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Original

Risk of bone fractures in patients with primary hyperparathyroidism: a systematic review and meta-analysis

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Abstract

Introduction: Primary hyperparathyroidism, a prevalent endocrine disorder, is known to cause osteoporosis. This study aims to examine the association between primary hyperparathyroidism and the risk of bone fracture.

Materials and Methods: A systematic review and meta-analysis approach was employed in this article. The databases ProQuest, PubMed, Web of Science, Cochrane, and the search engine Google Scholar were searched up to June 20, 2023. Data analysis was conducted applying STATA 14 software.

Results: Primary hyperparathyroidism increased the risk of any fractures overall (OR: 1.45, 95% CI: 1.26–1.67) in patients aged 50-59 years (OR: 1.37, 95% CI: 1.18–1.60) and in those aged 60-69 years (OR: 1.60, 95% CI: 1.25–2.05). Moreover, primary hyperparathyroidism led to an increased risk of vertebral fracture (OR: 1.90, 95% CI: 1.12–3.22), foot fracture (OR: 1.55, 95% CI: 1.09–2.20), femur fracture (OR: 1.51, 95% CI: 1.16–1.96), and osteoporotic fracture (OR: 1.42, 95% CI: 1.24–1.64). However, no statistically significant association was reported between primary hyperparathyroidism and the risk of hip fracture (OR: 1.11, 95% CI: 0.90–1.38), hand fracture (OR: 1.55, 95% CI: 0.88–2.75), forearm fracture (OR: 1.51, 95% CI: 0.52–4.39), femoral neck fracture (OR: 1.12, 95% CI: 0.56–2.25), and cervical fracture (OR: 1.40, 95% CI: 0.63–3.13).

Conclusion: The risk of any fractures in patients with primary hyperparathyroidism was 45% higher than in healthy individuals and increased with advancing age. Furthermore, primary hyperparathyroidism elevated the risk of vertebral fracture by 90%, foot fracture by 55%, femur fracture by 51%, and osteoporotic fracture by 42%.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024563393) and Research Registry (UIN: reviewregistry1851) websites.

Keywords: Fractures, Bone, Spiral fracture, Broken bones, Hyperparathyroidism, Primary hyperparathyroidism

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Introduction

Primary hyperparathyroidism is a common endocrine disorder characterized by elevated serum calcium levels and normal or high levels of parathyroid hormone in the blood (1). This condition predominantly affects patients aged 65 years and above in the United States, and its prevalence has risen over the past three decades (2). In 80%-85% of cases, primary hyperparathyroidism is caused by a single parathyroid adenoma (3).

Skeletal health is a significant concern for patients with hyperparathyroidism (4), since primary hyperparathyroidism leads to osteoporosis, fractures, nephrolithiasis, and complications of chronic kidney disease (5,6). Increased bone resorption and a higher risk of fracture in most skeletal sites, including the spine, wrist, ribs, and pelvis, are well-known concerns in primary hyperparathyroidism (7). Even asymptomatic patients with normocalcemia or mild hypercalcemia often experience decreased bone mineral density, resulting in osteoporosis and osteopenia (8,9).

Surgical treatment with parathyroidectomy is the definitive modality for primary hyperparathyroidism.

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Implication for health policy/practice/research/medical education

The meta-analysis findings indicated that patients with primary hyperparathyroidism face a 45% higher overall risk of fractures, which escalates with age, underscoring the urgent need for enhanced monitoring and preventive strategies in this population. Specifically, the dramatic increases in the risk of vertebral (90%), foot (55%), femur (51%), and osteoporotic fractures (42%) highlight the importance of implementing targeted interventions such as regular bone density assessments, fall prevention programs, and nutritional counseling to improve bone health. This multifaceted approach is essential for mitigating fracture risk and promoting better health outcomes in individuals with primary hyperparathyroidism, particularly among older adults who are already at a heightened risk for skeletal complications.

However, non-surgical therapy, in the form of conservative or medical management, serves as an alternative option for individuals who are not candidates for surgery (10). In addition to correcting hypercalcemia, parathyroidectomy increases bone density and reduces the risk of fracture in patients with osteoporosis and osteopenia (11-13). Observational studies have published conflicting results. Some studies have shown no significant relationship between primary hyperparathyroidism and fracture risk (14), while others have demonstrated that primary hyperparathyroidism increases the risk of fractures (15,16). Therefore, a systematic review and meta-analysis approach was employed to synthesize the results of various studies.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (17) was utilized to design the present study using a systematic review and meta-analysis approach. The study protocol was registered on the PROSPERO website (International Prospective Register of Systematic Reviews).

Search strategy

The ProQuest, PubMed, Web of Science, Cochrane databases, and Google Scholar search engine were searched without time limitation up to June 20, 2024. Medical Subject Headings (MeSH) keywords such as "Fractures, Bone", Spiral Fracture, Broken Bones, "Hyperparathyroidism, Primary", Primary Hyperparathyroidism, and their equivalents were used for the search. The keywords were combined using the operators (AND, OR). The reference lists of eligible studies were also reviewed for manual search. The search strategy on the Web of Science website was as follows: Fractures, Bone OR Spiral Fracture OR Broken Bones (Abstract) AND Hyperparathyroidism, Primary OR Primary Hyperparathyroidism (Abstract).

PICO components

- Population: Observational studies that investigated the association between primary hyperparathyroidism and fracture risk.
- Intervention/Exposure: Primary hyperparathyroidism.
- Comparison: Age- and sex-matched individuals with the target group.
- Outcomes: The association between primary hyperparathyroidism and fracture risk.

Inclusion and exclusion criteria

Observational studies that examined the association between primary hyperparathyroidism and fracture risk were included in the current study. However, duplicate studies, meta-analyses, studies published in conferences, low-quality studies, review studies, studies that investigated the relationship amid hypoparathyroidism and fracture risk, studies with unavailable full text, studies lacking the necessary information for data analysis, and studies that examined the association between parathyroidectomy and fracture risk were excluded from the current study.

Quality assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was conducted to evaluate observational studies (18). The above checklist has 22 questions with a minimum score of zero and a maximum score of 44. Then, two researchers evaluated the disagreements regarding the answers to the questions and reached a common answer through consultation.

Data extraction

Two individuals performed data extraction. Data such as the name of the first author, study type, sample size, age, study duration, location, year of publication, odds ratio (OR) between primary hyperparathyroidism and fracture risk with its upper and lower limits were extracted from the reviewed studies, and a third person reviewed the data extracted by the previous two individuals and resolved any discrepancies.

Analysis

The logarithm of each study's OR was used to combine the studies. The I^2 index was conducted to assess heterogeneity. The I^2 index has three classifications (less than 25% low heterogeneity, between 25% and 75% moderate heterogeneity, and more than 75% high heterogeneity). This study used a random-effects model (I^2=83.7%), and subgroup analysis was employed to investigate the association between primary hyperparathyroidism and fracture risk. Meta-regression was employed to examine the relationship between "the effect of primary hyperparathyroidism on fracture risk" with sample size and year of research publication. Data analysis was performed using STATA 14 software, and the significance level of the tests was considered $P < 0.05$.

Results

Study selection

A total of 1128 studies were searched from the databases.

After screening the study titles, 521 duplicate studies were removed. The abstracts of the subsequent studies were reviewed, and 92 studies with incomplete abstract information and unavailable full text were excluded. Out of 515 studies in the next stage, 81 studies were excluded due to incomplete data required for data analysis. Then, the full text of 434 studies was evaluated, and 420 more were excluded due to other exclusion criteria. Finally, 14 studies were included in the systematic review and meta-analysis process (Figure 1).

These 14 studies were published from 1992 to 2024. Three case-control studies and 11 cohort studies were examined in this meta-analysis, which collectively evaluated a total of 51,932 patients with primary hyperparathyroidism (Table 1).

Figure 2 revealed that the risk of any fractures in patients with primary hyperparathyroidism was higher than in normal individuals (OR: 1.45, 95% CI: 1.26–1.67). Moreover, primary hyperparathyroidism boosted the risk of fracture in patients aged 50-59 years (OR: 1.37, 95% CI: 1.18-1.60) and 60-69 years (OR: 1.60, 95% CI: 1.25–2.05). The results indicated that with increasing age, the risk of fracture in individuals with primary hyperparathyroidism increases.

However, there was no statistically significant association between primary hyperparathyroidism and the risk of hip fracture (OR: 1.11, 95% CI: 0.90–1.38), hand fracture (OR: 1.55, 95% CI: 0.88–2.75), forearm fracture (OR: 1.51, 95% CI: 0.52–4.39), femoral neck fracture (OR: 1.12, 95% CI: 0.56–2.25), and cervical fracture (OR: 1.40, 95% CI: 0.63–3.13) (Figures 3 to 7).

Primary hyperparathyroidism led to an increased risk of vertebral fracture (OR: 1.90, 95% CI: 1.12–3.22), foot fracture (OR: 1.55, 95% CI: 1.09–2.20), femur fracture (OR: 1.51, 95% CI: 1.16–1.96), and osteoporotic fracture (OR: 1.42, 95% CI: 1.24–1.64) (Figures 8 to 11).

In Figures 12 and 13, meta-regression showed no statistically significant association between "fracture risk in patients with primary hyperparathyroidism" and publication year ($P = 0.953$) or study sample size ($P = 0.437$).

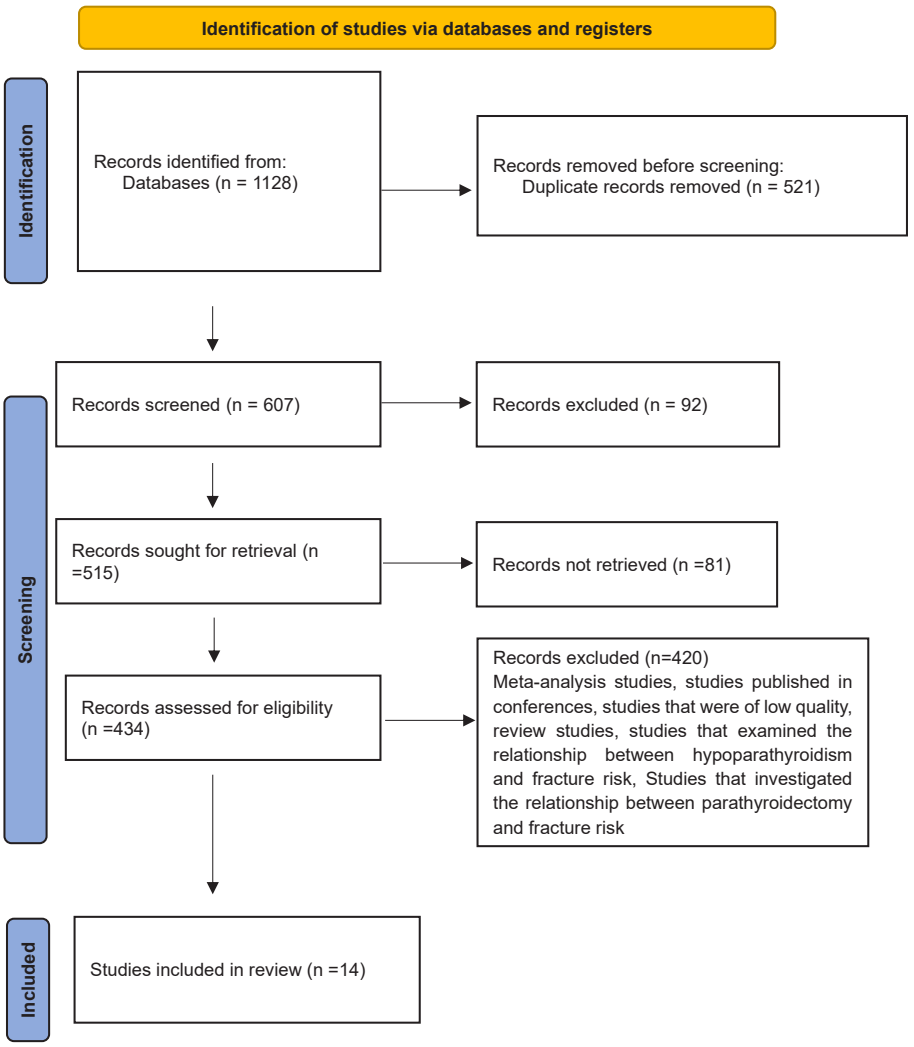

Figure 1. The PRISMA flow chart of study selection.

Table 1. Specifications of articles which entered into the meta-analysis process

Name, year	Index	Country	Type of study	Sample size in target group	Mean age in target group (year)	Sample size in compare group	Mean age in compare group (year)	Duration of study
Kim KJ, 2024 (19)	OR	South Korea	Cohort	6837	56	68370	56	2005-2020
Soto-Pedre E, 2023 (15)	HR	Scotland	Cohort	11616	55.7	34848	55.7	1997-2019
Kanis JA, 2023 (20)	HR	Denmark	Cohort	6884	65.2	68665	65.2	1997-2015
Axelsson KF, 2022 (16)	HR	Sweden	Cohort	16374	67.5	163740	67.5	2006-2017
Nilsson M, 2022 (21)	IRR	Sweden	Cohort	5009	61.7	14983	61.7	2003-2013
Ejlsmark-Svensson H, 2018 (22)	OR	Denmark	Case-Control	110	64	433	64	2005-2015
Vignali E, 2009 (23)	OR	Italy	Case-Control	150	61	300	61	2004-2006
Vestergaard P, 2003 (24)	IRR	Denmark	Cohort	360	65.5	NR	NR	1982-1996
Vestergaard P, 2000 (25)	RR	Denmark	Cohort	674	58.2	2021	58.2	1979-1997
Khosla S, 1999 (26)	SIR	USA	Cohort	407	57.8	NR	NR	1965–1992
Larsson K, 1993 (Women) (27)	RR	Sweden	Cohort	1373	62.6	NR	NR	1965–1983
Larsson K, 1993 (Men) (27)	RR	Sweden	Cohort	551	53.9	NR	NR	1965–1983
Melton LJ, 1992 (14)	RR	USA	Cohort	90	58.5	NR	NR	1965-1976
Romagnoli E, 2013 (28)	OR	Italy	Case-Control	73	63.6	74	63.1	2010-2011
Yu N, 2011 (29)	HR	UK	Cohort	1424	68.3	7120	68.3	1997–2006

NR: Not reported; OR: Odds ratio; RR: Risk ratio; HR: Hazard ratio; SIR: Standard incidence ratio; IRR: Incidence rate ratio.

Discussion

This study demonstrated that the risk of any fractures in patients with primary hyperparathyroidism was 45% higher than in normal individuals, with the fracture risk increasing as patients aged. Moreover, primary hyperparathyroidism led to an increased risk of vertebral fractures (90%), foot fractures (55%), femur fractures (51%), and osteoporotic fractures (42%). Therefore,

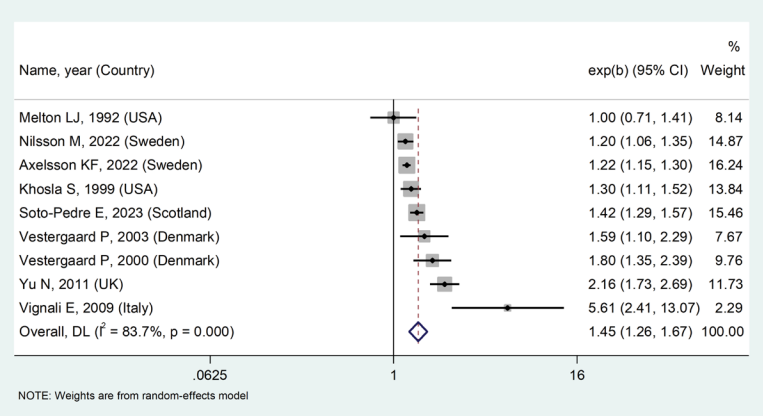

Figure 2. Forest diagram showing the risk of any fractures in individuals with primary hyperparathyroidism.

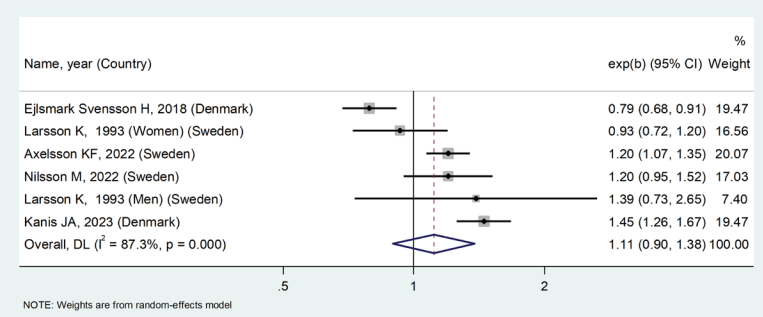

Figure 3. Forest diagram showing the risk of hip fracture in patients with primary hyperparathyroidism.

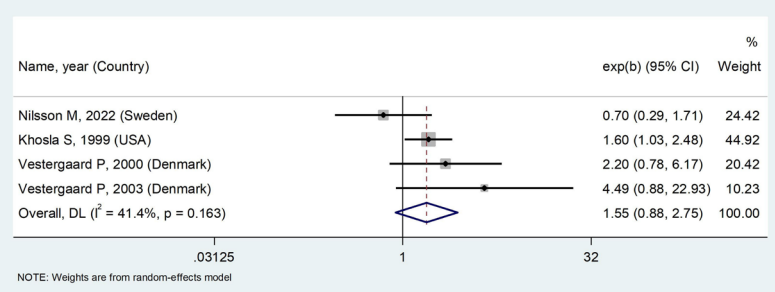

Figure 4. Forest diagram showing the risk of hand fracture in patients with primary hyperparathyroidism.

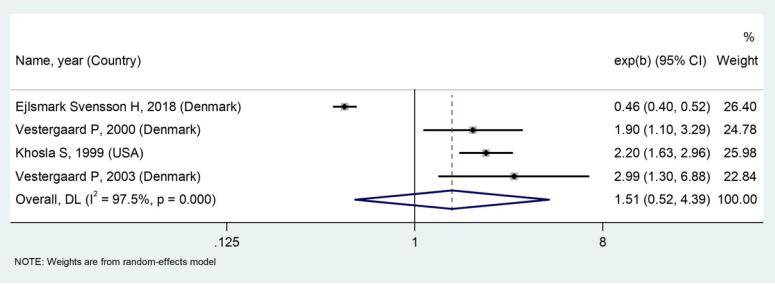

Figure 5. Forest diagram showing the risk of forearm fracture in patients with primary hyperparathyroidism.

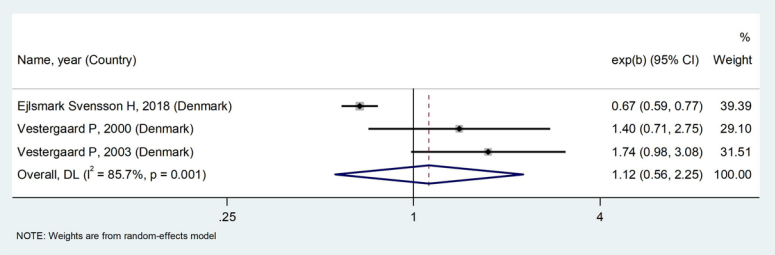

Figure 6. Forest diagram showing the risk of femoral neck fracture in patients with primary hyperparathyroidism.

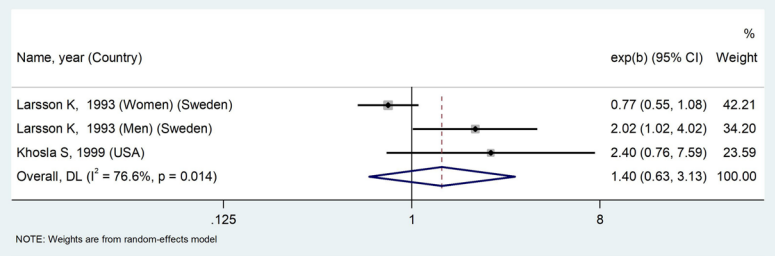

Figure 7. Forest diagram showing the risk of cervical fracture in individuals with primary hyperparathyroidism.

the highest fracture risk associated with primary hyperparathyroidism was observed in the vertebral region, followed by the foot and femur in second and third place, respectively. However, no significant correlation was found between primary hyperparathyroidism and the risk of fractures in the hip, hand, forearm, femoral neck, or cervical regions, indicating that the disease did not increase fracture risk in these areas.

A meta-analysis conducted by Ejlsmark-Svensson et al, aimed at examining fracture risk in primary hyperparathyroidism, revealed an increased risk of any fracture compared to the control group (OR: 2.01; 95% CI, 1.61-2.50). Elevated fracture risks were evident in the forearm (OR: 2.36; 95% CI, 1.64–3.38), spine (OR: 3.00; 95% CI, 1.41, 6.37), and vertebrae (OR: 5.76; 95% CI, 3.86–8.60). However, hip fractures were not associated with primary hyperparathyroidism (OR: 1.27; 95% CI, 0.97–1.66) (30). Another meta-analysis by Narayanan et

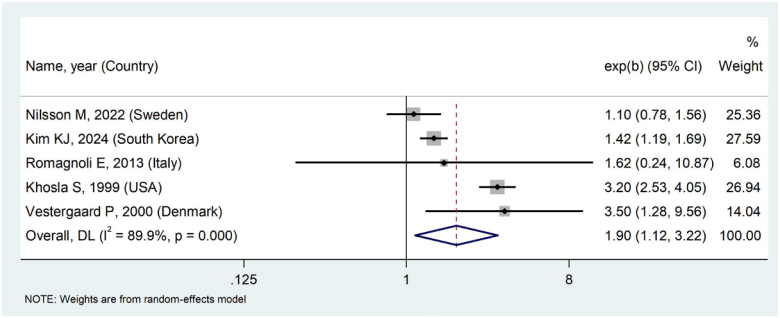

Figure 8. Forest diagram showing the risk of vertebral fracture in individuals with primary hyperparathyroidism.

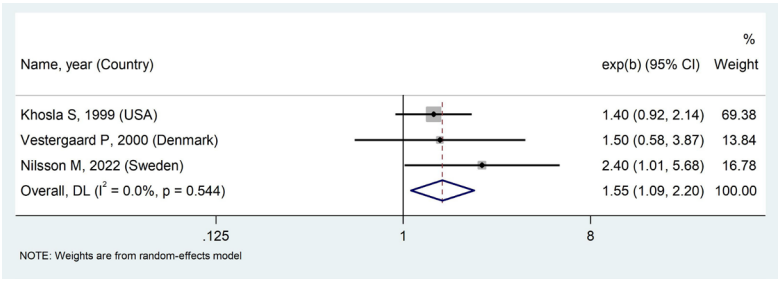

Figure 9. Forest diagram showing the risk of foot fracture in individuals with primary hyperparathyroidism.

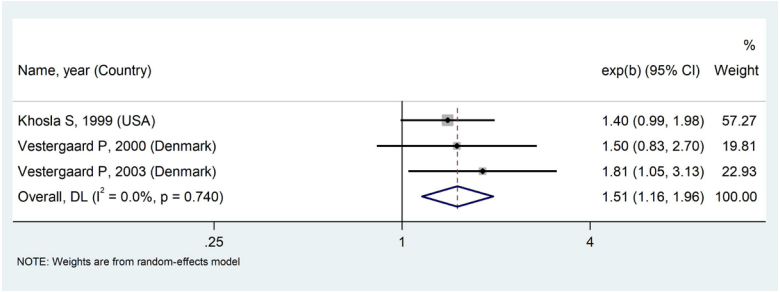

Figure 10. Forest diagram showing the risk of femur fracture in patients with primary hyperparathyroidism.

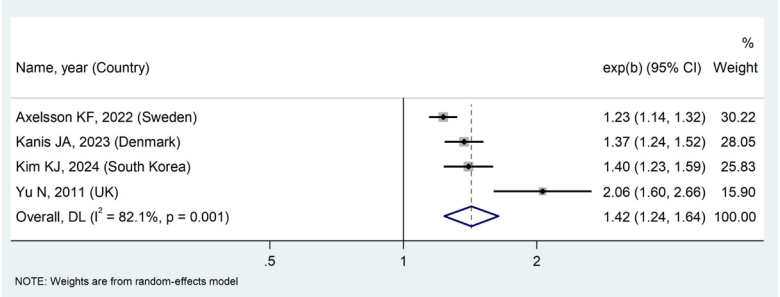

Figure 11. Forest diagram showing the risk of osteoporotic fracture in patients with primary hyperparathyroidism.

al in this field showed that the risk of vertebral fractures (relative risk [RR]: 2.57; 95% CI, 1.3–-5.09) and any fracture (RR: 1.71; 95% CI, 1.48–-1.97) was greater in individuals with primary hyperparathyroidism compared to the comparison group (31). The results of these studies aligned with our current findings, indicating that primary hyperparathyroidism is generally a risk factor for any type of fracture. It is worth noting that previous studies were published in 2021, making our current study more up-to-date. Furthermore, like our study, the aforementioned research concurred that vertebrae are at higher risk of fracture due to primary hyperparathyroidism compared to other bones.

Primary hyperparathyroidism affects not only bones but numerous body organs, increasing the risk of various diseases in affected individuals. Considering the results of similar meta-analysis, we find that primary hyperparathyroidism is a risk factor for gallstones, overall

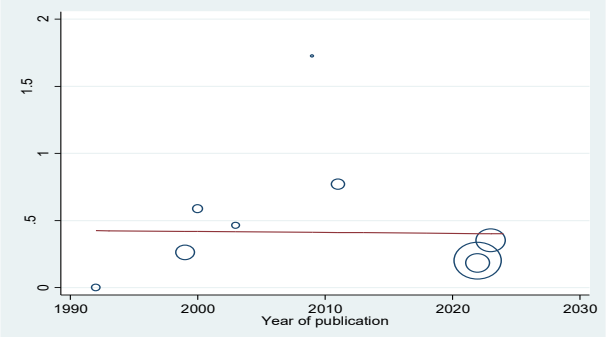

Figure 12. Meta-regression plot of association between fracture risk in individuals with primary hyperparathyroidism and year of study.

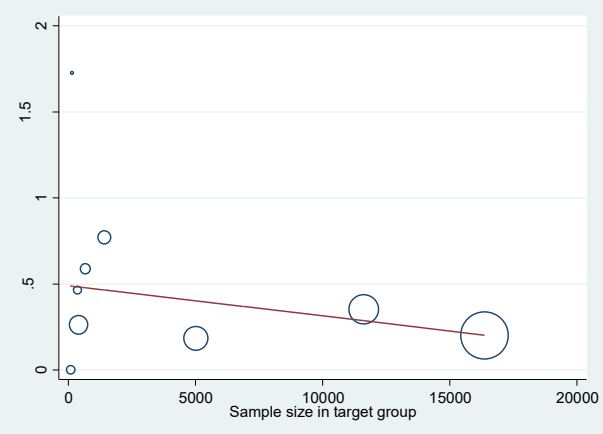

Figure 13. Meta-regression diagram of the relationship between fracture risk in patients with primary hyperparathyroidism and sample size.

mortality, and cardiovascular mortality, in addition to bone fractures. According to Kong et al, primary hyperparathyroidism increased the risk of overall mortality (RR: 1.39, 95% CI: 1.23–1.57) and cardiovascular mortality (RR: 1.61, 95% CI: 1.47–1.78) compared to the general population. However, no significant difference was observed in the risk of cardiovascular disease between patients with primary hyperparathyroidism and the general population (RR: 1.73, 95% CI: 0.87–3.47) (32). Pal et al reported the OR for gallstone disease in individuals with primary hyperparathyroidism compared to the control group as (OR: 1.77, 95% CI: 1.60–1.97) (1).

The following meta-analyses demonstrated that primary hyperparathyroidism increases the prevalence of diseases such as malignant cancer and gallstones. Additionally, Charoenngam et al conducted a study showing the prevalence of malignant cancer in patients with primary hyperparathyroidism was (0.19, 95% CI: 0.13–-0.25). Moreover, papillary thyroid cancer (pooled prevalence: 0.07; 95% CI: 0.06–-0.08) and breast cancer (pooled prevalence: 0.05; 95% CI: 0.03–-0.07) were the most common types of malignancies in these patients (33). Furthermore, Pal et al reported a pooled prevalence of gallstone disease in patients with primary hyperparathyroidism at 16% (1).

Conclusion

The risk of any fractures in patients with primary hyperparathyroidism was 45% higher than in normal individuals, with fracture risk increasing as age advanced. Furthermore, the highest fracture risk associated with primary hyperparathyroidism was observed in the vertebral region, followed by the foot and femur, respectively. Consequently, patients with primary hyperparathyroidism face a greater risk of bone fractures compared to the general population, underscoring the critical importance of identifying and treating these patients. This is particularly crucial for elderly patients or those exhibiting osteoporosis and low bone density.

Limitations of the study

The indices used in the reviewed studies varied, including RR, OR, hazard ratio (HR), incidence rate ratio (IRR), and standardized incidence ratio (SIR). The age group of patients was not mentioned in some studies. Except for one study, results were not presented by patient gender in other studies. Full texts of some studies were unavailable.

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Authors' contribution

Conceptualization: Yashar Shahbaz and Reza Noktehsanj.
Data curation: Yashar Shahbaz and Amin Norouzbeygi.
Formal analysis: Seyed Shahab Aldin Vaziri and Kiarash Tohidi.
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Methodology: Zahra Jamalafrouz and Kiarash Tohidi.
Project management: Reza Asadi.
Resources: All authors.
Supervision: Yashar Shahbaz.
Validation: Nazanin Hesari and Mobin Forghan.
Visualization: Seyed Shahab Aldin Vaziri and Kiarash Tohidi.
Writing–original draft: All authors.
Writing–reviewing and editing: All authors.

Conflicts of interest

There are no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42024563393) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1851). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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