Evidence synthesis for guideline development of a rare disease — chronic hypoparathyroidism

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy

McMaster University DOCTOR OF PHILOSOPHY (2023) Hamilton, Ontario (Health Research Methodology)

TITLE: Evidence synthesis for the guideline development of a rare disease — chronic hypoparathyroidism

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NUMBER OF PAGES: VIII, 106

Abstract

Rare diseases currently impact over 250 million people worldwide, accounting for over 3.5% of the global population. Clinicians caring for individuals living with rare diseases face difficulties providing accurate diagnosis and effective treatments. The low prevalence of individual rare diseases, and limited data and constrained resources available for research, makes it challenging to develop useful clinical guidelines.

The objective of this thesis is to share our experience in conducting evidence synthesis for the guideline development of a rare disease—chronic hypoparathyroidism, and show how we addressed the challenges encountered during the review process. The thesis begins by describing the challenges of evidence synthesis for guideline development in the context of rare diseases. I then present our strategies to overcome these challenges in three systematic reviews prepared for a chronic hypoparathyroidism guideline. The thesis ends by summarizing the challenges and solutions, highlighting strengths and limitations, and describing opportunities and challenges for future research in evidence synthesis for rare diseases.

Acknowledgements

It is an honor to express my sincere gratitude to all who have been instrumental in the completion of this PhD thesis.

First and foremost, my profound appreciation goes to my supervisor, Dr. Romina Brignardello-Petersen. Your unwavering support, encouragement, and guidance have been invaluable. Your expertise and insights were indispensable, and your confidence in me served as a continual source of inspiration. Particularly during the COVID-19 pandemic, which brought unprecedented challenges, your flexibility, support, and understanding were deeply valued and facilitated my progress during that difficult time.

I would also like to extend my heartfelt thanks to my advisory committee members, Dr. Gordon Guyatt and Dr. Lehana Thabane. Your constructive feedback and incisive questions were invaluable in molding this research. I am especially grateful for your advice, which has enriched not only my research but also my career.

I would like to extend special thanks to my colleagues and friends at HEI, McMaster University. Your company created an intellectually stimulating and enjoyable environment. The insightful discussions, shared moments over coffee, and unwavering support were indispensable.

To my fellow doctoral candidates, thank you for the camaraderie. The shared journey, with its diverse perspectives and challenges, has been a catalyst for my personal and professional growth.

My family deserves my deepest gratitude. To my parents, thank you for your boundless love, encouragement, and for instilling in me the values of hard work and perseverance. To my wife, Xiaoqin Wang, my heartfelt thanks for being my anchor and for the innumerable sacrifices you made on my behalf. To my little sweety, Emma Yao, your presence has been a source of immeasurable joy and happiness throughout my PhD journey.

Lastly, to all my friends and anyone I might have inadvertently overlooked, your support has been invaluable, and I am eternally grateful. Your contributions, in various forms, have not gone unnoticed and I appreciate them more than words can convey.

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Declaration of Academic Achievement

This is a “sandwich thesis” comprised of five chapters.

Chapter 1 is unpublished. LY is the sole author.

Chapter 2 is published in the Journal of Bone and Mineral Research. AAK, JPB, MM, MLB, BLC, GG conceived the idea; LY, GG, AAK compiled the content. LY drafted the first version of the article; LY, GG, AAK revised for important intellectual content. All authors approved the final version of the article.

Chapter 3 is published in the Journal of Bone and Mineral Research. LY, GHG and AAK conceived the idea; LY, XH, MXL, JL, CL, MK, AS, NM, DT, DSA, KD and KHY collected data; LY, XH, and MXL analyzed the data; LY, GHG and AAK interpreted the results; LY drafted the first version of the article; LY, GHG and AAK revised for important intellectual content. All authors approved the final version of the article.

Chapter 4 is published in the Journal of Bone and Mineral Research. LY, GHG and AAK conceived the idea; LY, JL, MXL, CL, XH, CL, DT, MK, AS, NM, DSA, KD, KHY collected data, LY, JL analyzed the data; LY, GHG and AAK interpreted the results; LY drafted the first version of the article; LY, GHG and AAK revised for important intellectual content. All authors approved the final version of the article.

Chapter 5 is unpublished. LY is the sole author.

Chapter 1: Introduction to This Thesis

In this first chapter of the thesis, I will provide an introduction to the challenge that rare diseases present. I will then describe that one-way authorities are addressing these challenges, is to develop formal guidelines for the diagnosis and management of rare diseases. Subsequently, I will introduce the role of systematic reviews in developing trustworthy guideline for a rare disease, the central theme of this thesis.

After introducing the issue of systematic reviews, I will summarize the methodologic challenges our team faced in producing the guideline and conducting evidence synthesis for a rare disease, chronic hypoparathyroidism, and how the subsequent chapters address these problems. The problems include the limited resources available (the solution described in Chapter 2); defining the outcomes on which the panel should focus (described in Chapter 3 (part 1)); and summarizing evidence when facing insufficient data (our reviews of both diagnosis and therapy addressing this issue in Chapter 3 (part 2) and Chapter 4). Finally, I will present the goals of Chapter 5, related to further reflections on the problems and solution.

I will now turn to summarizing the fundamental issues of rare diseases, the first of which is providing a definition, rare diseases are defined by the European Union as conditions affecting fewer than 1 in 2,000 individuals and by the United States as those affecting fewer than 200,000 Americans. [1,2] Despite their rarity, rare diseases collectively affect a significant number of patients. Currently, International Classification of Diseases (ICD) 11 recognizes over 5500 rare diseases,[3,4] which impact approximately 263-446 million people worldwide, accounting for 3.5–5.9% of the global population. [5] Approximately 80% of rare diseases have a genetic origin, and of those 70% begin in childhood. [4,5]

Individuals living with rare diseases face multiple challenges, the first of which is obtaining an accurate diagnosis. Due to the variability and non-specific nature of symptoms, rare diseases

are frequently misdiagnosed, or diagnosed late. Furthermore, due to the lack of effective treatments, many rare diseases can result in death in infancy or childhood. The U.S. Food and Drug Administration (FDA) has approved treatments for fewer than 10% of rare diseases. [6]

The number of clinical guidelines and systematic reviews related to rare diseases is limited, [7] and varies depending on the country or organization responsible for creating them. Due to the low number of those with each individual disease, limited data and constrained resources available for research, generating comprehensive clinical guidelines for rare diseases is often challenging.

However, many countries and organizations are striving to, by developing clinical guidelines, improve the diagnosis and management of rare diseases. The Orphanet database (https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN), for example, is an international consortium that aims to provide information on rare diseases and orphan drugs, including clinical guidelines. In 2021, the UK government and devolved administrations unveiled the "England Rare Diseases Action Plan," a framework designed to enhance the quality of life for individuals affected by rare diseases. Among the plan's many initiatives is a commitment to provide recommendations based on the best evidence available.

Evidence synthesis is crucial for the development of clinical guidelines and involves defining the PICO (P: Patient; I: Intervention; C: Comparison; O: Outcomes) questions, identifying studies, performing synthesis, rating the certainty of evidence, and integrating findings to draw appropriate conclusions. [7] However, given the limited available data and the complexities associated with understanding the rare diseases, conducting evidence synthesis is particularly challenging in this context.

The purpose of this thesis is to share our experience in conducting evidence synthesis for the guideline development of a rare disease, chronic hypoparathyroidism, and show how we addressed the challenges encountered during the evidence synthesis process.

The initial methodological challenge we confronted when conducting evidence synthesis for the chronic hypoparathyroidism guideline was, when faced with insufficient resources (i.e., limited resources of time, personnel, and money), how to develop recommendations for the entire spectrum of issues of clinical interest. It was only possible to conduct systematic reviews for a small proportion of those conditions. Since standards of trustworthy guidelines include conducting systematic reviews and then rating the certainty of evidence (ideally, in the view of many, using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach [8]), the implication was that most recommendations would not meet trustworthy guideline standards.

Chapter 2 describes how the methods team addressed this challenge, which was to define two very separate sets of recommendations (i.e., GRADEd and non-GRADEd recommendations). Furthermore, in this chapter, I introduced the methodology of evidence synthesis for guideline development of the two rare diseases on which the panel focused: chronic hypoparathyroidism and primary hyperparathyroidism. In this thesis, my primary focus is on chronic hypoparathyroidism.

An additional methodological challenge we met was how to define outcomes on which the panel should focus for a rare disease, specifically in establishing patient-important outcomes. Patients with chronic hypoparathyroidism present with a variety of symptoms, some of which may be due to hypoparathyroidism and some of which may not. Clearly, treatment for hypoparathyroidism

can only impact on the former, the most important of which should represent the focus of relevant randomized trials.

As it turns out, in the context of rare diseases in general, and chronic hypoparathyroidism in particular, differentiating between symptoms due to the disease and those that are not, is not altogether straightforward. Reaching consensus on patient-important outcomes, due to the disease is comparatively simpler for non-rare diseases. In the context of rare diseases in general and chronic hypoparathyroidism in particular, difficulties in understanding what complications and symptoms are causally associated with the rare condition include: 1) the complexity of the presentation of symptoms and complications, which can be influenced by multiple factors such as sex, age, parathyroid surgery, hypophosphatasia, and other comorbidities; [9-12] 2) the existing literature which reports an extensive list of over a hundred symptoms and complications in patients with chronic hypoparathyroidism, only a small proportion of which are likely to be causally related to chronic hypoparathyroidism.[13] Dealing with this issue required innovative methodologic thinking that **Chapter 3** (part 1) describes. In addition to conducting a systematic review, we developed criteria for distinguishing convincingly causal relations from those that were not.

The third significant challenge we tackled was how to mitigate the impact of insufficient data during evidence synthesis, a situation that frequently arises in the context of rare diseases. For example, the scarcity of patients with each particular rare disease often hampers the recruitment process for randomized trials (which are typically included in interventional systematic reviews for non-rare diseases), resulting in a paucity of evidence from such trials. Additionally, in rare diseases, the infrequent occurrence of patient-important outcomes (e.g., major adverse events consequent on the illness) and the prevailing culture among experts to focus on surrogate outcomes, make it challenging to find adequate data on patient-important

outcomes during evidence synthesis. In **Chapter 3** (part 2) and **Chapter 4**, I present an example of conducting a review related to diagnosis, and a systematic review related to management of chronic hypoparathyroidism. We adopted several approaches to maximize the wealth of information available including incorporating randomized studies irrespective of whether they were designed as parallel group, cluster, or crossover randomized studies and regardless of the publication status, and using indirect evidence from surrogate outcomes to infer patient-import outcomes.

Chapter 5 summarizes the methodology challenges in producing recommendations and conducting evidence synthesis for a particular rare disease present in Chapter 2 to 4, and discusses the strategies employed to address these challenges. Furthermore, Chapter 5 highlights strengths and limitations and reflects on opportunities and challenges for future evidence synthesis in the guideline development for rare diseases.

References

1. Global Genes. Rare Disease Facts and Figures 2021 [cited by 2023 April 10]. Retrieved from: https://globalgenes.org/rare-disease-facts/
2. EURORDIS. What is a rare disease? 2021 [cited by 2023 April 10]. Retrieved from https://www.eurordis.org/content/what-rare-disease
3. Aymé S, Bellet B, Rath A. Rare diseases in ICD11: making rare diseases visible in health information systems through appropriate coding. Orphanet J Rare Dis. 2015, 26;10:35.
4. The Lancet Diabetes Endocrinology. Rare diseases: individually rare, collectively common. Lancet Diabetes Endocrinol. 2023;11(3):139.
5. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, Murphy D, Le Cam Y, Rath A. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28(2):165-173.
6. FDA. Rare Disease Cures Accelerator 2023 [cited by 2023 April 10]. Retrieved from https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator
7. Pavan S, Rommel K, Mateo Marquina ME, Höhn S, Lanneau V, Rath A. Clinical Practice Guidelines for Rare Diseases: The Orphanet Database. PLoS One. 2017 Jan 18;12(1):e0170365.
8. Guyatt G H, Oxman A D, Vist G E, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. bmj, 2008, 336(7650): 924-926.
9. Clarke BL. Epidemiology and Complications of Hypoparathyroidism. Endocrinology and Metabolism Clinics of North America 2018;47(4):771-82.
10. Bilezikian JP, Khan A, Potts JT Jr, Brandi ML, Clarke BL, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res. 2011 Oct;26(10):2317-37.

11. Pasieka JL, Wentworth K, Yeo CT, Cremers S, Dempster D, et al. Etiology and Pathophysiology of Hypoparathyroidism: A Narrative Review. J Bone Miner Res. 2022;37(12):2586-2601.
12. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1-20.
13. Yao L, Hui X, Li M, Li J, Ahmed MM, et al. Complications, Symptoms, Presurgical Predictors in Patients With Chronic Hypoparathyroidism: A Systematic Review. J Bone Miner Res. 2022;37(12):2642-2653.

Chapter 2: Methodology for the Guidelines on Evaluation and Management of Hypoparathyroidism

ORIGINAL ARTICLE

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Methodology for the Guidelines on Evaluation and Management of Hypoparathyroidism and Primary Hyperparathyroidism

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ABSTRACT

To develop guidelines for hypoparathyroidism and primary hyperparathyroidism, the panel assembled a panel of experts in parathyroid disorders, general endocrinologists, representatives of the Hypoparathyroidism Association, and systematic review and guideline methodologists. The guideline panel referred to a formal process following the Recommendations, Assessment, Development, and Evaluation Working Group (GRADE) methodology to issue GRADEd recommendations. In this approach, panelists and methodologists formatted the questions, conducted systematic reviews, evaluated risk of bias, assessed certainty of evidence, and presented a summary of findings in a transparent fashion. For most recommendations, the task forces used a less structured approach largely based on narrative reviews to issue non-GRADEd recommendations. The panel issued Eight GRADEd recommendations (seven for hypoparathyroidism and one for hyperparathyroidism). Each GRADEd recommendation is linked to the underlying body of evidence and judgments regarding the certainty of evidence and strength of recommendations, values and preferences, and costs, feasibility, acceptability and equity. This article summarizes the methodology for issuing GRADEd and non-GRADEd recommendations for patients with hypoparathyroidism or hyperparathyroidism. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: THERAPEUTICS; HORMONE REPLACEMENT/RECEPTOR MODULATORS; EPIDEMIOLOGY; HEALTH SERVICES RESEARCH; DISORDERS OF CALCIUM/PHOSPHATE METABOLISM; PARATHYROID-RELATED DISORDERS

This article describes the methodology used for the development of hypoparathyroidism and primary hyperparathyroidism guidelines. In this series of articles summarizing the efforts of an international group of experts in hypoparathyroidism and primary hyperparathyroidism, the authors conducted systematic reviews of a small number of selected questions and narrative reviews for other questions. Ultimately, the panel produced two types of recommendations, GRADEd (from Recommendations, Assessment, Development, and Evaluation Working Group [GRADE]) and non-GRADEd, corresponding for the most part to issues for which systematic reviews were or were not undertaken. In this article, we describe the key elements of the methods the task forces used in developing their guidelines for hypoparathyroidism and primary hyperparathyroidism.

Composition, Selection, and Function of Guideline Task Forces

Six endocrinologists (JPB, MB, BLC, AAK, MM, JTP) made up the guideline steering committee. The honorary chair of the steering committee was John T. Potts. The cochairs of the steering committee were John P. Bilezikian and Aliya A. Khan. The steering committee met regularly and oversaw the entire guideline development

Received in original form July 22, 2022; revised form August 17, 2022; accepted August 24, 2022.
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Journal of Bone and Mineral Research, Vol. 37, No. 11, November 2022, pp 2404–2410.
DOI: 10.1002/jbmr.4687

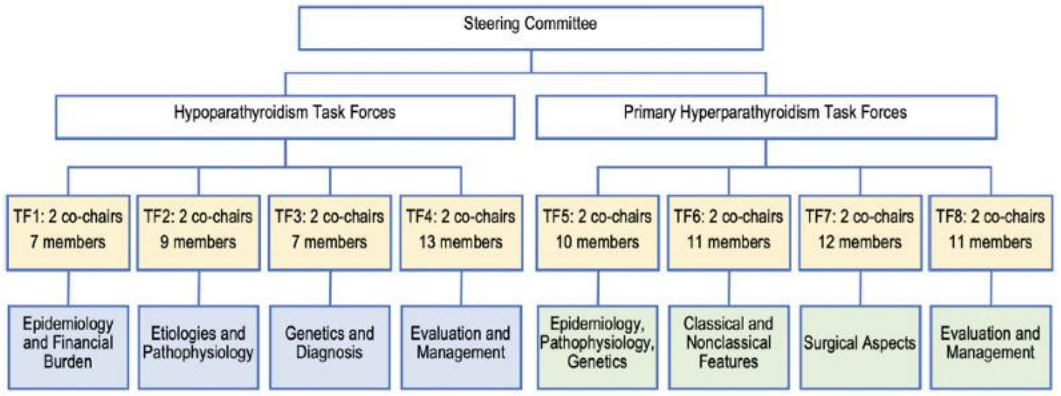

Fig. 1. Composition of guideline task forces.

process. The steering committee invited 11 endocrinologists to join them as cochairs, forming two task force groups, one for hypoparathyroidism (led by AAK) and the other for primary hyperparathyroidism (led by JPB). Each of these two task force groups consisted of four individual task forces (Fig. 1).

The task forces included specialists with expertise in parathyroid disease: endocrinologists, nephrologists, pathologists, epidemiologists, radiologists, pharmacologists, endocrine surgeons, and general endocrinologists. The steering committee selected task force members on the basis of their expertise and publications in the field with consideration given to international geographic representation. The steering committee gave equal preference to men and women. The Hypoparathyroidism Association was represented by two individuals. Fig. 1 describes the structure of the steering committee and the eight task forces.

The steering committee invited participation from methodologists from McMaster University with expertise in developing guidelines using the GRADE approach.[1,2] The full composition of the task forces included 93 experts in parathyroid disorders, four general endocrinologists, three methodologists, and two representatives of the Hypoparathyroidism Association. Seventeen countries and 45 institutions were represented. Industry employees were excluded.

All eight task forces held individual meetings on a regular basis to review the evidence, develop recommendations, and achieve consensus. Separate meetings were held regularly with the task force cochairs to guide and review the progress of the eight teams. The steering committee also met regularly to oversee the entire guideline development process.

Guideline Process

Each of the eight task forces focused on different aspects of the two diseases and developed a review paper. This series includes the four task force reviews on hypoparathyroidism and four task force reviews on primary hyperparathyroidism. In addition to the four reviews, the hypoparathyroidism task forces undertook four systematic reviews along with one survey evaluating monitoring practice for hypoparathyroidism. In addition to the four reviews, the primary hyperparathyroidism task forces undertook one systematic review. In total, five systematic reviews were completed and are published as part of this series. The cumulative repository of information from the aforementioned reviews were consolidated into two summary statement guideline papers: one for hypoparathyroidism and one for primary hyperparathyroidism. Those summary statements are also part of this series.

Recommendations of the Two Summary Statement Guidelines Papers

The guideline panel conducted systematic reviews for selected critical questions on hypoparathyroidism and primary hyperparathyroidism (Table 1) and issued a total of eight GRADEd recommendations (seven for hypoparathyroidism and one for hyperparathyroidism) based on one of the reviews related to primary hyperparathyroidism and four reviews and one survey related to hypoparathyroidism. The guideline panel also issued 59 non-GRADEd recommendations (20 for hypoparathyroidism and 39 for hyperparathyroidism) based on narrative reviews, which were labeled non-GRADEd recommendations.

GRADEd recommendations

GRADEd recommendations followed a structured process that we will describe in detail.[3,4]

Non-GRADEd recommendations

Non-GRADEd recommendations involved less structured approaches without formal specification of PICOs (P: Patient population, I: Intervention, C: Comparator group, O: Outcome), included conduct of traditional expert narrative literature reviews rather than systematic review approaches, and did not include tables summarizing the findings. Readers should interpret these non-GRADEd recommendations as they would other recommendations based on traditional approaches to guideline development.

Table 1. List of PICO/PECO Questions Used for GRADEd Recommendations

General questions	PICO/PECO format questions
1. In patients with chronic hypoparathyroidism, what are the symptoms and complications? This question did not directly inform a recommendation.	P: People with and without hypoparathyroidism, including both postsurgical and nonsurgical E (Exposure): Hypoparathyroidism C: People with normal parathyroid function O: Outcome or impact of hypoparathyroidism
2. In patients with chronic hypoparathyroidism, what are the desirable and undesirable consequences of PTH therapy versus conventional therapy?	P: Hypoparathyroidism from any cause (subgroups of postsurgical versus nonsurgical) I: PTH supplement therapy C: Conventional therapy (calcium, calcitriol, or alfa calcidol) O: Patient-important outcomes: nephrolithiasis, renal insufficiency, cataract, seizures, arrhythmia, ischemic heart disease, depression, infection, mortality, quality of life; surrogate outcomes: serum calcium, urine calcium, phosphate.
3. In patients with chronic hypoparathyroidism, what are the desirable and undesirable consequences of using different monitoring strategies?	P: Patients with chronic hypoparathyroidism I: More frequent monitoring with variety of tests C: Less frequent monitoring, with same or different tests O: Patient-important outcomes: nephrolithiasis, renal insufficiency, cataract, seizures, arrhythmia, ischemic heart disease, depression, infection, mortality, quality of life; surrogate outcomes: serum calcium, urine calcium, phosphate.
4. In patients undergoing total thyroidectomy, what is the value of measuring PTH or calcium shortly after surgery to predict the development of chronic hypoparathyroidism?	P: Patients that underwent total thyroidectomy I/C: Measuring early PTH or calcium levels within 12 or 24 hours after surgery O: Chronic hypoparathyroidism as defined by investigators 6 months or 1 year after surgery
5. In patients with asymptomatic primary hyperparathyroidism, what are the desirable and undesirable consequences of surgery versus nonsurgical management?	P: Patients with asymptomatic primary hyperparathyroidism I: Surgery with or without medical therapies C: No surgery with or without medical therapies O: Patient-important outcomes: Biochemical cure, fracture, kidney stones and renal failure, quality of life, mortality, surgical complications, cardiovascular events, cerebrovascular complications. Surrogate outcomes: Fractures as inferred from bone mineral density, biochemical cure as inferred from serum calcium, serum PTH, 24-hour urinary calcium excretion, serum creatinine and estimated glomerular filtration rate, systolic blood pressure or diastolic blood pressure, left ventricular mass index and ejection fraction.

Structured Questions—GRADEd Recommendations

Evidence review

A methods team led by GG, LY, and ZY, with substantial input from expert task force members, led the five systematic reviews. The reports of these systematic reviews, included as four separate articles in this series, provide all relevant details.

Defining the clinical questions

The steering committee defined the scope of the guidelines. Each task force took primary responsibility for proposing important clinical questions for systematic review. Five questions, four for hypoparathyroidism and one for primary hyperparathyroidism, were chosen. They were subjected to a structured process that included defining the relevant population, alternative management strategies (intervention/exposure and comparator), and outcomes (i.e., PICO/PECO (P: Patient population, E: Exposure, C: Comparator group, O: Outcome) format) (Table 1). Each clinical question provided the framework for formulating inclusion and exclusion criteria for systematic reviews and guided the search for relevant evidence.

Patient-important and surrogate outcomes

For GRADEd recommenadtions, the panel focused on outcomes that patients considered important rather than surrogate outcomes (e.g., fractures rather than bone density, renal stones rather than 24-hour urinary calcium excretion). In the hypoparathyroidism guideline, the panel focused on outcomes suggested, in the relevant systematic review, to be clearly causally related to hypoparathyroidism.

Identifying the literature

For each PICO/PECO question, the methods team searched Medline, EMBASE, and the Cochrane library. Paired reviewers independently screened the titles and abstracts retrieved from databases and further reviewed the full-text articles for eligibility

and resolved conflicts and disagreements by discussion. Searching the reference lists of publications of primary studies and relevant narrative reviews and guidelines provided another strategy for identifying additional references.

Assessing studies, summarizing evidence, and evaluating eligibility and risk of bias

Given the different types of questions addressed in the systematic reviews, eligibility differed: case series and cohort studies for the review of complications, diagnostic accuracy studies for the diagnostic review, and randomized trials for the comparisons between conventional therapy and PTH therapy of hypoparathyroidism, for comparisons between medical therapy and no medical therapy in primary hyperparathyroidism and for comparisons between surgery and no surgery for primary hyperparathyroidism. To assess the risk of bias of the different types of studies, the methodology team used the National Institutes of Health (NIH) Quality Assessment Tool for case series studies,[5] a modification of Newcastle-Ottawa Scale (NOS) for cohort studies,[6] a modified Cochrane risk-of-bias tool for randomized control trials,[7,8] and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for diagnostic accuracy studies.[9] Two reviewers independently rated the risk of bias, and a third senior reviewer resolved disagreements.

Evaluating certainty of bodies of evidence

For therapeutic and diagnostic systematic reviews, the methods team rated the certainty of evidence on an outcome-by-outcome basis using GRADE Working Group criteria (Fig. 2). When the certainty of evidence differed across outcomes, the methods team made an overall rating as the lowest certainty rating of the outcomes judged as critical.[3]

Defining subgroup analysis and assessing credibility

In each systematic review, the task force members defined possible subgroup analyses, including hypothesized direction of subgroup effects. To assess the credibility of subgroup effects, the methods team used the Credibility of Effect Modification Analyses (ICEMAN) criteria, a structured checklist consisting of nine items addressing design, analysis, and context of subgroup analysis.[10]

Conducting meta-analyses

We were unable to perform meta-analyses for two reviews: the complications review (first PICO in Table 1, the extremely diverse studies made it difficult to justify a meta-analysis to determine prevalence) and the monitoring review (third PICO in Table 1, only two studies described the monitoring frequency).

We performed meta-analyses for the other three reviews. We used bivariate analysis to calculate the pooled estimates of sensitivity, specificity for the predicting review (fourth PICO in Table 1). The other two reviews addressed management issues; the methods team used a random-effects model for all primary analyses. Chi-squared tests and I^2 statistics provided methods for assessing statistical heterogeneity.

Summary-of-findings tables

For GRADEd recommendations addressing therapeutic or diagnostic issues (recommendations based on systematic reviews), we summarized the certainty of evidence and estimates of relative and absolute effects of alternative management strategies in summary-of-findings tables.[11,12]

Recommendation direction and strength

GRADEd recommendations followed a structured process to classify recommendations as strong or weak.[11,12] Determinants of the strength and direction of recommendations included the balance between the desirable and undesirable consequences of an intervention, the certainty of evidence, patient values and preferences, and issues of feasibility, acceptability, and equity. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "We recommend." Recommendations were graded as weak either because of low certainty evidence or a close balance between desirable and undesirable outcomes and were worded as "We suggest."

Conducting a Survey Addressing Monitoring in Hypoparathyroidism

The methods team found very limited discussion in the systematic review addressing monitoring in hypoparathyroidism, so Task Force 4, in consultation with the methods team, designed a survey to evaluate the practice of the international experts who constituted the task forces on hypoparathyroidism. Respondents reported how frequently they assessed a wide variety of variables, including calcium, phosphorus, and magnesium levels. The task force identified a test as useful if a minimum of 70% of respondents used the test in >70% of their patients. Based on the survey, the panel issued three GRADEd recommendations. One of the papers in this series describes in detail the methods and results of the survey.[13]

Values and Preferences

The task force members considered patients' values and preferences in all recommendations. Patient partners provided formal input to two task force cochairs (AAK and LR), who ensured the panel considered their input. Important judgments included (i) patient important outcomes over surrogate outcomes and (ii) a higher value on comprehensive assessment and detecting possible problems than on parsimonious use of tests that might minimize costs, concern, and possibly unnecessary interventions.

Costs, Feasibility, Acceptability, Equity

Because cost issues were unlikely to change the direction or strength of the recommendations, the task forces did not conduct economic evaluations to consider resource use. In making their recommendations, the panel considered feasibility, equity for all patient populations including the pediatric and elderly patient populations, and practical issues.

Finalizing the Recommendations

For both GRADEd and non-GRADEd recommendations, the intent, successfully implemented, was to achieve consensus on all recommendations. There was no provision for voting. Chairs of each task force formulated the draft recommendations and scheduled discussions with all task force members to reach consensus. For GRADEd recommendations, the task forces reached

Study Design	Confidence in estimates	Lower if	Higher if
Randomized trials	High	Risk of bias −1 Serious −2 Very serious	Large effect + 1 Large + 1 Very large
	Moderate	Inconsistency −1 Serious −2 Very serious	Dose response +1 Evidence of a gradient
Observational studies	Low	Indirectness −1 Serious −2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or +1 would suggest a spurious effect when results show no effect
	Very Low	Imprecision −1 Serious −2 Very serious Publication bias −1 Likely −2 Very likely	

Fig. 2. GRADE approach for rating the certainty of evidence.

consensus on the wording of recommendations, the level on the certainty of evidence, and the direction and strength of recommendations; for non-GRADEd recommendations, the task forces reached agreement on expert practice.

Disclosing and Managing Conflicts of Interest

The individual disclosures of the steering committee and task force members are provided in papers in which they serve as coauthors. All panelists identified industry consultancies and advisory board memberships. Those who disclosed consultancies were not excluded. There was no other management of conflict of interest. The supplementary material includes the conflict-of-interest form that task force members completed. The following companies provided unrestricted educational support for the guideline process: Amolyt, Ascendis, Calcilytix, and Takeda. Although the companies were invited to attend the open sessions, they were not invited to make comments. The companies had no input into the design, leadership selection, task force membership, methods group constitution, implementation, conclusions, or the writing or review of manuscripts. The funds received were budgeted for methodology, knowledge translation, publication charges, young fellows' travel grants, meetings, and administrative costs. All members of the steering committee, cochairs, and task force members

served on a voluntary basis and did not receive any financial compensation.

Internal and External Presentations

The recommendations were presented to members of all task forces in two separate sessions: one for hypoparathyroidism and one for primary hyperparathyroidism. The steering committee and task force chairs considered all comments offered at the time of the presentations. In addition, all task force members had the opportunity to comment on and edit the draft manuscripts, including systematic reviews, narrative reviews, and guideline documents, in order to provide any clarification required. The recommendations did not require any modification following the presentations and feedback received by the attendees.

The recommendations were also presented to all societies, organizations, and patient advocacy groups that expressed interest in supporting these guidelines. The two summary-guideline papers were then distributed to all groups with invitation for comment and approval. All comments were considered by the steering committee and task force chairs. The groups that approved the guidelines emanating from this project are listed in the two summary statements. All guideline manuscripts, including this one, were submitted to the *Journal of Bone and Mineral Research*, where they underwent peer review. The peer review process will not result in any modification to the recommendations.

Limitations

The panel commissioned five systematic reviews to address particularly important and potentially controversial questions, two of which directly addressed management issues. Thus, the guidelines included a small number of GRADEd recommendations (one for hyperparathyroidism, seven for hypoparathyroidism). Recommendations regarding monitoring informed by the panel survey are also graded, but all are weak recommendations because they were based on very low-certainty evidence. For the remaining questions, the task forces issued 59 non-GRADEd recommendations (20 for hypoparathyroidism and 39 for hyperparathyroidism) based on narrative reviews. Though not graded or formalized by the process of a systematic review, those narrative reviews, nevertheless, were also based upon a careful review of the literature by the task force members.

Management of financial conflict of interest was restricted to exclusion of industry employees, declaration of financial conflicts by panelists, and declaration of funding for the guideline effort from pharmaceutical companies. Neither individual panel declarations nor funding for the guideline provided any indication of the magnitude of support. The panel did not consider nonfinancial conflicts of interest.

Plans for Updating

We plan to update the recommendations when important new data that will impact the recommendations become available.

Disclosures of Interests

AAK—Grants or speaker for Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx; consultant for Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx.

JPB—Consultant for Amgen, Radius, Ascendis, Calcilytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, Ipsen.

MLB has received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB; grants or speaker: Abiogen, Alexion, Amgen, Bruno Farmaceutici, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex, UCB; consultant: Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB.

BLC—Consultant for Takeda/Shire, Amolyt Pharma, Calcilytix; grants from Takeda/Shire, Ascendis.

MM—Consultant for Takeda, Amolyt, and Chugai; grants from Takeda and Chugai.

Acknowledgments

We acknowledge unrestricted financial support from Amolyt, Ascendis, Calcilytix, and Takeda. They had no input into the planning or design of the project, the conduct of the reviews, evaluation of the data, writing or review of the manuscript, its content, conclusions, or recommendations contained herein.

Author Contributions

Design/conceptualization of project: AAK, JPB, MM, MLB, BLC, GG. Data acquisition, review, analysis, methodology: LY, ZKY, GG, AAK, JPB. Project administration, including acquisition of funding: AAK, JPB, MM, MLB, BLC. Original drafting and preparation of manuscript: LY, GG. Review/editing of manuscript: LY, GG, AAK.

Ethical Statement

The study described the methods of guideline development and did not require ethics committee approval.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4687.

Data Availability Statement

This method study included no data.

References

1. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-406.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926.
3. Andrews J, Guyatt GH, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-725.
4. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a

recommendation's direction and strength. J Clin Epidemiol. 2013; 66(7):726-735.

5. National Heart L, and Blood Institute. Study Quality Assessment Tools. http://www.nhlbi.nih.gov/health-topics/study-qualityassessment-tools. 2020. Accessed Nov 16, 2020.
6. Guyatt G, Busse. J. Commentary: Risk of Bias in Cohort Studies. https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-in-cohort-studies/. 2011. Accessed Nov 10, 2020.
7. Guyatt G, Busse. J. Commentary: Risk of Bias in Randomized control trials. https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-in-cohort-studies/. 2011. Accessed Nov 10, 2020.
8. Higgins JPAD, Sterne JA, on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group, eds. Chapter 8: Assessing risk of bias in included studies. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017)*. Hamilton: Cochrane; 2017.
9. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-536.
10. Schandelmaier S, Briel M, Varadhan R, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. Can Med Assoc J. 2020;192(32):E901-E906.
11. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-172.
12. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol. 2013;66(2):173-183.
13. Van Uum S, Shrayyef M, M'Hiri I, et al. Initial assessment and monitoring of patients with chronic hypoparathyroidism: a systematic current practice survey. J Bone Med Res. 2022.

Chapter 3: Complications, Symptoms, Presurgical Predictors in Patients with Chronic Hypoparathyroidism: A Systematic Review

TASK FORCE

JBMR®

Complications, Symptoms, Presurgical Predictors in Patients With Chronic Hypoparathyroidism: A Systematic Review

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ABSTRACT

The complications and symptoms of hypoparathyroidism remain incompletely defined. Measuring serum parathyroid hormone (PTH) and calcium levels early after total thyroidectomy may predict the development of chronic hypoparathyroidism. The study aimed (i) to identify symptoms and complications associated with chronic hypoparathyroidism and determine the prevalence of those symptoms and complications (Part I), and (ii) to examine the utility of early postoperative measurements of PTH and calcium in predicting chronic hypoparathyroidism (Part II). We searched Medline, Medline In-Process, EMBASE, and Cochrane CENTRAL to identify complications and symptoms associated with chronic hypoparathyroidism. We used two predefined criteria (at least three studies reported the complication and symptom and had statistically significantly greater pooled relative estimates). To estimate prevalence, we used the median and interquartile range (IQR) of the studies reporting complications and symptoms. For testing the predictive values of early postoperative measurements of PTH and calcium, we used a bivariate model to perform diagnostic test meta-analysis. In Part I, the 93 eligible studies enrolled a total of 18,973 patients and reported on 170 complications and symptoms. We identified nine most common complications or symptoms probably associated with chronic hypoparathyroidism. The complications or symptoms and the prevalence are as follows: nephrocalcinosis/nephrolithiasis (median prevalence among all studies 15%), renal insufficiency (12%), cataract (17%), seizures (11%), arrhythmia (7%), ischemic heart disease (7%), depression (9%), infection (11%), and all-cause mortality (6%). In Part II, 18 studies with 4325 patients proved eligible. For PTH measurement, regarding the posttest probability, PTH values above 10 pg/mL 12–24 hours postsurgery virtually exclude chronic hypoparathyroidism irrespective of pretest probability (100%). When PTH values are below 10 pg/mL, posttest probabilities range from 3% to 64%. Nine complications and symptoms are probably associated with chronic hypoparathyroidism. A PTH value above a threshold of 10 pg/mL 12–24 hours after total thyroidectomy is a strong predictor that the patients will not develop chronic hypoparathyroidism. Patients with PTH values below the threshold need careful monitoring as some will develop chronic hypoparathyroidism. © 2022 American Society for Bone and Mineral Research (ASBMR).

Received in original form February 7, 2022; revised form July 22, 2022; accepted August 8, 2022.
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Additional Supporting Information may be found in the online version of this article.
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Journal of Bone and Mineral Research, Vol. 37, No. 12, December 2022, pp 2642–2653.
DOI: 10.1002/jbmr.4673

KEY WORDS: HYPOPARATHYROIDISM; PARATHYROID-RELATED DISORDERS; DISORDERS OF CALCIUM/PHOSPHATE METABOLISM; EPIDEMIOLOGY; HUMAN; GENETIC RESEARCH; ASSOCIATION STUDIES

Introduction

Chronic hypoparathyroidism is a rare endocrine disorder with an estimated prevalence of 37 per 100,000 person-years in the United States and of 22 per 100,000 person-years in Denmark.[1] It is characterized by low albumin-adjusted serum calcium in the presence of a low or inappropriately normal parathyroid hormone (PTH) level. Serum phosphorus may be normal or elevated. Total thyroidectomy is the most frequent cause of hypoparathyroidism. Most patients with postoperative hypoparathyroidism experience transient disease and recover within 6–12 months; 2%–10% will, however, develop chronic hypoparathyroidism and require long-term calcium and/or active vitamin D treatment.[2]

Given the low prevalence of chronic hypoparathyroidism, many questions of disease burden, early diagnosis, and optimal treatment and monitoring remain unanswered. Existing studies addressing these questions were often limited to small samples. In this study, we have used systematic reviews methods to address two essential questions.

Part I (complication and symptoms) aims to identify symptoms and complications associated with chronic hypoparathyroidism and determine the prevalence of those symptoms and complications. Part II aims to test the predictive value of using early PTH and calcium measurements to predict chronic hypoparathyroidism after total thyroidectomy. Owing to the significant variation that exists among studies regarding the timing of measurement, PTH/calcium thresholds, and the accuracy of these tests to predict permanent hypoparathyroidism, remain uncertain.

Methods

Protocol

We separately registered the two reviews in PROSPERO, with the registration number of Part I: CRD42021230757 and Part II: CRD42021236344.

Data sources

We searched PubMed, Embase, and Cochrane CENTRAL from inception to June 1, 2022. For Part I, we used the following keywords: hypoparathyroidism, hypocalcaemia, hypocal*, HypoPT, complications, symptoms (see details in Appendix S1). For Part II, we searched: "thyroidectomy," "parathyroid hormone/PTH" and "hypoparathyroidism" (see details in Appendix S2). The search was limited to human participants and used MeSH terms in various combinations to increase search sensitivity. Searching the reference lists of publications of primary studies, relevant narrative reviews, and guidelines provided another strategy for identifying additional references.

Study selection

Paired reviewers independently screened the studies in two stages: (i) title and abstract and (ii) full text. On retrieval of candidate abstracts, two reviewers evaluated each full-text publication for eligibility, resolving conflicts by discussion.

In Part I, we included studies reporting on the symptoms or complications of chronic hypoparathyroidism and their prevalence that were published in English. We categorized eligible studies as cohort studies (addressing patients with chronic hypoparathyroidism and people with normal parathyroid function) and single-arm studies (only addressing patients with chronic hypoparathyroidism, such as randomized controlled trials or case series). The following studies were excluded: (i) duplicate publications, reviews, or editorials; (ii) had more than 20% of patients with non-chronic hypoparathyroidism; and (iii) reported on fewer than 10 patients.

In Part II, eligible studies included patients who had undergone total thyroidectomy and had PTH/calcium levels performed within 7 days, examined the utility of PTH/calcium levels during or after total thyroidectomy, and were published in English. Studies were excluded if (i) more than 20% of patients underwent an operation other than total thyroidectomy; (ii) they were review articles, single-case articles, editorials, or letters; (iii) they examined only transient hypoparathyroidism as defined by the study.

Data extraction

In Part I, paired reviewers, using a standardized form, independently extracted data including author; year; study design; country; patient demographics; the number of patients in exposure and comparator (if there is one); diagnosis and duration of hypoparathyroidism; and incidence rate of complications or symptoms, including relative estimates and absolute estimates.

In Part II, for each included article, team members abstracted the following information: authors, year, patients source, number of patients, study design, sex, demographic data, final pathology, description of laboratory evaluations that each study deemed the best (cutoff levels for serum PTH and calcium, frequency and timing of evaluation), type of assay used, threshold and dose for calcium and/or active vitamin D treatment, all reported study outcomes, additional key findings, and notable study limitations. In studies in which investigators studied multiple thresholds and timing of PTH or calcium measurements, abstractors chose the measurement with the highest sensitivity and specificity corresponding to the maximum area under curve (AUC) value. For each study, we extracted or calculated the true positive, false positive, false negative, and true negative values.

Risk of bias assessment

In Part I, we used the National Institutes of Health (NIH) Quality Assessment Tool for single-arm studies[3] and a modification of Newcastle-Ottawa Scale (NOS) for cohort studies (those with a comparator of people with normal parathyroid function).[4,5] The NIH instrument poses nine questions and rates studies as low risk of bias if they meet seven to nine criteria, moderate risk of bias if they meet four to six criteria, and high risk of bias if they meet zero to three criteria. The modified NOS poses eight questions and rates the studies as low risk of bias if they meet seven to eight criteria, moderate risk of bias if they meet five to six criteria and low risk of bias if they meet fewer than five criteria.

In Part II, to assess the risk of bias, we used the QUADAS-2 scale (https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/), which assigns ratings based on four

key domains: patient selection; interpretation of index test; reference standard; the flow of patients through the study; and timing of the index test(s) and reference standards.[6] Each domain includes an assessment of the risk of bias, and the first three domains include an assessment of applicability.

Subgroup analysis

In Part I, considering that the etiology of chronic hypoparathyroidism differs across populations, we present the prevalence by different subgroups, including studies focusing on postsurgical adult patients (with >80% surgical adult patients), nonsurgical adult patients (with >80% nonsurgical adult patients), and children (with >80% population aged <18 years).

In Part II, we planned subgroup analyses to determine whether the following factors explained variation in the predictive performance of PTH and calcium: (i) PTH/calcium thresholds (PTH ≤ 10 pg/mL versus 10–15 pg/mL; calcium ≤ 1 mmol/L versus 1–2 mmol/L), anticipating the lower versus higher thresholds would result in higher specificity but lower sensitivity; (ii) timing of determination of chronic hypoparathyroidism (6 months versus 12 months), anticipating the longer duration would lead to higher sensitivity but lower specificity; (iii) timing of PTH/calcium measurement (≤12 versus 12–24 hours postoperative), anticipating the earlier measurement of PTH/calcium would result in the higher sensitivity but lower specificity. We restricted subgroup analyses to studies in which three or more studies existed for each subgroup. When this was the case, we compared sensitivity and specificity between these subgroups and explored the subgroup modification using Z test. We considered $p < 0.05$ as a significant difference between groups.

Data synthesis

In Part I, given not all the complications or symptoms reported by the included studies are truly associated with chronic hypoparathyroidism, to identify if complications and symptoms were associated with chronic hypoparathyroidism, we developed the following two criteria: (i) were reported by at least three studies, and (ii) had a statistically significantly greater pooled relative estimate in comparison to individuals with normal parathyroid function.

We used hazard ratios (HRs) or odds ratios (ORs) and 95% confidence intervals (CIs) to represent the association of complications or symptoms in studies comparing the frequency in patients with chronic hypoparathyroidism to individuals with normal parathyroid function. To minimize small study effects, we used the fixed-effect model to pool HRs/ORs and 95% CI through the inverse variance weighted method.

To determine the prevalence of complications and symptoms associated with chronic hypoparathyroidism, we included all patients from both single-arms studies and the cohort studies (case group). We described the median and interquartile range (IQR) for the complications and symptoms.

The following modifications were made to the planned data analysis in the protocol: (i) the complications and symptoms attributed to chronic hypoparathyroidism had to meet the two criteria described previously; (ii) as the studies were extremely diverse in sources of data (database data or clinical data) and population characteristics (adult or pediatric; surgical or nonsurgical patients; and comorbidities), it was difficult to justify a meta-analysis to determine prevalence. We, therefore, described the median, and IQR for all studies.

In Part II, we summarized the PTH and calcium characteristics by grouping them into categories of PTH (≤10, 10–15 pg/mL; change of >50% and change of ≤50%) and calcium (≤1, 1–2 mmol/L) thresholds, and timing of PTH/calcium measurement (intraoperative, 1–12 hours, 12–24 hours postoperative).

Table 1. Patients' Demographics and Study Characteristics in Part I

Demographics and characteristics	Number of patients (% or interquartile range)
Patients with chronic hypoparathyroidism ($n = 18,973$)	
Mean age (years), median (IQR)	48 (38, 51)
Female sex (%), median (IQR)	76 (62, 85)
Mean duration (years), median (IQR)	10 (7, 14)
Year	
<2000	51 (0)
2000–2005	103 (1)
2006–2010	219 (1)
2011–2015	2102 (11)
2016–2020	4652 (25)
2021–2022	11,846 (62)
Geographic area	
North America	10,088 (53)
Asia	3271 (17)
Europe	4250 (22)
South America	536 (3)
Africa	12 (0)
Oceania	20 (0)
Not specified	796 (4)
Design	
Single arm	8778 (46)
Cohort	10,195 (54)
Age	
Adults (≥18 years)	18,563 (98)
Children (<18 years)	153 (1)
Not specified	257 (1)
Mean duration of hypoparathyroidism	
≥10 years	4098 (22)
<10 years	4590 (24)
Not specified	10,285 (54)
Procedure	
Postsurgical	7427 (39)
Nonsurgical	3358 (18)
Not specified	8188 (43)
Receiving PTH therapy	
Yes	1204 (6)
No	17,769 (94)
Aiming at investigating complications or symptoms	
Yes	15,997 (84)
No	2976 (16)

We present the median and range of sensitivity and specificity for different PTH and calcium threshold categories.

Using MetaDiSc statistical software version 1.4 (https://meta-disc.software.informer.com/), we calculated diagnostic 2 × 2 tables and performance measures for the test.[7] We used bivariate analysis to calculate the pooled estimates of sensitivity, specificity, and likelihood ratios along with 95% CIs for the summary estimates.[8] The bivariate model preserves the two-dimensional nature of diagnostic data by analyzing the logit-transformed sensitivity and specificity of each study in a single model, and takes into account both within-study and between-study variability. When four or more studies addressing a specific index test proved available, we calculated pooled estimates of sensitivity and specificity.[8] For each pooled estimate, we calculated post-test probability stratified by varying pretest probability of chronic hypoparathyroidism after total thyroidectomy (eg, low 1%–5%, moderate 5%–10%, and high 10%–20%). We performed evaluation of funnel plot asymmetry with the midas commands and ran statistical analyses using STATA, version 17 (StataCorp, LLC, College Station, TX, USA). We assessed the overall certainty in pooled diagnostic effect estimates using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach.[9-11]

Results

Part I: Complications and symptoms in patients with chronic hypoparathyroidism

The search identified 7546 records; after removal of duplicates, 5764 remained. Of these 5764, 332 articles proved potentially eligible based on title and abstract review, of which 83 studies reported in 95 publications ultimately proved eligible (Fig. S1).

Table 1 summarizes the characteristics of eligible studies. Of the 93 eligible studies, 75 were single-arm studies (8778 cases) and 18 were cohort studies (10,195 cases versus 47,490 normal individuals) that compared symptoms or complications in patients with chronic hypoparathyroidism to individuals with normal parathyroid function. Table S1 presents additional details for each eligible study. A total of 69 of the 75 single-arm studies and 16 of the 18 cohort studies proved at low risk of bias (Tables S2 and S3).

Eighteen cohort studies reported relative estimates of 56 complications and symptoms in patients with chronic hypoparathyroidism in comparison to individuals with normal parathyroid function. Table 2 presents 19 complications and symptoms that were reported in more than two studies. Table S4 summarizes the remaining 37 complications and symptoms that were reported by only one or two studies. Of these 56 complications and symptoms, nine met the criteria defined in the methods and were considered to be associated with chronic hypoparathyroidism, including nephrocalcinosis/nephrolithiasis, renal insufficiency, seizures, arrhythmia, ischemic heart disease, depression, infection, cataracts and increased all-cause mortality (Table 2).

We identified a total of 170 complications and symptoms in the single-arm studies and cohort studies. The median prevalence of the nine identified complications and symptoms proven to be associated with chronic hypoparathyroidism amongst all studies are as follows: 15% of nephrocalcinosis/nephrolithiasis, 12% of renal insufficiency, 17% of cataract, 11% of seizures, 7% of arrhythmia, 7% of ischemic heart disease, 9% of depression, 11% of infection, and 6% of all-cause mortality (Table 3). We observed that the prevalence of the identified complications and symptoms varied among postsurgical adult patients in comparison to nonsurgical adult patients and pediatric patients (Table 3). Table S5 presents the complications and symptoms reported by more than two studies but did not prove associated with chronic hypoparathyroidism. Complications and symptoms reported by only one or two studies are not presented.

Table 2. Relative Effects of Complications/Symptoms (Reported by >2 Cohort Studies)

Complication/symptom	Number of studies	Number of patients/controls	Crude OR (95% CI)	Adjusted HR/OR (95% CI)
Nephrocalcinosis/nephrolithiasis	**8**[12-19]	**9414/45,463**	**2.63 (2.29–3.01)**	**1.88 (1.68–2.12)**
Renal insufficiency	**5**[12-14,18,20]	**9264/45,253**	**6.22 (5.74–6.74)**	**3.67 (2.44–5.52)**
Cataract	**6**[12,14,21-24]	**1466/6074**	**2.08 (1.66–2.61)**	**2.13 (1.65–2.75)**
Seizures	**5**[12-14,24,25]	**1500/6406**	**2.83 (2.26–3.53)**	**3.22 (2.51–4.11)**
Arrhythmia	**3**[12-14]	**1078/4679**	**1.62 (1.23–2.12)**	**1.37(1.05–1.79)**
Ischemic heart disease	**3**[12-14]	**1078/4679**	**1.55 (1.24–1.94)**	**1.26 (1.02–1.56)**
Depression	**4**[12,14,21,26]	**1140/4749**	**2.21 (1.69–2.89)**	**1.89 (1.37–2.61)**
Infection	**4**[12,20,21,24]	**9245/44,390**	**1.96 (1.82–2.11)**	**2.30 (1.75–3.02)**
All-cause mortality	**4**[12-14,24]	**1358/5980**	**1.47 (1.25–1.74)**	**1.80 (1.49–2.17)**
Anxiety	3[12,21,26]	930/2674	2.64 (1.46–4.78)	1.42 (0.26–7.76)
Any fracture	8[12,14,16,21,24,27-29]	1545/6118	1.20 (1.01–1.42)	1.05 (0.72–1.53)
Vertebra fracture	6[12,14,21,27-29]	1248/4800	1.95 (1.35–2.82)	1.25 (0.43–3.61)
Stroke	3[12-14]	1078/4679	1.49 (1.09–2.02)	1.31 (0.97–1.76)
Myocardial infarct	3[12-14]	1078/4679	1.18 (0.77–1.81)	0.98 (0.64–1.51)
Upper extremities fracture	3[12,14,21]	1078/4679	1.28 (0.95–1.74)	–
Lower extremities fracture	3[12,14,21]	1078/4679	1.35 (0.92–1.98)	–
Humerus or wrist fracture	3[12,14,21]	1078/4679	0.91 (0.58–1.41)	–
Intracranial calcification	3[14,23,25]	391/2515	5.92 (3.62–9.67)	–
Neuropsychiatric disease	3[12,21,29]	918/2644	1.69 (1.37–2.08)	–

The statistically significant complications and symptoms are in bold.

Table 3. Prevalence of Complications and Symptoms as Identified in 3 or More Studies in Patients With Chronic Hypoparathyroidism

Complications	Overall population[a]		Postsurgical adult patients		Nonsurgical adult patients		Children patients (<18 years)	
	Number of studies (number of patients)	Median (%, IQR)	Number of studies (number of patients)	Median (%, IQR)	Number of studies (number of patients)	Median (%, IQR)	Number of studies (number of patients)	Median (%, IQR)
Nephrocalcinosis/ nephrolithiasis	55 (13,710) [12-19,30-76]	15 (6, 29)	25 (2806) [13,15-18,32,33,36,37,39,42,43,48,50,51,53,60-62,66,67,69,71,72,75]	9 (4, 22)	10 (825) [12,14,31,38,42,62,65,67,69,72]	11 (6, 17)	5 (77) [38,44,54,55,76]	54 (38, 75)
Renal insufficiency	34 (6152) [12-15,18,31,32,34,37,38,40-42,44,46-48,53-56,60-62,66,67,70,72,73,77-81]	12 (4, 19)	17 (3633) [13,15,18,32,37,42,48,53,56,60,61,66,67,72,77,78,80]	10 (4, 16)	7 (744) [12,14,31,38,42,67,72]	13 (8, 36)	3 (57) [44,54,55]	0 (0, 21)
Cataract	26 (5463) [12,14,21-24,27,31,37,39,47,51,56,61,65,67,70,72,73,79,82-87]	17 (9, 44)	10 (2401) [21,22,24,37,39,51,61,67,72,79]	11 (3, 19)	14 (1278) [12,14,23,24,27,31,65,67,72,82,83,85-87]	43 (15, 46)	0	–
Seizures	26 (5613) [12-14,24-27,36,47,51,56,60,61,65,67,70,72,79,80,82,84,85,87-90]	11 (4, 54)	12 (3268) [13,24,25,36,51,60,61,67,72,79,80,90]	5 (2, 9)	11 (1042) [12,14,24,26,27,65,67,72,82,85,87]	33 (20, 64)	2 (63) [88,89]	42 (27, 57)
Arrhythmia	10 (3598) [12-14,37,47,56,70,72,73,79]	7 (5, 23)	4 (1811) [13,37,72,79]	7 (6, 18)	3 (534) [12,14,72]	6 (3, 9)	0	–
Ischemic heart disease	5 (2522) [12-14,70,72]	7 (5, 11)	2 (1374) [13,72]	8 (5, 11)	3 (534) [12,14,72]	7 (3, 19)	0	–
Depression	12 (3107) [12,14,15,21,26,36,47,48,56,60,70,73]	9 (3, 19)	5 (1026) [15,21,36,48,60]	4 (3, 12)	3 (452) [12,14,26]	21 (4, 40)	0	–
Infection	13 (11,474) [12,20,21,24,35,37,56,70,72,79,88,91,92]	11 (7, 21)	5 (1927) [21,24,37,72,79]	15 (12, 18)	3 (430) [12,24,72]	23 (8, 68)	1 (26) [88]	27
All-cause mortality	11 (2382) [12-14,24,33,35,37,77,91,93,94]	6 (0, 16)	7 (1645) [13,24,33,37,77,93,94]	11 (5, 16)	3 (496) [12,14,24]	29 (6, 39)	0	–

[a]Including studies of surgical adult patients, nonsurgical adult patients, mixed surgical and nonsurgical adult patients, and children patients.

Table 4. PTH Characteristics Related to Primary and Subgroup Analysis

PTH parameters ($n = 18$)	n (%)
Timing	
Intraoperative	1 (5)[106]
1–12 hours postoperative	5 (28)[96,98,103,109]
12–24 hours postoperative	12 (67)[95,97,99-102,104,105,107,108,110,111]
Threshold	
Absolute value, pg/mL (pmol/L)	
≤10 (1.05)	12 (66)[95,96,98,100-102,104,107,109-111]
10–15 (1.05–1.58)	4 (22)[99,103,105,108]
Change in value	
>50%	1 (6)[97]
<50%	0
Combination	
Absolute <9.3 pg/mL (0.98 pmol/L) and change of >86%	1 (6)[106]
Timing of determination of chronic hypoparathyroidism after surgery	
3 months	1 (6)[108]
6 months	8 (44)[95,99,102,103,105-107,111]
12 months	9 (50)[96-98,100,101,104,109,110]

Table 5. Calcium Characteristics Related to Primary and Subgroup Analysis

Serum calcium parameters ($n = 9$)	n (%)
Timing	
24 hours postoperative	9 (100)[95,99,101,102,104-107,109]
Threshold	
Absolute value, mmol/L	
≤1	1 (11)[101]
1–2	8 (89)[95,99,102,104-107,109]
Timing of determination of chronic hypoparathyroidism	
6 months	6 (67)[95,99,102,105-107]
12 months	3 (33)[101,104,109]

Part II: Predicting values of early parathyroid hormone and calcium levels with the development of chronic hypoparathyroidism in patients following total thyroidectomy

Screening identified 1619 abstracts of which 521 proved duplicates, leaving 1098 abstracts for review, of which 118 proved potentially eligible. Of these, 17 articles including 18 studies proved eligible[95-111] (Fig. S2).

The 18 studies (10 retrospective,[95,96,100-102,104,105,107,110,111] and eight prospective,[96-99,103,106,108,109]) included 4325 patients, most of whom were women ($n = 3457$, 80%). Studies varied in their inclusion of malignant disease as an indication for surgery; autotransplantation of parathyroid glands during surgery; consideration of both PTH and calcium as predictors; their definition of chronic hypoparathyroidism; and the prevalence of chronic hypoparathyroidism. Table S6 provides additional details.

Two studies[97,101] proved at high risk of bias in the "flow and timing" domain; 11 studies at unclear risk of bias in the "patient selection" domain; and all studies at low risk of bias in the "index test (PTH/calcium)" and "reference standard (chronic hypoparathyroidism)" domain (Fig. S3). Under applicability concerns, we rated high concerns in five studies[97,100,103,105,109] in the "patients' selection" domain and two studies[96,108] in the "reference standard (chronic hypoparathyroidism)" domain (Fig. S3).

Tables 4 and 5 present PTH and calcium characteristics and report varied timing, thresholds, and duration of chronic hypoparathyroidism. Most studies measured PTH levels at 12–24 hours after surgery ($n = 12$), used ≤10 pg/mL as the threshold ($n = 12$), and defined chronic hypoparathyroidism as at least 12 months' duration ($n = 9$). All studies measured calcium levels at 24 hours after surgery, of which six studies defined chronic hypoparathyroidism as at least 6 months' duration.

Eighteen studies reported PTH levels as a predictor. The median and range of sensitivity and specificity were similar between varying PTH thresholds (Table S7). For the pooled diagnostic accuracy, we found evidence of a subgroup effect: using 12 months versus 6 months as the standard reference for determining chronic hypoparathyroidism was associated with lower specificity (12 months: specificity 72%; 95% CI, 55%–84% versus 6 months: 87%; 95% CI, 79%–93%; p interaction = 0.04, Table 6).

Nine studies[95,99,101,102,104-107,109] including 2508 patients reported calcium as the predictor. The median and range of sensitivity and specificity proved similar across serum calcium thresholds (Table S8). Given only three studies in the group of 12 months to determine chronic hypoparathyroidism, we did not pool the data and instead presented the median and range; however, the nonoverlapping intervals between specificities of the 6 and 12 months groups, suggest a probable subgroup effect (Table 7).

The quality of evidence of findings proves at low to moderate (Table S8). Using evaluation of funnel plot asymmetry, we found no evidence of publication bias (Figs. S4 and S5).

The prevalence (in diagnostic terms, the pretest probability) of chronic hypoparathyroidism varied considerably across studies—from 1% to 29% (median 6.5%). We found a PTH test result above the threshold (10 or 10–15 pg/mL) virtually excludes chronic hypoparathyroidism (posttest probability near 100%) irrespective of pretest probability (moderate quality evidence, Table 8). When the PTH result was below the threshold (10 or 10–15 pg/mL), the stratifying prevalence (pretest probability) of chronic hypoparathyroidism results in posttest probabilities from as low as 3% to as high as 66% (low quality evidence, Table 8).

Discussion

Main findings

In Part I, eligible studies identified 170 complications and symptoms derived from 93 studies in 18,973 patients with chronic hypoparathyroidism. Of these, nine complications and symptoms were reported in three or more studies and occurred more often in patients with hypoparathyroidism than in individuals

Table 6. Diagnostic Accuracy and Subgroup Analysis of PTH

Parameters	Number of studies (number of patients)	Sensitivity (95% CI) %	*p*-interaction	Specificity (95% CI) %	*p*-interaction
Timing of determination of chronic hypoparathyroidism					
6 months	8 (1822)	99 (82–100)	1.00	87 (79–93)	0.04
12 months	9 (2451)	99 (86–100)		72 (55–84)	
Timing of measurement postoperatively					
≤12 hours	5 (1015)	97 (78–100)	1.00	82 (71–89)	0.65
12–24 hours	12 (3220)	97 (88–99)		79 (68–87)	
PTH threshold					
≤10 pg/mL	12 (3666)	97 (87–99)	0.76	80 (68–88)	1.11
10–15 pg/mL	4 (488)	95 (76–99)		81 (70–89)	

Table 7. Diagnostic Accuracy and Subgroup Analysis of Calcium

Parameters	Number of studies (number of patients)	Sensitivity (95% CI) %	*p*-interaction	Specificity (95% CI) %	*p*-interaction
Timing of determination of chronic hypoparathyroidism					
6 months	6 (1187)	89 (59–98)	0.92	80 (73–85)	0.01
12 months	3 (1321)	92 (58–99)		57 (50–65)	
Calcium threshold					
≤1 mmol/L	1 (481)	–	–	–	–
1–2 mmol/L	8 (2027)	88 (62–97)		74 (64–82)	

Table 8. Posttest Probability Given Varying Pretest Probabilities of Chronic Hypoparathyroidism

Measurement	Pretest probability			Quality of evidence
	Low (1%–5%)	Intermediate (5%–10%)	High (10%–20%)	
PTH (determination of chronic hypoparathyroidism at 6 months after surgery)				
Posttest probability test (below the threshold)	7–29	29–46	46–66	Low[a,b]
Posttest probability test (above the threshold)	100–100	100–100	100–100	Moderate[a]
PTH (determination of chronic hypoparathyroidism at 12 months after surgery)				
Posttest probability test (below the threshold)	**3–16**	**16–28**	**28–47**	Low[a,b]
Posttest probability test (above the threshold)	**100–100**	**100–100**	**100–100**	Moderate[a]
Calcium (determination of chronic hypoparathyroidism at 6 months after surgery)				
Posttest probability test (below the threshold)	4–19	19–33	33–52	Low[a,b]
Posttest probability test (above the threshold)	99–100	98–99	97–98	Moderate[a]

The most important results in this table are in bold.
[a]Most studies at unclear risk of bias in the patient selection.
[b]95% CI imprecise, lowering certainty in overall pooled estimate.

with normal parathyroid function: nephrocalcinosis/nephrolithiasis (median prevalence among all studies [15%]), renal insufficiency (12%), cataract (17%), seizures (11%), arrhythmia (7%), ischemic heart disease (7%), depression (9%), infection (11%), and all-cause mortality (6%) (Tables 2 and 3).

In Part II, we found that early PTH levels (within 24 hours) after total thyroidectomy provided higher sensitivity and specificity than serum calcium levels to predict chronic hypoparathyroidism. PTH values above the threshold of 10 pg/mL virtually rule out the development of chronic hypoparathyroidism with a sensitivity of close to 100% and assuming a low pretest probability (prevalence) of hypoparathyroidism. The specificity of the early PTH values, by contrast, is relatively low. Patients with a test of PTH values below the threshold have a likelihood to develop long-term hypoparathyroidism that ranges from 3% to 66% depending on the prevalence (pretest probability). We found no meaningful differences regarding the varying thresholds used in the individual studies (see Table 6) and timing of measurement (12 versus 24 hours after surgery).

Strengths and limitations

In Part I, strengths include a comprehensive search; registration of the study protocol before starting analysis with explicit explanation of subsequent changes to the protocol; and application of predefined criteria for the most credible and frequently occurring symptoms and complications.

Limitations include more than one-half of included studies did not aim to specifically investigate the complications or symptoms associated with chronic hypoparathyroidism and, as a result, may have failed to report on some of the complications and symptoms. Some studies reported the complications and symptoms based on International Classification of Diseases (ICD) codes or hospital records, which could underestimate their prevalence. Clinical heterogeneity among studies prevented us from pooling the prevalence data and limited our ability to draw accurate conclusions regarding the true prevalence of complications and symptoms in patients with chronic hypoparathyroidism. We did not include non-English-language publications and did not perform a substantial review of the gray literature for unpublished data. Last, when defining the complications related to chronic hypoparathyroidism, we used at least "three studies" reporting one criterion, which was based on the authors consensus and might lead to missing of some complications.

Part II represents the largest comprehensive review thus far addressing the diagnostic values of measuring PTH and calcium parameters to predict chronic hypoparathyroidism after total thyroidectomy. Other strengths included an extensive literature search; registering the study protocol before starting; evaluating the quality of evidence using the GRADE approach; and postulating several possible explanations of heterogeneity (timing of measurement, timing of determination of chronic hypoparathyroidism and thresholds) including a prior specification of direction. One of these proved compelling, demonstrating that specificity decreased when assessing the presence of chronic hypoparathyroidism at 12 rather than 6 months. This finding is consistent with some patients recovering between 6 and 12 months. By stratifying different intervals of pretest probability (disease prevalence), we calculated values for the posttest probability that are likely to be of use for clinicians and patients. Studies eligible for this review reported the prevalence of chronic hypoparathyroidism between 1% and 29%.

Limitations include, because of the limited number of studies in a planned subgroup analysis, inability to pool the sensitivity and specificity—we used instead median and range and compared overlap of CIs. Another limitation was that we restricted the review to English-language publications and did not perform a substantial review of the gray literature for unpublished data.

Comparison with other studies

In Part I, several previous reviews have addressed the symptoms or complications in patients with chronic hypoparathyroidism,[112-115] none, however, evaluated the prevalence of these symptoms and complications. In contrast, our review addressed both the prevalence of complications and symptoms and the relative estimates in comparison to individuals with normal parathyroid function.

In Part II, we identified one prior review that evaluated the predictive value of PTH and calcium for chronic hypoparathyroidism.[2] This study focused on the identification of preoperative, intraoperative, and postoperative factors that predict transient hypoparathyroidism. Authors included only one study[109] when addressing chronic hypoparathyroidism, limiting their power to detect predictive values. Our review added an additional 17 diagnostic accuracy studies with thousands of patients.

Interpretation and application

In Part I, the studies comparing patients with chronic hypoparathyroidism to individuals with normal parathyroid function enabled us to determine which complications and symptoms were associated with chronic hypoparathyroidism. The eligible studies suggest that the prevalence of a few identified symptoms and complications may vary among the patient populations. Existing guidelines[116-119] addressing the long-term complications of hypoparathyroidism were informed by limited case studies or narrow reviews. Our findings would provide useful information for the updating of future guidelines by reminding clinicians and patients what complications and symptoms should be avoided.

In Part II, to predict the risk of developing long-term hypoparathyroidism by biochemical parameters measured 12–24 hours after total thyroidectomy; PTH has a better predictive value than calcium; chronic hypoparathyroidism should be determined at 1 year rather than 6 months after surgery to avoid overdiagnosis. In using the PTH test, clinicians can choose any of the thresholds suggested in the existing studies (eg, <10 or 10–15 pg/mL). For patients with a test result of PTH above the threshold, the likelihood that patients' parathyroid function will recover is very high; they may not need postoperative treatment with active vitamin D and calcium long-term. Patients with immediate postoperative PTH values below the threshold may experience chronic hypoparathyroidism; the likelihood is influenced by the overall prevalence of chronic postoperative hypoparathyroidism in the clinicians' institution. When the prevalence is under 10%, no more than 30% of patients testing below the threshold will develop chronic hypoparathyroidism. When the prevalence is 20% less, less than 50% will experience chronic hypoparathyroidism (Table 8). Therefore, patients and clinicians should be vigilant to the possibility of long-term hypoparathyroidism in patients with a postoperative PTH test below the threshold. Although our results emphasize the value of PTH measurement in the diagnosis of postoperative hypoparathyroidism, postoperative parathyroid failure as an evolving process remains incompletely understood.

Conclusion

The Part I presents 170 symptoms and complications occurring in patients with chronic hypoparathyroidism and highlights the nine that are most likely associated with chronic hypoparathyroidism. The Part II supports the notion that a PTH value above a threshold of 10 pg/mL 12–24 hours after total thyroidectomy is a strong predictor that patients will not develop chronic hypoparathyroidism. Patients with PTH values below the threshold need careful monitoring as some of them will develop chronic hypoparathyroidism.

Acknowledgments

We acknowledge unrestricted financial support from: Amolyt, Ascendis, Calcilytix and Takeda. They had no input into the planning or design of the project, the conduct of the reviews, evaluation of the data, writing or review of the manuscript, its content, or conclusions.

AUTHOR CONTRIBUTIONS

Liang Yao: Formal analysis; methodology; writing – original draft; writing – review and editing. **Xu Hui:** Data curation; formal analysis; methodology; writing – review and editing. **Meixuan Li:** Data curation; writing – review and editing. **Jing Li:** Data curation; formal analysis; writing – review and editing. **Clement Lin:** Data curation; writing – review and editing. **Maryam Kandi:** Data curation; writing – review and editing. **Ashwini Sreekanta:** Data curation; writing – review and editing. **Nima Makhdami:** Data curation; writing – review and editing. **Divyalakshmi Tamilselvan:** Data curation; writing – review and editing. **Dalal S. Ali:** Data curation; writing – review and editing. **Karel Dandurand:** Data curation; writing – review and editing. **Kehu Yang:** Formal analysis; writing – review and editing. **John P. Bilezikian:** Conceptualization; writing – review and editing. **Maria Luisa Brandi:** Writing – review and editing. **Bart L. Clarke:** Writing – review and editing. **Michael Mannstadt:** Supervision; writing – review and editing. **Lars Rejnmark:** Formal analysis; supervision; writing – review and editing. **Aliya Aziz Khan:** Supervision; writing – review and editing. **Gordon Guyatt:** Conceptualization; methodology; supervision; writing – review and editing.

Conflicts of Interest

AAK: Speaker for Amgen, Shire/Takeda, Ultragenyx, Alexion, Chugai; grants from Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx; consultant for Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx. JPB: Consultant for Amgen, Radius, Ascendis, Calcilytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, Ipsen. MLB has received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB; grants and/or speaker: Abiogen, Alexion, Amgen, Bruno Farmaceutici, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex, UCB; consultant: Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB. BLC: Consultant for Takeda/Shire, Amolyt Pharma, Calcilytix; grants from Takeda/Shire, Ascendis. LR: Speaker for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, Ultragenyx; Consultant for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, Ultragenyx; Grants from Takeda and Kyowa Kirin. MM: Consultant for Takeda, Amolyt, and Chugai; Grants from Takeda and Chugai.

References

1. Clarke BL. Epidemiology and complications of hypoparathyroidism. Endocrinol Metab Clin North Am. 2018;47(4):771-782. https://doi.org/10.1016/j.ecl.2018.07.004.
2. Edafe O, Antakia R, Laskar N, et al. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014;101(4):307-320. https://doi.org/10.1002/bjs.9384.
3. National Heart Lung, and Blood Institute. Study quality assessment tools. 2020. Available from: https://www.nhlbi.nih.gov/health-topics/study-qualityassessment-tools. Accessed Aug 25, 2022.
4. Agarwal G, Guyatt G, Busse J. Methods commentary: risk of bias in cross-sectional surveys of attitudes and practices. 2011. Available from: https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-cross-sectional-surveys-of-attitudes-and-practices/ Accessed Aug 25, 2022.
5. Guyatt G, Busse J. Commentary: risk of bias in cohort studies. 2020. Available from: https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-in-cohort-studies/ Accessed Aug 25, 2022.
6. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.
7. Zamora J, Abraira V, Muriel A, et al. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6:31. https://doi.org/10.1186/1471-2288-6-31.
8. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005;58(10):982-990. https://doi.org/10.1016/j.jclinepi.2005.02.022.
9. Hultcrantz M, Mustafa RA, Leeflang MMG, et al. Defining ranges for certainty ratings of diagnostic accuracy: a GRADE concept paper. J Clin Epidemiol. 2020;117:138-148. https://doi.org/10.1016/j.jclinepi.2019.05.002.
10. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 22. The GRADE approach for tests and strategies-from test accuracy to patient-important outcomes and recommendations. J Clin Epidemiol. 2019;111:69-82. https://doi.org/10.1016/j.jclinepi.2019.02.003.
11. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336(7653):1106-1110. https://doi.org/10.1136/bmj.39500.677199.AE.
12. Underbjerg L, Sikjaer T, Mosekilde L, et al. The epidemiology of nonsurgical hypoparathyroidism in Denmark: a nationwide case finding study. J Bone Miner Res. 2015;30(9):1738-1744. https://doi.org/10.1002/jbmr.2501.
13. Underbjerg L, Sikjaer T, Mosekilde L, et al. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. J Bone Miner Res. 2013;28(11):2277-2285. https://doi.org/10.1002/jbmr.1979.
14. Kim SH, Rhee Y, Kim YM, et al. Prevalence and complications of nonsurgical hypoparathyroidism in Korea: a nationwide cohort study. PLoS One. 2020;15(5):e0232842. https://doi.org/10.1371/journal.pone.0232842.
15. Meola A, Vignali E, Matrone A, et al. Efficacy and safety of long-term management of patients with chronic post-surgical hypoparathyroidism. J Endocrinol Invest. 2018;41(10):1221-1226. https://doi.org/10.1007/s40618-018-0857-5.
16. Starr JR, Tabacco G, Majeed R, et al. PTH and bone material strength in hypoparathyroidism as measured by impact microindentation. Osteoporos Int. 2020;31(2):327-333. https://doi.org/10.1007/s00198-019-05177-2.
17. Tabacco G, Naciu AM, Maggi D, et al. Cardiovascular autonomic neuropathy as a new complication of postsurgical chronic hypoparathyroidism. J Bone Miner Res. 2019;34(3):475-481. https://doi.org/10.1002/jbmr.3623.
18. Mazoni L, Matrone A, Apicella M, et al. Renal complications and quality of life in postsurgical hypoparathyroidism: a case-control study. J Endocrinol Invest. 2022;45(3):573-582. https://doi.org/10.1007/s40618-021-01686-2.
19. Ketteler M, Chen K, Gosmanova EO, et al. Risk of nephrolithiasis and nephrocalcinosis in patients with chronic hypoparathyroidism: a retrospective cohort study. Adv Ther. 2021;38(4):1946-1957. https://doi.org/10.1007/s12325-021-01649-2.
20. Gosmanova EO, Chen K, Rejnmark L, et al. Risk of chronic kidney disease and estimated glomerular filtration rate decline in patients with chronic hypoparathyroidism: a retrospective cohort study. Adv Ther. 2021;38(4):1876-1888. https://doi.org/10.1007/s12325-021-01658-1.
21. Underbjerg L, Sikjaer T, Mosekilde L, et al. Postsurgical hypoparathyroidism—risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Mineral Res. 2014;29(11 S1):2504-2510. https://doi.org/10.1002/jbmr.2273.
22. Tasli NG, Akbas EM. Ocular findings associated with hypoparathyroidism. Ocul Immunol Inflamm. 2020;29(7–8):1287-1291. https://doi.org/10.1080/09273948.2020.1735451.
23. Goswami R, Ray D, Sharma R, et al. Presence of spondyloarthropathy and its clinical profile in patients with hypoparathyroidism. Clin Endocrinol (Oxf). 2008;68(2):258-263. https://doi.org/10.1111/j.1365-2265.2007.03032.x.

24. Vadiveloo T, Donnan PT, Leese CJ, et al. Increased mortality and morbidity in patients with chronic hypoparathyroidism: a population-based study. Clin Endocrinol (Oxf). 2019;90(2):285-292. https://doi.org/10.1111/cen.13895.
25. Zavatta G, Tebben PJ, McCollough CH, et al. Basal ganglia calcification is associated with local and systemic metabolic mechanisms in adult hypoparathyroidism. J Clin Endocrinol Metab. 2021;106(7):1900-1917. https://doi.org/10.1210/clinem/dgab162.
26. Aggarwal S, Kailash S, Sagar R, et al. Neuropsychological dysfunction in idiopathic hypoparathyroidism and its relationship with intracranial calcification and serum total calcium. Eur J Endocrinol. 2013;168(6):895-903. https://doi.org/10.1530/eje-12-0946.
27. Chawla H, Saha S, Kandasamy D, et al. Vertebral fractures and bone mineral density in patients with idiopathic hypoparathyroidism on long-term follow-up. J Clin Endocrinol Metabol. 2017;102(1):251-258. https://doi.org/10.1210/jc.2016-3292.
28. Mendonca ML, Pereira FA, Nogueira-Barbosa MH, et al. Increased vertebral morphometric fracture in patients with postsurgical hypoparathyroidism despite normal bone mineral density. BMC Endocr Disord. 2013;13(1):1. https://doi.org/10.1186/1472-6823-13-1.
29. Cipriani C, Minisola S, Bilezikian JP, et al. Vertebral fracture assessment in postmenopausal women with postsurgical hypoparathyroidism. J Clin Endocrinol Metab. 2021;106(5):1303-1311. https://doi.org/10.1210/clinem/dgab076.
30. Gafni RI, Langman CB, Guthrie LC, et al. Hypocitraturia is an untoward side effect of synthetic human parathyroid hormone (hPTH) 1-34 therapy in hypoparathyroidism that may increase renal morbidity. J Bone Miner Res. 2018;33(10):1741-1747. https://doi.org/10.1002/jbmr.3480.
31. Saha S, Kandasamy D, Sharma R, et al. Nephrocalcinosis, renal dysfunction, and calculi in patients with primary hypoparathyroidism on long-term conventional therapy. J Clin Endocrinol Metabol. 2020;105(4):E1215-E1224. https://doi.org/10.1210/clinem/dgz319.
32. Gronskaia S, Melnichenko G, Rozhinskaya L, et al. A registry for patients with chronic hypoparathyroidism in Russian adults. Endocr Connect. 2020;9(7):627-636. https://doi.org/10.1530/EC-20-0219.
33. Coudenys E, Meerhaeghe TV, Unuane D, et al. Long-term treatment with calcitriol in postsurgical hypoparathyroidism leads to renal function decline. Horm Metab Res. 2019;51(6):362-366. https://doi.org/10.1055/a-0902-8476.
34. Tay YKD, Tabacco G, Cusano NE, et al. Therapy of hypoparathyroidism with rhPTH(1-84): a prospective, 8-year investigation of efficacy and safety. J Clin Endocrinol Metabol. 2019;104(11):5601-5610. https://doi.org/10.1210/jc.2019-00893.
35. Mannstadt M, Clarke BL, Bilezikian JP, et al. Safety and efficacy of 5 years of treatment with recombinant human parathyroid hormone in adults with hypoparathyroidism. J Clin Endocrinol Metabol. 2019;104(11):5136-5147. https://doi.org/10.1210/jc.2019-01010.
36. Lopera JZ, Tabares SAL, Herrera DA, et al. Characteristics of hypoparathyroidism in Colombia: data from a single center in the city of Medellin. Arch Endocrinol Metab. 2020;64(3):282-289. https://doi.org/10.20945/2359-3997000000250.
37. Ponce de Leon-Ballesteros G, Bonilla-Ramirez C, Hernandez-Calderon FJ, et al. Mid-term and long-term impact of permanent hypoparathyroidism after Total thyroidectomy. World J Surg. 2020;44(8):2692-2698. https://doi.org/10.1007/s00268-020-05531-0.
38. Winer KK, Schmitt MM, Ferre EMN, et al. Impact of periprocedural subcutaneous parathyroid hormone on control of hypocalcaemia in APS-1/APECED patients undergoing invasive procedures. Clin Endocrinol (Oxf). 2021;94(3):377-383. https://doi.org/10.1111/cen.14335.
39. 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(2):215-222. https://doi.org/10.1530/eje.0.1460215.
40. Winer KK, Ko CW, Reynolds JC, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metabol. 2003;88(9):4214-4220. https://doi.org/10.1210/jc.2002-021736.
41. Lopes MP, Kliemann BS, Bini IB, et al. Hypoparathyroidism and pseudohypoparathyroidism: etiology, laboratory features and complications. Arch Endocrinol Metab. 2016;60(6):532-536. https://doi.org/10.1590/2359-3997000000221.
42. Winer KK, Yanovski JA, Cutler GB Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism: results of a short-term randomized crossover trial. JAMA. 1996;276(8):631-636. https://doi.org/10.1001/jama.276.8.631.
43. Winer KK, Yanovski JA, Sarani B, et al. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. J Clin Endocrinol Metab. 1998;83(10):3480-3486. https://doi.org/10.1210/jcem.83.10.5185.
44. Winer KK, Sinaii N, Peterson D, et al. Effects of once versus twice-daily parathyroid hormone 1-34 therapy in children with hypoparathyroidism. J Clin Endocrinol Metab. 2008;93(9):3389-3395. https://doi.org/10.1210/jc.2007-2552.
45. Rubin MR, Sliney J Jr, McMahon DJ, et al. Therapy of hypoparathyroidism with intact parathyroid hormone. Osteoporos Int. 2010;21(11):1927-1934. https://doi.org/10.1007/s00198-009-1149-x.
46. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metabol. 2012;97(12):4507-4514. https://doi.org/10.1210/jc.2012-1808.
47. 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(7):671-679. https://doi.org/10.4158/EP13328.OR.
48. Leidig-Bruckner G, Bruckner T, Raue F, et al. Long-term follow-up and treatment of postoperative permanent hypoparathyroidism in patients with medullary thyroid carcinoma: differences in complete and partial disease. Horm Metab Res. 2016;48(12):806-813. https://doi.org/10.1055/s-0042-118181.
49. 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 Metabol. 2016;101(7):2742-2750. https://doi.org/10.1210/jc.2015-4135.
50. Palermo A, Santonati A, Tabacco G, et al. PTH(1-34) for surgical hypoparathyroidism: a 2-year prospective, Open-Label investigation of efficacy and quality of life. J Clin Endocrinol Metab. 2018;103(1):271-280. https://doi.org/10.1210/jc.2017-01555.
51. David K, Moyson C, Vanderschueren D, et al. Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study. Eur J Endocrinol. 2019;180(1):71-78. https://doi.org/10.1530/EJE-18-0580.
52. Streeten EA, Mohtasebi Y, Konig M, et al. Hypoparathyroidism: less severe hypocalcemia with treatment with vitamin d2 compared with calcitriol. J Clin Endocrinol Metabol. 2017;102(5):1505-1510. https://doi.org/10.1210/jc.2016-3712.
53. Lorente-Poch L, Sancho JJ, Carballo L, et al. Clinical profile and long-term follow-up of 32 patients with postoperative permanent hypoparathyroidism. Gland Surg. 2017;6(Suppl 1):S3-S10. https://doi.org/10.21037/gs.2017.11.10.
54. 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(11):4106-4113. https://doi.org/10.1210/jc.2015-2257.
55. Winer KK, Kelly A, Johns A, et al. Long-term parathyroid hormone 1-34 replacement therapy in children with hypoparathyroidism. J Pediatr. 2018;203:391-399.e1. https://doi.org/10.1016/j.jpeds.2018.08.010.
56. Hamdy NAT, Decallonne B, Evenepoel P, et al. Burden of illness in patients with chronic hypoparathyroidism not adequately controlled with conventional therapy: a Belgium and The Netherlands survey. J Endocrinol Invest. 2021;44(7):1437-1446. https://doi.org/10.1007/s40618-020-01442-y.
57. 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(6):2356-2361. https://doi.org/10.1210/jc.2013-1239.
58. Rubin MR, Dempster DW, Zhou H, et al. Dynamic and structural properties of the skeleton in hypoparathyroidism. J Bone Mineral Res. 2008;23(12):2018-2024. https://doi.org/10.1359/jbmr.080803.

59. Rubin MR, Zwahlen A, Dempster DW, et al. Effects of parathyroid hormone administration on bone strength in hypoparathyroidism. J Bone Mineral Res. 2016;31(5):1082-1088. https://doi.org/10.1002/jbmr.2777.
60. Onder CE, Kuskonmaz SM, Koc G, et al. Evaluation of management of patients with postoperative permanent hypoparathyroidism. How close are we to the targets? [published online ahead of print December 3, 2020]. Minerva Endocrinol. 2020. https://doi.org/10.23736/s0391-1977.20.03291-5.
61. 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(1):e372-e385. https://doi.org/10.1210/clinem/dgab577.
62. Khan AA, AbuAlrob H, Punthakee Z, et al. Canadian national hypoparathyroidism registry: an overview of hypoparathyroidism in Canada. Endocrine. 2021;72(2):553-561. https://doi.org/10.1007/s12020-021-02629-w.
63. Cusano NE, Rubin MR, McMahon DJ, et al. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. J Clin Endocrinol Metab. 2014;99(10):3694-3699. https://doi.org/10.1210/jc.2014-2267.
64. Cusano NE, Rubin MR, McMahon DJ, et al. Therapy of hypoparathyroidism with PTH(1-84): a prospective four-year investigation of efficacy and safety. J Clin Endocrinol Metabol. 2013;98(1):137-144. https://doi.org/10.1210/jc.2012-2984.
65. Jain R, Singh SK, Agrawal NK. Idiopathic hypoparathyroidism: still a diagnostic conundrum - a tertiary centre experience. Horm Metab Res. 2020;52(10):708-711. https://doi.org/10.1055/a-1228-8199.
66. Acharya SV. Postoperative hypoparathyroidism: presentation, clinical features and long-term follow-up from tertiary care hospital. J Clin Diagn Res. 2021;15(1):OC18-OC20. https://doi.org/10.7860/JCDR/2021/46621.14423.
67. Zanchetta MB, Robbiani D, Oliveri B, et al. Hipopara-Red, real life experience in 322 patients with hypoparathyroidism. J Endocr Soc. 2021;5(2):bvaa181. https://doi.org/10.1210/jendso/bvaa181.
68. Marcucci G, Masi L, Cianferotti L, et al. Chronic hypoparathyroidism and treatment with teriparatide. Endocrine. 2021;72(1):249-259. https://doi.org/10.1007/s12020-020-02577-x.
69. Hepsen S, Akhanli P, Sakiz D, et al. The effects of patient and disease-related factors on the quality of life in patients with hypoparathyroidism. Arch Osteoporos. 2020;15(1):75. https://doi.org/10.1007/s11657-020-00759-8.
70. Chen K, Krasner A, Li N, et al. Clinical burden and healthcare resource utilization among patients with chronic hypoparathyroidism, overall and by adequately vs not adequately controlled disease: a multi-country chart review. J Med Econ. 2019;22(11):1141-1152. https://doi.org/10.1080/13696998.2019.1624081.
71. Marcucci G, Altieri P, Benvenga S, et al. Hypoparathyroidism and pseudohypoparathyroidism in pregnancy: an Italian retrospective observational study. Orphanet J Rare Dis. 2021;16(1):421. https://doi.org/10.1186/s13023-021-02053-3.
72. Konca Degertekin C, Gogas Yavuz D, Pekkolay Z, et al. Identifying clinical characteristics of hypoparathyroidism in Turkey: HIPOPARATURK-NET study. Calcif Tissue Int. 2022;110(2):204-214. https://doi.org/10.1007/s00223-021-00908-2.
73. Kovaleva EV, Eremkina AK, Elfimova AR, et al. The Russian registry of chronic hypoparathyroidism. Front Endocrinol. 2022;13:800119. https://doi.org/10.3389/fendo.2022.800119.
74. Marcucci G, Beccuti G, Carosi G, et al. Multicenter retro-prospective observational study on chronic hypoparathyroidism and rhPTH (1-84) treatment. J Endocrinol Invest. 2022;45(9):1653-1662. https://doi.org/10.1007/s40618-022-01800-y.
75. Bilginer MC, Aydin C, Polat B, et al. Assessment of calcium and vitamin D medications adherence in patients with hypoparathyroidism after thyroidectomy. Arch Osteoporos. 2022;17(1):22. https://doi.org/10.1007/s11657-022-01066-0.
76. Bernardor J, Flammier S, Cabet S, et al. Intermittent bi-daily subcutaneous teriparatide administration in children with hypoparathyroidism: a single-center experience. Front Pediatr. 2021;9:764040. https://doi.org/10.3389/fped.2021.764040.
77. Underbjerg L, Sikjaer T, Rejnmark L. Long-term complications in patients with hypoparathyroidism evaluated by biochemical findings: a case-control study. J Bone Miner Res. 2018;33(5):822-831. https://doi.org/10.1002/jbmr.3368.
78. 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(7):e10368. https://doi.org/10.1002/jbm4.10368.
79. Siggelkow H, Clarke BL, Germak J, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: findings from a 13-country patient and caregiver survey. Clin Endocrinol (Oxf). 2020;92(2):159-168. https://doi.org/10.1111/cen.14128.
80. Lui DTW, Fung MMH, Lee CH, et al. A territory-wide assessment of the incidence of persistent hypoparathyroidism after elective thyroid surgery and its impact on new fracture risk over time. Surgery. 2021;170(5):1369-1375. https://doi.org/10.1016/j.surg.2021.05.004.
81. Bertocchio JP, Grosset N, Groussin L, et al. Practice patterns for chronic hypoparathyroidism: data from patients and physicians in France. Endocr Connect. 2022;11(1):e210350. https://doi.org/10.1530/ec-21-0350.
82. Huddle KRL, Ally R. Idiopathic hypoparathyroidism in black South Africans. Q J Med. 1989;70(261):53-60.
83. Goswami R, Brown EM, Kochupillai N, et al. Prevalence of calcium sensing receptor autoantibodies in patients with sporadic idiopathic hypoparathyroidism. Eur J Endocrinol. 2004;150(1):9-18. https://doi.org/10.1530/eje.0.1500009.
84. Bhadada SK, Bhansali A, Upreti V, et al. Spectrum of neurological manifestations of idiopathic hypoparathyroidism and pseudohypoparathyroidism. Neurol India. 2011;59(4):586-589. https://doi.org/10.4103/0028-3886.84342.
85. Modi S, Tripathi M, Saha S, et al. Seizures in patients with idiopathic hypoparathyroidism: effect of antiepileptic drug withdrawal on recurrence of seizures and serum calcium control. Eur J Endocrinol. 2014;170(5):777-783. https://doi.org/10.1530/eje-14-0075.
86. Laway BA, Goswami R, Singh N, et al. Pattern of bone mineral density in patients with sporadic idiopathic hypoparathyroidism. Clin Endocrinol (Oxf). 2006;64(4):405-409. https://doi.org/10.1111/j.1365-2265.2006.02479.x.
87. Saha S, Goswami R. Auditing the efficacy and safety of alfacalcidol and calcium therapy in idiopathic hypoparathyroidism. J Clin Endocrinol Metab. 2019;104(4):1325-1335. https://doi.org/10.1210/jc.2018-02228.
88. Wang Y, Wang O, Nie M, et al. Clinical and genetic findings in a Chinese cohort of patients with DiGeorge syndrome-related hypoparathyroidism. Endocr Pract. 2020;26(6):642-650. https://doi.org/10.4158/EP-2019-0498.
89. Kim JH, Shin YL, Yang S, et al. Diverse genetic aetiologies and clinical outcomes of paediatric hypoparathyroidism. Clin Endocrinol (Oxf). 2015;83(6):790-796. https://doi.org/10.1111/cen.12944.
90. 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(2):151-162. https://doi.org/10.1007/s40271-019-00388-5.
91. 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(4):275-283. https://doi.org/10.1016/s2213-8587(13)70106-2.
92. Bilezikian JP, Clarke BL, Mannstadt M, et al. Safety and efficacy of recombinant human parathyroid hormone in adults with hypoparathyroidism randomly assigned to receive fixed 25-mug or 50-mug daily doses. Clin Ther. 2017;39(10):2096-2102. https://doi.org/10.1016/j.clinthera.2017.08.011.
93. Lakatos P, Bajnok L, Lagast H, et al. An open-label extension study of parathyroid hormone RHPTH(1-84) in adults with hypoparathyroidism. Endocr Pract. 2016;22(5):523-532. https://doi.org/10.4158/EP15936.OR.

94. Almquist M, Ivarsson K, Nordenstrom E, et al. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. Br J Surg. 2018;105(10):1313-1318. https://doi.org/10.1002/bjs.10843.
95. 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):300060520927199. https://doi.org/10.1177/0300060520927199.
96. Palmhag D, Brydolf J, Zedenius J, et al. A single parathyroid hormone measurement two hours after a thyroidectomy reliably predicts permanent hypoparathyroidism. Scand J Surg. 2021;110(3):322-328. https://doi.org/10.1177/1457496920913666.
97. Lončar I, Dulfer RR, Massolt ET, et al. Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism. Eur J Endocrinol. 2020;183(2):149-159. https://doi.org/10.1530/eje-20-0116.
98. Chang JW, Park KW, Jung SN, et al. The most reliable time point for intact parathyroid hormone measurement to predict hypoparathyroidism after total thyroidectomy with central neck dissection to treat papillary thyroid carcinoma: a prospective cohort study. Eur Arch Otorhinolaryngol. 2020;277(2):549-558. https://doi.org/10.1007/s00405-019-05693-1.
99. Sala DT, Muresan M, Voidazan S, et al. First day serum calcium and parathyroid hormone levels as predictive factors for safe discharge after thyroidectomy. Acta Endocrinol (Buchar). 2019;15(2):225-230. https://doi.org/10.4183/aeb.2019.225.
100. Canu GL, Medas F, Longheu A, et al. Correlation between iPTH levels on the first postoperative day after total thyroidectomy and permanent hypoparathyroidism: our experience. Open Med (Wars). 2019;14:437-442. https://doi.org/10.1515/med-2019-0047.
101. Calvo Espino P, Rivera Bautista J, Artés Caselles M, et al. Serum levels of intact parathyroid hormone on the first day after total thyroidectomy as predictor of permanent hypoparathyroidism. Endocrinol Diabetes Nutr. 2019;66(3):195-201. https://doi.org/10.1016/j.endinu.2018.08.006.
102. Wang W, Xia F, Meng C, et al. Prediction of permanent hypoparathyroidism by parathyroid hormone and serum calcium 24h after thyroidectomy. Am J Otolaryngol. 2018;39(6):746-750. https://doi.org/10.1016/j.amjoto.2018.08.005.
103. Suwannasarn M, Jongjaroenprasert W, Chayangsu P, et al. Single measurement of intact parathyroid hormone after thyroidectomy can predict transient and permanent hypoparathyroidism: a prospective study. Asian J Surg. 2017;40(5):350-356. https://doi.org/10.1016/j.asjsur.2015.11.005.
104. Wang JB, Sun HL, Song CY, et al. Association between decreased serum parathyroid hormone after total thyroidectomy and persistent hypoparathyroidism. Med Sci Monit. 2015;21:1223-1231. https://doi.org/10.12659/MSM.892867.
105. Selberherr A, Scheuba C, Riss P, et al. Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment. Surgery. 2015;157(2):349-353. https://doi.org/10.1016/j.surg.2014.09.007.
106. 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;18:150-153. https://doi.org/10.1016/j.ijsu.2015.04.074.
107. Julian 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. https://doi.org/10.1016/j.amjsurg.2013.01.038.
108. Ezzat WF, Fathey H, Fawaz S, et al. Intraoperative parathyroid hormone as an indicator for parathyroid gland preservation in thyroid surgery. Swiss Med Wkly. 2011;141:w13299. https://doi.org/10.4414/smw.2011.13299.
109. Hermann M, Ott J, Promberger R, et al. Kinetics of serum parathyroid hormone during and after thyroid surgery. Br J Surg. 2008;95(12):1480-1487. https://doi.org/10.1002/bjs.6410.
110. 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. https://doi.org/10.5603/EP.a2022.0005.
111. Riordan F, Brophy C, Murphy MS, et al. Predictive value of postoperative day 1 parathyroid hormone levels for early and late hypocalcaemia after thyroidectomy. Langenbecks Arch Surg. 2022;407(4):1653-1658. https://doi.org/10.1007/s00423-022-02480-1.
112. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. Nat Rev Disease Primers. 2017;3:17055. https://doi.org/10.1038/nrdp.2017.55.
113. Shoback DM, Bilezikian JP, Costa AG, et al. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metabol. 2016;101(6):2300-2312. https://doi.org/10.1210/jc.2015-3909.
114. Cianferotti L, Marcucci G, Brandi ML. Causes and pathophysiology of hypoparathyroidism. Best Pract Res Clin Endocrinol Metab. 2018;32(6):909-925. https://doi.org/10.1016/j.beem.2018.07.001.
115. Kakava K, Tournis S, Papadakis G, et al. Postsurgical hypoparathyroidism: a systematic review. In Vivo. 2016;30(3):171-180.
116. 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(2):G1-G20. https://doi.org/10.1530/eje-15-0628.
117. Khan AA, Koch CA, Van Uum S, et al. Standards of care for hypoparathyroidism in adults: a Canadian and international consensus. Eur J Endocrinol. 2019;180(3):P1-P22. https://doi.org/10.1530/eje-18-0609.
118. Castro A, Oleaga A, Parente Arias P, et al. Executive summary of the SEORL CCC-SEEN consensus statement on post-thyroidectomy hypoparathyroidism. Acta Otorrinolaringol Esp. 2019;70(5):301-305. https://doi.org/10.1016/j.otorri.2019.04.001.
119. 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. https://doi.org/10.1089/thy.2017.0309.

https://doi.org/10.1016/j.surg.2014.09.007

Online supplementary material

Complications, Symptoms, Pre-surgical Predictors in Patients with Chronic Hypoparathyroidism: A Systematic Review

Table of Contents

Supplemental appendix 1. Detailed search strategy for the PART I

MEDINE, MEDINE-in process (via OVID)

1. exp hypoparathyroidism/
2. HypoPT.mp.
3. hypoparathyroidism.tw.
4. 1 or 2 or 3
5. exp complication/
6. complication*.tw. or symptom*.tw.
7. exp adverse events/
8. adverse events.tw. or side effect*.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to humans

EMBASE (Via OVID)

1. exp hypoparathyroidism/
2. HypoPT.mp.
3. hypoparathyroidism.tw.
4. 1 or 2 or 3
5. exp complication/
6. complication*.tw. or symptom*.tw.
7. exp adverse events/
8. adverse events.tw. or side effect*.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to humans

Cochrane library

1. (HypoPT):ti,ab,kw
2. MeSH descriptor: [Hypoparathyroidism] explode all trees
3. (hypoparathyroidism):ti,ab,kw
4. #1 or #2 or #3

Supplemental appendix 2. Detailed search strategy for the PART II

MEDINE, MEDINE-in process (via OVID)

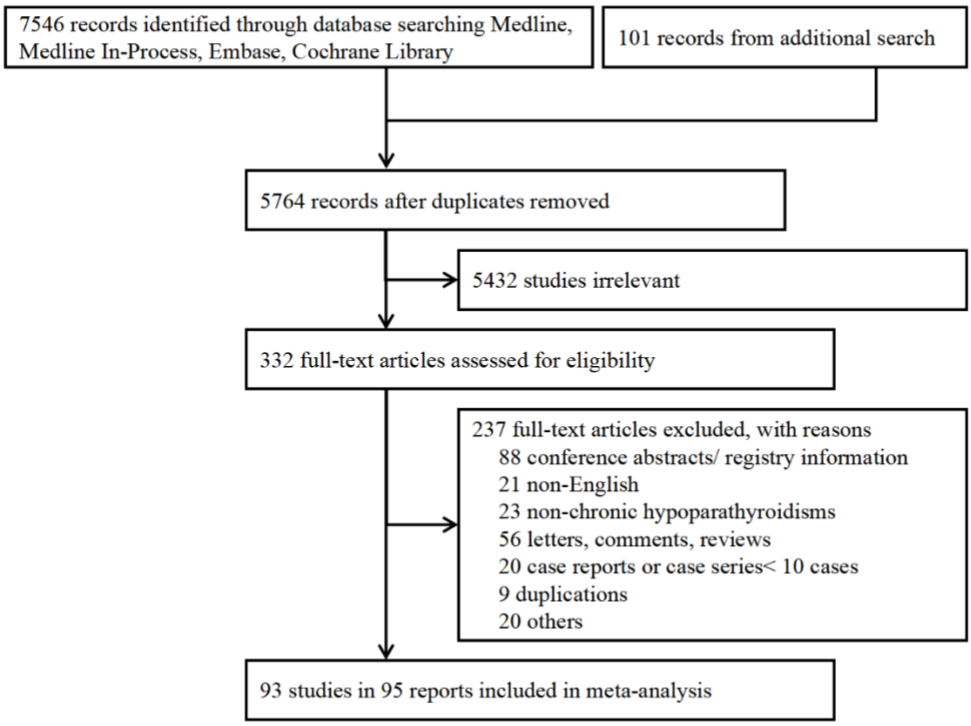
1. "Thyroidectomy"[Mesh] OR thyroid/surgery [mh] OR "thyroidectomy" OR "thyroidectomies" OR "thyroid surgery" OR "thyroid surgeries" OR "thyroid removal" OR “thyroid resection” [tiab]
2. "Parathyroid Hormone"[Mesh] OR "Parathyroid Hormone-Related Protein"[Mesh] OR "parathyroid hormone" OR "parathyroid hormones"[tiab]
3. "Calcium"[Mesh] or calcium [tiab]
4. Or/2-3
5. "hypoparathyroidism "[Mesh]) OR " HypoPT [tiab] OR hypoparathyroidism [tiab]
6. 1 and 4 and 5
7. #6 NOT ((animals NOT 'human'.sh)

Embase (via OVID)

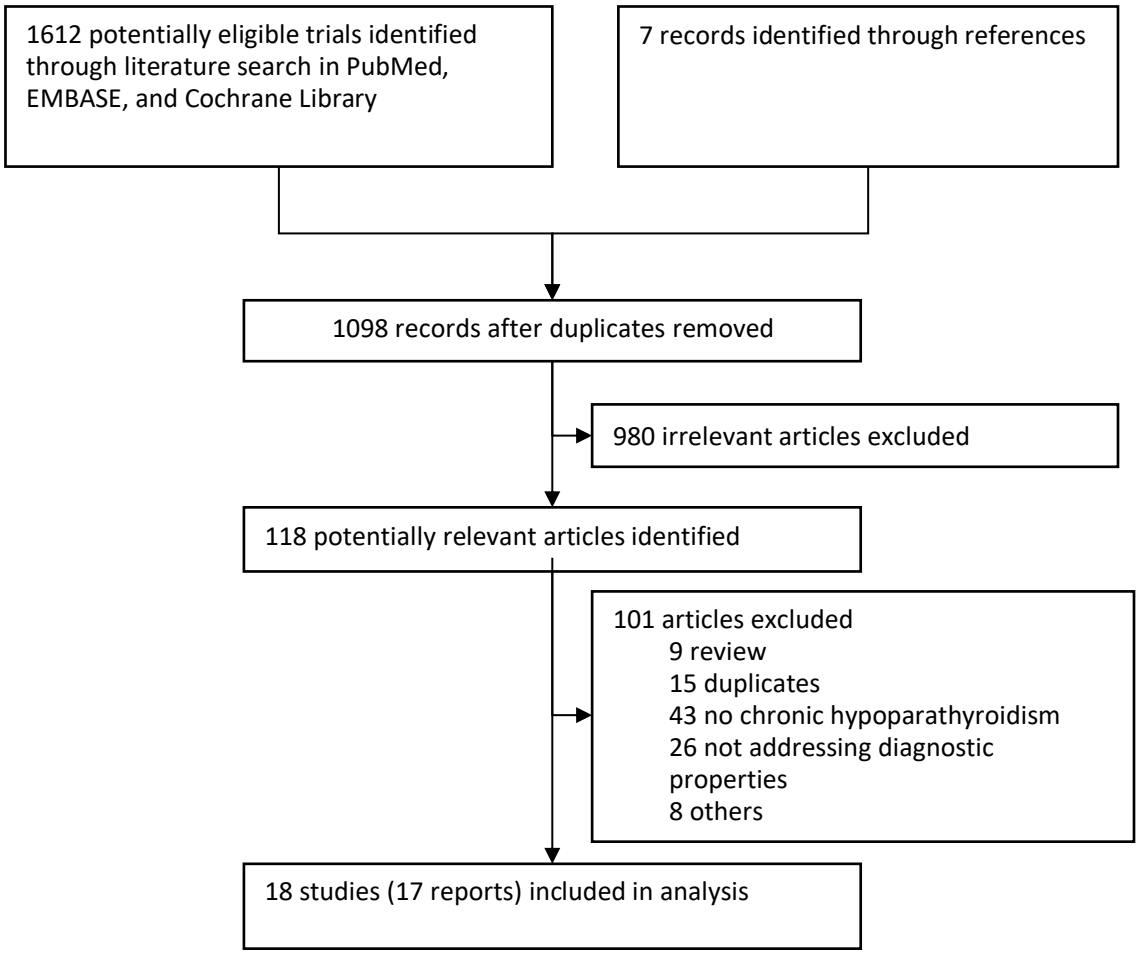
1. 'thyroid surgery'/exp OR 'thyroid surgery' OR thyroidectom*:ab,ti OR 'thyroid surgery':ab,ti OR 'thyroid surgeries':ab,ti OR 'thyroid removal':ab,ti or “thyroid resection” :ab,ti
2. 'parathyroid hormone'/exp OR 'parathyroid hormone-related protein':ab,ti OR 'parathyroid hormone':ab,ti OR 'parathyroid hormones':ab,ti
3. 'calcium'/exp and 'calcium':ab,ti
4. 2 or 3
5. hypoparathyroidism/exp OR HypoPT: ti/ab OR hypoparathyroidism.ab,ti.
6. 1 and 4 and 5
7. 'animal'/exp NOT 'human'.sh
8. 6 NOT 5

Cochrane library

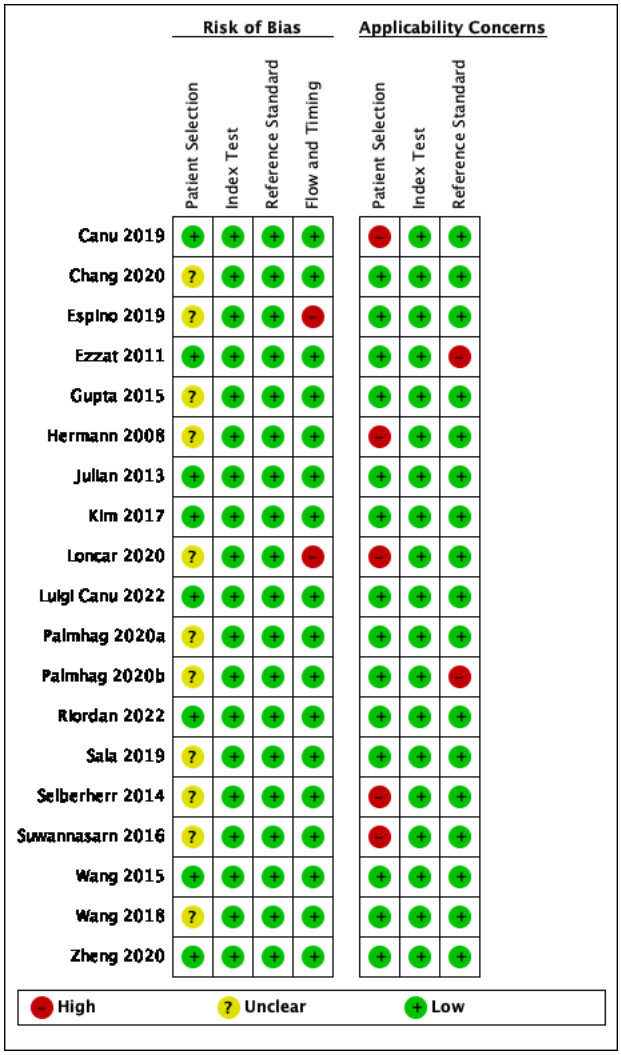
1. MeSH descriptor: [Thyroidectomy] explode all trees
2. MeSH descriptor: [Thyroid Gland] explode all trees and with qualifier(s): [Surgery - SU]
3. "thyroidectomy" or "thyroidectomies" or "thyroid surgery" or "thyroid surgeries" or "thyroid removal" :ti,ab,kw or “thyroid resection”: ti,ab,kw
4. OR/1-3
5. MeSH descriptor: [Parathyroid Hormone] explode all trees
6. MeSH descriptor: [Parathyroid Hormone-Related Protein] explode all trees
7. MeSH descriptor: [Calcium] explode all trees
8. "parathyroid hormone" or "parathyroid hormones" or “calcium”:ti,ab,kw
9. OR/5-8
10. MeSH descriptor: [hypoparathyroidism] explode all trees
11. Hypoparathyroidism or HypoPT: ":ti,ab,kw
12. OR/10-11
13. 4 and 9 and 12



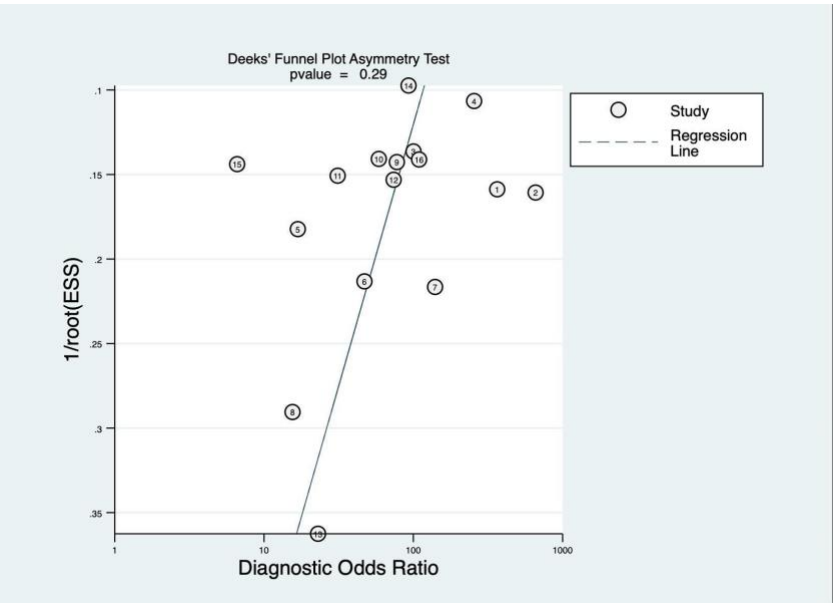
Supplemental Figure 1: Study selection of Part I



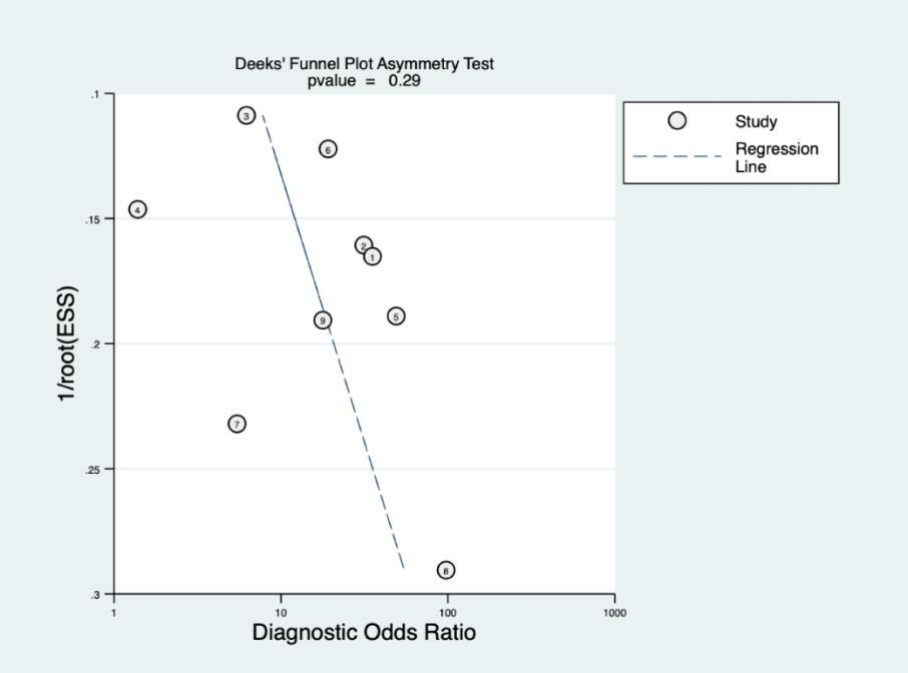
Supplemental Figure 2: Study selection of Part II



Supplemental Figure 3. Risk of bias assessment of Part II



Supplemental Figure 4. Publication bias to PTH test



Supplemental Figure 5. Publication bias to calcium test

Supplemental table 1. Characteristic of included studies (Part I)

Study	Design (single arm study/cohort study)	Site	Target at investigate complication	Patients' sources	No. of chronic HypoPT /control	Mean/ Median age (years)	Mean/ Median duration (years)	Female, N (%)	No. of post-surgical patients (%)	Adult/ Children	Clinical/ICD
Aggarwal 2013[1]	Cohort	India	No	Clinic	62/70	36.6	12	27 (44%)	0	Adult	Clinical
Arlt 2002[2]	Cohort	Germany	No	Hospital	25/25	48.4	3	25 (100%)	25 (100%)	Adult	Clinical
Chawla 2017[3]	Cohort	India	No	Clinic	104/64	37.2	15.1	48 (46%)	0	Adult	Clinical
Chou 2010[4]	Cohort	China	Yes	Hospital	19/38	56.4	9.3	14 (74%)	19 (100%)	Adult	Clinical
Cipriani 2021[5]	Cohort	Italy	Yes	University of Rome	50/40	65.4	19	50 (100%)	50 (100%)	Adult	Clinical
Goswami 2008[6]	Cohort	India	Yes	Hospital	40/14	35.1	9.6	23 (58%)	0	Adult	Clinical
Ketteler 2021[7] and Gosmanova 2021[8]	Cohort	USA	Yes	Database	8097/40485	58.6	>0.5	6173 (76%)	NR	Adult	ICD codes
Kim 2020[9]	Cohort	Korea	Yes	Database	210/2075	39.2	9.5	131 (62%)	0	Adult	ICD codes
Mazoni 2022[10]	Cohort	Italy	Yes	Clinic	89/89	49	7	70 (79%)	89 (100%)	Adult	Clinical
Mendonca 2013[11]	Cohort	Brazil	No	Hospital	16/17	62.3	15.3	16 (100%)	16 (100%)	Adult	Clinical
Meola 2018[12]	Cohort	Italy	No	Hospital	90/142	52	9	68 (76%)	90 (100%)	Adult	Clinical
Starr 2020[13]	Cohort	USA	No	Hospital	17/17	44.5	8.2	14 (82%)	14 (82%)	Adult	Clinical
Tabacco 2018[14]	Cohort	USA	Yes	Clinic	51/43	52.6	9.1	40 (92%)	51 (100%)	Adult	Clinical
Tasli 2020[15]	Cohort	Turkey	No	Hospital	35/40	48.1	0.6	23 (66%)	31 (89%)	Adult	Clinical

Underbjerg 2013[16] and Underbjerg 2014[17]	Cohort	Denmark	Yes	Database	688/2064	49	8.4	603 (88%)	688 (100%)	Adult	ICD codes
Underbjerg 2015[18]	Cohort	Denmark	Yes	Database	180/540	49.7	Chronic	95 (53%)	0	Adult	ICD codes
Vadiveloo 2019[19]	Cohort	UK	Yes	Database	280/1301	51.6	Chronic	194 (69%)	116 (41%)	Adult	ICD codes
Zavatta 2021[20]	Cohort	USA	Yes	Database	142/426	44	11	94 (66%)	114 (80%)	Adult	ICD codes
Almquist 2018[21]	Single arm	Sweden	No	Database	246	45.5	4.4	210 (85%)	246 (100%)	Adult	ICD codes
Ballesteros 2020[22]	Single arm	Mexico	Yes	Hospital	39	46.2	6.1	33 (85%)	39 (100%)	Adult	Clinical
Bernardor 2021[23]	Single arm	France	No	Hospital	10	10.7	>1	4 (40%)	1 (10%)	Children	Clinical
Bertocchio 2022[24]	Single arm	France	No	Hospital	107	51	10	76 (71%)	79 (74%)	Adult	Clinical
Bhadada 2011[25]	Single arm	India	Yes	Hospital	97	28.7	1.8	45 (46%)	0	both	Clinical
Bilezikian 2017[26]	Single arm	USA	No	11 US sites	42	48.4	≥1.5	35 (83%)	NR	Adult	Clinical
Bilginer 2022[27]	Single arm	Turkey	No	Clinic	64	48.6	5	52 (81%)	64 (100%)	Adult	Clinical
Brod 2020[28]	single arm	USA	Yes	NR	42	53	14	35 (83%)	36 (86%)	Adult	Clinical
Bruckner 2016[29]	Single arm	Germany	No	Hospital	33	37	15.9	18 (55%)	33 (100%)	Adult	Clinical
Chen 1998[30]	Single arm	China	No	Hospital	12	30.6	8.9	12 (100%)	7 (58%)	Adult	Clinical
Chen 2019[31]	Single arm	US, the UK, France, Germany, Italy, Spain, and Canada	Yes	Endocrinology practice setting	614	43.6	3.8	378 (62%)	457 (74%)	Adult	ICD codes

Coudenys 2019[32]	Single arm	Belgium	No	Hospital	101	50	6.6	80 (79%)	101 (100%)	Adult	Clinical
CusaNo 2013[33]	Single arm	USA	No	Hospital	54	46	13	40 (74%)	27 (50%)	Adult	Clinical
CusaNo 2013[34]	Single arm	USA	No	Medical Center	27	51	20	20 (74%)	16 (59%)	Adult	Clinical
CusaNo 2014[35]	Single arm	USA	No	Medical Center	69	46	12	55 (80%)	42 (61%)	Adult	Clinical
CusaNo 2020[36]	Single arm	USA	No	Hospital	33	47	6	24 (73%)	19 (58%)	Adult	Clinical
David 2019[37]	Single arm	Belgium	Yes	Hospital	170	58.1	16.6	103 (61%)	143 (84%)	Adult	Clinical
Gafni 2018[38]	Single arm	USA	No	NR	31	39.5	>1	25 (81%)	20 (65%)	Adult	Clinical
Gittoes 2021[39]	Single arm	North America, Europe	Yes	NR	737	49.1	10.1	587 (80%)	547 (74%)	Adult	Clinical
Goswami 2004[40]	Single arm	India	No	Clinic	51	33.1	7	22 (43%)	0	Adult	Clinical
Goswami 2012[41]	Single arm	India	Yes	Clinic	145	31.7	7.4	68 (47%)	0	Adult	Clinical
Gronskaia 2020[42]	Single arm	Russia	No	Hospital	200	45.4	>0.5	171 (86%)	165 (83%)	Adult	Clinical
Hadker 2014[43]	Single arm	USA	Yes	Association	374	49.4	12.6	318 (85%)	293 (78%)	Adult	Clinical
Hamdy 2020[44]	Single arm	Belgium, Netherlands	Yes	NR	97	48.5	5.1	66 (68%)	67 (69%)	Adult	Clinical
Hepsen 2020[45]	Single arm	Turkey	No	Hospital	160	47.2	7	141 (88%)	127 (79%)	Adult	Clinical
Huddle 1989[46]	Single arm	Black South Africans	Yes	NR	12	18-72	1-35	12 (100%)	0	Adult	Clinical
Karen 2020[47]	Single arm	USA	No	Clinic	27	4-67	17.6	18 (67%)	0	both	Clinical
Khan 2021[48]	Single arm	Canada	Yes	Universit	130	54	12	99 (76%)	91 (70%)	Adult	Clinical

				y, specialized academic and community centers							
Khan 2021b[49]	single arm	NR	No	NR	59	30.6	NR	48 (81%)	47 (80%)	Adult	Clinical
Kim 2015[50]	Single arm	Korea	Yes	NR	37	0.1	7	14 (38%)	0	Children	Clinical
KoncaDegertekin 2022[51]	Single arm	Turkey	Yes	Database	830	49.6	9.7	674 (81%)	686 (83%)	Adult	ICD codes
Kovaleva 2022[52]	Single arm	Russia	Yes	Database	544	55	>0.5	470 (86%)	480 (88%)	both	ICD codes
Lakatos 2016[53]	Single arm	Hungary	No	Hospital	24	52.7	15.1	21 (88%)	20 (83%)	Adult	Clinical
Laway 2006[54]	Single arm	India	No	Clinic	47	34.6	9.6	24 (51%)	0	Adult	Clinical
Levy 2015[55]	Single arm	Canada	Yes	Hospital	29	11.1	9.1	14 (48%)	1 (3%)	Children	Clinical
Leyre 2017[56]	Single arm	Spain	Yes	Hospital	32	51.2	6.5	29 (91%)	32 (100%)	Adult	Clinical
Liu 2020[57]	Single arm	China	Yes	Hospital	94	36.2	14	52 (55%)	0	Adult	Clinical
Lopera 2020[58]	Single arm	Colombia	Yes	Hospital	108	51.6	>0.5	99 (92%)	101 (94%)	Adult	Clinical
Lopes 2016[59]	Single arm	Brazil	Yes	Hospital	55	44.5	11.2	42 (76%)	41 (75%)	Adult	Clinical
Lui 2021[60]	Single arm	China	Yes	Database	460	49	NR	390 (85%)	460 (100%)	Adult	ICD codes
Mannstadt 2013[61]	Single arm	USA, Canada, Denmark, Hungary, Belgium, France, Italy, the UK	No	Hospital	134	47.5	13	105 (78%)	99 (74%)	Adult	Clinical
Mannstadt	Single arm	USA	No	12 US	49	48.1	15.9	40 (82%)	NR	Adult	Clinical

2019[62]				centers							
Marcucci 2021[63]	Single arm	USA	No	NR	12	48.6	12.6	7 (58%)	9 (75%)	Adult	Clinical
Marcucci 2021[64]	Single arm	Italy	No	9 Italian centers	25	32	>1	25 (100%)	21 (84%)	Adult	Clinical
Marcucci 2022[65]	Single arm	Italy	No	11 Italian centers	14	50.5	25.3	13 (93%)	11 (79%)	Adult	Clinical
Mitchell 2012[66]	Single arm	USA	Yes	Hospital	120	52	7.4	88 (73%)	79 (66%)	Adult	Clinical
Modi 2014[67]	Single arm	India	No	Hospital	70	23.5	13.5	37 (53%)	0	Adult	Clinical
Onder 2021[68]	single arm	Turkey	No	Medical Center	107	49.3	10	97 (91%)	107 (100%)	Adult	Clinical
Palermo 2018[69]	Single arm	Italy	No	9 Italian centers	42	55.8	2	38 (91%)	42 (100%)	Adult	Clinical
Rubin 2008[70]	Single arm	USA	No	Hospital	33	48.2	17	24 (73%)	18 (55%)	Adult	Clinical
Rubin 2010[71]	Single arm	USA	No	Hospital	30	49	19	22 (73%)	15 (50%)	Adult	Clinical
Rubin 2016[72]	Single arm	USA	No	Hospital	33	47	17.4	26 (79%)	20 (61%)	Adult	Clinical
Rubin 2016[73]	Single arm	USA	No	Medical Center	58	46	10	42 (72%)	34 (59%)	Adult	Clinical
Rujul 2020[74]	single arm	India	Yes	Hospital	32	27.2	5.9	12 (38%)	0	Adult	Clinical
Saha 2017[75]	Single arm	India	No	Clinic	101	34	14.1	NR	0	Adult	Clinical
Saha 2019[76]	Single arm	India	No	Clinic	92	25	15	45 (49%)	0	Adult	Clinical
Saha 2020[77]	Single arm	India	Yes	Clinic	165	40	15	75 (46%)	0	Adult	Clinical
Shrikrishna 2021[78]	single arm	India	Yes	Hospital	23	41.2	4	20 (87%)	23 (100%)	Adult	Clinical
Siggelkow 2020[79]	Single arm	Australia, Brazil, Canada, Denmark, France,	Yes	NR	398	51.7	8.7	310 (78%)	318 (80%)	Adult	ICD codes

		Germany, Italy, Japan, Norway, Spain, Sweden, UK, USA									
Storm 2021[80]	Single arm	Denmark	No	Hospital	24	54	>0.5	17 (71%)	24 (100%)	Adult	Clinical
Streeten 2017[81]	Single arm	USA	No	Hospital	30	55.2	13.5	23 (77%)	21 (70%)	Adult	Clinical
Sumida 2016[82]	Single arm	Japan	No	Hospital	19	71.3	1	9 (47%)	18 (95%)	Adult	Clinical
Tabacco 2019[83]	Single arm	Ireland	No	Hospital	20	49	8	16 (80%)	12 (60%)	Adult	Clinical
Tay 2019[84]	Single arm	USA	No	Hospital	24	46.2	29.9	18 (75%)	13 (54%)	Adult	Clinical
Underbjerg 2018[85]	Single arm	Danish	Yes	Database	431	41	12.7	351 (81%)	380 (88%)	Adult	Clinical
Wang 2009[86]	Single arm	China	No	Hospital	24	36.5	8.2	16 (67%)	6 (25%)	Adult	Clinical
Wang 2020[87]	Single arm	China	No	Hospital	160	20	>6	NR	0	Children	Clinical
Wilde 2020[88]	Single arm	Germany	No	Hospital	49	57.3	12.6	41 (84%)	49 (100%)	Adult	Clinical
Winer 1996[89]	Single arm	USA	No	National Institutes of Health (NIH) patients and outside physicians	10	46.5	16.5	4 (40%)	4 (40%)	Adult	Clinical
Winer 1998[90]	Single arm	USA	No	Hospital	17	41.5	19	13 (77%)	9 (53%)	Adult	Clinical
Winer 2003[91]	Single arm	USA	No	NR	27	18-27	1-36	17 (63%)	11 (41%)	Adult	Clinical
Winer 2008[92]	Single arm	USA	No	Clinical research	14	4–17	1-11	4 (29%)	1 (7%)	Children	Clinical

				center							
Winer 2010[93]	Single arm	USA	No	Hospital	12	5–14	NR	8 (75%)	0	Children	Clinical
Winer 2018[94]	Single arm	UK	Yes	Clinic	14	10.5	8.6	9 (64%)	0	Children	Clinical
Zanchetta 2021[95]	single arm	Argentina	Yes	Hospital	322	55.2	10.9	276 (86%)	292 (91%)	Adult	Clinical

Supplemental table 2. risk of bias of single-arm (case-series) studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score (risk of bias)
Aggarwal 2013[1]	Yes	Yes	CD	Yes	Yes	Yes	CD	Yes	Yes	7 (low)
Almquist 2018[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Arlt 2002[2]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Ballesteros 2020[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Bernardor 2021[23]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Bertocchio 2022 [24]	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	7 (low)
Bhadada 2011[25]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	7 (low)
Bilezikian 2017[26]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Bilginer 2022[27]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	9 (low)
Brod 2020[28]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7 (low)
Bruckner 2016[29]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Chawla 2017[3]	Yes	Yes	Yes	Yes	NA	Yes	CD	Yes	Yes	7 (low)
Chen 1998[30]	Yes	No	CD	CD	Yes	Yes	Yes	No	Yes	6 (moderate)
Chen 2019[31]	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	8 (low)
Chou 2010[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Cipriani 2021[5]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	9 (low)
Coudenys 2019[32]	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	8 (low)
Cusano 2013a[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Cusano 2013b[33]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Cusano 2014[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Cusano 2020[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
David 2019[37]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Gafni 2018[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Gittoes 2021[39]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Goswami 2004[40]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	7 (low)
Goswami 2008[6]	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	8 (low)
Goswami 2012[41]	Yes	Yes	Yes	No	NA	Yes	Yes	Yes	Yes	7 (low)
Gronskaia 2020[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Hadker 2014[43]	Yes	Yes	CD	No	NA	Yes	CD	Yes	Yes	5 (moderate)

Hamdy 2020[44]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7 (low)
Hepsen 2020[45]	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7 (low)
Huddle 1989[46]	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	7 (low)
Karen 2020[47]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Ketteler 2021[7]and Gosmanova 2021[8]	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	Yes	7 (low)
Khan 2021[48]	Yes	Yes	CD	Yes	NA	Yes	NA	Yes	Yes	6 (moderate)
Khan 2021b[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Kim 2015[50]	Yes	Yes	CD	Yes	NA	Yes	Yes	Yes	Yes	7 (low)
Kim 2020[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
KoncaDegertekin 2022[51]	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	Yes	7 (low)
Kovaleva 2022[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Lakatos 2016[53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Laway 2006[54]	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	8 (low)
Levy 2015[55]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Leyre 2017[56]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Liu 2020[57]	Yes	Yes	Yes	Yes	NA	Yes	CD	Yes	Yes	7 (low)
Lopera 2020[58]	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	8 (low)
Lopes 2016[59]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Lui 2021[60]	Yes	Yes	CD	CD	No	Yes	CD	Yes	Yes	5 (moderate)
Mannstadt 2013[61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Mannstadt 2019[62]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Marcucci 2021[64]	Yes	Yes	CD	CD	No	Yes	CD	Yes	Yes	5 (moderate)
Marcucci 2021[63]	Yes	Yes	CD	Yes	Yes	Yes	No	Yes	Yes	7 (low)
Marcucci 2022[65]	Yes	Yes	CD	CD	Yes	Yes	Yes	Yes	Yes	7 (low)
Mazoni 2022[10]	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	Yes	7 (low)
Mendonca 2013[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Meola 2018[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Mitchell 2012[66]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Modi 2014[67]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Onder 2021[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Palermo 2018[69]	Yes	Yes	CD	No	Yes	Yes	Yes	Yes	Yes	7 (low)
Rubin 2008[70]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)

Rubin 2010[71]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Rubin 2016a[72]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Rubin 2016b[73]	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	8 (low)
Rujul 2020[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Saha 2017[75]	Yes	Yes	Yes	No	NA	Yes	Yes	Yes	Yes	7 (low)
Saha 2019[76]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Saha 2020[77]	Yes	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	7 (low)
Shrikrishna 2021[78]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Siggelkow 2020[79]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Starr 2020[13]	Yes	Yes	CD	No	Yes	Yes	Yes	Yes	Yes	7 (low)
Storm 2021[80]	Yes	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	7 (low)
Streeten 2017[81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Sumida 2016[82]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Tabacco 2018[14]	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7 (low)
Tabacco 2019[83]	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Tasli 2020[15]	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Tay 2019[84]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Underbjerg 2013[16] and 2014[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Underbjerg 2015[18]	Yes	Yes	Yes	CD	Yes	Yes	CD	Yes	Yes	7 (low)
Underbjerg 2018[85]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Vadiveloo 2019[19]	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	8 (low)
Wang 2009[86]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Wang 2020[87]	Yes	Yes	Yes	No	No	No	Yes	Yes	No	5 (moderate)
Wilde 2020[88]	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	7 (low)
Winer 1996[89]	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes	8 (low)
Winer 1998[90]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8 (low)
Winer 2003[91]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Winer 2008[92]	Yes	Yes	CD	Yes	Yes	Yes	CD	Yes	Yes	7 (low)
Winer 2010[93]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)
Winer 2018[94]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)
Zanchetta 2021[95]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 (low)

Zavatta 2021[20]	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	8 (low)

CD = cannot determine

The NIH Quality Assessment Tool for Case Series Studies poses nine questions. Q1: Was the study question or objective clearly stated? Q2: Was the study population clearly and fully described, including a case definition? Q3: Were the cases consecutive? Q4: Were the subjects comparable? Q5: Was the intervention clearly described? Q6: Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? Q7: Was the length of follow-up adequate? Q8: Were the statistical methods well-described? Q9: Were the results well-described

Supplemental table 3. Risk of bias of cohort studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Score (risk of bias)
Aggarwal 2013[1]	definitely yes	definitely yes	probably no	definitely yes	probably no	definitely yes	definitely yes	definitely no	5 (moderate)
Arlt 2002[2]	definitely yes	definitely yes	probably no	definitely yes	probably no	definitely yes	definitely yes	definitely no	5 (moderate)
Chawla 2017[3]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	probably yes	definitely no	6 (moderate)
Chou 2010[4]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	definitely yes	definitely no	6 (moderate)
Cipriani 2021[5]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	definitely yes	definitely no	6 (moderate)
Goswami 2008[6]	definitely no	definitely yes	probably yes	probably yes	definitely yes	definitely yes	definitely yes	definitely no	6 (moderate)
Ketteler 2021[7]and Gosmanova 2021[8]	definitely yes	definitely yes	definitely no	definitely yes	probably no	definitely yes	definitely yes	definitely no	5 (moderate)
Kim 2020[9]	definitely no	definitely yes	definitely yes	definitely yes	definitely no	definitely yes	definitely yes	definitely no	5 (moderate)
Mazoni 2022[10]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	definitely yes	definitely no	6 (moderate)
Mendonca 2013[11]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	definitely yes	definitely no	6 (moderate)
Meola 2018[12]	definitely yes	definitely yes	definitely yes	definitely yes	definitely no	definitely yes	definitely yes	definitely no	6 (moderate)
Starr 2020[13]	definitely no	definitely yes	definitely no	definitely yes	definitely no	definitely yes	definitely yes	definitely no	4 (high)
Tabacco 2018[14]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	definitely yes	definitely no	6 (moderate)
Tasli 2020[15]	definitely no	probably yes	probably no	definitely yes	definitely yes	definitely yes	probably yes	definitely no	5 (moderate)
Underbjerg 2013[16] and 2014[17]	definitely no	definitely yes	probably no	definitely yes	probably yes	definitely yes	definitely yes	definitely no	5 (moderate)
Underbjerg 2015[18]	definitely yes	definitely	definitely yes	definitely	probably no	definitely yes	probably yes	definitely	7 (low)

		yes		yes				yes	
Vadiveloo 2019[19]	definitely no	definitely yes	definitely no	definitely yes	probably no	definitely yes	definitely yes	definitely no	4 (high)
Zavatta 2021[20]	definitely yes	definitely yes	definitely yes	definitely yes	probably no	definitely yes	definitely yes	definitely no	6 (moderate)

Note: Q1: Was selection of exposed and non-exposed cohorts drawn from the same population? Q2: Can we be confident in the assessment of exposure? Q3: Can we be confident that the outcome of interest was not present at start of study? Q4: Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Q5: Can we be confident in the assessment of the presence or absence of prognostic factors? Q6: Can we be confident in the assessment of outcome? Q7: Was the follow up of cohorts adequate? Q8: Were co-interventions similar between groups?

Supplemental table 4. Complications/symptoms (≤2 included studies) in patients with chronic hypoparathyroidism versus control population

Complication/symptom	No. of studies	No. of patients/ control	Crude OR (95%CI)	Adjusted HR/OR (95%CI)
Musculoskeletal and connective tissue disorders				
Ankle or foot fracture	2 [17 18]	868/2604	1.43 (0.81, 2.52)	
Atypical femur fracture	2 [17 18]	868/2604	1.29 (0.49, 3.36)	
Forearm fracture	2 [17 18]	868/2604	1.12 (0.74, 1.71)	
Proximal femur fracture	2 [17 18]	868/2604	1.00 (0.61, 1.63)	
Pelvic fracture	2 [17 18]	868/2604	9.03 (0.37, 222.74)	
Hip fracture	1 [9]	210/2075	0.43 (0.03, 7.26)	
Multiple vertebrae fracture	1 [3]	104/64	15.87 (0.92, 274.06)	
Sacroiliitis	1 [6]	40/14	9.98 (0.55, 182.37)	
Spondyloarthropathy	1 [6]	40/14	15.87 (0.88, 285.8)	
Musculoskeletal compromise	1 [20]	142/426	1.20 (0.80, 1.81)	
Pain				
Bone pain	1 [4]	19/38	1.20 (0.27, 5.30)	
Brain/central nervous system				
Basal ganglia calcification	2 [6 20]	181/440	5.61 (3.41, 9.22)	
Headache	1 [20]	142/426	0.84 (0.58, 1.24)	
Insomnia	1 [4]	19/38	0.51 (0.17, 1.59)	

Sleep disorders	1 [20]	142/426	1.38 (0.94, 2.03)	
Cardiovascular and metabolic disorders				
Heart failure	2 [8 9]	8307/42560	2.58 (2.31, 2.88)	2.43 (1.22, 4.83)
Hypertension	2 [8 20]	8239/40911	2.24 (2.13, 2.35)	
Neuropsychiatric				
Already significant impairment of mood	1 [2]	25/25	1.83 (0.39, 8.67)	
Ataxia/lack of coordination	1 [20]	142/426	0.83 (0.54, 1.27)	
Cognitive impairment or dementia	1 [20]	142/426	0.85 (0.51, 1.41)	
Hostility	1 [1]	25/25	11.29 (1.29, 98.89)	
Mannerism and posturing	1 [1]	25/25	5.43 (0.25, 118.96)	
Memory loss or forgetfulness	1 [20]	142/426	1.10 (0.60, 2.02)	
Parkinsonism	1 [20]	142/426	0.95 (0.37, 2.41)	
Presence of guilt feelings	1 [1]	25/25	4.57 (0.47, 44.17)	
Severe impairment of well-being and mood	1 [2]	25/25	2.92 (0.87, 9.78)	
Somatic concern	1 [1]	25/25	17.00 (0.90, 320.37)	
Tension	1 [1]	25/25	5.09 (1.45, 17.92)	
Metabolism and nutrition disorders				
Diabetes	2 [8 20]	8239/40911	2.23 (2.10, 2.37)	
Dyslipidemia	1 [20]	142/426	1.39 (0.95, 2.03)	
Hypocalcemia	1 [5]	50/40	54.44 (3.17, 936.02)	
Infections and infestations				
Infections in the upper airways	2 [17 18]	868/2604	1.96 (1.54, 2.49)	
Urinary tract infections	2 [17 18]	868/2604	1.93 (1.44, 2.58)	
Skin				
Skin itching	1 [4]	19/38	2.41 (0.76, 7.66)	
Eye				
Papilledema	1 [15]	70/80	0	
Other				
General weakness	1 [4]	19/38	0.72 (0.23, 2.23)	

Tremor	1 [20]	142/426	1.17 (0.66, 2.09)

Supplemental table 5. The prevalence of complications/symptoms (reported by >2 included studies) in all patients with chronic hypoparathyroidism

Complication/Symptom	No. of studies (No. of patients)	Median (IQR, %)
Musculoskeletal and connective tissue disorders		
Any fracture	29 (5091) [3 5 9 11 13 17-19 22 33 34 36 43 44 51 52 54 56 57 60 66 71-73 78 79 82 84 95]	13 (4, 19)
Vertebra fracture	9 (2666) [3 5 9 11 17 18 51 52 66]	4 (2, 18)
Upper extremities fracture	8 (2572) [9 17 18 33 51 52 66 73]	7 (3, 12)
Lower extremities fracture	7 (2028) [9 17 18 33 51 66 73]	4 (2, 9)
Ankle or foot fracture	6 (1532) [17 18 33 52 66 73]	4 (2, 5)
Humerus or wrist fracture	5 (1176) [9 17 18 33 66]	3 (2, 4)
Pelvic fracture	4 (1466) [17 18 33 52]	1 (0, 1)
Arm fracture	3 (912) [17 18 66]	9 (2, 11)
Muscle spasms	21 (3086) [5 25 26 28 29 39 40 42-44 46 53 54 58 61 62 64 74 86 87 95]	59 (20, 70)
Tetany	12 (2619) [5 29 39 42-44 46 53 54 61 64 95]	13 (11, 65)
Decreased bone mineral density	5 (1888) [5 22 38 43 51]	6 (4, 6)
Carpopedal spasm	4 (263) [25 58 74 87]	64 (38, 70)
Muscular weakness	4 (825) [28 39 86 87]	27 (9, 53)
Pain		
Bone pain	6 (858) [4 28 38 39 90 93]	11 (8, 29)
Muscle pain	6 (2223) [31 39 43 61 69 95]	12 (7, 23)

Joint pain	4 (1767) [28 31 39 43]	20 (14, 44)
Back pain	3 (920) [39 61 62]	16 (13, 20)
Extremity pain	3 (895) [39 53 61]	10 (8, 13)
Gastrointestinal disorders		
Constipation	5 (1861) [22 31 39 43 44]	11 (10, 22)
Nausea	4 (1262) [39 43 61 90]	14 (7, 25)
Brain/central nervous system		
Intracranial calcification	33 (3698) [3 5 6 9 20 34 37 40 41 44 46 48 50-52 54 58 59 63 66-68 70 72-77 79 84 94 95]	25 (9, 68)
Basal ganglia calcification	22 (1662) [3 5 6 20 34 41 46 48 50 52 58 59 63 66-68 70 72-74 84 95]	29 (9, 55)
Headache	7 (2067) [20 28 31 39 43 53 61]	17 (15, 42)
Sleep disorders	3 (1130) [5 20 43]	44 (9, 57)
Impaired neurological	3 (1050) [1 5 43]	27 (5, 35)
Cardiovascular and metabolic disorders		
Hypertension	10 (10519) [7 12 20 27 31 32 51 61 62 79]	23 (12, 41)
Heart failure	5 (8876) [7 9 44 46 60]	4 (3, 6)
Myocardial infarct	4 (1908) [9 16 18 51]	2 (1, 4)
Stroke	4 (1538) [9 16 18 60]	5 (4, 7)
Neuropsychiatric		
Anxiety	9 (2935) [1 17 18 31 39 43 44 61 62]	14 (4, 25)
Neuropschiatric disease	5 (1668) [5 18 27 51 52]	8 (5, 20)
Memory loss or forgetfulness	4 (1227) [20 25 31 43]	11 (10, 36)
Irritability	4 (1117) [25 31 43 74]	28 (15, 45)

Cognitive impairment or dementia	3 (1586) [5 20 51]	3 (0, 16)
Parkinsonism	3 (1034) [1 20 51]	3 (1, 4)
Impaired wellbeing	3 (432) [2 29 43]	48 (37, 61)
Inability to focus or concentrate	3 (1000) [31 43 63]	15 (8, 65)
Respiratory problems		
Sinusitis	3 (225) [26 61 62]	6 (2, 31)
Shortness of breath	3 (680) [5 28 53]	7 (1, 8)
Metabolism and nutrition disorders		
Diabetes	11 (10925) [3 7 12 20 27 31 32 51 60 64 79]	12 (4, 20)
Hypocalcemia	7 (1415) [5 10 23 51 52 65 80]	48 (40, 71)
Hypercalcemia	5 (1448) [23 51 52 80 83]	8 (3, 10)
Hypercalciuria	5 (8296) [7 48 59 65 89]	29 (24, 36)
Infections and infestations		
Infections in the upper airways	6 (1119) [17 18 26 61 62 87]	11 (7, 27)
Urinary tract infections	3 (917) [17 18 62]	17 (7, 18)
Other		
Paresthesia	13 (2813) [25 31 39 42-44 53 58 61 62 64 74 95]	31 (27, 54)
Fatigue	9 (2071) [28 31 39 43 44 53 61 74 90]	35 (17, 82)
Chvostek’s sign	4 (172) [30 58 74 86]	55 (20, 88)
Trousseau's sign	4 (172) [30 58 74 86]	77 (36, 98)
Hearing loss	4 (509) [3 43 50 87]	13 (7, 48)
Dental problems	3 (503) [25 43 74]	25 (8, 29)

Supplemental table 6. Characteristics of included studies (Part II)

Study	Country	Design	Total N	Mean age, y	N, % Female	N, % Children	N, % total thyroidectomy	Predictors	Diagnostic criteria of Chronic Hypoparathyroidism	N, % Chronic Hypoparathyroidism	N, % receiving auto transplantation	Monitoring by endocrinologist
Chang 2020[96]	China	prospective	143	56	114(80)	0	143(100)	PTH	serum PTH<15 pg/mL; Ca and/or vitamin D administration was required 12 months after surgery	11 (8)	0	NR
Loncar 2020[97]	Netherland	prospective	81	53	59(73)	0	64 (80)	PTH	Persistent need for calcium supplementation 12 months after surgery.	14 (17)	NR	Yes
Palmhag 2020a[98]	Sweden	prospective	39	46	31(79)	0	39(100)	PTH	Patients still in need of medication with active vitamin D and/or calcium at 12 months after surgery.	1 (3)	8 (20)	NR
Sala 2019[99]	Romania	prospective	134	52	118(88)	0	134(100)	PTH; Serum Ca	Patients with biochemical hypocalcemia at 6 months after surgery were confirmed to have permanent hypoparathyroidism.	8 (6)	NR	NR
Suwannasarn 2017[100]	Thailand	prospective	65	43	56 (86)	0	61(94)	PTH	ongoing requirement for supplementation of calcium and active vitamin D beyond 6 months.	19 (29)	0	NR
Gupta 2015[101]	India	prospective	90	41	76(85)	0	90(100)	PTH; Serum Ca	serum PTH <14 pg/ml; duration> 6months after surgery	10 (11)	NR	NR
Ezzat 2011[102]	Egypt	prospective	52	36	45(86)	0	52(100)	PTH;	serum PTH <15pg/mL, duration> 3 months after surgery.	5 (10)	NR	NR
Hermann 2008[103]	Austria	prospective	402	54	319(79)	0	343(85)	PTH; Serum Ca	serum PTH <6 pg/ ml, calcium < 2.1 mmol/L, or calcium and/or vitamin D treatment was necessary to treat for more than 12 months.	6(1)	41(10)	NR
Palmhag 2020b[98]	Sweden	retrospective	366	43	318(87)	0	366(100)	PTH	Patients still in need of active vitamin D and/or calcium at 12 months after surgery.	11 (3)	63(17)	NR

Zheng 2020[104]	China	retrospective	546	51	388(71)	0	546(100)	PTH; Serum Ca	serum PTH<15 pg/mL; requiring calcium and/or vitamin D supplementation for 6 months postoperatively	22(4)	0	NR
Canu 2019[105]	Italy	retrospective	75	49	59(79)	0	75(100)	PTH	serum PTH <10pg/mL for more than 12 months.	14 (19)	0	NR
Espino 2019[106]	Spain	retrospective	481	53	392(82)	0	481(100)	PTH; Serum Ca	serum PTH <15 pg/ml, need for calcium and vitamin D supplementation more than 12 months after surgery.	28(6)	0	Yes
Wang 2018 [107]	China	retrospective	110	42	78 (71)	0	110(100)	PTH; Serum Ca	serum PTH<15 pg/mL; serum calcium < 2.0 mmol/L; the need to receive calcium or vitamin D supplementation for more than 6 months.	10 (9)	NR	NR
Selberherr 2015[108]	Austria	retrospective	237	54	191(81)	0	237(100)	PTH; Serum Ca	serum PTH <15 pg/mL; serum calcium <2.0 mmol/L; for more than 6 months	2(1)	53(22)	NR
Wang 2015[109]	China	retrospective	438	47	352 (80)	0	438(100)	PTH; Serum Ca	serum PTH levels <15 pg/ml; calcium <2.00 mmol/L; calcium and/or vitamin D supplementation were necessary for more than 12 months.	12 (3)	39(9)	NR
Julian 2013[110]	Spain	retrospective	70	51	65(93)	0	70(100)	PTH; Serum Ca	serum PTH<15 pg/ ml; requiring calcium and/or vitamin D supplementation postoperatively for 6 months	5 (7)	0	Yes
Luigi Canu 2022[111]	Italy	retrospective	426	54	309 (72.54)	0	426(100)	PTH	PTH levels below the normal range for more than 12 months.	29(7)	7(1.64)	NR
Riordan 2022[112]	Ireland	retrospective	570	50	487 (85.4)	0	521(91)	PTH	any calcium level < 2.10 mmol/l > 6 months postoperatively, or any need for calcium and/or vitamin D >6 months postoperatively, irrespective of PTH or calcium levels.	30(5)	NR	NR

Supplemental table 7. descriptive analysis of diagnostic accuracy of measuring early PTH/calcium to predict chronic hypoparathyroidism.

PTH/calcium cut-off	No. of patients (No. of reports)	Sensitivity/ median (range), %	Specificity/ median (range), %
PTH ≤10	3666 (12)	100(90-100)	83(18-88)
PTH 10-15	488 (4)	97 (82-100)	82 (72-94)
PTH change of >50%	81 (1)	100	75
PTH absolute <9.3 & change >86%	90 (1)	100	98
Calcium ≤1	481 (1)	92	65
Calcium 1-2	2027 (8)	92(58-100)	78(50-88)

Supplemental table 8. Summary of findings (GRADE)

Outcome	No of studies (No of patients)	Study design	Test property, (95%)	Test result	Effect per 1,000 patients tested				Quality of evidence
					pre-test probability of 10 per 1000	pre-test probability of 50 per 1000	pre-test probability of 100 per 1000	pre-test probability of 200 per 1000	
PTH (determination of chronic hypoparathyroidism at 6- month after surgery)									
Sensitivity (TP + FN)	8 (1822)	Cohort	99 (82-100)	TPs	10 (8-10)	50 (41-50)	99(82-100)	198(164-200)	MODERATE [a]
				FNs	0 (0-2)	1 (0-9)	1 (0-18)	2 (0-36)	
Specificity (FP + TN)	8 (1822)	Cohort	87 (79-93)	FPs	129 (69-208)	124 (67-200)	117(63-189)	104 (56-168)	LOW [a,b]
				TNs	861(782-921)	827 (751-884)	783 (711-837)	696 (632-744)	
PTH (determination of chronic hypoparathyroidism at 12- month after surgery)									
Sensitivity (TP + FN)	9 (2451)	Cohort	99 (86-100)	TPs	10 (9-10)	50 (43-50)	99(86-100)	198(172-200)	MODERATE [a]
				FNs	0 (0-1)	1 (0-7)	1 (0-14)	2 (0-28)	
Specificity (FP + TN)	9 (2451)	Cohort	72 (55-84)	FPs	277 (158-446)	266 (152-428)	252 (144-405)	224 (128-360)	LOW [a,b]
				TNs	713(545-832)	684 (523-798)	648 (495-756)	576 (440-672)	
Calcium (determination of chronic hypoparathyroidism at 6- month after surgery)									
Sensitivity (TP + FN)	6 (1187)	Cohort	89 (59-98)	TPs	9 (6-10)	45(30-49)	89 (59-98)	178(118-196)	LOW [a,b]
				FNs	1 (0-4)	6 (1-21)	11 (2-41)	22 (4-82)	
Specificity (FP + TN)	6 (1187)	Cohort	80 (73-85)	FPs	198(149-267)	190(143-257)	180 (135-243)	160 (120-216)	LOW [a,b]
				TNs	792(723-842)	760(694-808)	720(657-765)	640 (584-680)	

TP: True positives (patients correctly classified as chronic hypoparathyroidism); FN: False negatives (patients incorrectly classified as not having chronic hypoparathyroidism); FP: False positives (patients incorrectly classified as having chronic hypoparathyroidism); TN: True negatives (patients correctly classified as not having chronic hypoparathyroidism)

Explanations

a. most studies at unclear risk of bias in the patient selection

b. 95% confidence interval imprecise lowering certainty in overall pooled estimate

References

1. Aggarwal S, Kailash S, Sagar R, et al. Neuropsychological dysfunction in idiopathic hypoparathyroidism and its relationship with intracranial calcification and serum total calcium. *Eur J Endocrinol* 2013;168(6):895-903. doi: 10.1530/eje-12-0946 [published Online First: 2013/03/14]

2. 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. *European Journal of Endocrinology* 2002;146(2):215-22. doi: http://dx.doi.org/10.1530/eje.0.1460215

3. Chawla H, Saha S, Kandasamy D, et al. Vertebral fractures and bone mineral density in patients with idiopathic hypoparathyroidism on long-term follow-up. *Journal of Clinical Endocrinology and Metabolism* 2017;102(1):251-58. doi: http://dx.doi.org/10.1210/jc.2016-3292

4. Chou FF, Chi SY, Hsieh KC. Hypoparathyroidism after total parathyroidectomy plus subcutaneous autotransplantation for secondary hyperparathyroidism--any side effects? *World journal of surgery* 2010;34(10):2350-54.

5. Cipriani C, Minisola S, Bilezikian JP, et al. Vertebral Fracture Assessment in Postmenopausal Women With Postsurgical Hypoparathyroidism. *J Clin Endocrinol Metab* 2021;106(5):1303-11. doi: 10.1210/clinem/dgab076 [published Online First: 2021/02/11]

6. Goswami R, Ray D, Sharma R, et al. Presence of spondyloarthropathy and its clinical profile in patients with hypoparathyroidism. *Clinical Endocrinology* 2008;68(2):258-63. doi: http://dx.doi.org/10.1111/j.1365-2265.2007.03032.x

7. Ketteler M, Chen K, Gosmanova EO, et al. Risk of Nephrolithiasis and Nephrocalcinosis in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. *Advances in therapy* 2021;38(4):1946-57. doi: 10.1007/s12325-021-01649-2 [published Online First:

2021/03/12]

8. Gosmanova EO, Chen K, Rejnmark L, et al. Risk of Chronic Kidney Disease and Estimated Glomerular Filtration Rate Decline in Patients with Chronic Hypoparathyroidism: A Retrospective Cohort Study. *Advances in therapy* 2021;38(4):1876-88. doi: 10.1007/s12325-021-01658-1 [published Online First: 2021/03/10]
9. Kim SH, Rhee Y, Kim YM, et al. Prevalence and complications of nonsurgical hypoparathyroidism in Korea: A nationwide cohort study. *PLoS ONE* 2020;15(5):e0232842. doi: http://dx.doi.org/10.1371/journal.pone.0232842
10. Mazoni L, Matrone A, Apicella M, et al. Renal complications and quality of life in postsurgical hypoparathyroidism: a case-control study. *J Endocrinol Invest* 2022;45(3):573-82. doi: 10.1007/s40618-021-01686-2 [published Online First: 2021/10/13]
11. Mendonca ML, Pereira FA, Nogueira-Barbosa MH, et al. Increased vertebral morphometric fracture in patients with postsurgical hypoparathyroidism despite normal bone mineral density. *BMC Endocrine Disorders* 2013;13((Mendonca, Pereira, Nogueira-Barbosa, Monsignore, Teixeira, Maciel, de Paula) Department of Internal Medicine, School of Medicine of Ribeirao Preto, University of Sao Paulo, Sao Paulo, Brazil(Watanabe) Department of Radiology, School of Dentistry of Ribei):1. doi: http://dx.doi.org/10.1186/1472-6823-13-1
12. Meola A, Vignali E, Matrone A, et al. Efficacy and safety of long-term management of patients with chronic post-surgical hypoparathyroidism. *Journal of Endocrinological Investigation* 2018;41(10):1221-26. doi: http://dx.doi.org/10.1007/s40618-018-0857-5
13. Starr JR, Tabacco G, Majeed R, et al. PTH and bone material strength in hypoparathyroidism as measured by impact microindentation. *Osteoporosis International* 2020;31(2):327-33. doi: http://dx.doi.org/10.1007/s00198-019-05177-2
14. Tabacco G, Naciu AM, Maggi D, et al. Cardiovascular Autonomic Neuropathy as a New Complication of Postsurgical Chronic Hypoparathyroidism. *Journal of Bone and Mineral*

Research 2019;34(3):475-81. doi: http://dx.doi.org/10.1002/jbmr.3623

15. Tasli NG, Akbas EM. Ocular Findings Associated with Hypoparathyroidism. *Ocular Immunology and Inflammation* 2020((Tasli) Department of Ophthalmology, College of Medicine, Erzincan Binali Yildirim University Hospital, Erzincan, Turkey(Akbas) Department of Internal Medicine, Division of Endocrinology, College of Medicine, Erzincan Binali Yildirim University Hospital) doi: http://dx.doi.org/10.1080/09273948.2020.1735451
16. Underbjerg L, Sikjaer T, Mosekilde L, et al. Cardiovascular and renal complications to postsurgical hypoparathyroidism: A Danish nationwide controlled historic follow-up study. *Journal of Bone and Mineral Research* 2013;28(11):2277-85. doi: http://dx.doi.org/10.1002/jbmr.1979
17. Underbjerg L, Sikjaer T, Mosekilde L, et al. Postsurgical hypoparathyroidism-Risk of fractures, Psychiatric Diseases, Cancer, Cataract, and Infections. *Journal of Bone and Mineral Research* 2014;29(11 S1):2504-10. doi: http://dx.doi.org/10.1002/jbmr.2273
18. Underbjerg L, Sikjaer T, Mosekilde L, et al. The epidemiology of nonsurgical hypoparathyroidism in Denmark: A nationwide case finding study. *Journal of Bone and Mineral Research* 2015;30(9):1738-44. doi: http://dx.doi.org/10.1002/jbmr.2501
19. Vadiveloo T, Donnan PT, Leese CJ, et al. Increased mortality and morbidity in patients with chronic hypoparathyroidism: A population-based study. *Clin Endocrinol (Oxf)* 2019;90(2):285-92. doi: 10.1111/cen.13895 [published Online First: 2018/10/31]
20. Zavatta G, Tebben PJ, McCollough CH, et al. Basal Ganglia Calcification Is Associated With Local and Systemic Metabolic Mechanisms in Adult Hypoparathyroidism. *J Clin Endocrinol Metab* 2021;106(7):1900-17. doi: 10.1210/clinem/dgab162 [published Online First: 2021/04/01]
21. Almquist M, Ivarsson K, Nordenstrom E, et al. Mortality in patients with permanent hypoparathyroidism after total thyroidectomy. *The British journal of surgery*

2018;105(10):1313-18. doi: http://dx.doi.org/10.1002/bjs.10843

22. Ponce de Leon-Ballesteros G, Bonilla-Ramirez C, Hernandez-Calderon FJ, et al. Mid-Term and Long-Term Impact of Permanent Hypoparathyroidism After Total Thyroidectomy. *World journal of surgery* 2020;44(8):2692-98. doi: http://dx.doi.org/10.1007/s00268-020-05531-0
23. Bernardor J, Flammier S, Cabet S, et al. Intermittent Bi-Daily Sub-cutaneous Teriparatide Administration in Children With Hypoparathyroidism: A Single-Center Experience. *Frontiers in pediatrics* 2021;9:764040. doi: 10.3389/fped.2021.764040 [published Online First: 2021/11/26]
24. Bertocchio JP, Grosset N, Groussin L, et al. Practice patterns for chronic hypoparathyroidism: data from patients and physicians in France. *Endocr Connect* 2022;11(1) doi: 10.1530/ec-21-0350 [published Online First: 2021/12/24]
25. Bhadada SK, Bhansali A, Upreti V, et al. Spectrum of neurological manifestations of idiopathic hypoparathyroidism and pseudohypoparathyroidism. *Neurology India* 2011;59(4):586-9. doi: 10.4103/0028-3886.84342 [published Online First: 2011/09/06]
26. Bilezikian JP, Clarke BL, Mannstadt M, et al. Safety and Efficacy of Recombinant Human Parathyroid Hormone in Adults With Hypoparathyroidism Randomly Assigned to Receive Fixed 25-mug or 50-mug Daily Doses. *Clinical Therapeutics* 2017;39(10):2096-102. doi: http://dx.doi.org/10.1016/j.clinthera.2017.08.011
27. Bilginer MC, Aydin C, Polat B, et al. Assessment of calcium and vitamin D medications adherence in patients with hypoparathyroidism after thyroidectomy. *Archives of osteoporosis* 2022;17(1):22. doi: 10.1007/s11657-022-01066-0 [published Online First: 2022/01/25]
28. 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(2):151-62. doi:

http://dx.doi.org/10.1007/s40271-019-00388-5

29. Leidig-Bruckner G, Bruckner T, Raue F, et al. Long-Term Follow-Up and Treatment of Postoperative Permanent Hypoparathyroidism in Patients with Medullary Thyroid Carcinoma: Differences in Complete and Partial Disease. *Hormone and Metabolic Research* 2016;48(12):806-13. doi: http://dx.doi.org/10.1055/s-0042-118181
30. Yuxin C, Fangqi L, Xiaoping W, et al. Parathyroid-thyroid transplantation without flushing or perfusion. *Transplantation proceedings* 1998;30(7):2931-2. doi: 10.1016/s0041-1345(98)00874-4 [published Online First: 1998/12/05]
31. Chen K, Krasner A, Li N, et al. Clinical burden and healthcare resource utilization among patients with chronic hypoparathyroidism, overall and by adequately vs not adequately controlled disease: a multi-country chart review. 2019 doi: 10.1080/13696998.2019.1624081
32. Coudenys E, Meerhaeghe TV, Unuane D, et al. Long-Term Treatment with Calcitriol in Postsurgical Hypoparathyroidism Leads to Renal Function Decline. *Hormone and Metabolic Research* 2019;51(6):362-66. doi: http://dx.doi.org/10.1055/a-0902-8476
33. 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(6):2356-61. doi: 10.1210/jc.2013-1239 [published Online First: 2013/04/19]
34. Cusano NE, Rubin MR, McMahon DJ, et al. Therapy of hypoparathyroidism with PTH(1-84): A prospective four-year investigation of efficacy and safety. *Journal of Clinical Endocrinology and Metabolism* 2013;98(1):137-44. doi: http://dx.doi.org/10.1210/jc.2012-2984
35. Cusano NE, Rubin MR, McMahon DJ, et al. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. *J Clin Endocrinol Metab* 2014;99(10):3694-9. doi: 10.1210/jc.2014-2267 [published Online First: 2014/07/01]
36. Cusano NE, Rubin MR, Williams JM, et al. Changes in Skeletal Microstructure Through Four

Continuous Years of rhPTH(1-84) Therapy in Hypoparathyroidism. *Journal of Bone and Mineral Research* 2020;35(7):1274-81. doi: http://dx.doi.org/10.1002/jbmr.4005

37. David K, Moyson C, Vanderschueren D, et al. Long-term complications in patients with chronic hypoparathyroidism: a cross-sectional study. *European journal of endocrinology* 2019;180(1):71-78. doi: https://dx.doi.org/10.1530/EJE-18-0580
38. Gafni RI, Langman CB, Guthrie LC, et al. Hypocitraturia Is an Untoward Side Effect of Synthetic Human Parathyroid Hormone (hPTH) 1-34 Therapy in Hypoparathyroidism That May Increase Renal Morbidity. *Journal of Bone and Mineral Research* 2018;33(10):1741-47. doi: http://dx.doi.org/10.1002/jbmr.3480
39. Gittoes N, Rejnmark L, Ing SW, et al. The PARADIGHM (physicians advancing disease knowledge in hypoparathyroidism) registry for patients with chronic hypoparathyroidism: study protocol and interim baseline patient characteristics. *BMC Endocr Disord* 2021;21(1):232. doi: 10.1186/s12902-021-00888-2 [published Online First: 2021/11/22]
40. Goswami R, Brown EM, Kochupillai N, et al. Prevalence of calcium sensing receptor autoantibodies in patients with sporadic idiopathic hypoparathyroidism. *European Journal of Endocrinology* 2004;150(1):9-18. doi: http://dx.doi.org/10.1530/eje.0.1500009
41. Goswami R, Sharma R, Sreenivas V, et al. Prevalence and progression of basal ganglia calcification and its pathogenic mechanism in patients with idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)* 2012;77(2):200-6. doi: 10.1111/j.1365-2265.2012.04353.x [published Online First: 2012/02/01]
42. Gronskaia S, Melnichenko G, Rozhinskaya L, et al. A registry for patients with chronic hypoparathyroidism in Russian adults. *Endocrine Connections* 2020;9(7):627-36. doi: http://dx.doi.org/10.1530/EC-20-0219
43. Hadker N, Egan J, Sanders J, et al. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the paradox study. *Endocrine Practice* 2014;20(7):671-79. doi: http://dx.doi.org/10.4158/EP13328.OR

44. Hamdy NAT, Decallonne B, Evenepoel P, et al. Burden of illness in patients with chronic hypoparathyroidism not adequately controlled with conventional therapy: a Belgium and the Netherlands survey. *J Endocrinol Invest* 2020 doi: 10.1007/s40618-020-01442-y [published Online First: 2020/11/01]

45. Hepsen S, Akhanli P, Sakiz D, et al. The effects of patient and disease-related factors on the quality of life in patients with hypoparathyroidism. *Archives of osteoporosis* 2020;15(1):75. doi: 10.1007/s11657-020-00759-8 [published Online First: 2020/05/21]

46. Huddle KRL, Ally R. Idiopathic hypoparathyroidism in black South Africans. *Quarterly Journal of Medicine* 1989;70(261):53-60.

47. Winer KK, Schmitt MM, Ferre EMN, et al. Impact of periprocedural subcutaneous parathyroid hormone on control of hypocalcaemia in APS-1/APECED patients undergoing invasive procedures. *Clin Endocrinol (Oxf)* 2021;94(3):377-83. doi: 10.1111/cen.14335 [published Online First: 2020/09/22]

48. Khan AA, AbuAlrob H, Punthakee Z, et al. Canadian national hypoparathyroidism registry: an overview of hypoparathyroidism in Canada. *Endocrine* 2021 doi: 10.1007/s12020-021-02629-w

49. 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(1):e372-e85. doi: 10.1210/clinem/dgab577 [published Online First: 2021/08/05]

50. Kim JH, Shin YL, Yang S, et al. Diverse genetic aetiologies and clinical outcomes of paediatric hypoparathyroidism. *Clinical Endocrinology* 2015;83(6):790-96. doi: http://dx.doi.org/10.1111/cen.12944

51. Konca Degertekin C, Gogas Yavuz D, Pekkolay Z, et al. Identifying Clinical Characteristics of Hypoparathyroidism in Turkey: HIPOPARATURK-NET Study. *Calcif Tissue Int* 2022;110(2):204-14. doi: 10.1007/s00223-021-00908-2 [published Online First:

2021/09/09]

52. Kovaleva EV, Eremkina AK, Elfimova AR, et al. The Russian Registry of Chronic Hypoparathyroidism. *Frontiers in endocrinology* 2022;13:800119. doi: 10.3389/fendo.2022.800119 [published Online First: 2022/03/08]
53. Lakatos P, Bajnok L, Lagast H, et al. AN OPEN-LABEL EXTENSION STUDY OF PARATHYROID HORMONE RHPTH(1-84) IN ADULTS WITH HYPOPARATHYROIDISM. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2016;22(5):523-32. doi: http://dx.doi.org/10.4158/EP15936.OR
54. Laway BA, Goswami R, Singh N, et al. Pattern of bone mineral density in patients with sporadic idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)* 2006;64(4):405-9. doi: 10.1111/j.1365-2265.2006.02479.x [published Online First: 2006/04/06]
55. 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(11):4106-13. doi: 10.1210/jc.2015-2257 [published Online First: 2015/09/01]
56. Lorente-Poch L, Sancho JJ, Carballo L, et al. Clinical profile and long-term follow-up of 32 patients with postoperative permanent hypoparathyroidism. *Gland surgery* 2017;6(Suppl 1):S3-s10. doi: 10.21037/gs.2017.11.10 [published Online First: 2018/01/13]
57. Liu J, Chen S, Quan T, et al. Bone microstructure of adult patients with non-surgical hypoparathyroidism assessed by high-resolution peripheral quantitative computed tomography. 2020 doi: 10.1007/s00198-020-05506-w
58. Lopera JZ, Tabares SAL, Herrera DA, et al. Characteristics of hypoparathyroidism in Colombia: data from a single center in the city of Medellin. *Archives of endocrinology and metabolism* 2020;64(3):282-89. doi: http://dx.doi.org/10.20945/2359-3997000000250
59. Lopes MP, Kliemann BS, Bini IB, et al. Hypoparathyroidism and pseudohypoparathyroidism:

etiology, laboratory features and complications. *Archives of endocrinology and metabolism* 2016;60(6):532-36. doi: http://dx.doi.org/10.1590/2359-3997000000221

60. Lui DTW, Fung MMH, Lee CH, et al. A territory-wide assessment of the incidence of persistent hypoparathyroidism after elective thyroid surgery and its impact on new fracture risk over time. *Surgery* 2021;170(5):1369-75. doi: 10.1016/j.surg.2021.05.004 [published Online First: 2021/06/13]
61. 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. *The Lancet Diabetes and Endocrinology* 2013;1(4):275-83. doi: http://dx.doi.org/10.1016/S2213-8587%2813%2970106-2
62. Mannstadt M, Clarke BL, Bilezikian JP, et al. Safety and Efficacy of 5 Years of Treatment with Recombinant Human Parathyroid Hormone in Adults with Hypoparathyroidism. *Journal of Clinical Endocrinology and Metabolism* 2019;104(11):5136-47. doi: http://dx.doi.org/10.1210/jc.2019-01010
63. Marcucci G, Masi L, Cianferotti L, et al. Chronic hypoparathyroidism and treatment with teriparatide. *Endocrine* 2021 doi: 10.1007/s12020-020-02577-x [published Online First: 2021/02/05]
64. Marcucci G, Altieri P, Benvenga S, et al. Hypoparathyroidism and pseudohypoparathyroidism in pregnancy: an Italian retrospective observational study. *Orphanet journal of rare diseases* 2021;16(1):421. doi: 10.1186/s13023-021-02053-3 [published Online First: 2021/10/11]
65. Marcucci G, Beccuti G, Carosi G, et al. Multicenter retro-prospective observational study on chronic hypoparathyroidism and rhPTH (1-84) treatment. *J Endocrinol Invest* 2022 doi: 10.1007/s40618-022-01800-y [published Online First: 2022/04/24]
66. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *Journal of Clinical Endocrinology and Metabolism*

2012;97(12):4507-14. doi: http://dx.doi.org/10.1210/jc.2012-1808

67. Modi S, Tripathi M, Saha S, et al. Seizures in patients with idiopathic hypoparathyroidism: effect of antiepileptic drug withdrawal on recurrence of seizures and serum calcium control. *Eur J Endocrinol* 2014;170(5):777-83. doi: 10.1530/eje-14-0075 [published Online First: 2014/03/22]
68. Onder CE, Kuskonmaz SM, Koc G, et al. Evaluation of management of patients with postoperative permanent hypoparathyroidism. How close are we to the targets? *Minerva endocrinologica* 2020 doi: 10.23736/s0391-1977.20.03291-5 [published Online First: 2020/12/04]
69. Palermo A, Santonati A, Tabacco G, et al. PTH(1-34) for Surgical Hypoparathyroidism: A 2-Year Prospective, Open-Label Investigation of Efficacy and Quality of Life. *The Journal of clinical endocrinology and metabolism* 2018;103(1):271-80. doi: https://dx.doi.org/10.1210/jc.2017-01555
70. Rubin MR, Dempster DW, Zhou H, et al. Dynamic and structural properties of the skeleton in hypoparathyroidism. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2008;23(12):2018-24. doi: 10.1359/jbmr.080803 [published Online First: 2008/08/08]
71. Rubin MR, Sliney Jr J, McMahon DJ, et al. Therapy of hypoparathyroidism with intact parathyroid hormone. *Osteoporosis International* 2010;21(11):1927-34. doi: http://dx.doi.org/10.1007/s00198-009-1149-x
72. Rubin MR, Cusano NE, Fan WW, et al. Therapy of hypoparathyroidism with PTH(1-84): A prospective six year investigation of efficacy and safety. *Journal of Clinical Endocrinology and Metabolism* 2016;101(7):2742-50. doi: http://dx.doi.org/10.1210/jc.2015-4135
73. Rubin MR, Zwahlen A, Dempster DW, et al. Effects of Parathyroid Hormone Administration on Bone Strength in Hypoparathyroidism. *Journal of bone and mineral research : the*

official journal of the American Society for Bone and Mineral Research 2016;31(5):1082-8. doi: 10.1002/jbmr.2777 [published Online First: 2016/01/03]

74. Jain R, Singh SK, Agrawal NK. Idiopathic Hypoparathyroidism: Still a Diagnostic Conundrum - A Tertiary Centre Experience. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme* 2020;52(10):708-11. doi: 10.1055/a-1228-8199 [published Online First: 2020/09/05]
75. 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. *Journal of Bone and Mineral Metabolism* 2017;35(4):405-11. doi: http://dx.doi.org/10.1007/s00774-016-0767-6
76. Saha S, Goswami R. Auditing the Efficacy and Safety of Alfacalcidol and Calcium Therapy in Idiopathic Hypoparathyroidism. *J Clin Endocrinol Metab* 2019;104(4):1325-35. doi: 10.1210/jc.2018-02228 [published Online First: 2019/01/05]
77. Saha S, Kandasamy D, Sharma R, et al. Nephrocalcinosis, renal dysfunction, and calculi in patients with primary hypoparathyroidism on long-term conventional therapy. *Journal of Clinical Endocrinology and Metabolism* 2020;105(4):E1215-E24. doi: http://dx.doi.org/10.1210/clinem/dgz319
78. Acharya SV. Postoperative hypoparathyroidism: Presentation, clinical features and long-term follow-up from tertiary care hospital. *Journal of Clinical and Diagnostic Research* 2021;15(1):OC18-OC20. doi: 10.7860/JCDR/2021/46621.14423
79. Siggelkow H, Clarke BL, Germak J, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: Findings from a 13-country patient and caregiver survey. *Clin Endocrinol (Oxf)* 2020;92(2):159-68. doi: 10.1111/cen.14128 [published Online First: 2019/11/14]
80. Storm P, Underbjerg L, Rejnmark L. Changes in treatment needs for chronic postoperative hypoparathyroidism during initiation of conventional treatment compared to stable phase

of treatment. *Endocrinology, diabetes & metabolism* 2021;4(3):e00269. doi: 10.1002/edm2.269 [published Online First: 2021/07/20]

81. Streeten EA, Mohtasebi Y, Konig M, et al. Hypoparathyroidism: Less severe hypocalcemia with treatment with vitamin d2 compared with calcitriol. *Journal of Clinical Endocrinology and Metabolism* 2017;102(5):1505-10. doi: http://dx.doi.org/10.1210/jc.2016-3712
82. Sumida K, Ubara Y, Hoshino J, et al. Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: a prospective study. *Osteoporosis International* 2016;27(4):1441-50. doi: http://dx.doi.org/10.1007/s00198-015-3377-6
83. Tabacco G, Tay YKD, Cusano NE, et al. Quality of Life in Hypoparathyroidism Improves with rhPTH(1-84) Throughout 8 Years of Therapy. *Journal of Clinical Endocrinology and Metabolism* 2019;104(7):2748-56. doi: http://dx.doi.org/10.1210/jc.2018-02430
84. Tay YKD, Tabacco G, Cusano NE, et al. Therapy of Hypoparathyroidism with rhPTH(1-84): A Prospective, 8-Year Investigation of Efficacy and Safety. *Journal of Clinical Endocrinology and Metabolism* 2019;104(11):5601-10. doi: http://dx.doi.org/10.1210/jc.2019-00893
85. Underbjerg L, Sikjaer T, Rejnmark L. Long-Term Complications in Patients With Hypoparathyroidism Evaluated by Biochemical Findings: A Case-Control Study. *Journal of Bone and Mineral Research* 2018;33(5):822-31. doi: http://dx.doi.org/10.1002/jbmr.3368
86. Wang O, Xing XP, Meng XW, et al. Treatment of hypocalcemia caused by hypoparathyroidism or pseudohypoparathyroidism with domestic-made calcitriol: Aprospective and self-controlled clinical trial. *Chinese Medical Journal* 2009;122(3):279-83. doi: http://dx.doi.org/10.3760/cma.j.issn.0366-6999.2009.03.008
87. Wang Y, Wang O, Nie M, et al. Clinical and genetic findings in a Chinese cohort of patients with DiGeorge syndrome-related hypoparathyroidism. *Endocrine Practice* 2020;26(6):642-50. doi: http://dx.doi.org/10.4158/EP-2019-0498

88. 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(7):e10368. doi: 10.1002/jbm4.10368 [published Online First: 2020/07/16]

89. Winer KK, Yanovski JA, Cutler Jr GB. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism: Results of a short-term randomized crossover trial. *Journal of the American Medical Association* 1996;276(8):631-36. doi: http://dx.doi.org/10.1001/jama.276.8.631

90. Winer KK, Yanovski JA, Sarani B, et al. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. *J Clin Endocrinol Metab* 1998;83(10):3480-6. doi: 10.1210/jcem.83.10.5185 [published Online First: 1998/10/13]

91. Winer KK, Ko CW, Reynolds JC, et al. Long-term treatment of hypoparathyroidism: A randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *Journal of Clinical Endocrinology and Metabolism* 2003;88(9):4214-20. doi: http://dx.doi.org/10.1210/jc.2002-021736

92. Winer KK, Sinaii N, Peterson D, et al. Effects of once versus twice-daily parathyroid hormone 1-34 therapy in children with hypoparathyroidism. *J Clin Endocrinol Metab* 2008;93(9):3389-95. doi: 10.1210/jc.2007-2552 [published Online First: 2008/05/22]

93. Winer KK, Sinaii N, Reynolds J, et al. Long-term treatment of 12 children with chronic hypoparathyroidism: A randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. *Journal of Clinical Endocrinology and Metabolism* 2010;95(6):2680-88. doi: http://dx.doi.org/10.1210/jc.2009-2464

94. Winer KK, Kelly A, Johns A, et al. Long-Term Parathyroid Hormone 1-34 Replacement Therapy in Children with Hypoparathyroidism. *The Journal of pediatrics* 2018;203:391-99.e1. doi: 10.1016/j.jpeds.2018.08.010 [published Online First: 2018/11/25]

95. Zanchetta MB, Robbiani D, Oliveri B, et al. Hipopara-Red, Real Life Experience in 322 Patients With Hypoparathyroidism. *Journal of the Endocrine Society* 2021;5(2):bvaa181. doi: 10.1210/jendso/bvaa181 [published Online First: 2021/01/08]

96. Chang JW, Park KW, Jung SN, et al. The most reliable time point for intact parathyroid hormone measurement to predict hypoparathyroidism after total thyroidectomy with central neck dissection to treat papillary thyroid carcinoma: a prospective cohort study. *Eur Arch Otorhinolaryngol* 2020;277(2):549-58. doi: http://dx.doi.org/10.1007/s00405-019-05693-1

97. Lončar I, Dulfer RR, Massolt ET, et al. Postoperative parathyroid hormone levels as a predictor for persistent hypoparathyroidism. *Eur J Endocrinol* 2020;183(2):149-59. doi: 10.1530/eje-20-0116 [published Online First: 2020/06/25]

98. Palmhag D, Brydolf J, Zedenius J, et al. A Single Parathyroid Hormone Measurement Two Hours after a Thyroidectomy Reliably Predicts Permanent Hypoparathyroidism. *Scand J Surg* 2020:1457496920913666. doi: http://dx.doi.org/10.1177/1457496920913666

99. Sala DT, Muresan M, Voidazan S, et al. First day serum calcium and parathyroid hormone levels as predictive factors for safe discharge after thyroidectomy. *Acta Endocrinol (Buchar)* 2019;15(2):225-30. doi: http://dx.doi.org/10.4183/aeb.2019.225

100. Suwannasarn M, Jongjaroenprasert W, Chayangsu P, et al. Single measurement of intact parathyroid hormone after thyroidectomy can predict transient and permanent hypoparathyroidism: a prospective study. *Asian J Surg* 2017;40(5):350-56. doi: http://dx.doi.org/10.1016/j.asjsur.2015.11.005

101. 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;18:150-53. doi: http://dx.doi.org/10.1016/j.ijsu.2015.04.074

102. Ezzat WF, Fathey H, Fawaz S, et al. Intraoperative parathyroid hormone as an indicator for

parathyroid gland preservation in thyroid surgery. *Swiss Med Wkly* 2011;141:w13299. doi: http://dx.doi.org/10.4414/smw.2011.13299

103. Hermann M, Ott J, Promberger R, et al. Kinetics of serum parathyroid hormone during and after thyroid surgery. *Br J Surg* 2008;95(12):1480-7. doi: 10.1002/bjs.6410 [published Online First: 2008/11/11]

104. 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):300060520927199. doi: http://dx.doi.org/10.1177/0300060520927199

105. Canu GL, Medas F, Longheu A, et al. Correlation between iPTH Levels on the First Postoperative Day After Total Thyroidectomy and Permanent Hypoparathyroidism: Our Experience. *Open Med (Wars)* 2019;14:437-42. doi: 10.1515/med-2019-0047 [published Online First: 2019/06/25]

106. Calvo Espino P, Rivera Bautista J, Artés Caselles M, et al. Serum levels of intact parathyroid hormone on the first day after total thyroidectomy as predictor of permanent hypoparathyroidism. *Endocrinol Diabetes Nutr* 2019;66(3):195-201. doi: 10.1016/j.endinu.2018.08.006 [published Online First: 2018/11/06]

107. Wang W, Xia F, Meng C, et al. Prediction of permanent hypoparathyroidism by parathyroid hormone and serum calcium 24h after thyroidectomy. *Am J Otolaryngol* 2018;39(6):746-50. doi: http://dx.doi.org/10.1016/j.amjoto.2018.08.005

108. Selberherr A, Scheuba C, Riss P, et al. Postoperative hypoparathyroidism after thyroidectomy: efficient and cost-effective diagnosis and treatment. *Surgery* 2015;157(2):349-53. doi: 10.1016/j.surg.2014.09.007 [published Online First: 2014/12/24]

109. Wang JB, Sun HL, Song CY, et al. Association between decreased serum parathyroid hormone after total thyroidectomy and persistent hypoparathyroidism. *Med Sci Monit*

2015;21:1223-31. doi: http://dx.doi.org/10.12659/MSM.892867

110. Julian 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):783-89. doi: http://dx.doi.org/10.1016/j.amjsurg.2013.01.038

111. 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. doi: 10.5603/EP.a2022.0005 [published Online First: 2022/02/15]

112. Riordan F, Brophy C, Murphy MS, et al. Predictive value of postoperative day 1 parathyroid hormone levels for early and late hypocalcaemia after thyroidectomy. *Langenbecks Arch Surg* 2022 doi: 10.1007/s00423-022-02480-1 [published Online First: 2022/03/06]

Chapter 4: Parathyroid Hormone Therapy for Managing Chronic Hypoparathyroidism: A Systematic Review and Meta-Analysis

TASK FORCE

JBMR®

Parathyroid Hormone Therapy for Managing Chronic Hypoparathyroidism: A Systematic Review and Meta-Analysis

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ABSTRACT

The efficacy and safety of parathyroid hormone (PTH) therapy for managing long-term hypoparathyroidism is being evaluated in ongoing clinical trials. We undertook a systematic review and meta-analysis of currently available randomized controlled trials to investigate the benefits and harms of PTH therapy and conventional therapy in the management of patients with chronic hypoparathyroidism. To identify eligible studies, published in English, we searched Embase, PubMed, and Cochrane CENTRAL from inception to May 2022. Two reviewers independently extracted data and assessed the risk of bias. We defined patients' important outcomes and used grading of recommendations, assessment, development, and evaluation (GRADE) to provide the structure for quantifying absolute effects and rating the quality of evidence. Seven randomized trials of 12 publications that enrolled a total of 386 patients proved eligible. The follow-up duration ranged from 1 to 36 months. Compared with conventional therapy, PTH therapy probably achieves a small improvement in physical health-related quality of life (mean difference [MD] 3.4, 95% confidence interval [CI] 1.5–5.3, minimally important difference 3.0, moderate certainty). PTH therapy results in more patients reaching 50% or greater reduction in the dose of active vitamin D and calcium (relative risk [RR] = 6.5, 95% CI 2.5–16.4, 385 more per 1000 patients, high certainty). PTH therapy may increase hypercalcemia (RR =2.4, 95% CI 1.2–5.04, low certainty). The findings may support the use of PTH therapy in patients with chronic hypoparathyroidism. Because of limitations of short duration and small sample size, evidence from randomized trials is limited regarding important benefits of PTH therapy compared with conventional therapy. Establishing such benefits will require further studies. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PARATHYROID HORMONE THERAPY; EPIDEMIOLOGY; HYPOPARATHYROIDISM

Received in original form February 5, 2022; revised form July 22, 2022; accepted August 8, 2022.
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Additional Supporting Information may be found in the online version of this article.
LY and JL are contributed equally to this study.
Journal of Bone and Mineral Research, Vol. 37, No. 12, December 2022, pp 2654–2662.
DOI: 10.1002/jbmr.4676

Introduction

Hypoparathyroidism (hypoPTH) is a rare disorder characterized by hypocalcemia in which the parathyroid glands fail to produce sufficient amounts of parathyroid hormone (PTH) or the parathyroid hormone produced lacks biologic activity. Long-term manifestations may include nephrocalcinosis/nephrolithiasis, renal failure, seizures, arrhythmia, ischemic heart disease, depression, cataracts, infection, increased mortality, and impaired quality of life.[1–4] Hypoparathyroidism occurs most commonly after neck surgery, accounting for 75% of patients with hypoparathyroidism.[5] The majority of postoperative cases of hypocalcemia resolve in the first weeks after surgery, and approximately 25% of such cases develop chronic or permanent hypoparathyroidism.[6,7]

The optimal treatment strategies for patients with chronic hypoparathyroidism remain uncertain. Conventional therapy with calcium and activated vitamin D analogs (calcitriol, alfacalcidol, or dihydrotachysterol) is necessary to maintain serum calcium and treat symptoms of hypocalcemia.[8,9] However, conventional therapy does not correct the underlying pathophysiology and is associated with long-term complications as cited above.[1–4,10]

PTH replacement therapy with either synthetic or recombinant human (rh) PTH(1–34) or intact rhPTH(1–84) has been evaluated in hypoparathyroidism. PTH(1–34) has been evaluated in both children and adults in varying treatment regimens. RhPTH(1–84) has also been evaluated in hypoparathyroidism and was approved in 2015 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an adjunctive treatment for patients with chronic hypoparathyroidism who cannot be well controlled on conventional therapy. TransCon PTH, a prodrug with rhPTH(1–34) transiently conjugated to polyethylene glycol, is not yet approved, but early data suggest it may provide stable PTH serum levels in the physiologic range for 24 hours.[11] This molecule has been evaluated in a phase 2 trial and a phase 3 trial in hypoparathyroidism.[12,13] PTH therapy is generally well tolerated with few adverse effects. In preclinical studies in rats, high doses of PTH(1–34) and PTH(1–84) were associated with dose- and duration-dependent osteosarcoma, which, however, has not been observed in humans.[14] The use of PTH therapy in chronic hypoparathyroidism patients should be based on evidence regarding potential benefit on patient-important outcomes.

With the goal to inform recommendations for the update of international guidelines on hypoparathyroidism,[7,15] we undertook this systematic review and meta-analysis to assess the effects of PTH therapy versus conventional therapy in managing patients with chronic hypoparathyroidism.

Methods

We submitted the systematic review protocol to PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=234774) for registration (CRD42021234774). This report follows the Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA)[16] (https://view.officeapps.live.com/op/view.aspx?src=http%3A%2F%2Fprisma-statement.org%2Fdocuments%2FPRISMA_2020_checklist.docx&wdOrigin=BROWSELINK).

Data sources

Relying in part on a prior review,[17] we searched Embase (https://www.elsevier.com/solutions/embase-biomedical-research), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and Cochrane CENTRAL (https://www.cochranelibrary.com/central) from inception to May 2022 using key words hypoparathyroidism, hypocalcemia, hypocal*, hypoPT, parathyroid hormone, PTH, rhPTH, PTH(1–34), teriparatide, PTH(1–84), TransCon PTH, and random*. MeSH terms implemented in various combinations increased search sensitivity. Searching the reference lists of publications of primary studies and relevant narrative reviews and guidelines provided another strategy for identifying additional references.

Study selection

We merged studies from the different sources and databases and removed duplicates. Paired reviewers screened the studies in two stages: (i) title and abstract and (ii) full text. For full-text review, two reviewers independently adjudicated eligibility and resolved conflicts by discussion.

Eligible studies included patients diagnosed with chronic hypoparathyroidism; compared PTH therapy versus conventional therapy (eg, calcium, calcitriol, alfacalcidol, vitamin D); used randomized controlled study trial design; and were published in English. Studies were excluded if they: (i) were intervention studies of <4 weeks' duration; (ii) were duplicate publications, review articles, single-case articles, editorials, or letters; and/or (iii) examined only temporary hypoparathyroidism as defined by the study.

Outcomes of interest

The selection of patient-important outcomes (defined as characteristics or variables that reflect how a patient feels, functions, or survives) referred to one systematic review that investigated the major complications related to chronic hypoparathyroidism, including nephrolithiasis, renal failure, seizures, arrhythmia, ischemic heart disease, depression, cataracts, infection, and all-cause mortality.[18] In addition, the guideline panel added another four outcomes as patient-important based on their experience managing patients (fracture, 50% or greater reduction in dose of active vitamin D and calcium, quality of life, and adverse events).

In the presence of limited evidence for patient-important outcomes, we also included the following surrogate outcomes: hypocalcemia, hypercalcemia, hypercalciuria, 24-hour urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxy vitamin D3, serum magnesium, serum alkaline phosphatase, serum osteocalcin, urine deoxypyridinoline, urine pyridinoline, mean creatinine clearance levels, and bone mineral density (BMD).

Data abstraction

For each included article, team members, using a standardized form, independently extracted author, year, country, patient demographics, interventions, doses, frequency, duration, and outcomes data. When one reviewer completed the data abstraction, a second reviewer independently reviewed the data.

Risk of bias and quality of evidence

A modified Cochrane risk of bias tool provided the basis for risk of bias assessment.[19,20] Two reviewers independently rated the risk of bias; a third senior reviewer resolved any disagreement. We used the grading of recommendations, assessment,

development, and evaluation (GRADE) system for assessing certainty in the evidence as high, moderate, low, or very low based on study design and considerations of risk of bias, consistency, precision, directness, and publication bias.[21,22]

Data synthesis

We performed a random-effects meta-analysis using DerSimonian and Laird approach,[23] which uses the inverse-variance method and assumes that studies are estimating different, yet related, intervention effects. We presented relative risks (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes. For continuous outcomes, weighted mean differences (WMD) and 95% CI using DerSimonian and Laird random-effects model provided pooled results. Chi-square tests and I^2 statistics provided methods for assessing statistical heterogeneity. All primary analyses were performed with STATA v15.1 (StataCorp, College Station, TX, USA).

Results

Study selection

The search identified 6835 records; after removal of duplicates, 5138 remained, among which 311 articles proved potentially eligible on the title and abstract review and 11 publications[12,13,24–33] reporting on seven studies (Fig. 1) met eligibility criteria.

Characteristics of included studies

Table 1 summarizes the characteristics of eligible studies, all randomized trials, of which six used parallel and one crossover design. The seven eligible studies included 386 patients, of whom 76% were female. The follow-up duration of the seven studies ranged from 1 to 36 months. Supplemental Table S1 presents the risk of bias assessment.

Main outcomes

None of the studies reported patient-important outcomes of nephrocalcinosis/ nephrolithiasis, seizures, arrhythmia, ischemic heart disease, cataracts, fracture, infection, or all-cause mortality. Three studies reported physical health-related quality of life by SF-36 instruments and suggested a very small possible benefit of treatment (MD 3.4, 95% CI 1.5–5.3, minimally important difference 3.0, moderate certainty, Table 2).[13,29,30] One study reported depression and suggested no important differences in the impact of interventions on depression (MD 0, 95% CI −0.2 to 0.1, moderate certainty, Table 2).[29] Two studies reported that PTH(1–84) therapy versus conventional therapy resulted in more patients reaching 50% or greater reduction in the doses of active vitamin D and calcium (RR = 6.5, 95% CI 2.5–16.4, 385 more per 1000 patients, high certainty evidence, Table 2).[12,25]

Five studies reported 21 (9%) patients had serious adverse events in the PTH group and 10 (9%) in the conventional group, including hypocalcemia, hypercalcemia, diarrhea, anaphylactic reaction, etc, but there was no evidence of important differences between groups based on the limited data available (RR = 1.14, 95% CI 0.6–2.2, 9 more per 1000 patients, low certainty evidence).[12,13,25,27,33] There were also no important differences in the discontinuation of the study due to adverse events (RR = 1.0, 95% CI 0.1–9.8, 0 more per 1000 patients, low certainty evidence).[13,25] Supplemental Table S2 presents a summary of the findings specifically reporting adverse events. Many adverse events were more frequently found in the PTH group than in the conventional therapy group; however, differences were

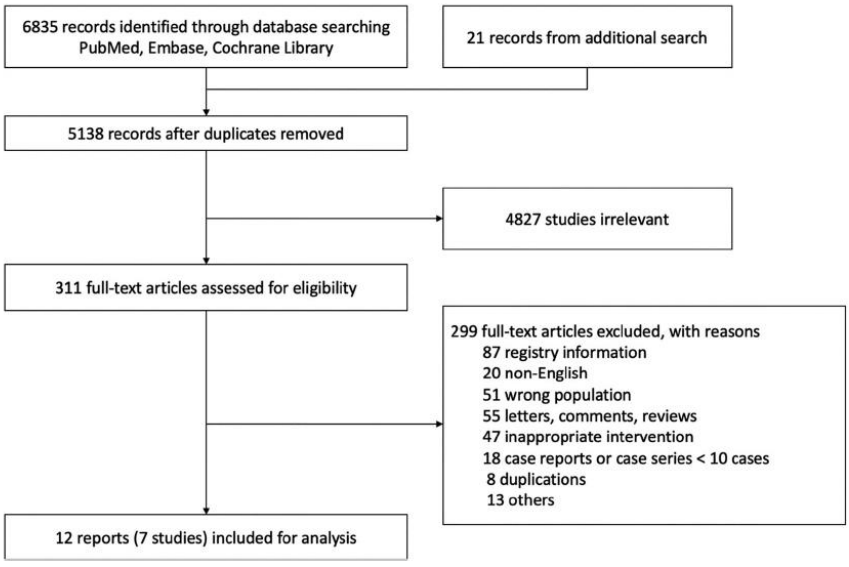

Fig. 1. Study selection.

Table 1. Characteristics of Included Studies

Study	Country	Study design	No. of patients in PTH/control	Age (mean)	Female	Surgical patients	Treatment group	Control group	Outcomes	Follow-up duration (months)	Key findings
REPLACE[24,25,30]	North America and Europe	Parallel RCT	90/44	47.5	78%	74%	rhPTH (1–84); active vitamin D; calcium	Placebo; active vitamin D; calcium	Patient important outcomes: adverse events, 50% or greater reduction in dose of vitamin D and calcium, quality of life Surrogate outcomes: hypocalcemia, hypercalcemia, hypercalciuria, 24-h urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-Dihydroxyvitamin D3	6	Serum phosphate levels decreased rapidly from the upper normal range and remained lower with rhPTH (1–84). At week 24, serum calcium–phosphate product was lower with rhPTH (1–84) vs. placebo. rhPTH (1–84) treatment resulted in significant reductions in oral calcium dose compared with placebo while maintaining serum calcium. The proportions of patients who had at least one adverse event and serious adverse events were similar between groups
Sikjaer, 2011-2014[26–29]	Denmark	Parallel RCT	32/30	52.0	85%	94%	rhPTH (1–84); alfacalcidol/ calcitriol/ ergocalciferol	Placebo; calcium and alfacalcidol/ calcitriol/ ergocalciferol	Patient important outcomes: adverse events, quality of life Surrogate outcomes: hypocalcemia, hypercalcemia, 24-h urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D3, serum magnesium, Serum alkaline phosphatase, Serum osteocalcin, BMD.	6	Asymptomatic hypercalcemia was present in 71% of the rhPTH (1-84) treated patients. Compared with placebo, 24-hour urinary calcium, phosphate, and magnesium did not change,
Winer, 2003[31]	USA	Parallel RCT	14/13	45.0	63%	41%	PTH (1–34); elemental calcium	Calcitriol and calcium	Patient important outcomes: adverse events Surrogate outcomes: 24-h urine calcium excretion, serum calcium, serum magnesium, phosphate excretion, mean creatinine clearance, Serum alkaline phosphatase, Serum osteocalcin, Urine deoxypyridinoline, Urine pyridinoline, BMD	36	(1) Serum calcium levels were similar in both treatment groups within or just below the normal range; (2) mean urinary calcium excretion was within the normal range from 1-3 yr in PTH-treated patients but remained above normal in the calcitriol group; (3) bone mineral content and bone mineral density showed no significant between-group differences over the 3-yr study period.
Winer,1996[32]	USA	Crossover RCT	10	46.5	40%	40%	PTH (1-34); dietary elemental calcium	Calcitriol; dietary elemental calcium	Patient important outcomes: adverse events Surrogate outcomes: hypercalcemia, 24-h urine calcium excretion, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D3, Serum alkaline phosphatase, Serum osteocalcin, Urine deoxypyridinoline, Urine pyridinoline	2.5	Once-daily treatment with PTH (1-34) maintained serum calcium in the normal range with decreased urine calcium excretion compared with calcitriol treatment. Biochemical markers of bone turnover increased significantly during PTH (1-34) treatment.

(Continues)

Table 1. Continued

Study	Country	Study design	No. of patients in PTH/ control	Age (mean)	Female	Surgical patients	Treatment group	Control group	Outcomes	Follow-up duration (months)	Key findings
Winer, 2010[33]	USA	Parallel RCT	7/5	9.6	33%	NR*	PTH (1-34); dietary elemental calcium; magnesium supplement	Calcitriol; calcium and cholecalciferol; magnesium supplement	Patient important outcomes: adverse events, Surrogate outcomes: hypocalcemia, 24-h urine calcium excretion, serum calcium, serum phosphate, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D3, serum magnesium, mean creatinine clearance, Serum alkaline phosphatase, Serum osteocalcin, Urine deoxypyridinoline, Urine pyridinoline, BMD	36	Mean predose serum calcium levels were maintained at, or just below, the normal range, and urine calcium levels remained in the normal range throughout the 3-yr study, with no significant differences between treatment groups. Creatinine clearance, corrected for body surface area, did not differ between groups and remained normal throughout the study.
Khan, 2021[12]	North America and Europe	Parallel RCT	44/15	49.2	81%	80%	TransCon PTH; oral elemental calcium; active vitamin D	Placebo; oral elemental calcium; active vitamin D	Patient important outcomes: adverse events, 50% or greater reduction in dose of vitamin D and calcium, quality of life Surrogate outcomes: hypocalcemia, hypercalcemia, serum calcium, serum phosphate	1	91% of participants treated with TransCon PTH achieved independence from standard of care. Mean 24-hour urine Ca decreased from a baseline mean of 415 mg/24h to 178 mg/24h by Week 26 while normal serum Ca (sCa) was maintained, and serum phosphate and serum calcium-phosphate product fell within the normal range. TransCon PTH was well tolerated with no treatment-related serious or severe adverse events.
Khan, 2022[13]	North America and Europe	Parallel RCT	61/21	48.6	78%	85%	TransCon PTH; oral elemental calcium; active vitamin D	Placebo; oral elemental calcium; active vitamin D	Patient important outcomes: adverse events, quality of life Surrogate outcomes: 24-h urine calcium excretion, serum calcium, hypocalcemia, hypercalcemia	6.5	93% of participants treated with TransCon PTH achieved independence from conventional therapy. Treatment with TransCon PTH over 26 weeks also normalized mean 24-hour urine calcium. Most adverse events were mild or moderate. No study drug-related withdrawals occurred.

NR = not reported.

Table 2. GRADE summary of findings

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence (quality of evidence)	Plain text summary
		Conventional therapy[a]	PTH[a]		
Quality of life (physical health)	Measured by: SF-36[b] Scale: 0–100 high better Based on data from 263 patients in 3 studies[13,29,30] Follow up 6 months	−0.1 Mean Difference: **MD 3.4 higher** (CI 95% 1.5 higher–5.3 higher)	3.3 Mean	**Moderate** Due to serious imprecision[c]	PTH therapy probably results in a small improvement in quality of life (physical health)
Quality of life (mental health)	Measured by: SF-36[b] Scale: 0–100 high better Based on data from 179 patients in 2 studies[29,30] Follow up 5 months	−2.8 Mean Difference: **MD 5.8 higher** (CI 95% 4.9 lower–16.5 higher)	3 Mean	**Low** Due to very serious imprecision[d]	PTH therapy may have small improvement in quality of life (mental health)
Depression	Measured by: WHO-5-well-being Scale: 0–5 high better Based on data from 59 patients in 1 study[29] Follow up 6 months	0.1 Mean Difference: **MD 0 lower** (CI 95% 0.2 lower–0.1 higher)	0.1 Mean	**Moderate** Due to serious imprecision[e]	PTH therapy probably has little or no impact on depression
50% or greater reduction in doses of active vitamin D and calcium	Relative risk: 6.5 (CI 95% 2.5–16.4) Based on data from 191 patients in 2 studies[12,25] Follow up 21 months	70 per 1000 Difference: **385 more per 1000** (CI 95% 200 more–744 more)	455 per 1000	**High**	PTH(1-84) and TransCon PTH therapy allow a 50% or greater reduction in doses of active vitamin D and calcium
Serious adverse events	Relative risk: 1.1 (CI 95% 0.6–2.2) Based on data from 349 patients in 5 studies[12,13,25,27,33] Follow up 6 months	90 per 1000 Difference: **9 more per 1000** (CI 95% 36 fewer–108 more)	99 per 1000	**Low** Due to very serious imprecision[d]	PTH therapy may have little or no impact on serious adverse events
Discontinued the study due to adverse events	Relative risk: 1.0 (CI 95% 0.1–9.8) Based on data from 216 patients in 2 study[13,25] Follow up 6 months	15 per 1000 Difference: **0 more per 1000** (CI 95% 42 fewer–72 more)	15 per 1000	**Low** Due to very serious imprecision[d]	PTH therapy may have little or no impact on discontinuation due to serious adverse events

[a]For continuous outcomes, absolute effect estimates in conventional therapy and PTH groups were difference of baseline and follow up.
[b]Minimally important difference (MID) is 3 points.[34]
[c]The confidence interval included trivial and small benefits.
[d]The confidence interval included serious harms and important benefits.
[e]The small sample sizes.

significant only for thirst during PTH(1–84) versus conventional therapy (RR = 6.5, 95% CI 1.2–34.2, 77 more per 1000 patients, low certainty evidence, Supplemental Table S2).

Supplemental Table S3 summarized the results of the surrogate outcomes and suggests that PTH therapy in comparison to conventional therapy is associated with higher serum calcium (MD 0.11 mmol/L, 95% CI 0.02, 0.20), lower serum phosphorus (MD −0.2 mmol/L 95% CI −0.4, −0.03), serum 25-hydroxyvitamin D (MD −9.2 ng/mL, 95% CI −12.2 to −6.1), serum magnesium (MD −0.06 mmol/L 95%CI −0.1, −0.01). Additionally, there was a higher incidence of hypercalcemia for patients receiving PTH(1–84) (RR = 2.4, 95% CI 1.2–5.04). We found no persuasive evidence of an impact of PTH (1–34) versus conventional therapy on creatinine clearance (MD 3.9 mL/min, 95% CI −2.4 to 10.3). Neither group demonstrated a difference in mean renal function.

Discussion

Main findings

Eligible studies did not report on patient-important outcomes of nephrocalcinosis/nephrolithiasis, seizures, arrhythmia, ischemic heart disease, cataracts, fracture, infection, and mortality. This may have been attributable to the small sample size of the studies and their relatively short-term duration. The study results obtained to date provide evidence that PTH(1–84) therapy allows more patients to reduce or stop taking calcium and active vitamin D. Reduction in dose or complete cessation of conventional therapy was not tracked in the controlled studies with PTH(1–34). There was a small or no impact on health-related quality of life (Table 2). Serious adverse events were infrequent, and although a number of adverse events occurred more frequently in the PTH group (Supplemental Table S2), the results were significant only for thirst. Regarding the surrogate outcomes, PTH therapy was associated with increased hypercalcemia, serum alkaline phosphatase, serum osteocalcin, and urine pyridinoline and reductions in serum phosphate, serum 25-hydroxyvitamin D, and serum magnesium (Supplemental Table S3).

Strengths and limitations

The strengths of this review include a comprehensive search; registration of our study protocol before starting; and evaluation of the quality of evidence using the GRADE approach. This review also has limitations. The most important limitation is the small sample size of the available studies, resulting in essentially insufficient evidence regarding many of the outcomes important to patients. The small sample size resulted in imprecision of estimates (there may be additional adverse effects that the studies were unable to detect) and precluded any subgroup analyses. Because of the short-term duration, the existing studies failed to address most patient-important outcomes. In addition, PTH may have effects in different etiologies of hypoparathyroidism.[35]

Comparison with other studies

One prior review included similar studies to our review and focused on the same questions.[36] However, the prior review did not include all publications based on the same population. For example, three publications addressed different outcomes for the REPLACE trial: one reported safety outcomes, one reported health-related quality of life, and one reported surrogate outcomes;[24,25,30] the prior review only included the first publication.[25] Similarly, we found another review addressing both adults and pediatric patients with chronic hypoparathyroidism that included five clinical trials; however, it only reported biochemical outcomes.[37] In comparison to prior reviews, our review adds additional studies and highlights the low-quality evidence measuring of most major patient-important outcomes and the likelihood that effects on physical health-related quality of life are small.

Interpretation and application

The available studies are small and provide limited evidence regarding major patient-important outcomes. The results suggest that benefits on quality of life may be small. PTH therapy (PTH(1–84) and TransCon PTH) might result in more patients being able to discontinue calcium and active vitamin D supplements, thus potentially reducing the pill burden of the disease, but because the quality of evidence is low, further study of this effect is needed. PTH therapy was also shown to lower serum phosphate. This may have potential benefits with respect to lowering the risk of ectopic calcification as well as nephrocalcinosis and declines in renal function. The impact of the reduction in serum phosphate requires further study. More definitive evidence requires considerably longer and larger studies, which may be challenging for clinical studies for a rare disease.

This review highlights the limitations in available evidence regarding the impact of PTH on patient-important outcomes. Results did, however, suggest a small impact of PTH therapy on physical health-related quality of life. The benefits include a reduction in serum phosphate. The reduction in phosphate may have important benefits on lowering the long-term complications of chronic hypoparathyroidism and requires further study. A reduction in the dose of the calcium and active D requirements was observed. The adverse events with PTH therapy in comparison to conventional therapy may be limited to a higher incidence of hypercalcemia. We found no other convincing evidence of important adverse events.

Disclosures

AAK: speaker and / or grants from Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, and Ultragenyx; consultant for Alexion, Amgen, Amolyt, Ascendis, Radius, Takeda, and Ultragenyx. JPB: consultant for Amgen, Radius, Ascendis, Calcilytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, and Ipsen. MLB: has received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, and UCB; grants and/or speaker: Abiogen, Alexion, Amgen, Bruno Farmaceutici, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex, and UCB; consultant: Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, and UCB. BLC: consultant for Takeda/Shire, Amolyt Pharma, and Calcilytix; grants from Takeda/Shire and Ascendis. LR: speaker for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, and Ultragenyx; consultant for Amgen, Lilly, Takeda, Alexion, Kyowa Kirin, Amolyt, Ascendis, and Ultragenyx; grants from Takeda and Kyowa Kirin. MM: consultant for Takeda, Amolyt, and Chugai; grants from Takeda and Chugai.

Acknowledgments

We acknowledge unrestricted financial support from Amolyt, Ascendis, Calcilytix, and Takeda. They had no input into the

planning or design of the project, the conduct of the reviews, evaluation of the data, writing or review of the manuscript, its content, or conclusions.

Authors' roles: Design/conceptualization of the project: AAK, JPB, MM, LR, MLB, BLC, and GG. Data acquisition, review, analysis, methodology: LY, MLB, XH, JL, KY, CL, DT, MK, AS, NM, DSA, KD, AAK, JPB, MM, LR, MLB, BLC, and GG. Project administration, including acquisition of funding: AAK, JPB, MM, LR, MLB, BLC. Original drafting and preparation of the manuscript: LY, JL, ML. Review/editing of the manuscript: LY, ML, XH, JL, KY, CL, DT, MK, AS, NM, DSA, KD, AAK, JPB, MM, LR, MLB, BLC, and GG.

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Liang Yao: Data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Jing Li:** Data curation; formal analysis; writing – original draft; writing – review and editing. **Meixuan Li:** Data curation; formal analysis; writing – review and editing. **Clement Lin:** Data curation; formal analysis; writing – review and editing. **Xu Hui:** Data curation; writing – review and editing. **Divyalakshmi Tamilselvan:** Data curation; writing – review and editing. **Maryam Kandi:** Data curation; writing – review and editing. **Ashwini Sreekanta:** Data curation; writing – review and editing. **Nima Makhdami:** Data curation; writing – review and editing. **Dalal S. Ali:** Data curation; project administration; writing – review and editing. **Karel Dandurand:** Data curation; project administration; writing – review and editing. **Kehu Yang:** Data curation; writing – review and editing. **John P. Bilezikian:** Methodology; writing – review and editing. **Maria Luisa Brandi:** Methodology; writing – review and editing. **Bart L. Clarke:** Methodology; writing – review and editing. **Michael Mannstadt:** Methodology; writing – review and editing. **Lars Rejnmark:** Formal analysis; writing – review and editing. **Aliya A. Khan:** Conceptualization; methodology; writing – review and editing. **Gordon Guyatt:** Conceptualization; methodology; supervision; writing – review and editing.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4676.

Data Availability Statement

NA

References

1. 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(10):2317-2337.
2. Cusano NE, Rubin MR, Sliney J Jr, Bilezikian JP. Mini-review: new therapeutic options in hypoparathyroidism. Endocrine. 2012;41(3):410-414.
3. Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med. 2008;359(4):391-403.
4. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(12):4507-4514.
5. Khan AA, Clarke B, Rejnmark L, Brandi ML. Management of endocrine disease: hypoparathyroidism in pregnancy: review and evidence-based recommendations for management. Eur J Endocrinol. 2019;180(2):R37-R44.
6. Shoback DM, Bilezikian JP, Costa AG, et al. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metab. 2016;101(6):2300-12.
7. 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(2):G1-G20.
8. 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(6):674-685.
9. 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.
10. Brandi ML, Bilezikian JP, Shoback D, et al. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101(6):2273-2283.
11. 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(8):1430-1440.
12. 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(1):e372-e385.
13. Khan A, Rubin M, Schwarz p, et al. Phase 3 PaTHway Trial: Participants Treated With TransCon PTH Achieved Independence From Conventional Therapy While Maintaining Normal Serum Calcium. 2022.
14. Gilsenan A, Harris D, Reynolds M, et al. Long-term cancer surveillance: results from the Forteo Patient Registry Surveillance Study. Osteoporos Int. 2021;32(4):645-651.
15. Khan AA, Koch CA, Van Uum S, et al. Standards of care for hypoparathyroidism in adults: a Canadian and international consensus. Eur J Endocrinol. 2019;180(3):p1-p22.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
17. Edafe O, Mech CE, Balasubramanian SP. Calcium, vitamin D or recombinant parathyroid hormone for managing post-thyroidectomy hypoparathyroidism. Cochrane Database Syst Rev. 2019;5:Cd012845.
18. Yao L. The complications, symptoms in adult patients with chronic hypoparathyroidism: a systematic review. J Bone Miner Res. 2021. https://asbmr.onlinelibrary.wiley.com/doi/10.1002/jbmr.4673?utm_source=google&utm_medium=paidsearch&utm_campaign=R3MR425&utm_content=LifeSciences
19. Higgins JP. Chapter 8: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Available at: https://training.cochrane.org/handbook/archive/v5.0.2/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm.
20. Guyatt GH, Busse JW. Risk of bias in randomized trials [Internet]. June 15, 2016. Available at: https://growthevidence.com/gordon-h-guyatt-md-msc-and-jason-w-busse-dc-phd/.
21. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-926.
22. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995-998.
23. Deeks JJ, Higgins PT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Available at: https://training.cochrane.org/handbook/current/chapter-10.
24. Clarke BL, Vokes TJ, Bilezikian JP, Shoback DM, Lagast H, Mannstadt M. Effects of parathyroid hormone rhPTH(1–84) on phosphate homeostasis and vitamin D metabolism in hypoparathyroidism: REPLACE phase 3 study. Endocrine. 2016;55(1):273-282.

25. 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(4):275-283.
26. Sikjaer T, Amstrup AK, Rolighed L, Kjaer SG, Mosekilde L, Rejnmark L. PTH(1-84) replacement therapy in hypoparathyroidism: a randomized controlled trial on pharmacokinetic and dynamic effects after 6 months of treatment. J Bone Miner Res. 2013;28(10):2232-2243.
27. Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. J Bone Miner Res. 2011;26(10):2358-2370.
28. Sikjaer T, Rejnmark L, Thomsen JS, et al. Changes in 3-dimensional bone structure indices in hypoparathyroid patients treated with PTH(1-84): a randomized controlled study. J Bone Miner Res. 2012;27(4):781-788.
29. Sikjaer T, Rolighed L, Hess A, Fuglsang-Frederiksen A, Mosekilde L, Rejnmark L. 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(6):1717-1726.
30. Vokes TJ, Mannstadt M, Levine MA, et al. Recombinant human parathyroid hormone effect on health-related quality of life in adults with chronic hypoparathyroidism. J Clin Endocrinol Metabol. 2018;103(2):722-731.
31. Winer KK, Ko CW, Reynolds JC, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1–34) versus calcitriol and calcium. J Clin Endocrinol Metabol. 2003;88(9):4214-4220.
32. Winer KK, Yanovski JA, Cutler GB Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. JAMA. 1996;276(8):631-636.
33. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler GB Jr. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. J Clin Endocrinol Metab. 2010;95(6):2680-2688.
34. Ware JE. User's manual for the SF-36v2 health survey. 2nd ed. Lincoln, RI: Quality Metric Inc; 2007.
35. Winer KK, Ye S, Ferré EMN, et al. Therapy with PTH 1-34 or calcitriol and calcium in diverse etiologies of hypoparathyroidism over 27 years at a single tertiary care center. Bone. 2021;149:115977.
36. Palui R, Das RR, Roy A, et al. Parathyroid hormone replacement versus oral calcium and active vitamin D supplementation in hypoparathyroidism: a meta-analysis. Indian J Endocrinol Metab. 2020;24(2):206-214.
37. Liu XX, Zhu XY, Mei GH. Parathyroid hormone replacement therapy in hypoparathyroidism: a meta-analysis. Horm Metab Res. 2016;48(6):377-383.

Online supplementary material

Parathyroid hormone therapy for managing chronic hypoparathyroidism: a systematic review and meta-analysis

Table of Contents

Table S1. Risk of bias of included studies

Study	Sequence generation	Allocation concealment	Blinding of patients and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
REPLACE [1-3]	Low	Low	Low	Low	Low	Probably low	Probably low
Sikjaer, 2011-2014 [4-7]	Low	Low	Low	Probably low	Low	Probably low	Probably low
Winer, 2003 [8]	Low	Probably low	Probably high	Probably high	Low	Probably low	Probably low
Winer, 1996 [9]	Probably low	Probably low	Probably high	Probably high	Low	Probably low	Probably low
Winer, 2010 [10]	Low	Probably low	Probably high	Probably high	Low	Probably low	Probably low
Khan 2021 [11]	Low	Probably low	Low	Probably low	Low	Probably low	Probably low
Khan 2022 [12]	Probably low	Probably low	Low	Probably low	Low	Probably low	Probably low

Table S2. GRADE summary of findings for specifically reported adverse events

Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		Conventional therapy	**PTH**		
Thirst	Relative risk: 6.5 (CI 95% 1.2 - 34.2) Based on data from 196 patients in 2 studies [1,4] Follow up 6 months	**14** per 1000	**91** per 1000	**Low** Due to very serious imprecision	PTH may increases thirst slightly
		Difference: **77 more per 1000** (CI 95% 3 more - 465 more)			
Tiredness	Relative risk: 0.9 (CI 95% 0.4 - 1.7) Based on data from 196 patients in 2 studies [1,4] Follow up 6 months	**162** per 1000	**146** per 1000	**Low** Due to very serious imprecision	PTH may decrease tiredness slightly
		Difference: **16 fewer per 1000** (CI 95% 97 fewer - 113 more)			

Dizziness	Relative risk: 1.7 (CI 95% 0.2 - 13.0) Based on data from 196 patients in 2 studies [1,4] Follow up 6 months	**68** per 1000	**116** per 1000 Difference: **48 more per 1000** (CI 95% 54 fewer - 816 more)	**Low** Due to very serious imprecision	PTH may increase dizziness
Headache	Relative risk: 1.3 (CI 95% 0.8 – 2.0) Based on data from 337 patients in 4 studies [1,4,11,12] Follow up 6 months	**191** per 1000	**248** per 1000 Difference: **57 more per 1000** (CI 95% 38 fewer - 191 more)	**Low** Due to very serious imprecision	PTH may result in a small increase in headache
Paresthesia	Relative risk: 1.3 (CI 95% 0.8 - 2.0) Based on data from 278 patients in 3 studies [1,4,12] Follow up 6 months	**242** per 1000	**315** per 1000 Difference: **73 more per 1000** (CI 95% 48 fewer - 242 more)	**Low** Due to very serious imprecision	PTH may increase paresthesia
Tetany	Relative risk: 1.2 (CI 95% 0.6 - 7.5) Based on data from 134 patients in 1 study [1] Follow up 6 months	**91** per 1000	**109** per 1000 Difference: **18 more per 1000** (CI 95% 36 fewer - 592 more)	**Low** Due to very serious imprecision	PTH may result in a small increase in tetany
Muscle spasms	Relative risk: 1.0 (CI 95% 0.6 - 1.6) Based on data from 216 patients in 2 study [1,12] Follow up 6 months	**262** per 1000	**262** per 1000 Difference: **0 fewer per 1000** (CI 95% 105 fewer 157 more)	**Very Low** Due to extremely serious imprecision	We are uncertain whether PTH increases or decreases muscle spasms
Pain in extremity	Relative risk: 1.9 (CI 95% 0.8 - 4.4) Based on data from 161 patients in 2 studies [1,8] Follow up 8 months	**105** per 1000	**200** per 1000 Difference: **95 more per 1000** (CI 95% 21 fewer - 357 more)	**Low** Due to very serious imprecision	PTH may increase pain in extremity
Myalgia	Relative risk: 1.2 (CI 95% 0.2 - 6.1) Based on data from 134 patients in 1 study [1] Follow up 6 months	**91** per 1000	**109** per 1000 Difference: **18 more per 1000** (CI 95% 73 fewer - 464 more)	**Low** Due to very serious imprecision	PTH may result in a small increase in myalgia
Musculoskeletal pain	Relative risk: 1.2 (CI 95% 0.2 - 6.1)	**45** per 1000	**54** per 1000	**Low** Due to very serious	PTH may have no or little impact on musculoskeletal pain

	Based on data from 134 patients in 1 study [1] Follow up 6 months	Difference: **9 more per 1000** (CI 95% 36 fewer - 230 more)		imprecision	
Back pain	Relative risk: 0.5 (CI 95% 0.2 - 1.2) Based on data from 134 patients in 1 study [1] Follow up 6 months	**204** per 1000	**102** per 1000	**Low** Due to very serious imprecision	PTH may decrease back pain
		Difference: **102 fewer per 1000** (CI 95% 163 fewer - 41 more)			
Neck pain	Relative risk: 1.5 (CI 95% 0.3 - 7.0) Based on data from 134 patients in 1 study [1] Follow up 6 months	**45** per 1000	**68** per 1000	**Low** Due to very serious imprecision	PTH may result in a small increase in neck pain
		Difference: **23 more per 1000** (CI 95% 31 fewer - 270 more)			
Upper abdominal pain	Relative risk: 1.7 (CI 95% 0.4 - 8.0) Based on data from 134 patients in 1 study [1] Follow up 6 months	**45** per 1000	**77** per 1000	**Low** Due to very serious imprecision	PTH may result in a small increase in upper abdominal pain
		Difference: **32 more per 1000** (CI 95% 27 fewer - 315 more)			
Diarrhea	Relative risk: 1.3 (CI 95% 0.5 – 3.2) Based on data from 216 patients in 2 study [1,12] Follow up 6 months	**92** per 1000	**120** per 1000	**Low** Due to very serious imprecision	PTH may result in a small increase in diarrhea
		Difference: **28 more per 1000** (CI 95% 46 fewer - 203 more)			
Nausea	Relative risk: 1.5 (CI 95% 0.7 – 3.2) Based on data from 337 patients in 4 studies [1,4,11,12] Follow up 6 months	**100** per 1000	**150** per 1000	**Low** Due to very serious imprecision	PTH may result in a small increase in nausea
		Difference: **50 more per 1000** (CI 95% 30 fewer - 220 more)			
Respiratory tract infection	Relative risk: 0.9 (CI 95% 0.2 - 5.5) Based on data from 196 patients in 2 studies [1,4] Follow up 6 months	**68** per 1000	**61** per 1000	**Low** Due to very serious imprecision	PTH may have little or no impact on respiratory tract infection
		Difference: **7 fewer per 1000** (CI 95% 54 fewer - 306 more)			
Nasopharyngitis	Relative risk: 0.4 (CI 95% 0.2 - 1.2) Based on data from 134 patients in 1 study [1] Follow up 6 months	**159** per 1000	**64** per 1000	**Low** Due to very serious imprecision	PTH may decrease nasopharyngitis
		Difference: **95 fewer per 1000** (CI 95% 127 fewer - 32 more)			

Sinusitis	Relative risk: 1.5 (CI 95% 0.3 - 7.0) Based on data from 134 patients in 1 study [1] Follow up 6 months	**45** per 1000	**68** per 1000	**Low** Due to very serious imprecision	PTH may result in a small increase sinusitis
		Difference: **23 more per 1000** (CI 95% 31 fewer - 270 more)			
Cardiovascular disease	Relative risk: 2.2 (CI 95% 0.6 - 7.7) Based on data from 62 patients in 1 study [4] Follow up 36 months	**67** per 1000	**147** per 1000	**Low** Due to very serious imprecision	PTH may increase cardiovascular disease
		Difference: **80 more per 1000** (CI 95% 27 fewer - 449 more)			

Table S3. Meta-analysis of surrogate outcomes

Outcomes	No of studies (No of patients)	Relative risk/Mean difference (95%CI)
Hypocalcemia (7 months)	5 (343) [1,7,10,11,12]	RR 0.7 (0.3 to 1.9)
Hypercalcemia (6 months)	**5 (341) [1,7,9,11,12]**	**RR 2.4 (1.2 to 5.0)**
Hypercalciuria (6 months)	1 (134) [1]	RR 3.4 (0.4 to 27)
24-h urine calcium excretion levels (mmol/24 h) (6 months)	6 (327) [1,4,8-10,12]	MD -0.13 (-0.49, 0.23)
Serum calcium, mmol/L (6 months)	**7 (376) [3,4,8-12]**	**MD 0.11 (0.02, 0.20**)
Serum phosphate (mmol/L) (6 months)	**5 (277)** [1,4,9-11]	**MD -0.2 (-0.4, -0.03)**
Serum 25-hydroxyvitamin D (ng/mL) (6 months)	**4 (218)** [1,4,9,10]	**MD -9.2 (-12.2, -6.1)**
Serum 1,25-Dihydroxyvitamin D3 (pg/mL) (6 months)	4 (218) [1,4,9,10]	MD 8.0 (-3.5 to 19.6)
Serum magnesium (mmol/L) (36 months)	**3 (101) [6,8,10]**	**MD -0.06 (-0.1, -0.01)**
Mean creatinine clearance levels (ml/min) (36 months)	2 (39) [8,10]	MD 3.9 (-2.4 to 10.3)
Serum alkaline phosphatase (u/l) (21 months)	**4 (111) [4,8-10]**	**MD 64.74 (8.1 to 121.4)**
Serum osteocalcin (ng/ml) (21 months)	**4 (111) [4,8-10]**	**MD 59.25 (11.6 to 106.9)**
Urine deoxypyridinoline (nmol/mmol) (36 months)	3 (49) [8-10]	MD 43.48 (-3.5 to 90.5)
Urine pyridinoline (nmol/mmol) (36 months)	**3 (49) [8-10]**	**MD 93.08 (15.9 to 170.2)**
BMD- total body (g/cm^2) (6 months)	3 (98) [4, 8,10]	MD -0.1 (-0.1, 0)
BMD- Hip-Femoral neck (g/cm^2) (21 months)	2 (86) [4, 8]	MD -2.4 (-7.3, 2.5)
BMD- Spine (g/cm^2) (6 months)	3 (98) [4, 8,10]	MD -0.1 (-0.4, 0.2)

*We bolded the significant results

References

1. 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. The Lancet Diabetes & Endocrinology. 2013;1(4):275-283.
2. Vokes TJ, Mannstadt M, Levine MA, et al. Recombinant Human Parathyroid Hormone Effect on Health-Related Quality of Life in Adults With Chronic Hypoparathyroidism. The Journal of Clinical Endocrinology & Metabolism. 2018;103(2):722-731.
3. Clarke BL, Vokes TJ, Bilezikian JP, Shoback DM, Lagast H, Mannstadt M. Effects of parathyroid hormone rhPTH(1–84) on phosphate homeostasis and vitamin D metabolism in hypoparathyroidism: REPLACE phase 3 study. Endocrine. 2016;55(1):273-282.
4. Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: A randomized, placebo-controlled study. Journal of Bone and Mineral Research. 2011;26(10):2358-2370.
5. Sikjaer T, Rejnmark L, Thomsen JS, et al. Changes in 3-dimensional bone structure indices in hypoparathyroid patients treated with PTH(1-84): A randomized controlled study. Journal of Bone and Mineral Research. 2012;27(4):781-788.
6. Sikjaer T, Amstrup AK, Rolighed L, Kjaer SG, Mosekilde L, Rejnmark L. PTH(1-84) replacement therapy in hypoparathyroidism: A randomized controlled trial on pharmacokinetic and dynamic effects after 6 months of treatment. Journal of Bone and Mineral Research. 2013;28(10):2232-2243.

7. Sikjaer T, Rolighed L, Hess A, Fuglsang-Frederiksen A, Mosekilde L, Rejnmark L. Effects of PTH(1–84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. Osteoporosis International. 2014;25(6):1717-1726.

8. Winer KK, Ko CW, Reynolds JC, et al. Long-Term Treatment of Hypoparathyroidism: A Randomized Controlled Study Comparing Parathyroid Hormone-(1–34)VersusCalcitriol and Calcium. The Journal of Clinical Endocrinology & Metabolism. 2003;88(9):4214-4220.

9. Winer KK, Yanovski JA, Cutler GB, Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. Jama. 1996;276(8):631-636.

10. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler GB, Jr. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. J Clin Endocrinol Metab. 2010;95(6):2680-2688.

11. 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. 2021 Aug 4:dgab577. doi: 10.1210/clinem/dgab577. Epub ahead of print. PMID: 34347093.

12. Khan A, Rubin M, Schwarz P, et al. Phase 3 PaTHway Trial: Participants Treated With TransCon PTH Achieved Independence From Conventional Therapy While Maintaining Normal Serum Calcium. 2022.

Chapter 5: Discussion and Conclusion to This Thesis

This thesis both describes an approach to addressing the challenges inherent when resources are unavailable to conduct systematic reviews for all the relevant questions the guideline panel wishes to address, and presents a series of investigations focused on evidence synthesis for the development of a guideline on a rare disease, chronic hypoparathyroidism. In this concluding chapter, I review the methodological challenges first presented in Chapter 1 and discuss how I have addressed them (described in detail in Chapters 2 to 4). Additionally, I highlight the strengths and limitations of our approach to differentiating recommendations based on systematic reviews and those that were not; of our reviews themselves; and explore potential opportunities and challenges that may arise when we look toward future directions in this field.

Challenges and solutions

During the evidence synthesis for guideline development for chronic hypoparathyroidism, we encountered several methodological challenges. The first challenge we met was confronting the limited resources - financial, temporal, and human - for the guideline development.

In **Chapter 2**, our methods team described the solution employed to address this problem, which involved engaging the leaders of the guideline in defining a restricted number of issues for which systematic reviews would be conducted, and for which would not. Subsequently, the leadership of the panel collaborated with the panel members and defined four critical PICO questions for conducting systematic reviews. The panel leaders assigned the methods team to ensure that when these reviews were conducted, trustworthiness standards of articulation of values and preferences, rating of evidence certainty, and the resultant process of moving from evidence to recommendations and grading the strength of recommendations were met. In this dissertation, this particular type of recommendations are termed as GRADEd recommendations.[1,2]

The clinical experts within the guideline panel assumed responsibility for the residual questions that were not subjected to systematic reviews. For these questions, the panel issued recommendations that were based on the narrative reviews [3-5] and less clearly defined criteria for moving from evidence to recommendations. The process of these recommendations, termed herein as non-GRADEd recommendations, involved a less structured approach without formal specifications of PICOs, conduct of traditional expert narrative literature reviews rather than systematic review approaches and did not include tables summarizing the findings.[6]

The methods team was, however, also charged with explaining these two different types of recommendations to the guideline users by differentiating them one from the other and ensuring that the two categories were clear. We specified formal GRADEd recommendations, and non-GRADEd recommendations in different places in the guideline and using wording and presentation of GRADEd recommendation as suggested by the GRADE working group,[7] while using quite different language and presentation for non-GRADEd recommendations.

In **Chapter 3,** I present our approach to help determine patient-important outcomes for the guideline panel by inferring causation between the process of this rare disease and the symptoms and complications in patients with chronic hypoparathyroidism experience. To address the causality issue, we conducted a systematic review based on cohort and case-control studies that addressed patients with chronic hypoparathyroidism and people with normal parathyroid function. Developing criteria for distinguishing between convincingly causal relations from those that were not, involved methodologic innovation. We established two criteria to determine the symptoms and complications causally related to hypoparathyroidism: 1) those reported by at least 3 studies, and 2) those where patients with chronic hypoparathyroidism exhibited a statistically higher risk compared to individuals with normal parathyroid function.

By applying these criteria, we were able to filter down from 170 complications and symptoms reported in the existing literature, ultimately identifying the nine complications and symptoms that met our criteria for being causally related to chronic hypoparathyroidism (reported in detail in Chapter 3). By referring the findings from this review and in conjunction with the consideration of experts' clinical experience and patients' values, the panel members were able to define patient-important outcomes. This, in turn, aided with execution of evidence synthesis and guideline recommendations.

The third challenge we confronted during the evidence synthesis for rare disease involved minimizing the impact of insufficient evidence for patient-important outcomes. In **Chapter 3** (part 2), we present a diagnosis review that addressed the predicting values of early parathyroid hormone and calcium levels with the development of chronic hypoparathyroidism in patients following total thyroidectomy, to obtain as much information as possible, we incorporated data from both prospective and retrospective cohort studies. Using this approach, we were able to include an additional ten retrospective cohort studies, which facilitated data pooling for sensitivity, specificity, and post-test probabilities.

Chapter 4 presents a management review that compares parathyroid hormone therapy versus conventional therapy for chronic hypoparathyroidism. To maximize the wealth of information available, we endeavored to incorporate randomized studies irrespective of whether they were designed as parallel group, cluster, or crossover randomized studies and regardless of the publication status (i.e., published peer reviewed journals, pre-publications, conferences posters, or ongoing studies), and if there is no or very few studies or data sources from randomized trials, we were prepared to incorporating observational studies.

Using this comprehensive approach, we identified seven small, randomized trials with a total of 386 patients, comprising four parallel group published studies, one crossover published study, and two unpublished parallel group trials (trial authors have completed their study but not published their data when we were extracting the data). The authors of the unpublished trials generously shared data, allowing us to perform a meta-analysis based on the optimal study design (randomized trials) for a rare disease.

Further, in the management review, because limited direct evidence for patient-important outcomes proved available, we utilized indirect evidence from surrogate outcomes to infer patient-import outcomes. For example, we utilized 24-hour urinary calcium excretion as a surrogate for nephrocalcinosis/nephrolithiasis, and bone mineral density for fracture. We used the often neglected GRADE strategy: rather than rating certainty regarding the surrogate, we rated certainty in the patient-important outcome for which the surrogate was standing in, in the process rating down the certainty of evidence because of indirectness. We referred to prior publications [8-11] to ascertain if there is a relationship between the surrogate outcome and inferred patient-import outcomes. If a relationship was present, we rated down once for indirectness if the population in the referred studies was similar to that in our reviews. If there was no evidence of a relationship, we rated down twice for indirectness. Because non-randomized studies of interventions also infrequently reported data for patient-import outcomes, we did not incorporate data from these studies.

In addition to the primary challenges, we also met some secondary challenges conducting the reviews. One such challenge is whether to pool data, especially in light of the considerably heterogeneous presentations among the population under study. In the review investigating the prevalence of symptoms and complications causally related to chronic hypoparathyroidism, we confronted numerous factors, such as age, duration of hypoparathyroidism, whether the patient

has undergone parathyroid surgery or not, and whether they have received treatments or not, which could influence the prevalence of symptoms or complications resulting from chronic hypoparathyroidism. [3,12-16] These factors rendered the findings difficult to interpret. Even pooling the data into pre-defined subgroups did not satisfactorily explain the extremely high heterogeneity across studies.

Working with the expert panel, we decided to abandon pooling the prevalence data by performing meta-analysis. Instead, we opted to present the prevalence using median and interquartile range, stratified by general population, postsurgical adult population, non-surgical population, and pediatric patients.

Strengths and limitations

In addition to the strengths described in the included publications, a principal strength of this thesis lies in our exploration of diverse methods for conducting evidence synthesis and issuing recommendations. We did not yield to the challenges inherent in conducting evidence synthesis for rare diseases. Instead, we explored diverse methods to overcome these obstacles, including clear differentiation between evidence-based and traditional guideline development approaches, empirically addressing issues of causation between disease and potential disease manifestations, and with respect to diagnostic and management issues rigorously and persistently working to obtain all relevant evidence and where necessary appropriately basing inferences on surrogate endpoints. These methods could potentially be generalized to the evidence synthesis process for the development of guidelines for other rare diseases.

Despite the strengths, our work has limitations. Firstly, this thesis represents only a segment of the guideline development for chronic hypoparathyroidism. We did not present the publications

of systematic review with no eligible studies and the narrative literature reviews that support non-GRADEd recommendations. This omission might make it difficult for researchers to gain a comprehensive understanding of the entire guideline development process for chronic hypoparathyroidism. To mitigate this limitation, I attached a summary of all the publications related to the guideline development for chronic hypoparathyroidism.[3-6,15-20]

Secondly, our use of different methodologies in one guideline, encompassing both the GRADEd and non-GRADEd approach for issuing recommendations, may potentially lead to misleading or misunderstanding. While ideally, the use of GRADEd approach for issuing recommendations would be optimal for all guideline questions, the guideline panel needs to consider the constraints of limited time, financial resources, and human resources. This is particularly pertinent in the context of a rare disease in which the target population is relatively small compared to common diseases.

Further, based on our prior research, compared with GRADEd approach, guideline panels foregoing trustworthiness standards and using non-GRADEd approach, what they often call “consensus” approach, are more likely to issue inappropriate strong recommendations. This could result in unnecessary harms to patients. [21-23] However, sometimes foregoing full trustworthy guideline standards for rare diseases may be unavoidable. In such situations, the approach we have adopted to clearly differentiate between more and less rigorous approaches has the merit of at least making vivid to clinicians what is more and less trustworthy.

Thirdly, not all challenges outlined in this thesis are exclusive to the evidence synthesis process for rare diseases. For instance, the second challenge we confronted during the reviews - defining patient-important outcomes- is a consideration relevant to guidelines for both rare and

non-rare diseases. In the context of rare diseases, however, there exists a particular need to educate both panel members and patients about the complications and symptoms causally linked to the rare condition, differentiating that is usually much more evident in commonly occurring diseases. This understanding forms the bedrock of defining relevant and significant patient-important outcomes, thereby aiding in more effective shared decision-making.

Additionally, in two of our reviews, we employed both prospective and retrospective cohort studies in the review of identifying symptoms and complications related to the rare condition (Chapter 3, part 1), and in the reviewing of addressing the diagnostic question (Chapter 3, part 2). However, the reliability of this approach is contingent upon the risk of bias inherent in the included studies, as well as the magnitude of their sample sizes. It is crucial to acknowledge that the observational nature of these studies, particularly in retrospective studies, could increase the risk of bias. For instance, the absence of appropriate adjusted analysis in comparisons between exposure and non-exposure groups, could increase likelihood of identifying false symptoms and complications.

Sample size could also impact the reliability of findings. For example, in the systematic review addressing the causality between chronic hypoparathyroidism and symptoms/complications, we included 18 cohort/case-control studies with a total of 10,195 cases and 47,490 normal individuals. However, for other rare diseases, obtaining a large sample size of cases from cohort and case-control studies can be challenging. In such cases, researchers might need to think about other approaches to help identify the complications and symptoms causally linked to a rare disease.

Furthermore, our approach of restricting eligibility to randomized trials to address the management question of chronic hypoparathyroidism might not be feasible for other rare

diseases. The unavailability of randomized trials may obligate researchers addressing other rare disease to consider broadening their evidence sources to obtain as much data as possible. This could involve including observational studies such as cohort studies, case-control studies, case studies, cross-sectional studies, as well as including studies for which limited data are available such as those reported only in conferences abstracts. Broadening eligibility criteria could also include using indirect evidence from surrogate outcomes, but also evidence with indirectness related to population, interventions, and comparison. Lastly, the guideline panel did not involve any implement specialists, which may lead to challenging to apply the guideline in real-world settings.

Opportunities and future directions

The process of evidence synthesis for rare diseases, as exemplified by our work on chronic hypoparathyroidism, not only illuminates the obstacles within the research landscape but also highlights potential avenues for future exploration. These difficulties provide innovative opportunities for researchers and guideline developers to further explore and refine their methodologies for evidence synthesis in rare diseases.

Firstly, it is vital that researchers and guideline developers, whenever feasible, harness innovation to deliver recommendations following trustworthiness standards for rare diseases. This objective demands a cooperative effort to garner more resources for guideline development for such diseases and readiness to confront the challenges associated with conducting systematic reviews. While it is undeniably true that at times that compromising on standards of trustworthiness when making recommendations for rare diseases, such as, in our case, chronic hypoparathyroidism, might be unavoidable, guideline developers should only make these compromises when limitation of time and cost are insurmountable. If faced with this situation, clearly differentiating between more and less trustworthy recommendations optimally

serves clinical and patient consumers of the guideline. However, compromising trustworthiness standards resorting to a “consensus” approach should be viewed as a measure of last resort when resources are severely limited.

Secondly, identifying complications and symptoms causally related to the rare disease could be an important aspect of managing rare diseases. This understanding can educate panel members and patients, helping them comprehend the intricacies of the rare condition, and informing the right patient-important outcomes to guide the completion of systematic reviews and recommendations. Bringing empirical evidence to bear on this issue involves conducting a systematic review, focusing on cohort and case-control studies, thus helping to clarify the causality between the disease and associated symptoms/complications. However, in circumstances where the available studies are insufficient to establish causality, our approach may fall short.

Thirdly, when faced with insufficient evidence for a rare disease, the incorporation of more extensive compendium of studies, irrespective of study design, as well as the inclusion of indirect evidence, can be advantageous in acquiring more information. During our reviews for the guideline of chronic hypoparathyroidism, we incorporated indirect evidence from surrogate outcomes to infer patient-important outcomes. If necessary, indirect evidence relating to population, interventions, and comparisons could also be beneficial, though the certainty of this evidence should be rated down for potential indirectness.

In conclusion, our solutions to address the challenges, as encountered during the process of conducting evidence synthesis and developing recommendations for chronic hypoparathyroidism, may only cover a segment of the potential issues and do have their

limitations. Nevertheless, the insights and experiences derived from our work may hold potential applicability to other rare diseases. In this way, our work contributes to the development of robust, evidence-based guidelines for rare conditions. Future research should focus on these identified opportunities, aiming to continuously improve and refine the process of evidence synthesis and moving from evidence to recommendations in the formation of guidelines for rare diseases.

References

1. Andrews J, Guyatt GH, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-725.
2. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013; 66(7):726-735.
3. Pasieka JL, Wentworth K, Yeo CT, Cremers S, Dempster D, et al. Etiology and Pathophysiology of Hypoparathyroidism: A Narrative Review. J Bone Miner Res. 2022;37(12):2586-2601.
4. Mannstadt M, Cianferotti L, Gafni RI, Giusti F, Kemp EH, et al. Hypoparathyroidism: Genetics and Diagnosis. J Bone Miner Res. 2022;37(12):2615-2629.
5. Bjornsdottir S, Ing S, Mitchell DM, Sikjaer T, Underbjerg L, et al. Epidemiology and Financial Burden of Adult Chronic Hypoparathyroidism. J Bone Miner Res. 2022;37(12):2602-2614.
6. Yao L, Guyatt G, Ye Z, Bilezikian JP, Brandi ML, et al. Methodology for the Guidelines on Evaluation and Management of Hypoparathyroidism and Primary Hyperparathyroidism. J Bone Miner Res. 2022;37(11):2404-2410.
7. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020;119:126-135.
8. Saponaro F, Cetani F, Mazoni L, Apicella M, Di Giulio M, et al. Hypercalciuria: its value as a predictive risk factor for nephrolithiasis in asymptomatic primary hyperparathyroidism? J Endocrinol Invest. 2020;43(5):677-682.
9. Rejnmark L, Vestergaard P, Mosekilde L. Nephrolithiasis and renal calcifications in primary hyperparathyroidism. J Clin Endocrinol Metab. 2011;96(8):2377-85.

10. Tay YD, Liu M, Bandeira L, Bucovsky M, Lee JA, et al. Occult urolithiasis in asymptomatic primary hyperparathyroidism. Endocr Res. 2018 May;43(2):106-115.
11. Bouxsein ML, Eastell R, Lui LY, Wu LA, de Papp AE, Grauer A, Marin F, Cauley JA, Bauer DC, Black DM; FNIH Bone Quality Project. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials. J Bone Miner Res. 2019;34(4):632-642.
12. Clarke BL. Epidemiology and Complications of Hypoparathyroidism. Endocrinology and Metabolism Clinics of North America 2018;47(4):771-82.
13. Bilezikian JP, Khan A, Potts JT Jr, Brandi ML, Clarke BL, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res. 2011;26(10):2317-37.
14. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173(2):G1-20.
15. Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Gittoes NJ, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. J Bone Miner Res. 2022;37(12):2568-2585.
16. Khan AA, Bilezikian JP, Brandi ML, Clarke BL, Potts JJ, Mannstadt M; et al. The Second International Workshop on the Evaluation and Management of Hypoparathyroidism. J Bone Miner Res. 2022;37(12):2566-2567.
17. Van Uum S, Shrayyef M, M'Hiri I, Dandurand K, Ali DS, Bilezikian JP, et al. Initial Assessment and Monitoring of Patients with Chronic Hypoparathyroidism: A Systematic Current Practice Survey. J Bone Miner Res. 2022;37(12):2630-2641.
18. Khan AA, Guyatt G, Ali DS, Bilezikian JP, Collins MT, et al. Management of Hypoparathyroidism. J Bone Miner Res. 2022;37(12):2663-2677.

19. Yao L, Hui X, Li M, Li J, Ahmed MM, et al. Complications, Symptoms, Presurgical Predictors in Patients With Chronic Hypoparathyroidism: A Systematic Review. J Bone Miner Res. 2022;37(12):2642-2653.
20. Yao L, Li J, Li M, Lin C, Hui X, et al. Parathyroid Hormone Therapy for Managing Chronic Hypoparathyroidism: A Systematic Review and Meta-Analysis. J Bone Miner Res. 2022;37(12):2654-2662.
21. Yao L, Guyatt GH, Djulbegovic B. Can we trust strong recommendations based on low quality evidence? BMJ. 2021;25;375:n2833.
22. Yao L, Ahmed MM, Guyatt GH, Yan P, Hui X, et al. Discordant and inappropriate discordant recommendations in consensus and evidence-based guidelines: empirical analysis. BMJ. 2021;25;375:e066045.
23. Djulbegovic B, Guyatt G. Evidence vs Consensus in Clinical Practice Guidelines. JAMA. 2019; 27;322(8):725-726.