 7.4%), RET mutation (8, 11.8%), Malignancy (15, 22.1%), Thyroid nodule and lymphadenopathy (2, 2.9%)	Total thyroid (100%)	Post-op only	Oral calcium carbonate, Oral vitamin D	Postoperative hypoparathyroidism (transient and permanent)	Hypocalcemia: inpatient serum calcium <8.0 mg/dL Temporary hypoparathyroidism: Calcium and vitamin D requirement <12 mo postoperatively Permanent hypoparathyroidism: Calcium and vitamin D requirement beyond 1 y postoperatively	Transient: 41% Permanent: 2.9%

of parathyroid manipulation on post-operative hypocalcemia rates. Chen et al. described that they did not observe higher rates of hypocalcemia in cases with parathyroid autotransplantation or unintentional parathyroidectomy [5]. Conversely, Morris et al. found that inadvertent parathyroid resection was associated with temporary ($p = 0.03$) but not permanent ($p = 0.07$) hypoparathyroidism [19].

3. Discussion

Our study reveals that there are significant variations in the definition, management, and prevention of hypocalcemia following thyroidectomy in the pediatric population. Our study sought to review current practices in prevention and treatment of hypocalcemia after thyroid surgery in children and to evaluate the role of calcium and Vitamin D in prevention of hypocalcemia. Our review identified 15 studies spanning 1552 pediatric patients who underwent thyroidectomy. Among pediatric patients, transient or permanent hypocalcemia is the most common endocrine complication after thyroidectomy. Rates of this complication range from 1.6% to 50% [27,28]. Our review found a pooled incidence of 35.5% (24.7, 47.9) and 4.2% (1.9, 9.1) for transient and permanent hypocalcemia, respectively.

In addition to pediatric patients being at an increased risk of developing hypocalcemia after thyroidectomy due to their age [6], there are other well described risk factors. Central and bilateral lymph node dissection [5,14,18,19,21,23–25], the presence of Grave's disease [5,14,24] or malignancy [5,14,23–25] as indications for surgery, and total thyroidectomy [5,14,18,24] were identified as independent predictors of post-operative hypocalcemia in multiple studies in this review. This is similarly reflected in the adult literature. Roh et al. showed that, in adults, central lymph node dissection significantly increased the rate of post-operative hypocalcemia compared with total thyroidectomy alone, and that this could be prevented by routine post-operative supplementation with oral calcium and vitamin D [29]. Similarly, Wang et al. identified seven factors that were significantly related to post-operative hypocalcemia in adults: age, gender, lymph node dissection, operation type, pre-operative PTH level, operation time, and application of carbon nanoparticles [30]. With an understanding of risk factors for post-operative hypocalcemia, there is an opportunity to prophylactically supplement high-risk patients.

There were three studies (Breuer et al.,Yu et al., and Tsai et al.) that preemptively started a subset of their study participants on pre-operative calcium and /or calcitriol supplementation. Tsai et al. describe a unique supplementation strategy based on risk stratification by intra-operative PTH, which proved to be a useful means of stratification given the inverse correlation between time of parathyroid function recovery and risk of hypocalcemia [26]. It is difficult to interpret if such a strategy was effective in reducing rates of hypocalcemia, given that the study instead focused on establishing the validity of using intraoperative PTH as a means of risk stratification. The study by Breuer et al., demonstrates that pre-operative supplementation may be effective in reducing rates of hypocalcemia [15]. In contrast, the study by Yu et al. demonstrates a possibly inadequate supplementation despite an aggressive preventative approach, as well as the challenge in properly choosing high-risk individuals as candidates for pre-operative supplementation [24]. While there are currently no studies regarding this type of protocol in the pediatric population, there is discussion, albeit limited, in the adult population. Sun et al. [31] describe a classification of 132 patients into 4 groups (A-D) based on the National Comprehensive Cancer Network (NCCN) risk stratification system. Low-risk (Group A) group was defined as patients undergoing limited thyroidectomy, and high-risk groups (B-D) were patients undergoing total thyroidectomy and/or neck dissection. After surgery, patients in groups C and D (of highest risk) were prophylactically put on oral and IV calcium gluconate, respectively. Of note, IV calcium supplementation in group D resulted in a more rapid recovery in serum calcium levels ($p < 0.05$).

There is significant variation in post-operative management of hypocalcemia in the pediatric population, with more of a consensus in the adult population. American Thyroid Association (ATA) guidelines recommend that effective management of mild to moderate post-operative hypoparathyroidism in adults can be achieved by administering either prophylactic oral calcium or vitamin D, selective oral calcium, and vitamin D based on rapid post-operative PTH levels or serial serum calcium levels as a guide. Inpatient management is recommended for more severe cases of hypocalcemia [32]. This is in contrast to the management of the pediatric population such as in studies in this review, with the majority of institutions requiring patient admission for IV calcium therapy as treatment for post-operative hypocalcemia regardless of severity. It is unclear if the adult ATA guidelines can be applied to the pediatric population. This review highlights that additional studies are needed to facilitate creation of clear guidelines and practices surrounding peri-operative calcium management for children undergoing thyroidectomy.

Table 2
Statistically significant risk factors for development of transient or permanent postoperative hypocalcemia (available odds ratios (OR) and p-values are reported).

	Central and/or bilateral lymph node dissection	Graves' disease	Malignancy	Total thyroidectomy (versus partial thyroidectomy)	Previous thyroid surgery	Younger age
Akkari et al.	+	+	+	−	+	+
Chen et al.	+ OR 22.25, $p = 0.01$	+ OR 3.99, $p = 0.02$	+ OR = 2.96, $p = 0.03$	+ OR 7.39, $p < 0.01$	−	−
De Jong et al.	+	−	−			−
Jiang et al.	+ $p = 0.04$		−	+ $p = 0.01$	−	
Morris et al.	+ $p = 0.002$* $p = 0.04$^	−	−	−	−	−
Nordenstrom et al.	−	−	−	−	−	−
Patel et al.	+	−	−	−	−	−
Wu et al.	+ OR 4.26, $p < 0.001$		+ OR 6.65, $p < 0.001$			−
Yu et al.	+ $p = 0.04$	+	+ $p = 0.05$	+	−	+ $p = 0.01$
Zobel et al	+ OR 12.6, $p < 0.01$	−	+ OR 6.7, $p = 0.02$			

+ = variable is a risk factor for post-operative hypocalcemia.
- = variable is not a risk factor for post-operative hypocalcemia.
Empty cell = the study did not evaluate that particular variable as a risk factor post-operative hypocalcemia.
* Temporary post-operative hypocalcemia.
^ Permanent post-operative hypocalcemia.

Two key recommendations are suggested by the findings of our review. First, there is a need for research that evaluates the efficacy of prophylactic calcium and/or Vitamin D supplementation in the pre-operative, peri-operative, and/or post-operative periods of thyroidectomy, particularly in high-risk groups. Second, given the high rates of post-thyroidectomy hypocalcemia reported in the literature, calcium management protocols should be introduced and tested. Patel 2018, Overman 2019, and Tsai 2019 demonstrate examples of protocols with patient stratification into high- and low-risk groups by intra-operative and/or post-operative PTH levels, to allow for targeted management [20,21,26].

There are several limitations of this systematic review. The studies included have a total of 1552 patients each with small numbers of study participants. The study done by Nordenstrom et al. represents the largest study cohort, with 274 patients. The overall quality of the studies was poor to fair, with most studies being single center studies and case series. The 15 studies included are quite heterogeneous in definitions of hypocalcemia/hypoparathyroidism, outcome measures, and management practices. Additionally, our review included studies of both total and hemi-thyroidectomies. These surgeries can vary in extent of hypocalcemia given the varied extents of dissection. Given the sparsity of available literature, we included both types of surgeries in our review. Lastly, there was also limited long-term follow-up in most of the included studies. As a result, direct comparisons between studies was difficult and formal meta-analyses could not be performed. Despite these limitations, our study adds to the limited data and knowledge in the management of post-operative hypocalcemia following thyroid surgery in children.

4. Conclusion

We identified 15 studies that described prevalence, prevention, and management of hypocalcemia after thyroidectomy in pediatric patients. This review not only demonstrates that post-thyroidectomy hypocalcemia is common in the pediatric population, particularly in high-risk groups, but also that there is significant practice variation in calcium management in pediatric patients. Further investigation is needed to evaluate screening of high-risk pediatric patients who may be candidates for prophylactic supplementation, as well as whether supplementation should be given to patients pre-operatively and/or post-operatively. The introduction of standardized protocols for calcium management should be considered.

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