International Urology and Nephrology (2024) 56:1217–1225
https://doi.org/10.1007/s11255-023-03882-w

UROLOGY - REVIEW

Systematic review of the risk of urolithiasis following parathyroidectomy in patients with primary hyperparathyroidism

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Received: 14 September 2023 / Accepted: 4 November 2023 / Published online: 1 December 2023

Abstract

Objective Parathyroidectomy (PTX) is the conclusive therapy for primary hyperparathyroidism (PHPT), but its effect on the risk of urolithiasis is inconclusive. We comprehensively reviewed the currently available research to investigate the impact of PTX on the likelihood of urolithiasis among individuals suffering PHPT.

Methods Internet-based articles in English language released on Cochrane, PubMed, Scopus, Web of knowledge, and Embase up to September, 2023 were comprehensively reviewed. Each publication in contrast to the incidence, occurrence, or recurrence of urolithiasis after PTX versus medical treatment in PHPT patients was included. The outcome with pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) was examined employing DerSimonian and Laird's model of random effects. To determine the range of the real effect size of a future study in 95% of all populations, a prediction interval (PI) was also established.

Results Finally, ten studies involving 74,190 patients were included. Results from randomized-controlled trials (RCTs) and observational studies (OSs) both revealed that PTX did not substantially lessen the vulnerability of urolithiasis among individuals with PHPT (RCTs: pooled relative risk [RR] 0.42, 95%CI 0.13–1.41, $p = 0.163$; OSs: pooled RR 1.37, 95%CI 0.96 to 1.97, $p = 0.084$). The PI (RCT: 0.03 to 5.96; OSs: 0.44–4.20) containing 1.0 suggested the possibility of consistent results in future studies. Subgroup and sensitivity analyses supported the above findings, and no evidence showed publication bias.

Conclusion Our analysis from the available RCTs or OSs did not give adequate or exact proof that the average effect of PTX lowers the incidence of urolithiasis among PHPT persons based on the random-effects model. Future research shall take into account the common effect of PTX as well as the prerequisites of preventive stone procedures, which will further help us assess the effectiveness of PTX in reducing kidney calculus comorbidity and develop techniques to avoid stone sequelae in these individuals.

Keywords Parathyroidectomy · Urolithiasis · Risk · Primary hyperparathyroidism · Meta-analysis · Systematic review

Introduction

Primary hyperparathyroidism (PHPT), a prevalent endocrine illness, is characterized by excessive parathyroid hormone (PTH) production by multiple parathyroid glands. PHPT seems to be the third leading metabolic problem following diabetic mellitus and hypothyroidism [1, 2]. PHPT affects women nearly three times more frequently than males worldwide. Postmenopausal (post-M) women account for a sizable proportion of PHPT patients in Western countries, owing to both the earlier screening for osteoporosis [3] and estrogen withdrawal for parathyroid tumorigenesis and intestinal calcium absorption reductions [4, 5]. A large US investigation showed that PHPT attacked 0.86% of the total population

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[6]. The approximate incidence was 1 per 400 females and 1 per 1000 males from 1995 to 2010, and was 233 per 100,000 females and 85 per 100,000 males in 2010 [7]. Like in the United States [8, 9], individuals in Western Europe experiencing silent minor hypercalcemia are frequently identified with PHPT as per multichannel biochemical tests. PHPT was detected in 3.4% of postmenopausal women in Sweden according to a community health survey [10]. The incidence rates of PHPT in Scotland increased between 1986 and 2013, and from 1998 to 2006 [11, 12], because of increased disease knowledge, faster detection, and an increase in life expectancy. A community historical follow-up research project from 2007 to 2018 across Tayside, Scotland [13], discovered 4–6 cases of PHPT per 10,000 person-years on average each year. This population-based survey reveals a 0.84% occurrence of PHPT and confirms that PHPT seems to be a widespread metabolic problem in the general population, especially among postmenopausal females. The higher life expectancy of the Scottish population, particularly elderly people who are still most prone to PHPT, has led to a rise in predominance, despite stable incidence rates.

The frequency of PHPT among Chinese seniors and middle-aged people ($n = 2451$) was disclosed to be 0.2% [14]. Nevertheless, as a result of the rising measurement of ionized calcium level, the annual incidence and prevalence in nations outside North America and Europe are soaring, which seems to be linked to a shift in patient presentation of disease from having symptoms to being asymptomatic. Consequently, it is reasonable to expect that the incidence and prevalence of PHPT will rise globally [15]. Unlike in Western countries, PHPT was more common in premenopausal (pre-M) women in Asian countries, such as China [16] and India [17], which could be attributed to the disease's aggressive character in this region of the world, which is exacerbated by the related severe vitamin D deficiency [17].

PHPT clinically results in a number of co-morbidities, including osteoporosis, fractures, urolithiasis, muscle weakness, cardiac abnormality, psychiatric abnormality, cancers, and increased mortality [18]. Among them, urolithiasis with a reported prevalence of 3–5% [19] is a major concern for PHPT patients, and contributes to chronic kidney disease and reduced life quality [20, 21]. Urolithiasis can cause severe pain, infection, obstruction, and kidney damage, and its recurrence rate is high due to the lack of proper treatment [22]. Both parathyroidectomy (PTX) and medical treatment are proposed to decrease serum intact PTH (iPTH) and resolve PHPT. PTX can be administered to individuals experiencing hypercalciuria (24 h urine calcium > 400 mg), demonstrative kidney calculi disorder, or imaging-confirmed silent stones [23]. The mechanism underlying the decrease in stone formation following PTX is most likely due to the correction of hypercalcemia and hyperparathyroidism, both of which are known risk factors of stone development [24]. However, in America, the majority of PHPT patients are handled non-operatively, as only 50% of individuals suffering from renal stones and 38.9% of overall patients receive PTX within a year after PHPT diagnosis [25]. In addition, the effect of PTX on urolithiasis development in PHPT patients has not been well established. Some studies show that PTX reduces the likelihood of developing urinary stones by lowering serum calcium and PTH levels [26, 27], while other studies find no significant change in stone incidence after PTX [28, 29]. This inconsistency can be explained by the variations in research demographics and designs.

Given the concerns above, we carried out a meta-analysis to examine the possibility of urolithiasis among PHPT individuals treated by PTX versus medical method.

Methods

Search strategy and selection criteria

We looked for medical studies released prior to September 2023 in EMBASE, Web of Knowledge, PubMed, Scopus, and Cochrane pursuing Preferred Reporting Items for Systematic Reviews and Meta-Analyses [30]. The following search terms were used: "primary hyperparathyroidism", or "PHPT"; "parathyroidectomy", or "parathyroid gland surgery", or "PTX"; "renal calculi", or "kidney stones", or "urolithiasis", or "nephrolithiasis". GS and XMW sought for possible studies individually, and any discord between them was resolved by GLT. We communicated with the researchers, whenever necessary, for clarification of the information being provided.

Inclusion and exclusion criteria

Reports that satisfied further prerequisites were included: (1) randomized-controlled trials (RCTs) or observational studies (OSs) involving adults (age ≥ 18) and (2) assessments of the likelihood of urolithiasis (incidence, prevalence, or recurrence) or provision of sufficient information for calculating relative risks (RRs) and 95% confidence intervals (CIs) comparing PTX-treated versus medically treated PHPT patients.

Studies were excluded if they were reviews, commentaries, editorials, letters, unpublished studies, quasi-experiments, animal studies, comparisons among many forms of PTX or various medicinal therapies, or comparisons between PTX treatments, or studies with a sample size less than 50 patients.

Data extraction and quality assessment

The titles and abstracts of all discovered papers were examined for consideration by two distinct reviewers. Full-text

articles were obtained for further assessment. Discrepancies were resolved through discussion and consensus.

The selection of studies and retrieval of information followed a normal Cochrane process. The following information was collected: study methodology, representative sample, patient characteristics, period of follow-up, PTX technique, severity of PHPT, type of urolithiasis, and outcomes.

Two reviewers (GS and XMW) individually appraised the merits of articles. With the Risk of Bias Tool developed by the Cochrane Collaboration, the risk of bias (low, unclear or high) in six categories was judged for each RCT with three tiers per category: sequence generation; allocation hiding; blinding participants, personnel, and outcome assessors; partial outcome data; selective result reporting; and other biases. Provided a minimum of one category was "high risk of bias," the general likelihood of bias was high, while it was low when all categories remained “low risk” [31]. The quality of OSs was surveyed using the Newcastle–Ottawa Scale (NOS). The NOS consists of three quality criteria for cohort studies: choice, consistency, and result. The maximum rating for each of these three categories is 4, 2, and 3 stars, respectively. Therefore, the highest quality comprises 9 stars, and a study featuring 6 stars or more is considered to be of good quality [31]. The 11-item Agency for Healthcare Research and Quality (AHRQ) checklist can be used to evaluate the quality of cross-sectional research articles [32]. The possible answers for each item are "Yes," "No," and "Unclear". If the response to a question is "yes," one point is awarded; otherwise, no point is given. A study with a total score of 0–5, 6–7, and 8–11 is deemed to be of low, moderate, and high quality, respectively. Disagreements were resolved through dialogue.

Statistical analysis

We combined dichotomous outcomes (e.g., probability of urolithiasis) utilizing relative risk (RR) with 95%CI. With I^2 statistic, heterogeneity across studies was quantified as minor ($I^2 < 25\%$), modest (25–50%), or significant ($\geq 50\%$). Considering the intrinsic variation with research methodology, we predetermined individual analysis for the RCTs and OSs. For RCTs (or OSs), the primary or secondary analysis comprised all the included trials. Each participant who started to receive therapy, whether he/she completed it or not, was counted as a patient in the RCTs that employed the intent-to-treat criterion. A prediction interval (PI) was calculated to indicate the range of a true effect size of a future study in 95% of all populations [33]. Given the anticipated heterogeneity of OSs, we subjected the patients with or without prior record of urolithiasis at the time of PHPT diagnosis to distinct subanalysis. We also ran sensitivity tests to clarify if the heterogeneity may be attributed to observable sources. Funnel plot inequality was studied with visual representation, and Begg's, and Egger's assessment when at least five studies were available for investigation. All analyses except for the PI were finished on Review Manager 5.3.5 from the Cochrane Collaboration with STATA 14.0 (STATA College Station, USA). The PI were performed with R software Version 4.1.3. The significance threshold was $p < 0.05$, except for publication bias test ($p < 0.10$).

Results

Study selection and characteristics

We first found 3366 possibly relevant publications, of which 31 were retrieved for further inspection. Two RCTs [34, 35] represented an identical group or organization, but their results were different. One study [36] was removed from the meta-analysis, because its reported occurrence rates of urolithiasis were zero in both the PTX and medical therapy groups. Finally, four RCTs [34, 35, 37, 38] with 485 patients as well as six OSs (one cross-sectional study[39] and five cohort studies [40–44]) with 73,705 individuals were included (Fig. 1). The four RCTs had sample sizes between 50 and 191 patients, follow-up periods from 1.0 to 10.0 years, 79.24% to 92.00% females, and mean age of 63.10 to 64.89 years. Individuals with mild PHPT were enrolled in all RCTs.

In the six OSs, the sample sizes ranged from 265 to 44,978 patients, the follow-up period ranged from 1.15 to 8.01 years, the female percentage was 12.2% to 78.20%, and the mean age was 52.02 to 67.50 years. Apart from two investigations on multinational origins, the remaining nine trials were from either the United States or European countries. Table 1 outlines the key elements of the ten studies.

Quality assessment

Figure S1 and Table S1 show the methodological quality ratings of RCTs and OSs, respectively. As a result of the absence of respondent blindness or hiding of assignment, research staff, and result judgement, we classified the four RCTs as a medium level of bias risk. Three of the five CSs have NOS scores ≥ 7 (mean of 8.2). According to AHRQ, the cross-sectional study was of intermediate quality (Table S1).

Risk of urolithiasis

The combined relative risk (RR) of urolithiasis following PTX versus medical treatment in the four RCTs was 0.42 (95%CI 0.13–1.41; $p = 0.163$) in the random-effects model, showing no heterogeneity. The PI was 0.03 to 5.96. The six relevant OSs had similar minuscule-integrated estimates

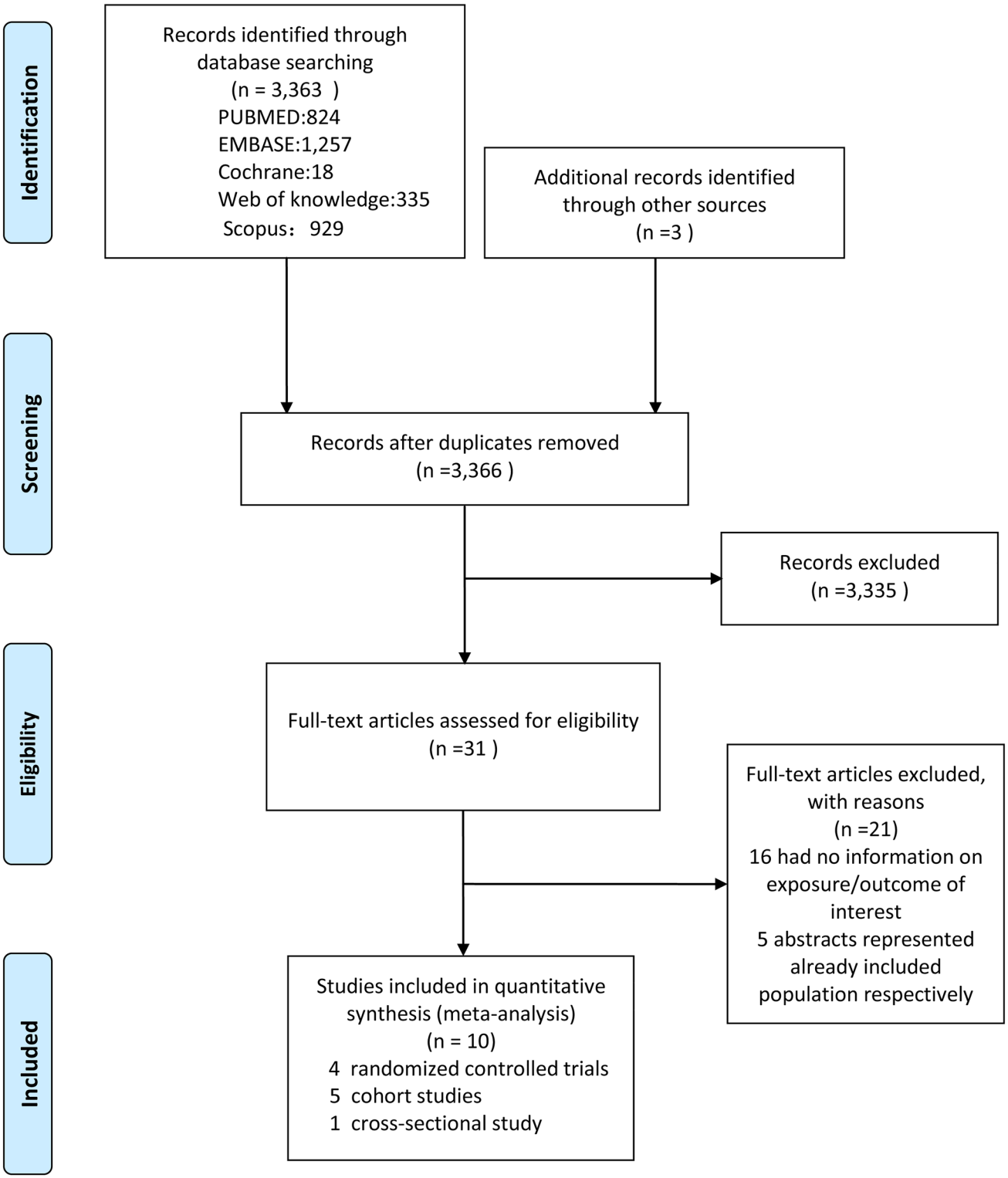

Fig. 1 Flow diagram of study selection

regarding the impact (pooled RR, 1.37; 95%CI 0.96–1.97; $p = 0.084$; PI: 0.44 to 4.20; Fig. 2), with notable heterogeneity ($I^2 = 85.7\%$; $p < 0.001$). History of urolithiasis at PHPT diagnosis yielded similar results by separate subanalyses (Fig. 3). Sensitivity analysis showed that heterogeneity did not vanish after removing individual studies. Neither Egger's

Table 1 Detailed demographic characteristics and outcomes of studies included in the meta-analysis

Study	Data source/ country, region	Sample size	Mean age (years)	Female (%Total)	Duration of follow-up (years)	Severity of PHPT	Type of urolithiasis	Effect estimate of urolithiasis risk
Randomized-controlled trials								
Rao et al. [38]	The Henry Ford Health System/ The United States	53	64.89	79.24	NR	Mild Asymptomatic	Kidney stones	OR (Calc)
Ambrogini et al. [37]	The Department of Endocrinology at the University Hospital of Pisa/Italy	50	64.52	92.0	1.0	Mild Asymptomatic	Kidney stone	OR (Calc)
Lundstam et al. [34]	SIPH study/ Denmark, Sweden, Norway	191	64.20	86.39	5	Mild	Urinary tract stones	OR (Calc)
Pretorius et al. [35]	SIPH study/ Denmark, Sweden, Norway	191	63.10	86.39	10	Mild	Kidney stones	HR
Cross-sectional studies								
Posen et al. [39]	NR/Australia	265	52.02	64.91	6.77	Any	Kidney stones	OR (Calc)
Cohort Studies								
Vestergaard et al. [40]	The Danish national hospital discharge database/ Denmark	3,213	61.00	75.32	NR	Any	Kidney stones	HR
Seib et al. [41]	Optum's deidentified Clinformatics Data Mart Database/ The United States	7,623	66.50	78.1	5	Any	Kidney Stone	aOR
Seib et al. [42]	The VA Corporate Data Warehouse/ The United States	44, 978	66.0	12.2	5.07	Any	Kidney Stone	aHR
Axelsson et al. [44]	The Swedish Patient Register/ Sweden	16,374	67.50	78.20	1.15	Any	Kidney stone	aHR
Huang et al. [43]	Kaiser Permanente Southern California databases/ The United States	1,252	60.2	56.2	8.01	Any	Nephrolithiasis	HR

PHPT primary hyperparathyroidism; *HR* hazard ratio; *OR* odds ratio; *aHR* adjusted hazard ratio; *aOR* adjusted odds ratio; *Calc* calculated; *SIPH* Scandinavian investigation on primary hyperparathyroidism; *NR* not reported

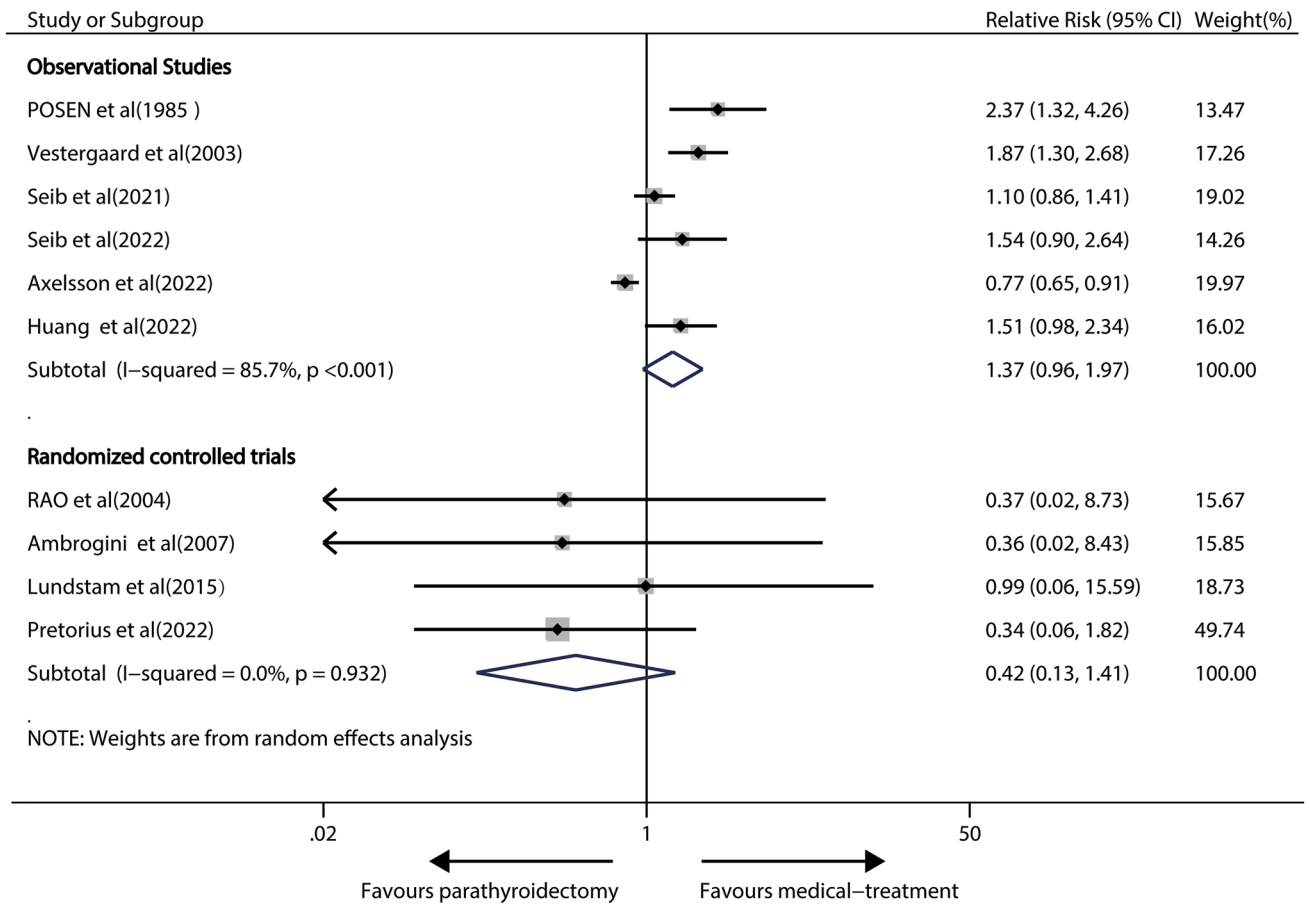

Fig. 2 Forest plot for effect of PTX treatment versus medical treatment on risk of urolithiasis

nor Begg's tests showed clear systematic bias in the urolithiasis risk analyses (both $p > 0.1$; Fig. S2).

Discussion

The current meta-analysis provides a thorough examination of the relationship between PTX and urinary stone development in PHPT patients. Results show that neither RCTs nor OSs prove PTX significantly reduce the vulnerability of urolithiasis among PHPT patients. The PI (RCT: 0.03–5.96; OSs: 0.44–4.20) containing 1.0 suggested the possibility of consistent results in future studies. Subgroup analyses were carried out to determine if the risk of urolithiasis varied with the history of urolithiasis when PHPT was first diagnosed. Separate subanalyses revealed underwhelming results for the history of kidney stones during PHPT diagnosis. The finding is similar with the majority of previous studies, which reveal no substantial reduction in the risk of urolithiasis after PTX in PHPT patients. Moreover, the risk of urolithiasis was elevated in individuals receiving PTX versus medical therapy, but not significantly (pooled RR, 1.37; 95% CI 0.96–1.97; $p = 0.084$). Multivariable analysis by Vestergard et al. [40] also found that PTX-treated patients had a higher incident of any kidney stone. They thought that the reason was due to the residual treatment selection bias with more advanced disease (a large preexisting stone burden and worse PHPT biochemical profiles) in surgically treated patients. Posen et al. [39] discovered individuals with history of renal stones had a 50% likelihood of recurring episodes, whether they received PTX or not. Even if they remained hypercalcaemic and hypercalciuric, patients without history of calculi were unlikely to produce stones.

At the same hand, because stones that appear soon after PTX may be formed before the therapy, the advantages regarding operative treatment may emerge only after long time. According to Seib et al., patients experiencing kidney calculi had a twofold adjusted likelihood of a clinically noteworthy recurrence following PTX, as opposed to those receiving non-operative treatment [42]. However, the occurrence of kidney stones following PTX decreased over time. They also discovered no discernible difference in the probability for fresh stone occurrence based on therapy for PHPT individuals without experiencing kidney calculi. It

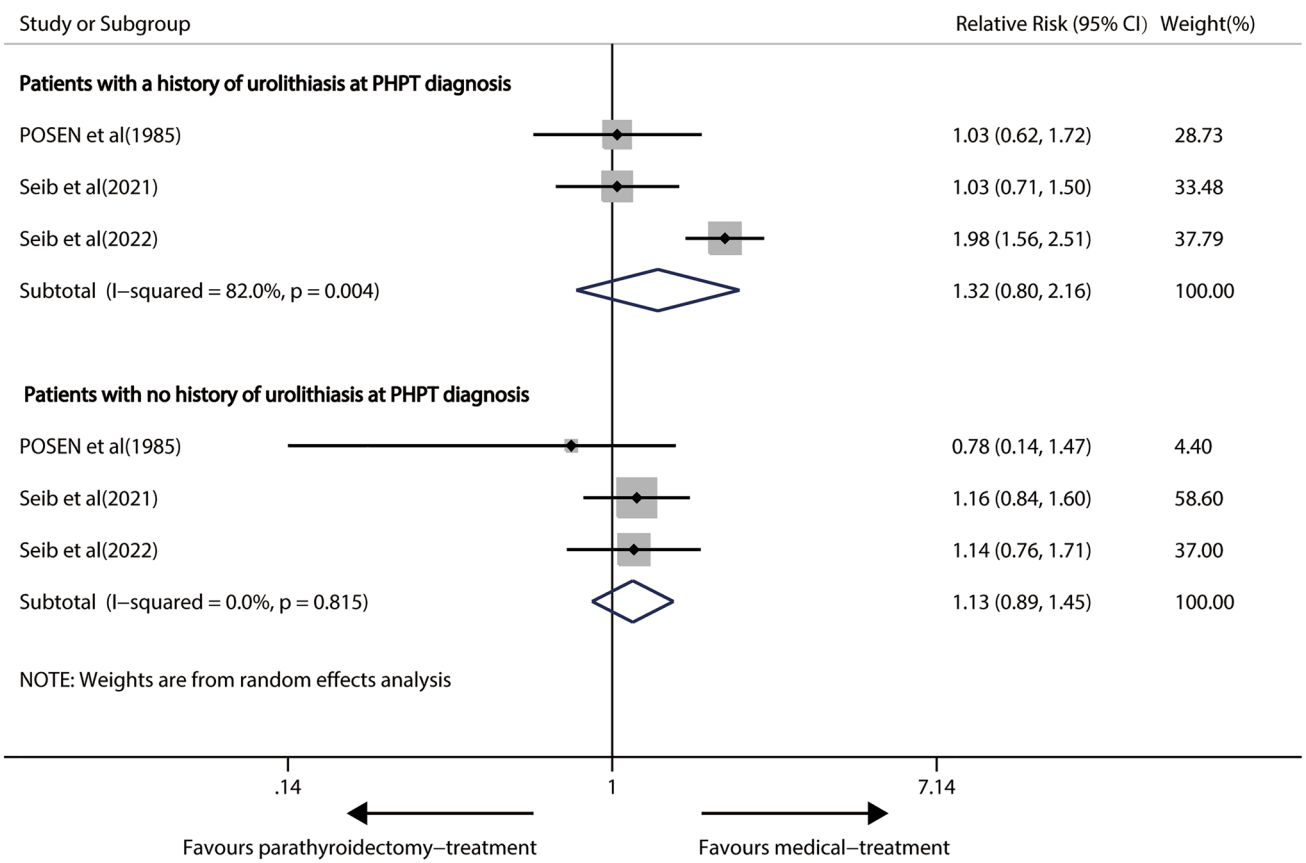

Fig. 3 Forest plot for effect of PTX treatment versus medical treatment on risk of urolithiasis, according to urolithiasis history at PHPT diagnosis

is implied that PTX has no meaningful advantage on the principal avoidance of kidney calculi and that PTX reduces or delays the prospective likelihood of reoccurring kidney calculi, but does not prevent kidney stones.

Another probable explanation is that the formation of urolithiasis is a systemic disorder. Hypercalciuria is a factor, but it is not the only way PHPT patients develop urolithiasis. Reducing PHPT-related risk factors, such as hypercalcaemia, phosphate excretion, and urine pH after PTX, may have a favorable influence on the recurrence of urolithiasis. Other factors influencing stone formation besides hypercalcaemia include low urine volume, elevated pH, oxalate and citrate excretion, younger age and male gender, and predisposing genetic factors [45, 46]. Apart from hypercalciuria, the lithogenic factors associated with PHPT patients may differ depending on the demographic and geographic region analyzed [47]. Despite a successful PTX, the overall risk of urolithiasis is still higher because of other co-occurring factors [29]. Future research shall take into account diet modification, pharmaceutical intervention, as well as the elimination of risk factors for urolithiasis formation, regardless of whether they undergo PTX.

The comprehensive search method based on typical Cochrane protocols, and the relatively large sample size, are two strengths of this review. However, there are some restrictions. First, we are unable to uncover unreleased documents that may have skewed our findings. Second, because the meta-analysis is based partially on OSs, the possibility of confounding cannot be totally eliminated. Third, the included studies differ in patient characteristics, research design, and follow-up duration, which can have contributed to the observed heterogeneity. Furthermore, no data regarding the initial degree of hypercalciuria or related stone risk factors were gathered, which can have influenced the results.

Conclusions

In conclusion, based on the random-effects model, our investigation from the available RCTs or OSs does not provide adequate or exact proof that the average effect of PTX lowers the likelihood of urolithiasis among PHPT individuals. However, this finding must be regarded with caution, because the true variation in effects between studies could be attributable to uncharacterised or unexplained factors. Future research shall take into account the common effect of PTX as well as the prerequisites of preventive stone procedures, which will further help us assess the effectiveness of PTX in reducing

kidney calculus comorbidity and develop techniques to avoid stone sequelae in these individuals.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-023-03882-w.

Acknowledgements The authors would like to thank all authors of the included studies in our meta-analysis.

Data availability The datasets used and analyzed in this investigation are accessible from the corresponding author in response to a legitimate request.

Declarations

Conflict of interest No potential conflict of interest relevant to this article was reported.

Ethical approval As the study was a meta-analysis based on the existing population-based studies, we did not apply for the approval of institutional review board.

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