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REVIEW

Fracture risk in hypoparathyroidism: a systematic review and meta-analysis

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Abstract

Summary In this meta-analysis, we analyzed 7 observational studies for assessing the fracture risk in patients with hypoparathyroidism (hypoPT). We found that the risk of vertebral fractures is increased by almost 2-fold, especially those with nonsurgical hypoPT.

Purpose Patients with hypoPT have higher bone mineral density than age- and sex-matched controls. This would theoretically translate into a lower risk of fractures, although available clinical evidence is contradictory. Hence, the present systematic review and meta-analysis was undertaken to collate and provide a precise summary of fracture risk in hypoPT.

Methods PubMed, Scopus, and Web of Science databases were systematically searched using appropriate keywords till March 8, 2021, to identify observational studies reporting the rate of occurrence of fractures among hypoPT patients (nonsurgical and/or postsurgical) compared to non-hypoPT subjects (controls). Study quality was assessed using Newcastle-Ottawa Scale. Pooled odds ratio (OR) with 95% confidence intervals (CI) was calculated. Subgroup analyses of nonsurgical and postsurgical hypoPT patients were also conducted.

Results We identified 7 observational studies of high-quality pooling data retrieved from 1470 patients with hypoPT. When stratified based on the skeletal site, pooled analyses showed that hypoPT patients were at an increased risk of vertebral fractures compared to non-hypoPT controls (OR 2.22, 95% CI: 1.23, 4.03, $p = 0.009$, $I^2 = 49\%$, random-effects model). The increased risk of vertebral fractures was seen only in patients with nonsurgical hypoPT (OR 2.31, 95% CI: 1.32, 4.03, $p = 0.003$, $I^2 = 3\%$, random-effects model) but not in those with postsurgical hypoPT. hypoPT patients were not at an increased or decreased risk of any, humerus, or proximal femur/hip fractures than controls.

Conclusions Nonsurgical hypoPT patients are at an almost 2-fold increased risk of vertebral fractures and thus need to be actively screened irrespective of the underlying BMD.

Keywords Fracture · Hypoparathyroidism · Vertebral fracture

Introduction

Hypoparathyroidism (hypoPT) is a rare endocrine disorder characterized by hypocalcemia and low or undetectable levels of parathyroid hormone (PTH). Removal of or inadvertent damage to the parathyroid glands at the time of anterior neck surgery is, by far, the most common etiology of hypoPT [1]. Other etiologies include autoimmune destruction of the parathyroid glands and hereditary causes. The prevalence of hypoPT in the USA has been estimated to be 37/100,000 population [2, 3].

The major symptomatic features of hypoPT relate to neuromuscular irritability and include paresthesias of the extremities and around the mouth, laryngospasm, and frank seizures [1, 4, 5]. Skeletal health is also affected in hypoPT. In normal physiology, PTH is required in adults for skeletal remodeling. In the absence of PTH, skeletal remodeling is impaired leading to a state of low bone turnover [6], as represented by circulating markers of bone formation and bone resorption which are generally in the lower half of the normal range [7]. Expectedly, being a low bone turnover state, areal bone mineral density (BMD), as measured by dual-energy X-ray

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absorptiometry (DXA), is generally higher than age- and sex-matched controls [8, 9]. However, as assessed by trabecular bone score (TBS), bone microarchitecture is compromised in patients with hypoparathyroidism regardless of the BMD [10]. Consistent with poor bone microarchitecture, an increased prevalence of fractures in hypoPT has been reported in a few case-control studies [11–15]. Nevertheless, the data is inconsistent, and some studies have shown no increase in fracture risk in patients with hypoPT [16, 17]. In fact, the risk of fractures at the upper extremities was significantly decreased in postsurgical hypoPT patients [17].

Considering the lack of granularity and the remarkable heterogeneity in the available clinical evidence, the present systematic review and meta-analysis was undertaken to collate and provide a precise summary of fracture risk in hypoPT.

Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [18].

Search strategy

Two investigators (RP and MB) independently performed a systematic search of the literature across the PubMed, Scopus, and Web of Science databases from inception until March 8, 2021, using the following keywords interposed with appropriate Boolean operators: "hypoparathyroidism" AND "fractures." The language was restricted to English only. The references of relevant reviews and retrieved articles were also screened for potentially eligible articles. For missing data, the corresponding authors of the potentially eligible studies were contacted wherever possible.

Eligibility and exclusion criteria

Eligibility criteria were set as follows:

1. Observational studies (prospective or retrospective, cohort or case-control design).
2. Studies should include patients with hypoPT (either nonsurgical or postsurgical or both) and subjects without hypoPT (controls) for comparison.
3. Studies should report the rate of occurrence of fractures (as the number of "events") among hypoPT patients compared to non-hypoPT subjects.

Exclusion criteria were set as follows:

1. Studies that had included subjects with pseudohypoparathyroidism, functional hypoparathyroidism, normocalcemic hypoparathyroidism, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).
2. Studies that lacked a non-hypoPT control group.
3. Studies where fracture data had not been reported.
4. Reviews, comments, editorials, letters to the editor, or case reports.

Data extraction

Two investigators (RP and MB) independently scanned titles and/or abstracts to exclude duplicate studies and studies that failed to meet the aforementioned eligibility criteria. Potentially eligible studies were full-text assessed. Any discrepancies between the aforementioned investigators were solved by discussion, consensus, or arbitration by a third senior investigator (SKB). Studies hence selected were reviewed, and the following data were extracted from full-text reports for further assessment: study characteristics, type of hypoPT (nonsurgical and/or postsurgical), the number of patients with hypoPT, the number of subjects without hypoPT, the site of fracture (any, vertebral, humerus, wrist, proximal femur, or hip), the type of fracture (clinical or morphometric), and the reported number of fractures in hypoPT patients vs. non-hypoPT subjects (i.e., the number of events in hypoPT patients *vs.* non-hypoPT subjects).

Assessment of study quality and risk of bias

The Newcastle-Ottawa Scale (NOS) was used to assess the quality and risk of bias of the included observational studies. The scale assesses three quality parameters: selection, comparability, and outcome divided across eight specific items that slightly differ when scoring case-control and cohort studies [19]. The maximum score on NOS is 9. Any score ≥7 qualifies as high-quality with a low risk of bias, while a score <5 is categorized as low-quality with a high risk of inherent bias. Any score in between is rated as moderate-quality [20]. The assessment of study quality was conducted independently by two investigators (RP and SM). Any discrepancy was solved by a discussion with a third senior investigator (SKB).

Statistical analysis

The difference in the rate of occurrence of fractures (events) in hypoPT patients vs. non-hypoPT subjects was calculated using the OR with 95% confidence intervals (CI) after implementation of the Mantel-Haenszel (M-H) fixed-effects model. Separate analyses were performed based on the fracture site (any, vertebral, humerus, and proximal femoral/hip). We also conducted subgroup analyses of nonsurgical and postsurgical hypoPT patients.

In addition to the fracture risk, we calculated the mean differences (MD) in BMD at various sites between the hypoPT and control group with 95% CI, using an inverse-variance weighted fixed-effects model.

Statistical heterogeneity among studies was assessed using I^2 statistics. Heterogeneity was quantified as low, moderate, and high with upper limits of 25%, 50%, and 75% for I^2, respectively [21]. In the present meta-analysis, significant heterogeneity was considered when the I^2 value was ≥50%, with a p value <0.05. Outcomes with significant heterogeneity were reanalyzed and reported using the random-effects model. A p <0.05 was considered to be statistically significant.

Statistical analysis was performed using the RevMan 5.4 software (Cochrane Collaboration).

Results

After a thorough literature search and a meticulous study selection process, we included seven observational studies in our meta-analysis, pooling data retrieved from 1470 patients with hypoPT and 6101 subjects without hypoPT [11–17]. The study selection process has been summarized in the PRISMA flowchart (Fig. 1).

The primary characteristics of the included studies and the NOS scores have been summarized in Table 1. All the studies were of high quality. Three studies catered to postsurgical [11, 15, 17] and nonsurgical hypoPT [12–14], each. Vadiveloo et al. had included patients with both postsurgical and nonsurgical hypoPT [16]. Clinical fractures were reported in four studies [12, 14, 16, 17], while data on morphometric vertebral fractures were presented in three studies [11, 13, 15]. The subjects without hypoPT (controls) were invariably matched for age and sex in all the studies. None of the studies explicitly mention about the use of recombinant human PTH (1-84) as a treatment option in the hypoPT patients; nevertheless, Cipriani et al. had clearly mentioned that hypoPT patients with previous use of teriparatide or recombinant human PTH (1-84) were excluded [15].

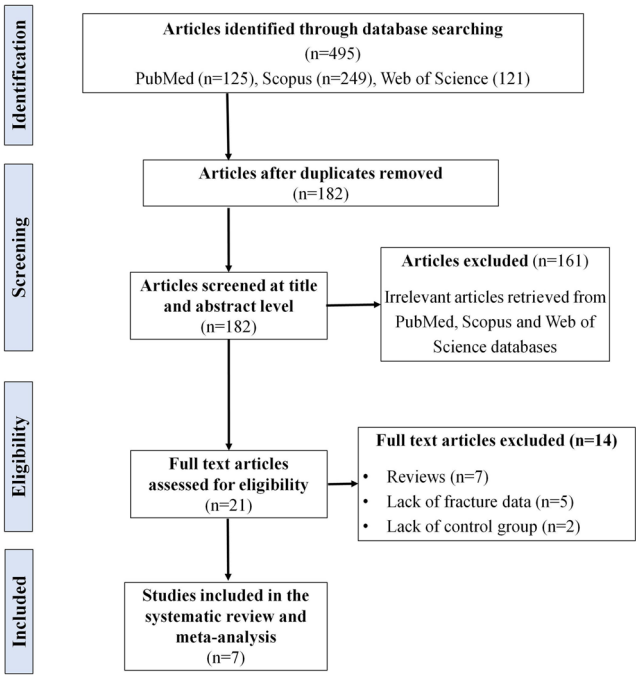

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart showing the study selection process

The results of the meta-analysis have been summarized under the following heads based on the reported site of fracture.

Risk of any fractures

Data on *any* fractures were reported in four studies [12, 14, 16, 17]. The pooled analysis did not show any significant increase or decrease in the risk of *any* fractures in hypoPT patients than controls (OR 1.06, 95% CI: 0.88, 1.27, p=0.54, I^2=25%, fixed-effects model). Subgroup analysis also showed that neither patients with nonsurgical hypoPT nor those with postsurgical hypoPT are at an increased or decreased risk of *any* fractures (Fig. 2).

Risk of vertebral fractures

Data on vertebral fractures were reported in six studies [11–15, 17]. Pooled data revealed that patients with hypoPT were at an almost 2-fold increased risk of vertebral fractures compared to controls (OR 2.22, 95% CI: 1.23, 4.03, p=0.009, I^2=49%, random-effects model). The increased risk of vertebral fractures was observed only in patients with nonsurgical hypoPT (OR 2.31, 95% CI: 1.32, 4.03, p=0.003, I^2=3%, random-effects model) and not in those with postsurgical hypoPT (OR 2.58, 95% CI: 0.69, 9.64, p=0.16, I^2=71%, random-effects model) (Fig. 3).

Risk of humerus fracture

Data on humerus fracture were reported in only three studies [12, 14, 17]. On pooled analysis, patients with hypoPT were not at an increased or decreased risk of humerus fractures compared to non-hypoPT controls (OR 1.47, 95% CI: 0.14, 15.55, p=0.75, I^2=96%, random-effects model) (Fig. 4).

Risk of proximal femur/hip fractures

Data on proximal femur fractures reported in two studies [12, 17] and hip fractures reported in one study [14] were pooled together. Patients with hypoPT were not at an increased or decreased risk of proximal femur/hip fractures compared to non-hypoPT controls (OR 1.59, 95% CI: 0.24, 10.73, p=0.63, I^2=90%, random-effects model) (Fig. 5).

Table 1 Summarizing the studies included in the systematic review and meta-analysis

Author (reference)	Study design/Place of study	Type of hypoPT	Characteristics of study population	Clinical/ morphometric fractures	Fracture site	Number of fractures/ number of cases	Number of fractures/ number of controls	NOS*
Mendonça et al. (2013) [11]	Observational cross-sectional case--control study∞ Brazil	Postsurgical hypoPT	Cases *n*=16 Mean age 62.3 years All women Controls *n*=17 Mean age 58.0 years All women	Morphometric	Vertebral	10/16 (62.5%)	2/17 (11.7%)	8
Underbjerg et al. (2015) [12]	Observational case-finding study** Denmark	Nonsurgical hypoPT	Cases *n*=180 Median age 49.7 years Women 53.0% Controls *n*=540 ^	Clinical	Any Vertebral Proximal humerus Proximal femur fractures	34/180 (18.9%) 5/180 (2.7%) 14/180 (7.8%) 9/180 (5.0%)	70/540 (13.0%) 11/540 (2.0%) 14/540 (2.6%) 15/540 (2.8%)	8
Chawla et al. (2016) [13]	Observational cohort study§ India	Nonsurgical hypoPT	Cases *n*=104 Mean age 37.2 years Women 46.1% Controls *n*=64 Mean age 37.5 years Women 39.1%	Morphometric	Vertebral	19/104 (18.3%)	3/64 (4.7%)	7
Kim et al. (2020) [14]	Observational retrospective cohort study# Korea	Nonsurgical hypoPT	Cases n=210 Mean age 39.2 years Women 62.4% Controls *n*=2075 Mean age 39.2 years Women 62.6%	Clinical	Any Vertebral Humerus or wrist Hip	15/210 (7.1%) 9/210 (4.3%) 7/210 (3.3%) 0/210 (0.0%)	116/2075 (5.6%) 39/2075 (1.9%) 71/2075 (3.4%) 11/2075 (0.5%)	8
Cipriani et al. (2021) [15]	Observational cross-sectional case control study⌘ Italy	Postsurgical hypoPT	Cases *n*=50 Mean age 65.4 years All postmenopausal women Controls *n*=40 Mean age 64.2 years All postmenopausal women	Morphometric	Vertebral	8/50	3/40	8
Vadiveloo et al. (2018) [16]	Observational retrospective population-based study@ UK	Postsurgical hypoPT Nonsurgical hypoPT	Postsurgical cases *n*=116 Mean age 47.1 years Women 80.2% Nonsurgical cases *n*=106 Mean age 50.5 years Women 64.2% Controls *n*=1301 Mean age 49.6 years Women 71.2%	Clinical	Any	10/116 (8.6%) 11/106 (10.4%)	153/1301 (11.8%) 153/1301 (11.8%)	8
Underbjerg et al. (2014) [17]	Observational case-finding study¶ Denmark	Postsurgical hypoPT	Cases *n*=688 Median age 49 years Women 88.0% Controls *n*=2064	Clinical	Any Vertebral Proximal humerus	102/688 (14.8%) 13/688 (1.9%) 4/688 (0.6%) 13/688 (1.9%)	305/2064 (14.8%) 36/2064 (1.7%) 47/2064 (2.3%) 51/2064 (2.5%)	7

Table 1 (continued)

Author (reference)	Study design/Place of study	Type of hypoPT	Characteristics of study population	Clinical/ morphometric fractures	Fracture site	Number of fractures/ number of cases	Number of fractures/ number of controls	NOS*
			Median age 49 years Women 88.0%		Proximal femur fractures			

*Newcastle-Ottawa Scale with a maximum score of 9

$^{\infty}$ Age-, height-, and weight-matched controls

**Sex and year of birth (± 2 years) matched controls

^Median age and proportion of women not mentioned

§ Controls (age- and sex-matched) were family members of hypoPT patients who consented to participate

Propensity score matched controls based on age, sex, and comorbid disease

⌘Age-matched controls

@ Matched for sex, age (± 5 years), and diabetes status

¶Sex and year of birth (± 2 years) matched controls

HypoPT hypoparathyroidism

The data on BMD were reported in three studies [11, 13, 15]. Pooled analysis showed that compared to controls, patients with hypoPT had increased BMD at the lumbar spine (MD 0.140 g/cm^2, 95% CI: 0.050, 0.240, p=0.004, I^2=81%, random-effects model) (Supplementary Figure 1A), femoral neck (MD 0.090 g/cm^2, 95% CI: 0.050, 0.130, p<0.001, I^2=8%, fixed-effects model) (Supplementary Figure 1B), and total hip (MD 0.070 g/cm^2, 95% CI: 0.040, 0.100, p<0.001, I^2=18%, fixed-effects model) (Supplementary Figure 1C). Data on forearm BMD were inadequately reported and, hence, could not be pooled together. In addition, two studies had compared the BMD in hypoPT patients with and without vertebral fractures. Notably, there was no statistically significant difference in BMD at the lumbar spine, femoral neck, or total hip between the two groups [13, 15].

Discussion

The present systematic review and meta-analysis shows that patients with hypoPT are at an increased risk of vertebral fractures compared to age- and sex-matched non-hypoPT controls. The increased risk was evident only in patients with nonsurgical hypoPT and not in those with postsurgical hypoPT, necessitating active surveillance for vertebral fractures in the former subgroup.

Hypoparathyroidism is characterized by hypocalcemia and low or undetectable levels of PTH. Hypocalcemia manifests as neuromuscular irritability clinically presenting as paresthesias, tetany, and refractory seizures [4, 5]. Other manifestations of hypoPT include cataracts [22], basal ganglia calcifications [23], and cardiovascular autonomic neuropathy [1]. Skeletal manifestations in hypoPT include an increased risk of fracture, although available clinical evidence is limited and contradictory. An increased prevalence of fractures in hypoPT has been reported in a few case-control studies [11–15], while some studies have shown no increase in fracture risk [16, 17]. On the contrary, the risk of fractures at the upper extremities was reported to be significantly decreased in postsurgical hypoPT patients [17].

Skeletal dynamics in hypoPT is characterized by low bone turnover, resulting in a higher bone mass than age- and gender-matched controls [6, 8, 9, 24]. Accordingly, areal BMD, measured by DXA, and volumetric BMD, measured by peripheral quantitative computed tomography (pQCT), have been reported to be greater in hypoPT patients than controls. It is evident in both cancellous and cortical bone [25, 26]. Even in the present meta-analysis, pooled data from 3 studies showed that BMD was higher at the lumbar spine, femoral neck, and total hip in hypoPT patients as compared to non-hypoPT controls. Thus, in accordance with an increased bone mass, hypoPT patients are unlikely to be at an

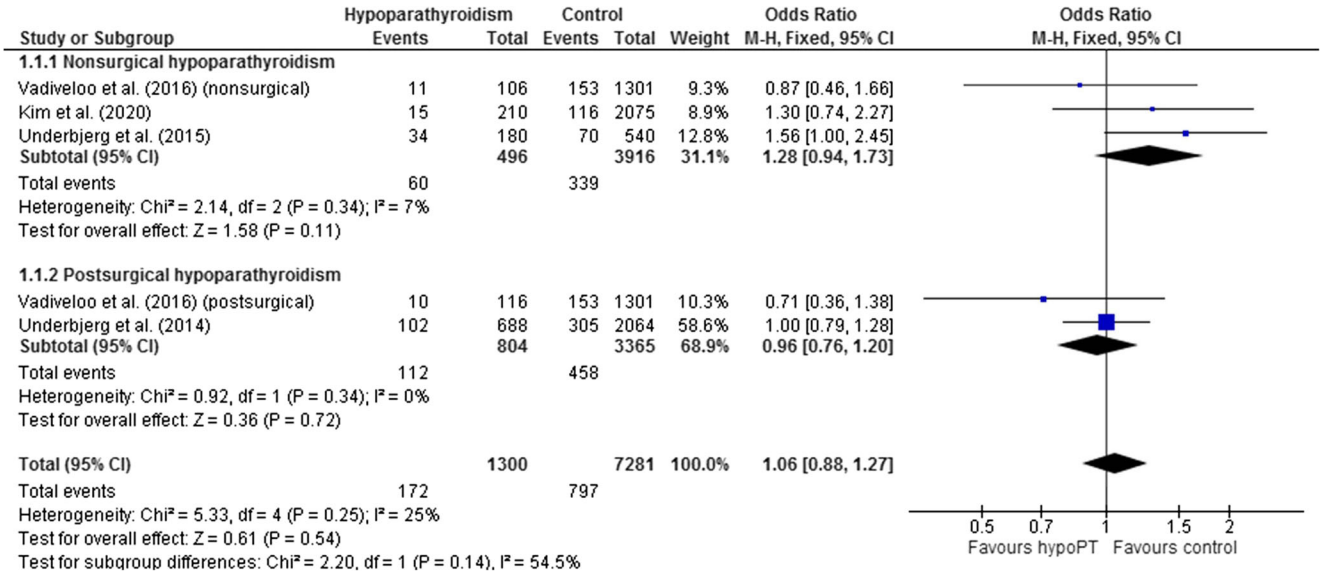

Fig. 2 Forest plot with subgroup analysis showing the risk of *any* fractures in patients with hypoparathyroidism (hypoPT) as compared to non-hypoPT controls

increased risk of fractures or might even be at a lower risk of fractures compared to non-hypoPT subjects [17].

Nevertheless, higher bone mass does not necessarily translate into increased bone strength. A typical example of this paradox is type 2 diabetes mellitus (T2D). The areal BMD in patients with T2D is usually increased by 5 to 10% above an aged-matched non-diabetic population; nonetheless, they are at an increased risk of incident fragility fractures [27]. The same has been attributed to a deteriorated bone microarchitecture seen in patients with T2D that translates into an increased fracture risk regardless of the areal BMD. Besides, T2D also represents a low bone turnover state, and most of the recent studies have confirmed decreased levels of bone turnover markers in patients with diabetic mellitus [28].

Similarly, despite an increase in bone mass, bone microarchitecture is compromised in patients with hypoPT. Among 62 postsurgical hypoPT patients who underwent estimation of TBS at the lumbar spine, 32.2% of the patients presented values below the normal range (<1.310) [10]. In another recent report, the TBS values of 50 postmenopausal women with postsurgical hypoPT fitted in the classification of degraded microarchitecture even though areal BMD at the

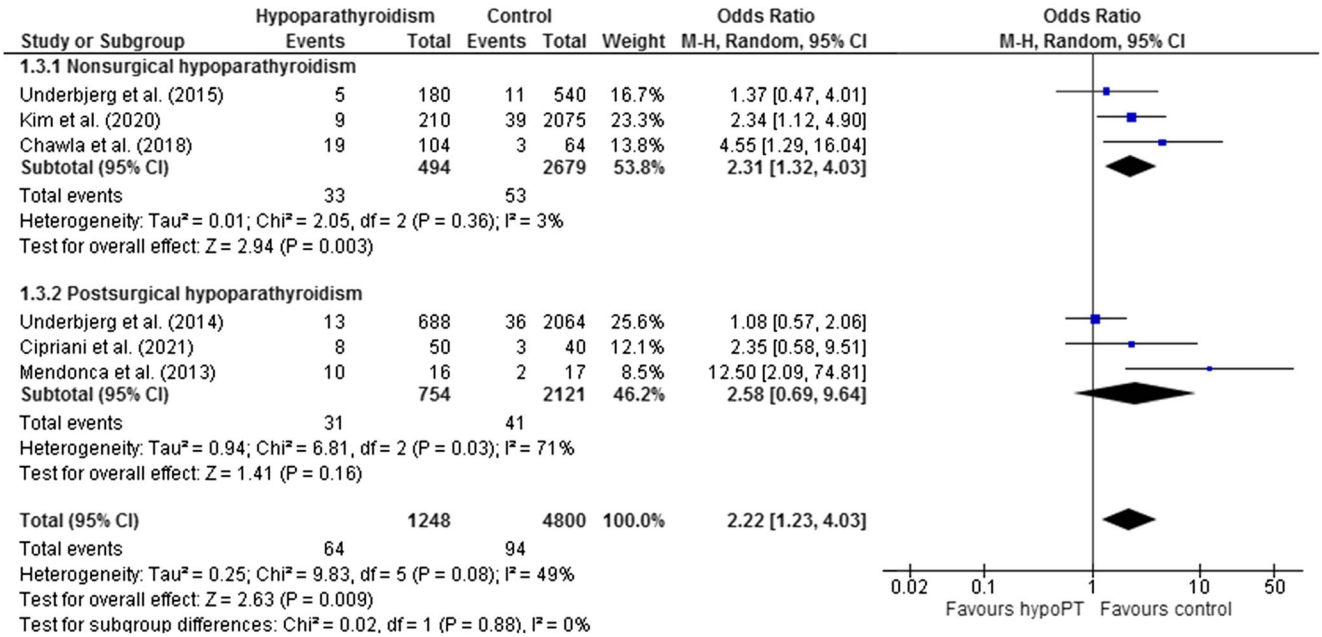

Fig. 3 Forest plot with subgroup analysis showing the risk of *vertebral* fractures in patients with hypoparathyroidism (hypoPT) as compared to non-hypoPT controls

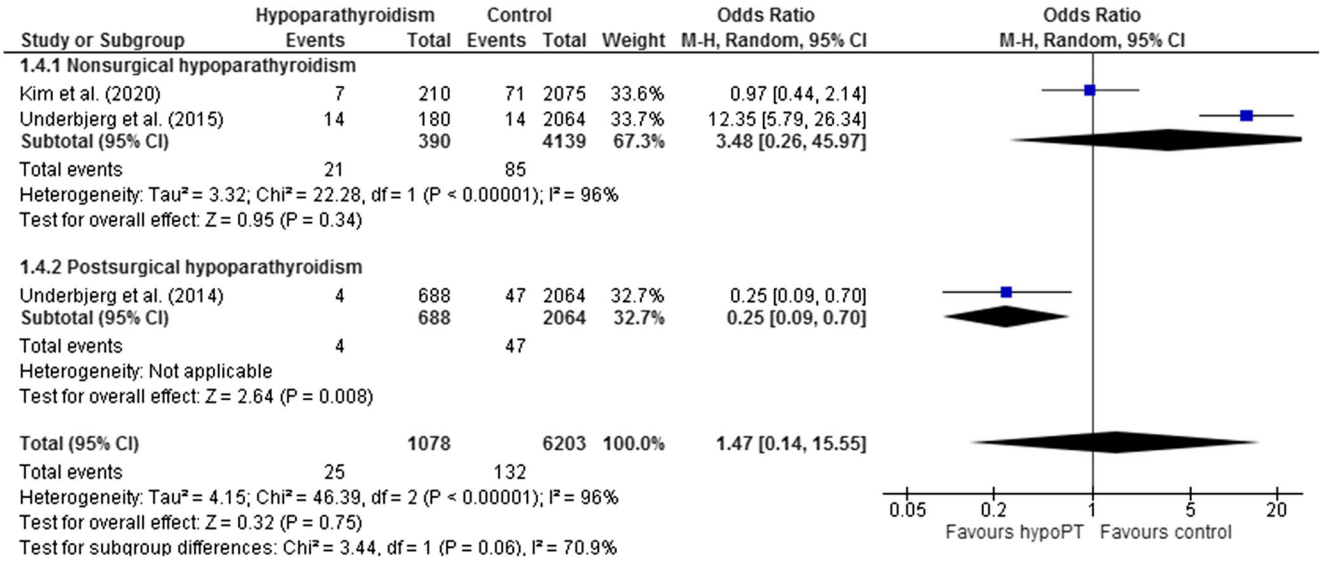

Fig. 4 Forest plot with subgroup analysis showing the risk of *humerus* fractures in patients with hypoparathyroidism (hypoPT) as compared to non-hypoPT controls

lumbar spine (L1–L4), femoral neck, and total hip were significantly higher than an age-matched control group [15]. Besides, resistance to microfracture, measured by bone material strength index (BMSi), is lower in hypoPT patients than in controls [29]. Consistent with these findings, the present meta-analysis did find an increased risk of vertebral fractures in patients with hypoPT, although, on subgroup analysis, the risk remained statistically significant only in patients with nonsurgical hypoPT but not in those with postsurgical hypoPT. The possible explanation for the disparity is that patients with nonsurgical hypoPT (autoimmune or genetic causes) are more likely to have longer disease duration than those with iatrogenic postsurgical hypoPT. Besides, onset of disease at an early age as in patients with nonsurgical hypoPT is likely to affect bone mass and bone architecture at the time of acquisition of peak bone mass, thereby possibly further increasing the risk of fractures. In addition, the longer duration of anticonvulsant therapy in patients with nonsurgical hypoPT compared to patients with postsurgical hypoPT may augment the risk of fractures in the former group.

Further indirect evidence on bone fragility is derived from bone histomorphometry. In a cohort of 33 hypoPT patients who underwent histomorphometric analysis, an increase in cortical and trabecular width, along with a reduction in cortical porosity, was reported. Altogether, the results suggested that in hypoPT, bone remodeling activity and the reabsorption rate are reduced in all bone compartments, namely, cancellous, endocortical, and intracortical [30]. Interestingly, bone mineralization was not different in hypoPT patients compared to euparathyroid controls; hence, possibly, hypoPT patients apparently display

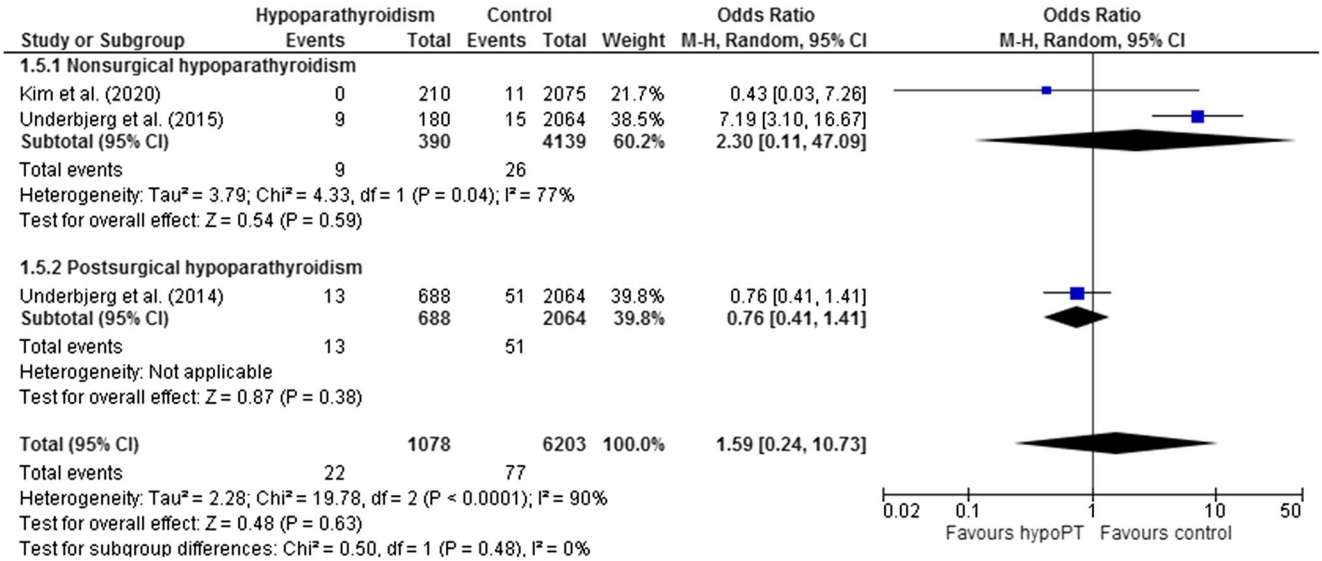

Fig. 5 Forest plot with subgroup analysis showing the risk of *proximal femur/hip* fractures in patients with hypoparathyroidism (hypoPT) as compared to non-hypoPT controls

an increase in bone volume, but not of its mineral component. Supposedly, these changes decrease the bone mineral component to bone surface ratio, a possible factor underlying increased bone fragility in hypoPT patients [31].

Although the risk of vertebral fractures is increased, the present meta-analysis did not reveal a significant risk of *any*, humerus or proximal femur/hip fractures. Vertebrae are predominantly composed of trabecular bone; compared to cortical bone, the surface to volume ratio of trabecular bone is much higher [32]. Thus, trabecular bone has a large surface exposed to the bone marrow and blood flow, and hence, the turnover is higher than in cortical bone [33]. Accordingly, bone remodeling levels are higher in the trabecular bone as compared to cortical bone [34]. Thus, hypoPT, a condition characterized by a state of suppressed bone remodeling, is more likely to affect the trabecular than the cortical compartment. Whatever may be the underlying cause, it is prudent to actively screen patients with nonsurgical hypoPT for vertebral fractures irrespective of the underlying BMD. Screening with vertebral fracture assessment (VFA) during DXA examination represents a valid, safe, and cost-effective method to complete the assessment of the vertebral spine in patients with hypoPT [15].

The present systematic review and meta-analysis happens to be the first pooled data summarizing the hitherto available clinical evidence on fracture risk in patients with hypoPT. In addition, we have provided subgroup analysis of fracture risk in patients with nonsurgical and postsurgical hypoPT as the two represent distinct clinical entities. Furthermore, data on stratified analyses on the risk of fracture at different skeletal sites have also been presented.

The meta-analysis does have certain limitations. First, the number of included studies was limited to only seven. Second, the included data were all extracted from observational studies in the absence of any available randomized clinical trials. Third, in most of the included studies, fractures were not explicitly categorized as low-trauma or fragility fractures. Fourth, in most of the included studies, the selection of the control group was solely based on the absence of hypoPT, and other diseases that could potentially affect bone metabolism were not excluded; this might have influenced the fracture risk in the control group and might have accordingly altered the risk estimates in the present meta-analysis. Fifth, some of the studies investigating the fracture risk in hypoPT patients might have underestimated the actual number of fractures as data on fracture prevalence was solely based either on hospital discharge codes or nationwide/regional claims databases. As radiographs were not carefully performed, one cannot exclude the possibility of underlying morphometric vertebral fractures. Lastly, some of the analyses showed relatively high heterogeneity. For example, pooled analyses of fracture risk at the humerus or proximal femur/hip showed a considerable heterogeneity of 96% and 90%, respectively. However, since a very limited number of studies were included in each of the two analyses, we did not perform any sensitivity analyses. Instead, we used the random-effects model (and not the fixed-effects model) to make the results more generalizable.

Conclusions

The present meta-analysis suggests that the risk of vertebral fractures is increased by almost 2-fold in patients with hypoPT, especially those with nonsurgical hypoPT, probably because of a longer duration of disease. Thus, patients with nonsurgical hypoPT need to be actively screened for vertebral fractures, preferably with VFA, irrespective of the underlying BMD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-05966-8.

Author contribution Study design was conceived by Sanjay Kumar Bhadada. Literature search and data extraction were performed by Rimesh Pal and Mainak Banerjee. Study quality and risk of bias assessment was performed by Rimesh Pal and Soham Mukherjee. Statistical analysis was performed by Rimesh Pal, Mainak Banerjee, and Ashok Kumar. The initial version of the manuscript was drafted by Rimesh Pal. The manuscript was revised by Sanjay Kumar Bhadada. All authors read and approved the final version of the manuscript.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Being a meta-analysis, ethical committee approval was not required.

Consent to participate Not applicable.

Conflict of interest None.

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