Original Article

Effect of postsurgical chronic hypoparathyroidism on morbidity and mortality: a systematic review and meta-analysis

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Background: Hypoparathyroidism (HypoPT) is a common sequela of anterior neck surgeries. While the acute risks of HypoPT are well known, emerging evidence is beginning to define the risks chronic HypoPT poses to patients. This meta-analysis aims to evaluate that risk and give more insight into its consequences.

Methods: A systematic review and meta-analysis were performed, searching EMBASE, Web of Science, and Scopus for studies published up to July 1, 2020 and reported following PRISMA guidelines. Pooled analysis was estimated using the Mantel-Haenszel method and a random-effects model. A sub-analysis of the pooled data for each morbidity was performed and demonstrated in forest plots.

Results: Patients with postsurgical chronic HypoPT had a high risk of cardiac morbidities [odds ratio (OR) =1.43; 95% confidence interval (95% CI): 1.21 to 1.70; P<0.001] in the absence of elevated risk of cardiac arrhythmias (OR =1.35, 95% CI: 0.96 to 1.79, P=0.08). Analysis also showed higher odds of developing renal disease (OR =4.85, 95% CI: 3.54 to 6.67, P<0.001), renal stones (OR =3.86, 95% CI: 1.81 to 8.23, P<0.001), seizures (OR =2.41, 95% CI: 1.66 to 3.5, P<0.001), mental health problems (OR =1.46, 95% CI: 1.21 to 1.77, P<0.001), and infections (OR =1.51, 95% CI: 1.28 to 1.78, P<0.001). Conversely, HypoPT has no effect on mortality risk (OR =1.19, 95% CI: 0.96 to 1.49, P=0.12).

Conclusions: Postsurgical HypoPT patients are vulnerable to a variety of medical and psychiatric diseases. This meta-analysis should guide surgeons in preoperative counseling and postoperative care for patients undergoing anterior neck surgeries.

Keywords: Hypoparathyroidism (HypoPT); morbidity; mortality; chronic hypoparathyroidism; meta-analysis

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Introduction

Chronic hypoparathyroidism is a rare endocrine disorder which can be transient or permanent. Hypoparathyroidism (HypoPT) has an incidence of 24–40 per 100,000 in the United States and Europe, with a lower prevalence (10.1 per 100,000) in Norway (1-8). The most common cause of chronic HypoPT is parathyroidectomy or accidental removal of parathyroid glands during thyroid

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Table 1 Electronic search criteria for systematic review for postsurgical chronic hypoparathyroidism

Database	Search criteria	Citations
EMBASE	((‘hypoparathyroidism’) AND (‘mortality’ OR ‘morbidity’ OR ‘cardiovascular disease’ OR ‘heart disease’ OR ‘cardiac complications’ OR ‘cardiovascular’ OR ‘heart’ OR ‘renal’ OR ‘renal complications’ OR ‘complications’ or ‘death’))	4,056
Web of Science	TS=((‘hypoparathyroidism’) AND (‘mortality’ OR ‘morbidity’ OR ‘cardiovascular disease’ OR ‘heart disease’ OR ‘cardiac complications’ OR ‘cardiovascular’ OR ‘heart’ OR ‘renal’ OR ‘renal complications’ OR ‘complications’ or ‘death’))	2,029
Scopus	((‘hypoparathyroidism’) AND (‘mortality’ OR ‘morbidity’ OR ‘cardiovascular disease’ OR ‘heart disease’ OR ‘cardiac complications’ OR ‘cardiovascular’ OR ‘heart’ OR ‘renal’ OR ‘renal complications’ OR ‘complications’ or ‘death’))	17,685

Table 2 PICOS criteria for the systematic search

Parameters	Inclusion criteria	Exclusion criteria
Population	Males and non-pregnant females >18 years old	Prior chronic kidney disease
Intervention/exposure	Diagnosis of hypoparathyroidism	–
Comparator	Normal parathyroid function	–
Outcome	Development of a comorbid condition or mortality	–
Study design	Case-control, cohort studies, and randomized controlled trials	Case reports, commentary, non-English studies, book chapters, pilot studies, literature reviews, articles without full text available

PICOS, Population, Intervention, Comparator, Outcome, and Study Design.

surgery (1-5,8). Postsurgical HypoPT was estimated at 6.4-29 per 100,000, compared to 2.3–17 per 100,000 in non-surgical patients (1-5,8). Chronic HypoPT is defined as the use of vitamin D or calcium supplements for more than six months to maintain normocalcemia (9). The incidence rate of postsurgical HypoPT ranges from 1.17% to 12.1% in some reports (10-13).

Little data is available on the effect of postsurgical chronic HypoPT on morbidity and mortality. Several studies with small sample sizes have reported the effects of HypoPT on cardiovascular, renal, and cerebrovascular systems. The same reports have described chronic HypoPT as a potential cause of fracture, cataract, malignancy, infection, psychiatric disorders, and death (2,3,14-18). To our knowledge, this is the first meta-analysis to evaluate the impact of chronic HypoPT on developing morbidities and mortality. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/gs-21-181).

Methods

Literature search

A comprehensive web-based literature search was performed on the EMBASE, Web of Science, and Scopus databases for articles published up to July 1, 2020, using a widespread literature screening. The primary objective was to determine the risk of developing morbidities and mortality among patients with postsurgical chronic HypoPT. The search algorithm included all occurrences in the title or abstract of the terms: “hypoparathyroidism” and “mortality” or “morbidity” or “cardiovascular disease” or “heart disease” or “cardiac complications” or “cardiovascular” or “heart” or “renal” or “renal complications” or “complications” or “death.” Exact search terms are shown in *Table 1*. Inclusion criteria were defined using the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) approach (*Table 2*). Males and non-pregnant females over the age of 18 diagnosed with

postsurgical chronic HypoPT without prior renal disease were compared to those without postsurgical chronic HypoPT. The outcomes of interest were the development of any comorbid condition or mortality. The study designs included randomized controlled trials (RCT), case-control studies, and cohort studies. We excluded case reports, commentary, non-English articles, book chapters, pilot studies, and literature reviews from the study. Conference proceedings and unpublished studies were included if they provided sufficient information, including demographics and outcomes. The Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were used to ensure adequate reporting of this meta-analysis (19).

Data extraction and selection

All included citations were extracted and compiled into a citation management software (Endnote X9.2) by title, author, journal, year of publication, and article type. Duplicate articles were removed. A manual review of the articles was performed independently by two co-investigators (DH and MS). Articles were screened in two stages. First, articles were manually screened for inclusion by title/abstract, followed by full-text review for exclusion. For potentially repetitive data presented in two separate publications by a single institution, the more recent publication was included. Bibliographies of the selected articles were reviewed to ensure the inclusion of all relevant literature. No data was repeated or shared between selected articles. All disputes over inclusion or exclusion were first discussed among two authors (DH, MS). Any unresolved discrepancy was then solved by the corresponding investigator (EK).

We extracted data from the relevant articles, including demographics, type of morbidity, and mortality. Frequency data were collected as fractions of exposures over outcomes. Relative risk and odds ratios were collected with calculations for validity, such as confidence intervals and P values. Data for morbidities were further divided into subgroups based on disease process: (I) cardiovascular, (II) renal, (III) neuropsychiatric, (IV) immunologic and oncologic, (V) skeletal, and (VI) ophthalmic. Risk of mortality was also assessed.

Cases and control population

Cases were identified as patients who needed vitamin D or calcium supplements for more than 6 months to maintain normocalcemia following thyroidectomy or parathyroidectomy. The control group included the following: (I) normal population, (II) patients who developed non-surgical hypoparathyroidism, and (III) post-surgical patients with preserved parathyroid function.

Quality assessment

Quality was assessed at the study level by evaluating the authors' stated purpose, study design, and source of data collection for all included studies. This was performed independently by two co-investigators (JK and MS), and any discrepancies were reviewed by the senior investigator (EK). Tools for methodological quality were used to assess articles individually. The Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies was used (20). This instrument comprises nine points that determine the selection, comparability, and exposure. In this meta-analysis, articles were considered to have a high methodologic quality if they scored between 7–9; moderate-quality between 4–6; and low quality less than 4. Investigators were also asked to independently assess the overall relevance and overall validity of the included studies. Each of these categories was ranked as either high, moderate, or low.

Statistical analysis

Data were analyzed using Comprehensive Meta-Analysis version 3.0. For dichotomous scales, the effect size was pooled by Mantel-Haenszel (M-H) test and expressed as odds ratio (OR) along with a 95% confidence interval (95% CI). Heterogeneity was assessed by Cochran's Q test and its magnitude defined by I^2 statistic. In the case of significant heterogeneity, a random-effects model was applied, and potential clinical and methodological differences between studies were examined. Sensitivity analysis was performed by removing individual studies and rechecking heterogeneity.

Results

Characteristics of included studies

A PRISMA flow chart for the selection of articles in this study can be found in *Figure 1*. The initial literature search returned 23,770 records. After removal of duplicates and application of inclusion criteria, 27 unique full-text

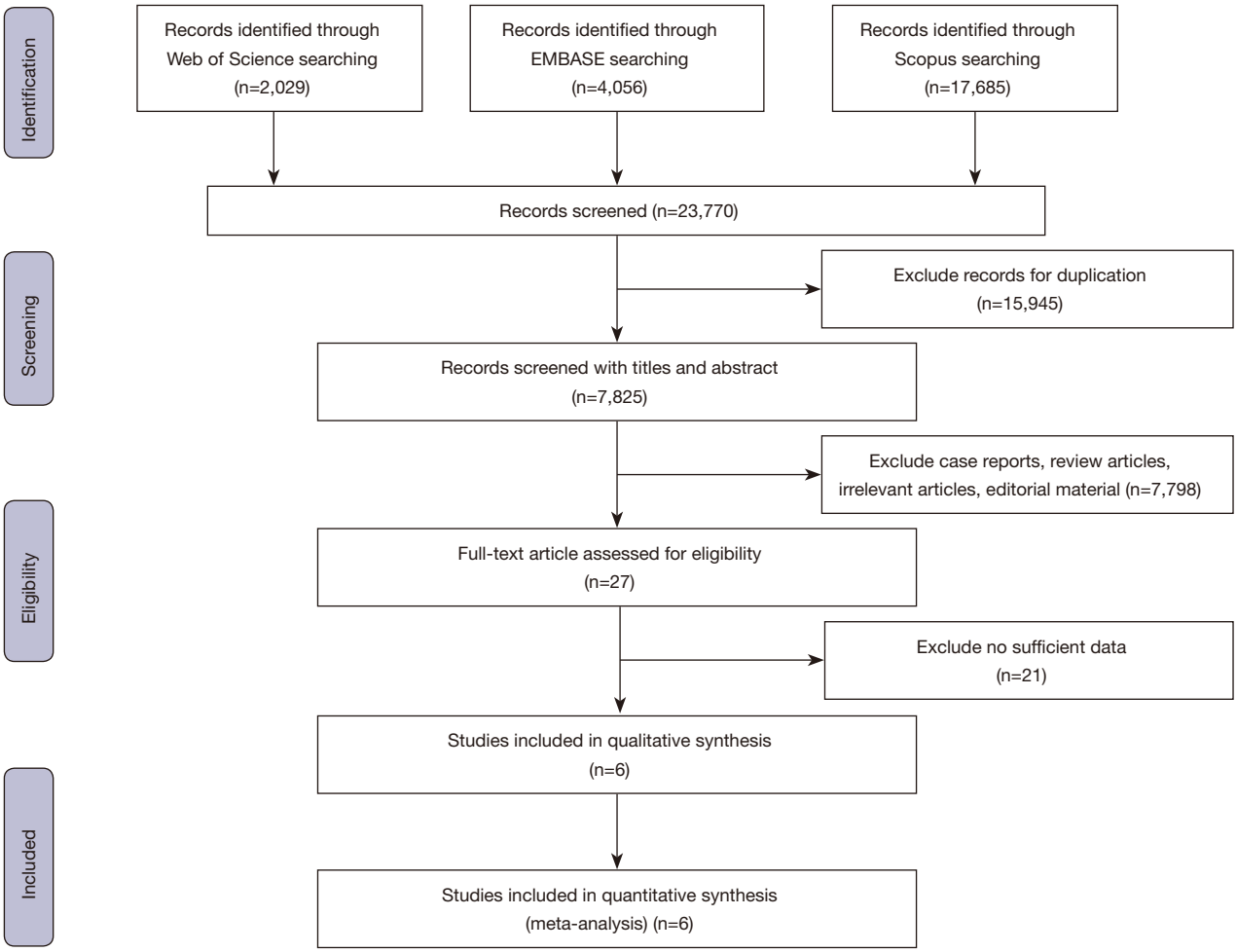

Figure 1 The workflow of literature search and study selection process.

Table 3 Characteristics of the selected studies

Authors (reference)	Year of publication	Study design	Population	Sample size (n)	Case (n)	Control (n)	Female case (n)	Female control (n)
Vadiveloo (14)	2018	Retrospective cohort	Scottish	1,417	116	1,301	93	926
Underbjerg (2)	2013	Retrospective cohort	Denmark	2,752	688	2,064	603	1,816
Underbjerg (3)	2014	Retrospective cohort	Denmark	2,752	688	2,064	603	1,816
Bergenfelz (15)	2019	Retrospective cohort	Sweden	4,828	239	4,589	206	3,813
David (17)	2019	Cross sectional study	Belgium	159	143	16	91	7
Almquist (18)	2018	Retrospective cohort	Sweden	4,899	246	4,653	210	3,861

Table 4 Summary of quality assessment of cohort and case-control studies

Authors (reference)	Overall relevance*	Follow-up length	NOS score#	Overall validity&	Selection	Comparability	Outcome
Vadiveloo (14)	H	9 years	9	H	★★★★	★★	★★★
Underbjerg (2)	H	<25 years	8	H	★★★★	★★	★★
Underbjerg (3)	H	<24 years	8	H	★★★★	★★	★★
Bergenfelz (15)	H	4.5 years	7	M	★★★	★	★★★
David (17)	H	n/a	7	M	★★★	★★	★★
Almquist (18)	H	4.4 years	7	L	★★★	★	★★★

*, author assessment of overall relevance to the study; #, Newcastle-Ottawa Scale score, maximum of 9; &, overall author assessment of validity. Graded high (H), medium (M), or low (L). H, high; M, moderate; L, low.

Table 5 Effect of postsurgical chronic hypoparathyroidism on morbidity and mortality

Morbidity and mortality	No of studies	Sample size		Effect size			Heterogeneity			Variance
		Case	Control	Pooled OR	95% CI	P value	Q	P value	I^2	T^2
Cardiac disease	3	1,023	7,541	1.33	1.07, 1.66	0.011	1.89	0.38	0%	0.000
Arrhythmia	2	920	6,514	1.32	0.96, 1.80	0.08	0.56	0.45	0%	0.00
Renal disease	2	927	6,647	4.85	3.54, 6.65	<0.001	0.09	0.76	0%	0.00
Renal stone	3	1,069	6,604	3.17	1.55, 6.52	0.002	2.86	0.24	30%	0.48
Seizure	3	947	3,381	1.99	1.35, 2.92	<0.001	19.73	<0.001	89.8%	1.10
Mental health	2	804	3,365	1.39	1.13, 1.70	0.002	0.25	0.61	0%	0.00
Fracture	3	1,027	7,625	0.95	0.75, 1.19	0.62	3.06	0.21	35%	0.25
Malignancy	2	918	6,453	0.95	0.71, 1.28	0.75	4.16	0.041	75.9%	0.49
Infection	2	804	3,365	1.04	0.81, 1.34	0.77	0.01	0.93	0%	0.00
Cataract	2	804	3,365	1.21	0.78, 1.87	0.39	0.00	0.98	0%	0.00
Mortality	3	804	3,365	1.19	0.96, 1.49	0.11	4.86	0.08	58.8%	0.27

A comparison of failure rate relative to success rate was applied. Heterogeneity was significant if P value <0.1 or I^2>50%. CI, confidence interval; Q statistic, a measure of weighted squared deviations that denotes the ratio of the observed variation to the within-study error; I^2, the ratio of true heterogeneity to total observed variation; T^2, Tau squared and it is referred to the extent of variation among the effects observed in different studies.

publications were assessed for full-text review. Articles were excluded for irrelevant topics, lack of relevant data, or excluded study design. Ultimately, six retrospective cohort studies with a total of 14,055 patients were included for systematic review and meta-analysis. Characteristics of the included studies are listed in *Table 3*. The six citations included 1,432 patients with postsurgical chronic HypoPT and 12,623 controls. Of these, females accounted for 1,203 cases and 10,423 controls.

Quality assessment of reviewed studies

All included studies were of a moderate to high methodological quality with a median NOS score of 7.5 [interquartile range (IQR) 7.0 to 8.25] (*Table 4*). Studies primarily included European populations from 2013–2019, specifically, Denmark (2), Sweden (2), Belgium (1), and United Kingdom (1).

Pooled analysis of demographic characteristics

Pairwise comparison between cases and controls revealed no significant difference in age (P=0.41) or gender (P=0.07). Studies showed no evidence of heterogeneity for age (I^2=0%) or gender (I^2=28.9%).

Pooled analysis for the effect of chronic hypoparathyroidism on morbidities

Table 5 summarizes the pooled effect size of chronic HypoPT on the development of multiple morbidities and mortality.

Cardiac morbidity

"Cardiovascular disease" comprises ischemic heart disease and strokes. Patients with postsurgical chronic HypoPT were more likely to have cardiac morbidities (OR =1.33, 95% CI: 1.06 to 1.65, P=0.011) (*Figure 2A*). Overall, 124 out of 1023 postsurgical chronic HypoPT patients developed cardiac problems (12.1%), double the rate of the control group (521/7,541, 6.9%). However, a pooled analysis showed no significant difference in the risk of developing cardiac arrhythmia (OR =1.32, 95% CI: 0.96 to 1.79, P=0.08) (*Figure 2B*).

Renal morbidity

Pairwise comparison showed a fourfold higher likelihood of renal disease (OR =4.85, 95% CI: 3.54 to 6.65, P<0.001) (*Figure 2C*) and threefold higher risk of developing renal stones (OR=3.17, 95% CI: 1.55 to 6.52, P=0.002) (*Figure 2D*). The risk of renal disease was 10.5% (97/927) in postsurgical chronic HypoPT compared to 1.4% (91/6,647) among controls. Similarly, 3.4% (36/1,069) developed renal stones compared to 0.3% (23/6,604) in the control population.

Neuropsychiatric morbidity

"Mental health concerns" include psychosis, schizophrenia, depression, affective disorders, and anxiety. "Neurologic morbidities" describe seizure. Forty-nine out of 947 HypoPT patients (5.2%) developed seizures (OR =1.99, 95% CI: 1.35 to 2.92, P<0.001) compared to the control group (145/338, 4.3%) (*Figure 3A*). Postsurgical chronic HypoPT patients were also more likely to develop mental health disorders such as generalized anxiety or depression (OR =1.39, 95% CI: 1.33 to 1.69, P=0.002) (*Figure 3B*).

Immunologic and oncologic morbidity

Pooled data showed no effect on immune status. 10.8% (87/804) of patients with chronic HypoPT were hospitalized with infections such as pneumonia compared to 11.6% (390/3,365) in the control group (OR =1.04, 95% CI: 0.81 to 1.33, P=0.77) (*Figure 4A*). Data did not show any difference related to malignancy (OR =0.82, 95% CI: 0.663 to 1.025, P=0.08) (*Figure 4B*).

Skeletal morbidity

Analysis did not show increased risk of developing fracture (OR =0.94, 95% CI: 0.75 to 1.18, P=0.62) with 11% (113/1027) developing fractures in postsurgical chronic HypoPT patients (*Figure 5A*).

Ophthalmic morbidity

Pooled data showed no increase in the risk of developing cataract in postsurgical chronic HypoPT patients (OR =1.21, 95% CI: 0.78 to 1.87, P=0.39) (*Figure 5B*).

Pooled analysis for the effect of chronic HypoPT on mortality

In terms of crude mortality rate, our study showed no significant difference between the two groups (OR =1.19, 95% CI: 0.96 to 1.49, P=0.12) (*Figure 6*).

Heterogeneity assessment for morbidities and mortality

As depicted in *Table 5*, there was homogeneity across the studies for all variables except seizure (I^2 =89.8%), malignancy (I^2 =75.9%), and mortality (I^2 =58.8%).

Discussion

Chronic HypoPT increased the risk of developing comorbidities across multiple organ systems. The mechanisms causing these adverse effects are poorly understood; however, basic science studies have suggested that high calcium/phosphate products in tissues can lead to the formation of crystals that may deposit in different systems (21,22). Another theory is that long-term hypocalcemia may indirectly damage various body systems through poorly understood cellular pathways (23). This meta-analysis showed an increased risk of developing cardiac diseases, renal diseases, renal stones, seizures, mental health disorders, and infections in patients with postsurgical chronic HypoPT, but there was no significant impact on cardiac arrhythmia, bony fractures, malignancy, cataracts, or mortality.

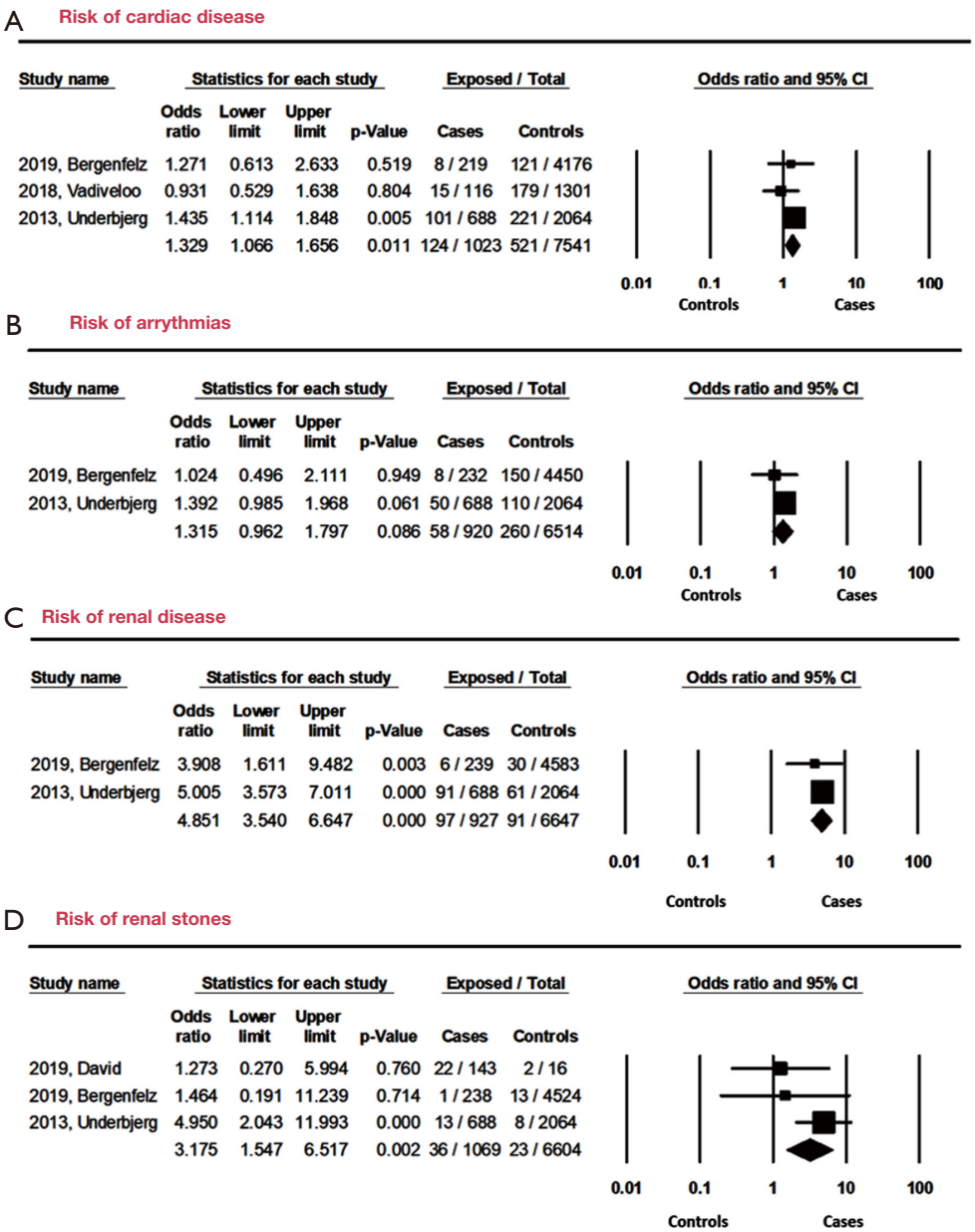

Figure 2 Forest plot presenting the effect of chronic HypoPT on cardiac and renal morbidities. (A) Cardiac disease; (B) developing arrhythmia; (C) renal disease; (D) renal stones. HypoPT, hypoparathyroidism.

Our study showed an increase in the risk of developing cardiovascular diseases (CVD) in postsurgical chronic HypoPT patients. Long-term hypocalcemia can lead to cardiomyopathy, long Q-T syndrome, arrhythmia, and increased levels of cardiac enzymes (23,24). These results contradict other studies suggesting that postsurgical chronic HypoPT does not affect the cardiovascular system in patients without a previous history of CVD (2,15,22). The same studies showed that chronic HypoPT increased the risk of cardiovascular events in patients with known underlying cardiovascular comorbidity prior to surgery (15,22). This risk may increase by twofold or more on long-term follow-up (15). The risk of CVD was proven to be higher in non-surgical chronic HypoPT patients compared

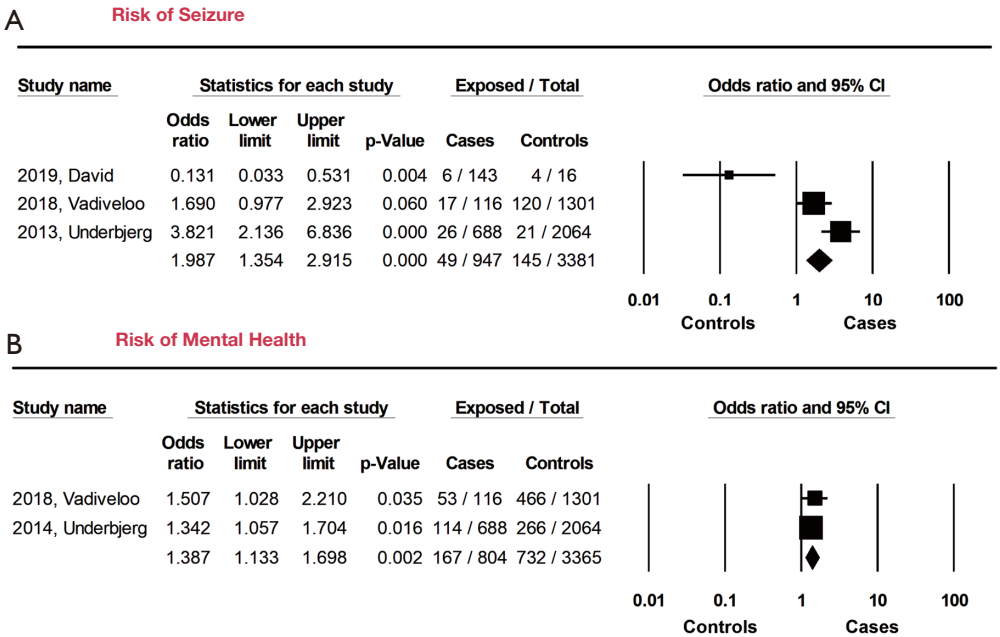

Figure 3 Forest plot presenting the effect of chronic HypoPT on neuropsychiatric morbidity: (A) seizure and (B) mental health. HypoPT, hypoparathyroidism.

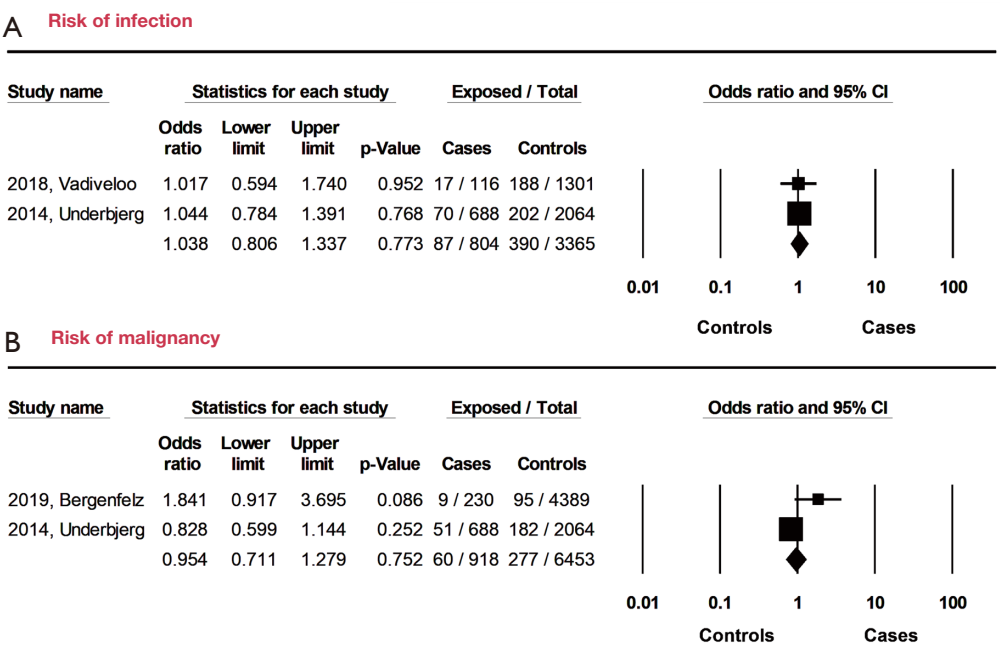

Figure 4 Forest plot presenting the effect of chronic HypoPT on immunologic and oncologic morbidity: (A) infection and (B) malignancy. HypoPT, hypoparathyroidism.

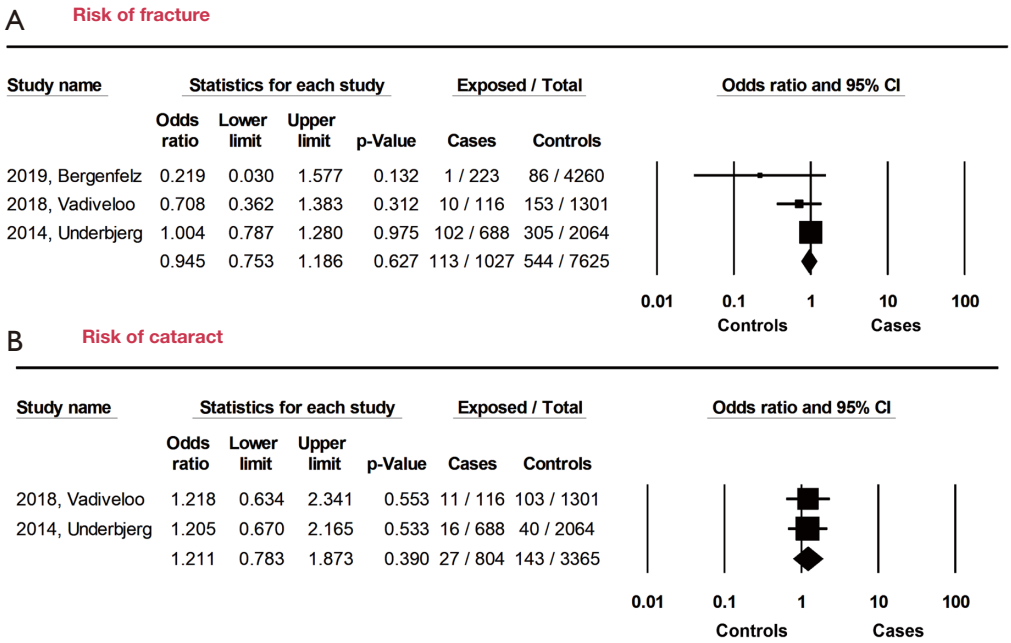

Figure 5 Forest plot presenting the effect of chronic HypoPT on skeletal and ophthalmological morbidities: (A) fracture, (B) cataract. HypoPT, hypoparathyroidism.

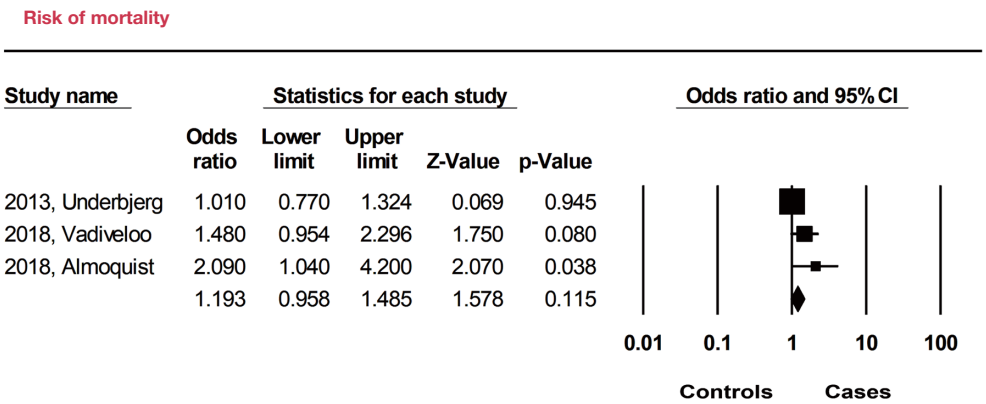

Figure 6 Forest plot presenting the effect of chronic HypoPT on the risk of mortality. HypoPT, hypoparathyroidism.

to postsurgical chronic HypoPT (4,22).

Like CVD, postsurgical chronic HypoPT was shown to have a significant effect on the renal system. Bergenfelz *et al.* reported that permanent HypoPT increases the risk of renal insufficiency, which is consistent with the findings of Mitchell *et al.* (15,25). The latter also reported an increased risk of renal calcifications and stones, which was supported by the cohort study conducted by David *et al.* (17,25). Postsurgical chronic HypoPT patients are at five times higher risk of developing renal stones than the normal population (2,25). A positive correlation between high phosphate and calcium/phosphate levels and the increased risk of renal disease in general was reported (22). The risk of developing long-term renal morbidities is the same in postoperative HypoPT as in the non-surgical chronic HypoPT (4). Our meta-analysis supported the association between chronic HypoPT and developing renal morbidities.

Postsurgical chronic HypoPT has also been shown

to increase the risk of seizure (2,17,25). The mechanism underlying the development of seizure is not yet understood, but it could be due to the effect of intracellular calcium stabilizing cell membranes (14). David *et al.* and Mitchell *et al.* reported increased risk of seizure as high as 8.8%, which was consistent with the findings of this meta-analysis (9.9%) (17,25). Underbjerg *et al.* found that the risk of developing seizures could increase by fourfold compared to the normal population, and these episodes could carry debilitating consequences (2). The risk is the same in the non-surgical chronic HypoPT group (4).

Our meta-analysis, which included 1,027 patients who underwent neck surgeries and developed chronic HypoPT, showed no increased risk of developing bone fractures. This is supported by the findings in Danish and Scottish studies (3,14). Underbjerg *et al.* reported a protective effect of chronic HypoPT against upper extremity fractures (3). Similarly, Bergenfelz *et al.* found the risk of fracture post-thyroidectomy to be 0.5% compared to 2% in the normal population (15). The same findings were reported by Underbjerg *et al.* for non-surgical patients with chronic HypoPT, except for the proximal humerus and forearm where the risk increased (4). Even so, this effect is poorly characterized and not well understood. Parathyroid hormone (PTH) plays an essential role in bone metabolism (26). Patients with chronic HypoPT often have a relatively low bone turnover status and high body mass index (27). This could explain the decreased risk of fracture in chronic HypoPT patients. In addition, the use of vitamin D supplements often affects muscle function and calcium resorption (28,29).

It is well known that PTH also plays a regulatory role in the immune system; thus, a lack of PTH may impair the immune system and increase the risk of infection (30). Vitamin D also plays an important role in the regulation and expression of multiple genes responsible for activating the immune system (31,32). Studies show that treating chronic HypoPT patients with a high dose of vitamin D can improve immunity and decrease the rate of infection (31-33). Phosphate hemostasis can also play a role in infection control (22). Studies showed that chronic HypoPT can increase the risk of infection by 1.4-2.0-fold in both post-surgical and non-surgical groups compared to the normal population (31,32). Underbjerg *et al.* showed that four or more hypocalcemic episodes increased the risk of infection by 2.7-fold (22). The most common infection associated with chronic HypoPT was urinary tract infection (22). Median phosphate level above 1.21 mmol/L was associated with an increase in the risk of upper respiratory tract infection but not urinary tract infection; moreover, disease duration increases the risk of infection (22). Underbjerg *et al.* reported that even after excluding urinary tract infection, the risk of other infections increased in patients with chronic HypoPT (22). This association was also observed for the risk of hospitalization secondary to infection. Results were not homogenous among the studies. Vadiveloo *et al.* did not report an increased risk of infection in their published series among surgical patients but reported a significant increase in the rate of infection in non-surgical chronic HypoPT patients (14). This is in contrast to our results, which showed an increased risk of infection as an effect in postsurgical chronic HypoPT.

Vitamin D receptors are found almost in every tissue type in the body (34-37). Several studies suggested that vitamin D can protect against gastrointestinal malignancies. Interestingly, some reports showed that chronic HypoPT could decrease the risk of gastrointestinal malignancies with increasing doses of calcium and vitamin D supplements (3,34-37). Bergenfelz *et al.* reported this finding, which showed an increased risk of malignancy in postsurgical chronic HypoPT patients compared to a population with normal parathyroid function. They did not reach definitive conclusions on causality but suggested that the finding could be due to chance, a causal relationship with hypoparathyroidism, medical treatment, or oversurveillance (15). Overall, the risk of malignancy was decreased in the non-surgical chronic HypoPT group per Underbjerg *et al.* (4). Our analysis could not find a relationship between postsurgical chronic HypoPT and developing cancers.

Our meta-analysis could not establish an association between postsurgical chronic HypoPT and the development of cataract. Chronic postsurgical HypoPT may lead to cataract due to calcium phosphate deposition in the lens (38). Our results are consistent with the results of Underbjerg *et al.* (3). Studies showed that HypoPT might increase the risk of mortality as well (22). However, our study could not establish a statistically significant increased risk of mortality among the postoperative chronic HypoPT patients. These results are consistent with Vadiveloo *et al.* (14).

Limitations and future recommendations

Our study has some limitations, including inevitable heterogeneity across studies in three variables reported,

inconsistent follow-up period, and lack of information about the treatment protocol of vitamin D and calcium supplements. The limited geographical distribution (almost 80% of the postsurgical hypocalcemia cohort is from Northern Europe) is an important limitation to our study. Several factors can attribute to development of postsurgical hypocalcemia in Europeans including surgical techniques such as extensive dissection, limited sun exposure with higher prevalence of vitamin D deficiency. Studies investigating the complication of chronic post-surgical hypoparathyroidism among non-European populations should be conducted. Future studies from large databases (SEER, UKRETS, EUROCRINE) can investigate the impact on the postsurgical chronic HypoPT among North American population and help validate our study results. Due to the limited numbers of study published, an analysis comparing post-surgical chronic HypoPT *vs.* normal population with no hypoparathyroidism, then post-surgical chronic HypoPT *vs.* non-surgical chronic HypoPT could not be performed. Future studies and meta-analysis should estimate the risk of developing morbidities among these groups when enough studies are available in the literature.

Finally, due to the presence of few eligible studies, authors were not able to perform meta-regression analysis to test the magnitude of impact of study covariates.

Implications on current clinical practice

Given the higher risk of comorbidities in chronic postsurgical HypoPT patients, endocrinologist, family physicians, and primary care providers should give particular attention to this group of patients. Chronic postsurgical HypoPT patients should be educated about the symptoms of these sequalae especially ischemic heart diseases, stroke, and mental health diseases including anxiety and depression. Future studies may investigate if proper treatment of the chronic postsurgical HypoPT will normalize the risk.

Conclusions

To our knowledge, this is the first meta-analysis that reveals how postsurgical chronic HypoPT can increase the risk of morbidities. Our findings show chronic HypoPT to be associated with an increased risk of cardiac, renal, neurologic, immunologic, and psychiatric complications. Surgeons should be aware of the long-term development of such adverse events and use this knowledge when counseling patients preoperatively. Postoperative follow-up management and medical treatment administration should be strictly observed to avoid and manage such events.

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