Review Article

Beyond hypocalcemia: the impact of permanent post-operative hypoparathyroidism on patient quality of life—a narrative review

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Background and Objectives: Iatrogenic hypoparathyroidism with subsequent hypocalcemia can be a debilitating consequence of thyroidectomy that often requires substantial medical management. While temporary hypocalcemia can be treated effectively in the short-term, the sequelae of long-term hypoparathyroidism and hypocalcemia is not well understood and the means to treat require a broader understanding of the complications of permanent hypocalcemia. The reduction in patient quality of life (QOL) with longstanding hypoparathyroidism is likely underestimated and underreported, though emerging studies aim to address this important topic which prioritize patient factors in addition to biochemical measures.

Methods: A literature review was performed using PubMed to search all original articles published in the English language over between 2000 and March 2022 that included terms such as 'calcium', 'hypocalcemia', 'hypoparathyroidism', 'long-term management', 'quality of life', and 'supplementation'.

Key Content and Findings: Hypocalcemia will be discussed as it pertains to post-operative clinical assessment, temporary and permanent medical management, and, importantly, QOL parameters related to persistent hypocalcemia. Implementation of treatment modalities to improve QOL in patients with persistent hypocalcemia will be discussed in order to outline the means by which these patients are followed in the long-term.

Conclusions: This article aims to update the reader on the long-term medical and psychosocial considerations in patients with iatrogenic hypoparathyroidism which will motivate communication and treatment strategies in those who live with hypocalcemia following thyroid surgery.

Keywords: Hypocalcemia; hypoparathyroidism; long-term management; quality of life (QOL); supplementation

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Introduction

Hypocalcemia secondary to hypoparathyroidism is one of the most common post-operative complications following thyroidectomy. Low serum calcium levels, defined as a low total serum calcium level below normal range (1), are thought to drive the mental and physical impairment leading to a reduction in patient quality of life (QOL). Whereas there are many conditions predisposing individuals to hypocalcemia, for the purposes of this paper, only hypoparathyroidism will be considered. Hypoparathyroidism involves a low intact parathyroid hormone (PTH) level that is below the level of the normal range (2). Hypoparathyroidism is related to direct injury or excision of parathyroid glands during thyroid surgery, and hypocalcemia will be mentioned here in direct relationship to a diagnosis of post-operative hypoparathyroidism.

The management of hypocalcemia following thyroid surgery can be medically complex, challenging both the patient and the provider. Patient-reported QOL associated with hypocalcemia is poor and is, unfortunately, often-underestimated by the medical community (3). Rates of post-operative hypocalcemia vary across multiple studies, with temporary hypocalcemia ranging from 7.6–35% and permanent hypocalcemia 1–3% (4,5). According to the American Thyroid Association (ATA) guidelines, temporary hypocalcemia is defined as low serum calcium 6-months or less following surgery, with permanence defined beyond that threshold (2). The American Society of Bone and Mineral Research (ASBMR) and other institutions do recognize that the risk of post-operative hypocalcemia is lower in high volume centers with more experienced endocrine surgeons (6).

The aim of this article is to summarize the treatment of hypocalcemia in both the immediate and late post-operative periods, and consider sequelae and symptoms related to hypocalcemia after thyroidectomy, both in the temporary and permanent post-operative scenario. The literature surrounding QOL in these patients is sparse, and there are more contemporary studies that appear to focus on this as a topic for future evaluation. We will highlight the current paradigms and guidelines for medical treatment of hypocalcemia in the post-operative setting, and end the article on measures to identify, assess and improve QOL for patients afflicted with this condition. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aot.amegroups.com/article/view/10.21037/aot-22-10/rc).

Methods

A PubMed search was completed on English only literature spanning the dates of 2000–2022. One study published in 1952 was added separately. Types of literature included case series, case-controlled studies, cohort studies, randomized control studies and systematic reviews. Key words included 'calcium', 'hypocalcemia', 'hypoparathyroidism', 'long-term management', 'quality of life', 'supplementation'. *Table 1* provides a summary of the above.

Postoperative hypocalcemia: diagnosis and symptomatology

According to the ATA Surgical Affairs Committee Statement published in 2017, the absolute value, trend and slope of calcium and PTH values after surgery, can be used to predict permanent hypoparathyroidism (2). One study measured calcium levels at 6 and 12 hours after surgery and noted that patients with a rise in calcium levels at 12 hours were safe for discharge without additional calcium supplementation for home. Patients who had calcium levels equal to or above 8 mg/dL were also safe for discharge, but with supplementation on board (7). This study did not comment on PTH levels. Low post-operative PTH, age, female gender, vitamin D deficiency, the presence of malignancy, obesity and thyrotoxicosis were considered risk factors for transient hypocalcemia (8,9).

Prediction of transient hypoparathyroidism that evolves into in a permanent state is not well established. Postoperative PTH values, a gradient in PTH values between preoperative and postoperative measurements, decrease in magnesium levels, and the presence of parathyroid autotransplantation, have been associated with the risk of permanent hypoparathyroidism (10-13). Other known risk factors include re-operative thyroid surgery, and inclusion of central neck dissection in thyroidectomy. At the most recent ASBMR meeting in 2021, the workshop consortium responsible for the updated guidelines made a strong recommendation to measure PTH in the hours immediately after surgery. Levels higher than 10 pg/mL were considered low risk for hypocalcemia while those with levels less than 10 pg/mL, the risk for hypocalcemia was 50% or lower (14).

The presence of symptoms of hypocalcemia is related to the acuity of the serum calcium drop and the serum calcium level. Patients with chronic hypocalcemia are therefore less symptomatic (15). Symptoms associated with post-operative hypocalcemia can include paraesthesias of the perioral

Table 1 The search strategy summary

Items	Specification
Date of search	March 1, 2022
Databases and other sources searched	PubMed
Search terms used	'Calcium', 'hypocalcemia', 'hypoparathyroidism', 'long-term management', 'quality of life', 'supplementation'
Timeframe	Any publication between 2000 and March 2022 was included
Inclusion and exclusion criteria	Inclusion criteria: English only literature, case studies, case control studies, randomized control studies, systematic reviews
	Exclusion criteria: non-English literature
Selection process	Both authors (K.F.M. and V.K.D.) were involved in the selection process of articles, and consensus was obtained prior to review of articles and data collection
Any additional considerations, if applicable	V.K.D. provided additional articles as needed including one study from 1952

Table 2 Approaches to management of postoperative hypoparathyroidism

Category of treatment based upon symptoms	Calcium (po)	Calcitriol (po)	Calcium (intravenous)
Empiric treatment	Calcium carbonate: 0.5–1.25 g bid-tid	Calcitriol 0.15–0.5 ug bid	N/A
Mild-moderate hypoparathyroidism (serum calcium <8.5 mg/dL, new onset symptoms)	Calcium carbonate: 1–3 g daily divided doses bid-tid	Calcitriol: 0.25–0.5 ug bid	N/A
Progressive/symptomatic hypoparathyroidism (serum calcium <7.0 mg/dL, OR persistent/severe symptoms despite therapy; ALSO check EKG for QT interval prolongation)	Calcium carbonate: 3–4 g daily divided doses bid-tid	Calcitriol: 0.25–1.0 ug bid	IV bolus: 1–2 g calcium gluconate along with intravenous fluid infusion

EKG, electrocardiogram; N/A, not applicable; IV, intravenous.

region and extremities, muscle stiffness, cramps and spasms.

Postoperative hypocalcemia: inpatient management recommendations

The ATA Surgical Affairs Committee summarized the current recommendations in the management of postoperative hypoparathyroidism (*Table 2*) (2). The two primary forms of calcium supplementation are calcium carbonate and calcium citrate. Oral calcium carbonate is the most common form, with recommendations to give between 500–625 mg to 1,000–1,250 mg two to three times a day. Calcium citrate is better absorbed, though not always available on hospital formularies. Adding the active form of vitamin D, also known as calcitriol [1,25-(OH)2-D3] increases the absorption of calcium in the gastrointestinal (GI) tract. A typically dose recommendation is 0.5–1.0 mcg per day.

In the event of symptomatic or clinical hypoparathyroidism associated with calcium levels of <8.0 mg/dL that decline despite oral therapy, intravenous (IV) calcium repletion may be required. Initiation of an IV calcium gluconate drip requires a patient be monitored via electrocardiogram (EKG) because of the risk for QT interval prolongation and cardiac arrythmia which may potentially develop into torsades de pointes (2). Calcium given by IV bolus (1–2 g of calcium) is the fastest way to rapidly raise serum calcium. The IV bolus is often followed by a continuous drip to maintain normal serum calcium levels in the low-normal reference range. Oral supplementation should be continued and titrated upwards with the goal of weaning off IV repletion as soon as possible.

Postoperative hypocalcemia: hospital discharge recommendations

Following discharge, and while the provider and patient await parathyroid gland recovery which can take weeks, higher doses of calcium may be required. Some studies have recommended the use of pre- and post-operative PTH levels to determine whether or not calcium supplementation is needed (2). Many centers have specialized protocols for post-operative management of calcium when patients return home. Calcium supplementation doses can start at 1,500 mg daily and go as high as 3,500 mg of elemental calcium per day if divided into multiple doses throughout the day for better absorption. Calcitriol is also generally recommended, starting at 0.25 mcg of calcitriol 1–2 times daily (0.25–4.0 mcg/day). Vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) are longer-term derivatives of calcitriol and used as well. Vitamin D increases intestinal phosphate absorption, but intestinal phosphate binders may be necessary if phosphorus is high (2). Close follow up with the surgical team and/or endocrinologist is advised for biochemical surveillance and medication titration.

Management of permanent hypocalcemia

The current guidelines for treatment of permanent hypoparathyroidism recommend targeting serum calcium within the low-normal range (less than or equal to 8.8 mg/dL), and serum phosphorus within the high-normal range (higher than or equal to 4.5 mg/dL). The goal of therapy is to reduce symptoms, minimize risk of kidney stones and kidney dysfunction, and prevent ectopic soft tissue calcium deposition (1,16,17). Given the complexity of post-operative hypoparathyroidism, patients are generally managed by a metabolic bone specialist. Conventional therapy includes calcium supplementation as well as activated vitamin D supplementation (such a calcitriol or an analog similar to it, sometimes in combination). According to guidelines, most patient require at least 1 g of elemental calcium daily, with those forms of calcium including calcium carbonate, calcium citrate and calcium lactate. Calcium citrate is recommended for patients who have impaired gastric acid secretion such as those on proton pump inhibitors. The use of activated vitamin D, or calcitriol [1,25(OH)2D] increases intestinal calcium absorption.

Patients being actively managed for post-operative hypoparathyroidism require close monitoring of calcium and vitamin D levels. According to major guidelines, lab testing should occur at regular intervals, or anywhere from every 3–6 months (17). The ultimate goal is to prevent complications of hypoparathyroidism medical management using calcium and D, such as high levels of calcium in urine, soft tissue calcifications and renal failure. With dosage adjustment, providers must also monitor phosphate and magnesium levels, with initiation of adjunct treatment for any of these electrolyte abnormalities should they arise. The consensus remains that serum calcium levels should be maintained such that the calcium-phosphate product is <55 mg/dL. This is important in order to prevent ectopic soft tissue calcifications in the brain, kidneys and vascular system. Phosphate binders or a low-phosphate diet are generally used when serum phosphate levels are very high. Serum phosphate and magnesium levels should be monitored when thiazide diuretics are used as a first line treatment to prevent or minimize hypercalciuria (17,18).

Long-term management of hypoparathyroidism has turned towards PTH replacement therapy. Emerging treatments in the form of recombinant PTH [1–84] was introduced for hypoparathyroidism that was not adequately controlled with calcium and vitamin D supplementation, approved by the Food and Drug Administration (FDA) in 2015 (19) as Natpara®. PTH [1–84] is given as a subcutaneous injection daily which resulted in improvement in serum calcium for 24 hours in the study (19). Multiple studies assessing this novel therapy, including the most well-known randomized controlled study, REPLACE, demonstrated reduction in calcium and vitamin D supplementation, with patients maintaining normal serum calcium levels (20). The results of studies assessing QOL in patients receiving PTH [1–84] were mixed (21). Unfortunately, the FDA recalled PTH [1–84] in 2019 due to concern for rubber particulate matter within the medication vials so it is currently off the market.

Currently, there is a phase 2 randomized clinical trial investigating a new PTH analog called TransCon PTH for the treatment of hypoparathyroidism. It is a once-daily hormone replacement therapy, replacing PTH over 24 hours (22). TransCon PTH is delivered subcutaneously, and an active PTH is released in a controlled manner (22). Data from the phase two study demonstrated that 82% of TransCon PTH-treated participants at one month, and 91% of those treated with TransCon at over 6 weeks, achieved independence from conventional calcium and vitamin D supplementation, compared with 15% of participants who were in the placebo group. Additionally, there was a statistically significant improvement in 36 Item

Table 3 Complaints of patients with hypoparathyroidism that suggest poor quality of life

Visceral	Neurocognitive	Mood
Pain	Inability to multitask	Depression
Fatigue	Poor memory and concentration	Anxiety
Cramping	Cognitive fog	Personality disorder
Paresthesia	Slow processing	
Seizures		

Health Survey (SF-36) scores as well as its sub-domains regarding QOL, for patients in the treated versus placebo group (23).

Symptoms and end-organ damage of permanent disease

Management goals of permanent hypocalcemia are to maintain calcium and vitamin D levels in order to avoid significant hypocalcemia or hypercalcemia, and decrease the risk of long-term end-organ complications resulting from both the disease as well as treatment. States of neuromuscular excitability and unstable cardiac electrical signaling can affect cardiac rhythm, and are associated with late onset symptoms. Neuropsychiatric symptoms can include cognitive changes, mood changes, lightheadedness, and irritability. Sustained muscle contraction may also lead to laryngospasm, and severe neural excitability may lead to seizures (2).

According to the new 2021 ABSMR guidelines on hypoparathyroidism, a meta-analysis of 81 studies identified that the most common symptoms/complications of chronic hypoparathyroidism were, in descending order, cataract (24%), infection (18%), nephrolithiasis, renal failure, seizures, depression, ischemic heart disease and arrhythmias (14). Hypoparathyroidism is associated with an increased risk of cataracts, with reported prevalence rates of 27–55% based on some studies (24-26). Cataract formation in patients with hypocalcemia appears to have a different pathophysiology than that of age-related cataract formation, namely, that there appears to be an association with chronic hypocalcemia. Papilledema is also a common ophthalmologic finding, and can be reversed with the hypocalcemia is corrected. Renal insufficiency with increased hypercalciuria and kidney stones is secondary to the conventional medical therapy used to treat the hypoparathyroidism, with rates as high as 12–57% (27,28). Calcium and activated vitamin D metabolites lead to increased excretion of calcium into the urine because of the lack of PTH-mediated reabsorption in the kidney (17). Neuropsychiatric sequelae are also prevalent in chronic hypoparathyroidism. Lastly, cardiac sequelae such as dilated cardiomyopathy and arrhythmias occur secondary to prolongation of the corrected QT interval on electrocardiogram, along with prominent U wave and T wave abnormalities (17).

QOL issues with permanent disease

QOL in patients with hypocalcemia is currently measured via general health related quality of life (HRQOL) metrics. These include the widely-used SF-36 (29-31). To date, all studies using SF-36 to qualify the effects of Hypoparathyroidism do not necessarily encompass all of the symptoms reported by patients living with permanent hypoparathyroidism. Symptoms such as cognitive deficits, fatigue, or decreased muscle strength are not part of the current metrics. Moreover, the concurrence of Hypoparathyroidism with hypothyroidism for some of these patients makes it more difficult to assess HRQOL related to Hypoparathyroidism or due to the combination of Hypoparathyroidism and hypothyroidism (32,33). Therefore, further studies are required that quantify the effect of Hypoparathyroidism on patients' QOL using disease-specific questionnaires (34).

The relevant symptoms associated with chronic hypocalcemia span multiple domains of patient reported HRQOL. The SF-36 includes eight domains of health status: physical functioning (10 items); physical role limitations (four items); bodily pain (two items); general health perceptions (five items); energy/vitality (four items); social functioning (two items); emotional role limitations (three items) and mental health (five items). The scoring algorithm incorporates an additive score which is divided out of a 100, where by the worst possible score is zero and 100 is the best possible health (35). While patients may have a variety of different physical and emotional challenges, in a study by Frey *et al.*, patients with permanent hypoparathyroidism had reduced mental and voice scores after thyroid surgery on top of symptoms such as myalgia, joint pain, paresthesia, tetany, anxiety attack, and exhaustion which were the most common (36). Other parameters related to QOL with permanent hypocalcemia are summarized in *Table 3*.

In evaluating post-surgical or iatrogenic

hypoparathyroidism, it is important to consider other aspects of patient resilience and well-being that may contribute to the QOL score for patients which may influence or confound the impact of hypocalcemia. For example, a diagnosis of thyroid cancer has a negative impact on QOL and therefore needs to be considered in patients who may also Hypoparathyroidism (37,38). Many patients with post-surgical hypoparathyroidism have a diagnosis of cancer compared to benign disease (33), an overlap that can challenge causality assumptions. We take a further look into the roles of medical management and physician involvement in QOL parameters for patients with hypoparathyroidism.

Medical management and QOL parameters

It is presently unclear to what degree QOL challenges are a function of the serum calcium level itself, the rate of change in serum calcium compared to pre-surgical levels, and/or the variability in the serum calcium level throughout the day. Post-operative hypoparathyroidism appears to correlate with worse QOL for patients compared to idiopathic forms, suggesting that long-term habituation to low serum calcium level has a significant influence on disease signs and symptoms (34). There is an ongoing debate about whether the lack of PTH—rather than calcium—may have some effect on the presence of symptoms that are detrimental to QOL for patients with hypoparathyroidism.

With the development of PTH replacement as standard of care on the horizon as an alternative to conventional therapy for permanent hypoparathyroidism, many studies have looked at the role of these agents on mental and physical QOL in patients compared to calcium and vitamin D alone. Studies looking at PTH [1–84] and PTH [1–34], respectively, for post-surgical hypoparathyroidism demonstrated an improvement in QOL in patients using SF-36 questionnaires (39). In both studies however, authors correlated PTH replacement directly with improvement in QOL scores, rather than calcium and vitamin D supplementation with improvement in QOL scores. A steady increase in serum calcium along with a reduction of supplemental calcium and calcitriol daily may represent the main reason for both the physical and mental QOL improvements, suggesting that QOL improvement is directly related to less daily medication burden (40). In summary, decreasing the need for supplementation and decreasing fluctuations in serum calcium levels may be the main sources of improved QOL. Additional studies are needed, however, to determine whether PTH replacement versus conventional medical management should motivate the selection of agent in patients with a reduced QOL.

Physician involvement in QOL parameters and treatment

For patients with hypoparathyroidism, there appears to be a disconnect between health care provider perception of hypoparathyroidism as a disease state and the patient experience as an individual living with permanent hypocalcemia. A large web-based survey of 374 patients revealed that healthcare providers often do not clearly understand the QOL issues associated with hypoparathyroidism and that patients feel that they are lacking support (41). In a study comparing surgeon and patient perception of postsurgical hypoparathyroidism, 47% of 340 postsurgical patients with permanent hypoparathyroidism believed that their health was much worse post-operatively compared to before surgery, which was a contrast to the majority of surgeons who believed QOL improved post-operatively for patients (42). Communication between patients and providers with regard to diagnosis and management of post-operative hypoparathyroidism and hypocalcemia warrants improvement. Seventy-nine percent of 374 patients in the PARADOX study strongly agreed that most physicians do not understand hypoparathyroidism (41). One study demonstrated that symptom management in patients with hypocalcemia after surgery was acceptable if patients were given preoperative and post-operative education and assurance in the form of verbal teaching (43). Many patients move through multiple providers until they are satisfied (at most 50%) with their provider. Communication and strong and consistent follow up for patients with hypocalcemia is crucial. Improved informed consent and preoperative education by the health care team may assist in symptom management and QOL improvement for patients with hypocalcemia following thyroid surgery.

Future directions*: *a more accurate measure of patient QOL

There is a current effort to validate hypoparathyroid-specific instruments to assess QOL for patients, many of them in primary stages of evaluation (44-47). A disease-specific measure of the signs and symptoms of hypoparathyroidism, the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom) was developed a few years ago, is currently endorsed by the FDA, but undergoing serial validation studies. This 17-item survey includes symptoms within two domains: physical

and cognitive. Preliminary work identified this survey as potentially valuable not only in assessment of QOL, but also in allowing the assessment of treatment impact, and the risk/benefit ratio of the treatments themselves (45).

Another questionnaire is the 28-item Hypoparathyroid Patient Questionnaire (HPQ 28). The questionnaire qualifies the symptoms surrounding hypoparathyroidism on five scales including pain and cramps; loss of vitality; GI symptoms; depression and anxiety; and neurovegetative complaints (46). Preliminary responses to the questionnaire reflected variation in calcium and vitamin D treatment regimens. The conclusion was that reduced may be caused by one or a combination of the conventional treatment modalities, and overall improvement in QOL is related to less treatments overall (47).

Conclusions

Although normalization of biochemical parameters in patients with hypoparathyroidism is an important goal for post-operative management, the medical community must also address the impact of permanent hypocalcemia on patient QOL. There is much work to be done in identifying those symptoms characteristic of hypoparathyroidism as well as in creating an algorithm for managing the social, functional and emotional effects of having a lack of PTH. Improvement in QOL measurements will help to quantify the scope of the problem and will better guide education, communication and resource generation for patients with permanent disease.

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References

1. Stack BC Jr, Bimston DN, Bodenner DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: Postoperative Hypoparathyroidism--Definitions and Management. Endocr Pract 2015;21:674-85.
2. Orloff LA, Wiseman SM, Bernet VJ, et al. American Thyroid Association Statement on Postoperative Hypoparathyroidism: Diagnosis, Prevention, and Management in Adults. Thyroid 2018;28:830-41.
3. James BC, Aschebrook-Kilfoy B, White MG, et al. Quality of life in thyroid cancer-assessment of physician perceptions. J Surg Res 2018;226:94-9.
4. Edafe O, Antakia R, Laskar N, et al. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg 2014;101:307-20.
5. Cho JN, Park WS, Min SY. Predictors and risk factors of hypoparathyroidism after total thyroidectomy. Int J Surg 2016;34:47-52.
6. Bilezikian JP, Khan A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res 2011;26:2317-37.

7. Güllüoğlu BM, Manukyan MN, Cingi A, et al. Early prediction of normocalcemia after thyroid surgery. World J Surg 2005;29:1288-93.
8. Noureldine SI, Genther DJ, Lopez M, et al. Early predictors of hypocalcemia after total thyroidectomy: an analysis of 304 patients using a short-stay monitoring protocol. JAMA Otolaryngol Head Neck Surg 2014;140:1006-13.
9. Falcone TE, Stein DJ, Jumaily JS, et al. Correlating pre-operative vitamin D status with post-thyroidectomy hypocalcemia. Endocr Pract 2015;21:348-54.
10. Lee DR, Hinson AM, Siegel ER, et al. Comparison of Intraoperative versus Postoperative Parathyroid Hormone Levels to Predict Hypocalcemia Earlier after Total Thyroidectomy. Otolaryngol Head Neck Surg 2015;153:343-9.
11. Hammerstad SS, Norheim I, Paulsen T, et al. Excessive decrease in serum magnesium after total thyroidectomy for Graves' disease is related to development of permanent hypocalcemia. World J Surg 2013;37:369-75.
12. Gupta S, Chaudhary P, Durga CK, et al. 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;18:150-3.
13. Almquist M, Hallgrimsson P, Nordenström E, et al. Prediction of permanent hypoparathyroidism after total thyroidectomy. World J Surg 2014;38:2613-20.
14. Khan AA, Bilezikian JP, Brandi ML, et al. Guidelines on Diagnosis, Evaluation and Management of Hypoparathyroidism: 2021. ASBMR 2021; Abstract LB-1101.
15. Abate EG, Clarke BL. Review of Hypoparathyroidism. Front Endocrinol (Lausanne) 2016;7:172.
16. Bollerslev J, Rejnmark L, Marcocci C, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol 2015;173:G1-20.
17. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. Nat Rev Dis Primers 2017;3:17055.
18. Brandi ML, Bilezikian JP, Shoback D, et al. Management of Hypoparathyroidism: Summary Statement and Guidelines. J Clin Endocrinol Metab 2016;101:2273-83.
19. Sikjaer T, Rejnmark L, Rolighed L, et al. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. J Bone Miner Res 2011;26:2358-70.
20. Mannstadt M, Clarke BL, Vokes T, et al. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol 2013;1:275-83.
21. Rubin MR, Cusano NE, Fan WW, et al. Therapy of Hypoparathyroidism With PTH(1-84): A Prospective Six Year Investigation of Efficacy and Safety. J Clin Endocrinol Metab 2016;101:2742-50.
22. Karpf DB, Pihl S, Mourya S, et al. A Randomized Double-Blind Placebo-Controlled First-In-Human Phase 1 Trial of TransCon PTH in Healthy Adults. J Bone Miner Res 2020;35:1430-40.
23. Khan AA, Rejnmark L, Rubin M, et al. PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism. J Clin Endocrinol Metab 2022;107:e372-85.
24. STEINBERG H, WALDRON BR. Idiopathic hypoparathyroidism; an analysis of fifty-two cases, including the report of a new case. Medicine (Baltimore) 1952;31:133-54.
25. Arlt W, Fremerey C, Callies F, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. Eur J Endocrinol 2002;146:215-22.
26. Saha S, Gantyala SP, Aggarwal S, et al. Long-term outcome of cataract surgery in patients with idiopathic hypoparathyroidism and its relationship with their calcemic status. J Bone Miner Metab 2017;35:405-11.
27. Lienhardt A, Bai M, Lagarde JP, et al. Activating mutations of the calcium-sensing receptor: management of hypocalcemia. J Clin Endocrinol Metab 2001;86:5313-23.
28. Levy I, Licht C, Daneman A, et al. The Impact of Hypoparathyroidism Treatment on the Kidney in Children: Long-Term Retrospective Follow-Up Study. J Clin Endocrinol Metab 2015;100:4106-13.
29. Cusano NE, Rubin MR, McMahon DJ, et al. The effect of PTH(1-84) on quality of life in hypoparathyroidism. J Clin Endocrinol Metab 2013;98:2356-61.
30. Sikjaer T, Rolighed L, Hess A, et al. Effects of PTH(1-84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. Osteoporos Int 2014;25:1717-26.
31. Astor MC, Løvås K, Debowska A, et al. Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. J Clin Endocrinol Metab 2016;101:3045-53.
32. Winer KK. Advances in the treatment of hypoparathyroidism with PTH 1-34. Bone 2019;120:535-41.
33. Sikjaer T, Moser E, Rolighed L, et al. Concurrent

Hypoparathyroidism Is Associated With Impaired Physical Function and Quality of Life in Hypothyroidism. J Bone Miner Res 2016;31:1440-8.
34. Vokes TJ. Quality of Life in Hypoparathyroidism. Endocrinol Metab Clin North Am 2018;47:855-64.
35. Burholt V, Nash P. Short Form 36 (SF-36) Health Survey Questionnaire: normative data for Wales. J Public Health (Oxf) 2011;33:587-603.
36. Frey S, Figueres L, Pattou F, et al. Impact of Permanent Post-thyroidectomy Hypoparathyroidism on Self-evaluation of Quality of Life and Voice: Results From the National QoL-Hypopara Study. Ann Surg 2021;274:851-8.
37. Hoftijzer HC, Heemstra KA, Corssmit EP, et al. Quality of life in cured patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:200-3.
38. Singer S, Lincke T, Gamper E, et al. Quality of life in patients with thyroid cancer compared with the general population. Thyroid 2012;22:117-24.
39. Tabacco G, Tay YD, Cusano NE, et al. Quality of Life in Hypoparathyroidism Improves With rhPTH(1-84) Throughout 8 Years of Therapy. J Clin Endocrinol Metab 2019;104:2748-56.
40. Santonati A, Palermo A, Maddaloni E, et al. PTH(1-34) for Surgical Hypoparathyroidism: A Prospective, Open-Label Investigation of Efficacy and Quality of Life. J Clin Endocrinol Metab 2015;100:3590-7.
41. Hadker N, Egan J, Sanders J, et al. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. Endocr Pract 2014;20:671-9.
42. Cho NL, Moalem J, Chen L, et al. Surgeons and patients disagree on the potential consequences from hypoparathyroidism. Endocr Pract 2014;20:427-46.
43. Doubleday AR, Robbins SE, Macdonald CL, et al. What is the experience of our patients with transient hypoparathyroidism after total thyroidectomy? Surgery 2021;169:70-6.
44. Coles T, Chen K, Nelson L, et al. Psychometric evaluation of the hypoparathyroidism symptom diary. Patient Relat Outcome Meas 2019;10:25-36.
45. Brod M, Waldman LT, Smith A, et al. Assessing the Patient Experience of Hypoparathyroidism Symptoms: Development of the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom). Patient 2020;13:151-62.
46. Wilde D, Wilken L, Stamm B, et al. The HPQ-Development and First Administration of a Questionnaire for Hypoparathyroid Patients. JBMR Plus 2020;4:e10245.
47. Wilde D, Wilken L, Stamm B, et al. Quantification of Symptom Load by a Disease-Specific Questionnaire HPQ 28 and Analysis of Associated Biochemical Parameters in Patients With Postsurgical Hypoparathyroidism. JBMR Plus 2020;4:e10368.

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