

Peer Review File

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Reviewer A

Comment 1: Please avoid the term “incidence”, and use “risk”. Incidence is standard presented in person-years and not as %. F.e. ‘incidence’ vs ‘risk’ of renal disease in the paragraph on renal morbidity

Response 1: We thank the reviewer to pointing this out and we edited the manuscript to adopt the reviewer comment” Line 166-168

Changes in the text: We changed the text from “The incidence of renal disease was” to “The risk of renal disease was 10.5% (97/927) in postsurgical chronic HypoPT compared to 1.4% (91/6647) among controls. Similarly, 3.4% (36/1069) developed renal stones compared to 0.3% (23/6604) in the control population.”

Comment 2: The authors state in the PRISMA overview that the registration of a study protocol is N/A. Can the authors confirm no study protocol was written or registered (f.e. in PROSPERO)? It is advisable in the future to write/register a study protocol before starting a systematic review/meta-analysis.

Response 2: We thank the author for this recommendation. We have previously submitted the study protocol to Prospero. The submission number is 269843. However, it is currently under review as Prospero takes longer than expected since the COVID Pandemic.

Changes in the text: N/A

Comment 3: Please mention the specific reason for only including studies from 1/2000

Response 3: We appreciated the reviewer comment highlighting this important recommendation. We searched the same databases prior to 2000. However, we could not identify any further studies that align with our inclusion criteria that can be included in the data analysis. Line 30-31, and Line 75-77. We deleted the literature date limitation.

Changes in the text: We deleted the literature date limitation “from January 2000”. The text now read as “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.” Line 75-77

And “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” Line 75-77

Comment 4: At the “quality assessment” part, the last sentence is not finished

Response 4: The sentence has been completed

Changes in the text: The Text has been completed to become “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”. Line 123-126

Comment 5: Could the authors please comment on the fact whether the selected studies adjusted for the same confounding variables (age, comorbidity...)?

Response 5: We appreciate the authors input to elaborate the impact of confounding variables. 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. Therefore, authors mentioned this point in the limitation. This section has been included in the limitations as well. Line 291-292

Changes in the text: We added the following statement to the limitations section: “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.” Line 291-292

Comment 6: At the “Pooled analysis of demographic characteristics” part, the second I² should be in superscript (I²).

Response 6: The typo has been corrected. Line 152

Changes in the text: Text has been corrected to “Studies showed no evidence of heterogeneity for age (I² = 0%) or gender (I² = 28.9%).”

Comment 7: Limitations: could the authors comment a little bit more on the limited geography (almost 80% of the postsurgical hypocalcemia cohort is from Northern Europe) and possible confounders associated with this limited geography f.e. differences in indication for surgery and pre- and postoperative Vit D status. All included studies have a retrospective study design

Response 7: We appreciated the reviewer comment. We have added a small paragraph to the limitations section. Line 279-286.

Changes in the text: The following paragraph has been added “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”

Comment 8: Limitations: please change Vitamin D and Calcium ‘supplement’ to ‘supplements’

Response 8: Typo has been corrected. Line 279

Changes in the text: We changed the text from “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 supplement” to “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”

Comment 9: Please add a small paragraph on the usefulness and/or implications of the study results on current clinical practice.

Response 9: We appreciate the reviewer comment. We added the recommended paragraph. Line 293-299

Changes in the text: We added the following paragraph to the manuscript
“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 sequelae 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.”

Comment 10: Please add a small paragraph on (possible) future studies and the importance of big data analyses (SEER, UKRETS, EUROCRINE...) in collecting data to support/confirm these data

Response 10: The recommended changes had been added to the limitation Line 283-286.

Changes in the text: We added the following paragraph to the manuscript “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”

Comment 11: The authors state that their meta-analysis included 1,027 patients with HypoPT after total thyroidectomy. Can the authors comment on the fact whether redo surgery or completion thyroidectomies were included? This statement also implies that no studies on morbidity of HypoPT after parathyroidectomy are available. Can the authors comment if this is indeed the case?

Response 11: We appreciate the reviewer comment. Underbjerg et al. included patients who had neck surgery without pointing out the detailed of surgeries (2,3). Vadiveloo et al. also collectively described the postsurgical HypoPT following neck surgeries with no further explanation if these patients had redo surgeries or completion thyroidectomy (14).

On the other hand, Bergenfelz et al. described their experience among post thyroidectomy patients (15). The authors excluded patients who had previous thyroid surgery therefore completion thyroidectomy are not included (15). David et al. included patients who developed the disease following lobectomy, total thyroidectomy, neck dissection, partial or total parathyroidectomy (17). Almquist et al. included only patients who developed the disease following parathyroidectomy (18). Therefore, we edited the manuscript as below. Line 230

Changes in the text: We changed the manuscript from “Our meta-analysis, which included 1,027 patients who underwent total thyroidectomy and developed chronic HypoPT” to “Our meta-analysis, which included 1,027 patients who underwent neck surgeries and developed chronic HypoPT ” Line 230

Comment 12: Please check the spelling of ‘Underbjerg’, when mentioned in the manuscript. Several variations (Underbrjerg, Underbiereg et al...) are noted throughout the manuscript.

Response 12: We thank the reviewer for pointing this out. We thoroughly revised the manuscript and made the recommended corrections.

Changes in the text: Underbjerg et al. reported a protective effect of chronic HypoPT against upper extremity fractures. Line 232

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. Line 234-236

Underbjerg et al. showed that four or more hypocalcemic episodes increased the risk of infection by 2.7-fold. Line 249

Comment 13: Table 3-4: Some author names are written in full; others are not. Try to be consistent

Response 13: We included the full name of authors in table 3, and table 4.

Changes in the text: The full name has been included as Karel David, Martin Almquist

Comment 14: Table 4: In the legend, rephrase to 'Newcastle-Ottawa Scale score'.

Response 14: Corrected the table legend as recommended

Changes in the text: Newcastle-Ottawa Scale score

Comment 15: Table 5: The title of the tables uses capital letters mid-sentence. Please adjust. The abbreviation 'NA: Not applicable' is not used. Please remove.

Response 15: The title has been corrected. The NA abbreviation has been deleted.

Changes in the text: Effect of postsurgical chronic hypoparathyroidism on morbidity and mortality

Comment 16: Figure 1: Please change 'n=21' to 'n = 21'.

Response 16: Figure has been corrected as recommended

Changes in the text: n = 21

Comment 17: Figure 3: Please remove the capital letters in 'Seizure' and 'Mental Health'.

Response 17: Typo is corrected in the figure 3, and capital letters are corrected

Changes in the text: Risk of seizure, Risk of mental health

Comment 18: Figure 6: Please change Almoquist to Almquist.

Response 18: Typo is corrected in the figure 6

Changes in the text: Almquist

Reviewer B

Comment 1: In this study, authors put the patients who developed non-surgical hypoparathyroidism in the control population, along with normal patients, and post-surgical patients with preserved parathyroid function

In this way, you would get two types of comparison:

Type 1: hypoparathyroidism (by surgical) vs. no hypoparathyroidism

Type 2: hypoparathyroidism (by surgical) vs. hypoparathyroidism by (non-surgical)

I am a bit concerned that the authors put these two different types of comparison into one meta-analysis. It would make the results difficult to explain.

Response 1: We would love to thank the reviewer and appreciate his insightful comment. Having two types of comparison; hypoparathyroidism (by surgical) vs. no hypoparathyroidism, then hypoparathyroidism (by surgical) vs. hypoparathyroidism by (non-surgical) would make help estimating specific Odds ratio of every disease (cardiovascular, infection, cataract, renal stone, seizure, ... etc.) among different groups of comparison. However, due to the limited numbers of study published on every group, an analysis looking comparing these different groups separately could not be performed. We highlighted this part in the limitations section. Line 286-290

Changes in the text: We added the following paragraph to the limitation section “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.”

Comment 2: Please check in Table 3, the number in control (n), Female case(n), female control (n) are duplicated in reference 14 and 17

Response 2: We correct the typo included in table 3.

Changes in the text:

Authors/Reference	Year of publication	Study Design	Population	Sample size (n)	Case (n)	Control (n)	Female Case (n)	Female Control (n)
Thenmalar Vadiveloo ¹⁴	2018	retrospective cohort	Scottish	1417	116	1301	93	926
Line Underbjerg ²	2013	retrospective cohort	Denmark	2752	688	2064	603	1816
Line Underbjerg ³	2014	retrospective cohort	Denmark	2752	688	2064	603	1816
Anders Bergenfelz ¹⁵	2019	retrospective cohort	Sweden	4828	239	4589	206	3813
Karel David ¹⁷	2019	cross sectional study	Belgium	159	143	16	91	7
Martin Almquist ¹⁸	2018	retrospective cohort	Sweden	4899	246	4653	210	3861