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# 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).

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## 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://metadisc.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

| | Overall population[a] | | Postsurgical adult patients | | Nonsurgical adult patients | | Children patients (<18 years) | |
|---|---|---|---|---|---|---|---|---|
| Complications | 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.

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## 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.

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