Journal of Endocrinological Investigation (2024) 47:593–601
https://doi.org/10.1007/s40618-023-02177-2

ORIGINAL ARTICLE

Features of patients and fracture risk in hypoparathyroidism; a single center study

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Received: 9 April 2023 / Accepted: 16 August 2023 / Published online: 23 August 2023

Abstract

Purpose Patients with hypoparathyroidism (hypoPT) have low bone turnover and high bone mineral density (BMD). However, data on fracture risk are conflicting. The objectives of this study were: 1. To describe clinical/biochemical characteristics of hypoPT patients followed at a single medical center. 2. To identify postsurgical hypoPT patients and investigate their fracture rate compared with gender/age-matched post-surgical normocalcemic patients.

Methods Retrospective analysis of patient's medical records treated at the tertiary medical center in 2010–2021 identified by computerized medical database search.

Results The cohort included 133 patients (91% women, mean age 64 ± 13 years) of whom 105 (79%) had post-thyroidectomy hypoparathyroidism and the remainder had an autoimmune/idiopathic/other etiology. Mean follow-up time was 21 ± 12 and 27 ± 12 years, respectively. The control group included 142 post-thyroidectomy patients without hypoparathyroidism. Patients in the postsurgical hypoparathyroidism group were older and had higher calcium and PTH levels at diagnosis than the non-surgical hypoPT patients. Comparing the postsurgical hypoPT and postsurgical normocalcemic control patients revealed a significantly higher BMD in the hypoPT group. Yet, fracture rates were 31% in the postsurgical hypoparathyroidism group and 21% in the control group ($P = 0.1$) over a similar median follow-up period (17 and 18.4 years, respectively). In both groups the most common fracture site was the spine (50% and 70%, respectively; $p = 0.33$), mainly nonclinical morphometric fractures. Higher phosphorus blood level was associated with increased fracture risk.

Conclusions The relatively high BMD in patients with postsurgical hypoparathyroidism is not associated with lower fracture risk. Silent morphometric fractures are quite common in this group of patients.

Keywords Hypoparathyroidism · Fractures · Hypocalcemia · Osteoporosis · Bone Mineral Density

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Introduction

Hypoparathyroidism is a rare disorder of parathyroid hormone (PTH) deficiency, with an estimated prevalence of 23–37 per 100,000 population [1, 2]. It is associated with an increased risk of comorbidities, including renal stones, cardiovascular disease, seizures, and neuropsychiatric diseases [3–6].

PTH is essential for bone turnover and maintenance of calcium homeostasis. It regulates circulating calcium levels through a direct action on kidney and bone, and an indirect effect on vitamin D absorption in the intestine [2, 7]. Generally, the lack of PTH-mediated bone resorption in hypoPT patients causes low bone turnover and substantially higher bone density than in age- and sex- matched control subjects [8–10]. Nevertheless, fracture risk remains controversial in this group of patients [5]. Despite the increase in bone mineral density (BMD), markedly abnormal skeletal microstructure has been found in patients with chronic HypoPT on transiliac biopsy, histomorphometric analysis, and micro-computed tomography [11]. In clinical studies, some investigators found low or no risk of fractures in patients with HypoPT [3, 12] whereas others reported an increased fracture risk, mostly vertebral fractures, despite normal/high BMD [13–17]. Most of the uncertainty in the existing data probably stems from the heterogeneous etiology of HypoPT and different population groups.

In adults, approximately 75% of cases of HypoPT occur secondary to neck surgery, mainly thyroidectomy [2, 5]. The risk of fracture may vary between patients with postsurgical HypoPT and HypoPT due to an idiopathic/genetic/autoimmune etiology. In the present study we describe a cohort of patients with hypoparathyroidism followed at a large single endocrine institute in Israel. The aims of the study were: 1. to describe clinical/biochemical characteristics of all hypoPT patients followed at our medical center. 2. to identify the group of postsurgical hypoPTH patients and investigate their fracture rate compared with gender/age-matched post-surgical normocalcemic patients.

Materials and methods

The study was conducted at a university-affiliated tertiary hospital in Israel, and the protocol was approved by The Ethics (Helsinki) Committee at the Rabin Medical Center (Reference 0784-21-RMC) without the need of informed consent.

The electronic healthcare database of the Endocrine Institute of Rabin Medical Center was retrospectively screened for adult patients diagnosed with HypoPT between 2010 and 2021. Only those with permanent HypoPT were included. Exclusion criteria were transient HypoPT, pseudo-HypoPT, persistent thyroid cancer with distant metastases, chronic glucocorticoid treatment. Data were retrieved from the electronic medical files of the eligible patients, as follows: demographic characteristics, age of onset of HypoPT, etiology of HypoPT, BMD evaluation by dual-energy X-ray absorptiometry, number and location of non-traumatic fractures after the diagnosis of HypoPT, pharmacological treatment for hypocalcemia, presence of osteoporosis, and presence of kidney stones. Mean levels of biochemical parameters at the first year after the diagnosis of HypoPT were recorded, including serum and urine calcium, serum creatinine and phosphorus, PTH and 25-hydroxyvitamin D [25(OH)D], and serum thyroid-stimulating hormone (TSH) .

Hypocalcemia was defined as an albumin-adjusted serum calcium concentration lower than 8.5 mg/dL. Corrected calcium-phosphorus (Ca-P) product was calculated according mean corrected serum calcium levels and mean phosphorus levels at the first year after the diagnosis.

The diagnosis of nephrolithiasis was based on clear documentation of past events and/or imaging studies revealing kidney stones.

The full cohort of hypoPT patients was divided by etiology. The patients in whom HypoPT occurred following neck surgery were matched for age, sex, and date of surgery to a control group of patients derived from the hospital's Thyroid Cancer Registry who underwent thyroidectomy due to thyroid cancer, had normal postoperative levels of calcium and PTH and had no evidence of persistent/ metastatic disease (flowchart of the study design and cohort description is depicted in Figure 1).

Most thyroid cancer patients were treated with a suppressive dose of levothyroxine. Suppressed TSH level was defined as level < 0.5 mIU/l.

All available digital radiological scans, ordered for different clinical indications, were independently reviewed by two members of the study team (G.T., I.S.S.) using the Clalit Health Services' PACS software. Presence of morphometric vertebral fractures was assessed according to the Genant method [18]. Only moderate and severe (grade 2 and 3) fractures were included. As the majority of the images were obtained for indications other than osteoporosis and were not always specifically targeted at the spine, we frequently couldn't confirm or exclude mild deformities (Grade 1 Genant criteria).

The first BMD evaluation was done after menopause and/or at an age older than 50 years in most patients. Osteoporosis was defined as a BMD T score of ≤ – 2.5SD in at least one skeletal site (lumbar spine, femoral neck, total hip, or distal radius) on dual energy X-ray absorptiometry. Since

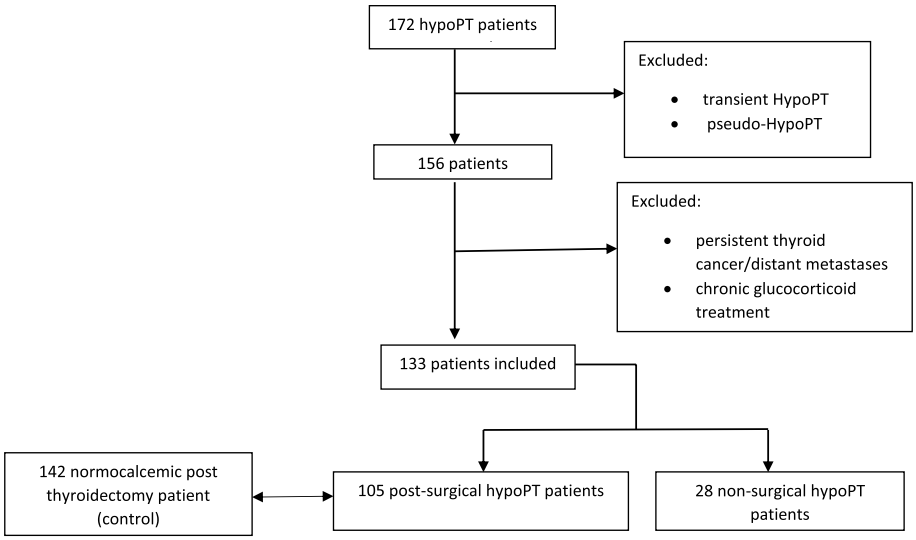

Fig. 1 Flowchart of study design and cohort description. *hypoPT* hypoparathyroid

BMD measurements were performed in different centers, only T-score results were analyzed. Due to a small number of examinations conducted at a younger age, tests with a Z-score were not included in the analysis.

Creatinine (normal range: males 0.67–1.17 mg/dl, females 0.51–0.95 mg/dl), serum phosphorus levels (normal range: 2.5–5 mg/dl), and serum and urine calcium levels (normal range: 8.5–10.5 mg/dl and 100–250 mg/24h, respectively) were measured using the AU5430 (until January 2014) or the 5800AU (since January 2014) chemistry analyzers (Beckman Coulter Inc., Atlanta, GA, USA). Corrected calcium-phosphorus (Ca-P) product was calculated according mean corrected serum calcium levels and mean phosphorus levels at the first year after the diagnosis.

Serum 25(OH) D level was measured using the LIAISON® 25 OH Vitamin D TOTAL assay (DiaSorin, Saluggia, Italy; normal range 75-250.0 nmol/L). Levels of TSH were measured by chemiluminescence assay (DPC 2000 Immulite; Siemens Healthcare Diagnostics, Eschborn, Germany; normal range 0.5–4.7 mIU/L). Serum PTH measurements were performed in different laboratories using different assays throughout the follow-up period. Therefore, PTH level is presented as a value above the lower normal limit (xLNL).

Statistical analysis

The statistical analysis for this paper was generated using SAS software, version 9.4.

Continuous variables are presented by means and standard deviations (SD), and categorical variables by number and percent. T-test was used to compare baseline continuous normally distributed variables between groups, and Wilcoxon test was used for continuous skewed variables. Fisher exact test was used to compare categorical variables between groups. The Kaplan Meier model with the Fine and Gray correction for death with no fracture as a competing risk was used to plot the cumulative incidence of fractures. Hazard ratios for fracture risk were computed using the Cox PH model with the Fine and Gray correction for the competing risk of death with no fracture. Two-sided *P* values less than .05 were considered statistically significant.

Results

Clinical and biochemical characteristics of the full cohort

A total of 133 patients (91% women, mean age 64 ± 13) met the inclusion criteria; 105 (79%) had post-thyroidectomy HypoPT (postsurgical HypoPT group) and in the remainder, HypoPT was due to various etiologies (nonsurgical HypoPT group). The baseline clinical and biochemical features stratified by HypoPT etiology are shown in Table 1.

Within the postsurgical HypoPT group, thyroid cancer was the most common reason for surgery, in 77 patients (73%). The remaining patients were operated for multinodular goiter (n = 20, 19%) and Graves' disease (n = 8, 8%). Within the nonsurgical HypoPT group, 14 patients had idiopathic HypoPT (50%); in 9 patients, HypoPT was due to autoimmune polyglandular syndrome type 1, in 2 patients, to autosomal dominant hypocalcemia, in other 2, to DiGeorge syndrome and in 1 patient, to thalassemia-major-induced hemosiderosis.

The postsurgical group was significantly older than the non-surgical group (mean age 47 vs 21 years, respectively, $p < 0.01$) with a predominance of females (80% vs 36%, $p < 0.05$). Biochemically, hypoPT in the non-surgical group was more severe, as reflected in lower serum calcium (7.2

Table 1 Clinical and biochemical characteristics of 133 patients with HypoPT stratified by etiology

Characteristics	Postsurgical HypoPT	Non-surgical HypoPT	*P* value
Number of patients, n (%)	105 (79)	28 (21)	
Female, n (%)	87 (80)	10 (36)	< 0.05
Age at diagnosis (years)	47 ± 13	21 ± 10	< 0.01
Follow-up (years)	21 ± 12	27 ± 12	0.09
Serum Ca at diagnosis (mg/dl)[a]	7.9 ± 0.6	7.2 ± 0.9	0.01
Minimal serum Ca (mg/dl)	6.9 ± 0.7	6.1 ± 0.9	< 0.01
Serum P at diagnosis (mg/dl)	4.7 ± 0.6	5.7 ± 1.1	< 0.01
Mean serum creatinine (mg/dl)	0.8 ± 0.3	0.8 ± 0.2	0.7
PTH level[b]	1.3 ± 1.3	0.5 ± 0.6	< 0.01
Vitamin 25(OH) D (nmol/l)	59 ± 27	54 ± 25	0.36
Urinary Calcium (mg/24 h)	273 ± 145	309 ± 176	0.02
Nephrolithiasis, n (%)	15 (14)	7 (25)	0.01
BMD evaluation n (%)	69 (66%)	7(25%)	< 0.01
Lumbar spine T score (SD)	−0.5 ± 2.1	−0.4 ± 1.5	0.47
Femoral neck T score (SD)	−0.6 ± 1.4	−0.5 ± 1.8	0.88
Fractures, n (%)	32 (31)	2 (7)	0.01
Treatment			
Mean Ca dose (mg)	1697 ± 884	2080 ± 942	0.17
Mean alphaD3 dose (mcg)	0.8 ± 0.5	1.5 ± 0.8	0.02
Patients prescribed HCTZ, n (%)	33 (30)	5 (18)	

Values are mean ± SD unless otherwise indicated

[a]Calcium values are corrected to albumin levels

[b]Data presented in values above low normal level (xLNL)

BMD bone mineral density; *Ca* calcium; *HypoPT* hypoparathyroidism; *P* phosphorus; *PTH* parathyroid hormone, *HCTZ* hydrochlorothiazide, *25(OH) D* 25-hydroxyvitamin D

± 0.9 vs 7.9 ± 0.6 mg/dl, p = 0.01), and PTH levels (0.5 ± 0.6 vs 1.3 ± 1.3 (xLNL), p < 0.01) and higher serum phosphorus (5.7 ± 1.1 vs 4.7 ± 0.6 mg/dl, < 0.01) and urinary calcium levels (309 ± 176 vs 273 ± 145 mg/24h, p = 0.02), respectively.

Clinically, nephrolithiasis was detected more frequently in the non-surgical group (25% vs 14%, p = 0.01). The mean BMD T scores were similar in both groups.

During the follow-up, fractures occurred in 32 patients (31%) in the postsurgical group and 2 (7%) in the nonsurgical group. Due to substantial differences in patients' features, mainly the much younger age of the non-surgical hypoPT patients, the variance in the pathophysiology of bone health between the surgical/nonsurgical hypoPT groups, and the very low number of fractures in the nonsurgical group (2 fractures throughout the study period), this group of patients was not included in the fracture risk analysis.

Postsurgical HypoPT vs postsurgical normocalcemic group, fracture risk analysis

The group of 105 patients with chronic postsurgical HypoPT was compared to a control group of 142 patients with a normal calcium and PTH levels after thyroidectomy, matched for age, sex, and date of surgery (table 2). There was no significant difference in the age at menopause between the two groups.

All patients were on levothyroxine therapy. As compared to normocalcemic patients, the HypoPT group had significantly higher levels of serum thyroid-stimulating hormone (TSH) because of a lower percentage of patients with a suppressed TSH < 0.5 mIU/l (57 (54%) vs 101 (71%) respectively, p = 0.008.

The mean BMD Tscores were significantly higher in the HypoPT group.

Spine imaging was available in 69 postsurgical HypoPT patients (66%) and in 90 (64%) control patients.

The fracture rate was 31% in the postsurgical hypoPT patients and 21% in the control group, but this difference did not reach statistical significance (p = 0.1). A higher percentage of fractures occurred after menopause in both groups: 78% in the HypoPT group and 67% in the control group.

On Cox proportional hazards regression analysis with correction for the competing risk of death with no fracture, older age and higher serum phosphorus levels, especially more than 5 mg/dl, were associated with an increased risk of fractures. Conversely, higher BMD and an older age at menopause had a protective effect (table 3).

Table 2 Clinical and biochemical characteristics of patients with postsurgical HypoPT and normocalcemic control patients

	HypoPT N = 105	Control N = 142	*P*-value
Female n (%)	83 (79)	117(82)	0.5
Age of diagnosis (years)[a]	47 ± 17	48 ± 15	0.3
Age of menopause (years)	49.4 ± 5.2	50 ± 4.1	0.3
Follow up to 1st fracture (years)	21 ± 15	19 ± 9	0.4
Serum calcium (mg/dl)[b]	7.9 ± 0.6	9.3 ± 0.5	< 0.01
Serum phosphorus (mg/dl)	4.7 ± 08	3.7 ± 0.6	< 0.01
Serum creatinine (mg/dl)	0.8 ± 0.3	0.8 ± 0.3	0.3
25(OH)D (nmol/l)	59 ± 27	51 ± 20	**0.03**
PTH[c]	1.3 ± 1.3	4.9 ± 3.4	< 0.01
TSH (mIU/l)	1.7 ± 4.5	0.6 ± 0.9	**0.01**
BMD evaluation n (%)	69 (63)	60 (40)	**< 0.05**
Lumbar spine T score (SD)	−0.5 ± 2.1	−1.5 ± 1.0	**< 0.01**
Femoral neck T score(SD)	−0.6 ± 1.4	−1.4 ± 0.9	**< 0.01**
Osteoporosis, n (%)	20 (19)	35 (24.6)	0.35
Fractures, n (%)	32 (31)	30 (21)	0.1
Fractures after menopause, n (%)	25 (78)	20 (67)	0.2

Bold value indicates significant finding (p<0.05)

Data are presented as mean ± SD unless otherwise indicated

[a]Date of diagnosis = date of surgery

[b]Calcium values are corrected to albumin levels

[c]Data presented in value above low normal level (xLNL)

The mean corrected Ca-P product was 37±5 mg^2/dl^2. It was not associated with fracture risk.

The mean duration of follow-up from the date of diagnosis to the first event of fracture was 21±15 and 19±9 years, respectively ($P = 0.4$).

The distribution of fracture sites is shown in Figure 2. The spine was the most common site of fractures in both HypoPT (n = 16, 50%) and the control group (n = 21, 70%). The majority of vertebral fractures were non-clinical morphometric: 10 (63%) and 17 (81%), respectively. The rate of femoral neck fracture was low in both groups (n = 4, 11% and n = 3, 9%, respectively), and rib fractures were more common in the HypoPT group (n = 6, 17%) than in the control group (n = 2, 6%).

Osteoporosis treatment was administered to 25 patients (24%) in the HypoPT group and 34 (24%) in the control group. Seven patients with HypoPT (28%) and 1 control patient (3%) received teriparatide. The remaining patients with HypoPT received bisphosphonates, for a mean duration of 5.2±3.1 years. Among the remaining patients in the control group, 30 received oral and parenteral bisphosphonates and 4 were treated with denosumab.

The annual incidence of fractures was similar in both groups also after excluding patients who received bone-active therapy. (Figure 3).

During follow-up, 42 patients died: 18 in the HypoPT group (17.1%), and 24 in the control group (16.9%) The main causes of death were cardiovascular disease and malignancy.

Table 3 Risk of fractures according to hypoparathyroidism in patients after total thyroidectomy

Parameter	Hazard ratio	95% Confidence interval	*P*-value
Sex male	0.23	0.069–1.303	0.079
Smoking	1.77	0.554–5.67	0.33
Age at diagnosis	1.05	1.02–1.07	< 0.01
Age at menopause	0.88	0.77–0.99	0.037
PTH	0.87	0.65–1.16	0.35
Vitamin 25(OH)D[a]	0.99	0.98–1.01	0.39
TSH level	1.01	0.95–1.08	0.65
Calcium blood level[b]	0.66	0.36–1.19	0.17
Phosphorus blood level[b]	1.56	1.08–2.27	0.02
Phosphorus blood level > 5 mg/dl	2.23	1.06–4.67	0.03
Calcium-Phosphorus product[c]	1.06	0.99–1.12	0.07
Spine T score	0.73	0.57–0.92	< 0.01
Femoral neck T score	0.69	0.49–1.00	0.05

PTH parathyroid hormone; *TSH* thyroid stimulation hormone

[a]First available biochemical value after the date of diagnosis

[b]Mean level at the first year after thyroidectomy

[c] Corrected Ca-P product of mean corrected blood calcium and mean phosphorus levels at the first year after thyroidectomy

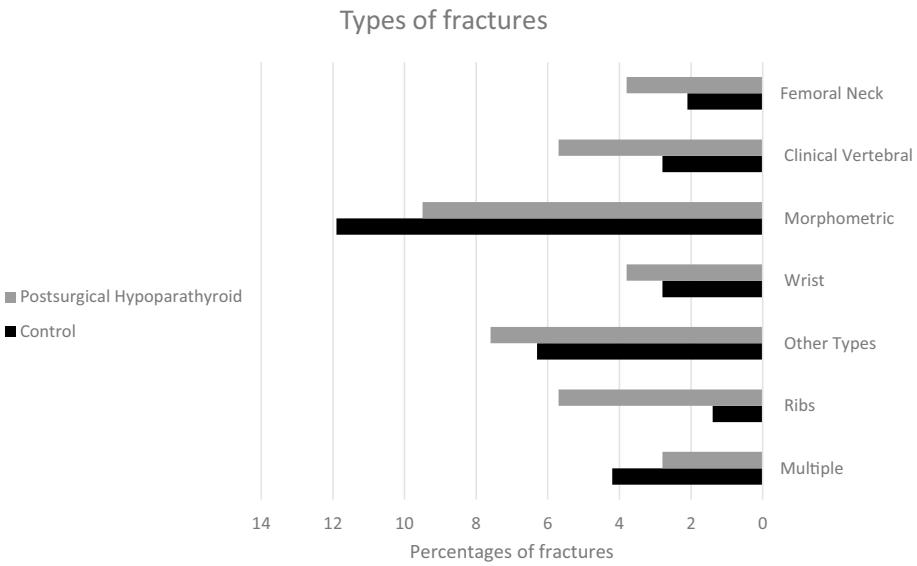

Fig. 2 Distribution and types of fractures in patients with postsurgical HypoPT and postsurgical normocalcemic control subjects. Other types included fractures of the humerus, pelvis, and ankle

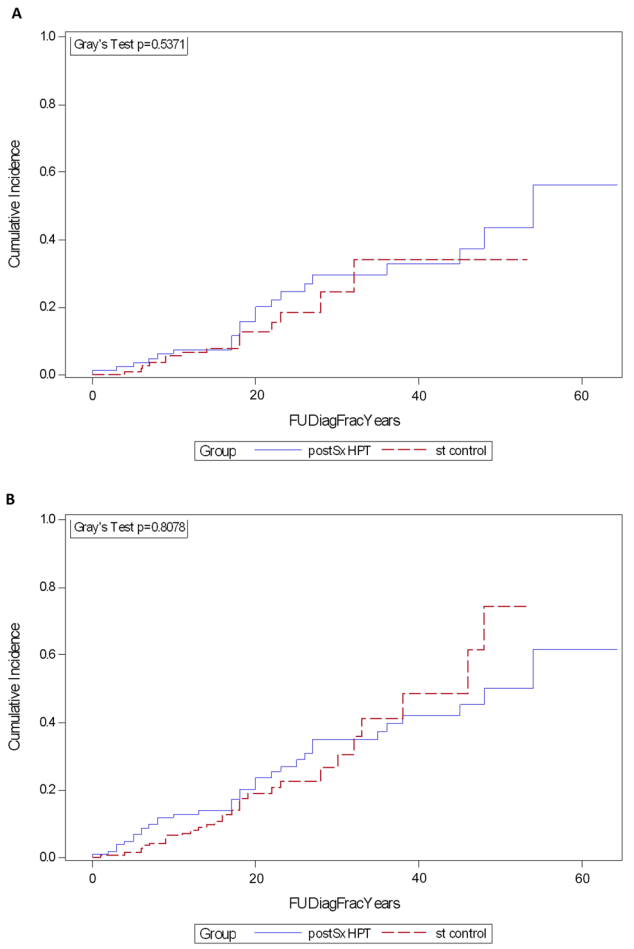

Fig. 3 Incidence of all types of fractures in patients with postsurgical HypoPT compared to postsurgical normocalcemic control subjects. **A** including patients who received bone-active treatment. **B** excluding patients who received bone-active drugs

Discussion

The present study showed that although patients with postsurgical HypoPT had generally higher BMD than patients who were normocalcemic after thyroidectomy, there was no significant difference in the fracture rate between the two groups over a long-term follow-up period.

Data in the literature on the association of fracture risk with HypoPT are non-conclusive. Several large retrospective population-based studies investigated complications of HypoPT, including fracture incidence. One of the studies reported a reduced risk of upper extremity fractures in patients with postsurgical HypoPT, but the incidence of fractures in other skeletal sites did not differ from the control group [3]. Another study, limited to patients with nonsurgical HypoPT, found no overall increase in fracture risk [17]. In two smaller studies, the prevalence of morphometric vertebral fractures was increased in postmenopausal women with chronic postsurgical HypoPT [14, 15]. A recently published small cross -sectional study did not find a higher risk of morphometric vertebral fractures in postsurgical hypoPT women compared to controls. However, the absolute number of fractures was very low in both groups [20]. Chawla et al. [16] detected a high prevalence of silent vertebral fractures in patients with idiopathic HypoPT. Factors associated with fractures in this study were prolonged use of anticonvulsants and menopause. A meta-analysis of pooled data revealed a twofold increased risk of vertebral fractures in patients with nonsurgical HypoPT but not in patients with postsurgical HypoPT [21]. However, this analysis showed relatively high heterogeneity. In some studies, data on fractures was solely based on hospital discharge codes, and not categorized as high-trauma/osteoporotic fractures.

In the whole cohort of patients with HypoPT in the present study, 79% had surgical etiology of HypoPT. Most patients in our postsurgical HypoPT group were women (80% vs 36% in the nonsurgical group). These findings are in concordance with other studies regarding hypoPT and gender distribution in surgical/nonsurgical hypoPT [3, 19].

Of 28 patients with nonsurgical HypoPT, only 2 (7%) sustained fractures during follow-up. The younger age of these patients and the different pathophysiology of bone health could explain the low prevalence of fractures in our study.

We found relatively high fractures rate in HypoPT group and normocalcemic control (31% and 21% respectively).

In a large nationwide survey of 688 Danish patients with postsurgical HypoPT, a 15% incidence of any fractures in the HypoPT and control groups was reported [3]. Longer follow up and prolonged suppressive levothyroxine treatment for thyroid cancer in most of the hypoPT and control group patients may explain the higher rate of fractures in our study.

Fujiyama et al. [10] suggested that hypoparathyroidism provides protection against accelerated bone loss in postmenopausal women, resulting in reduced bone fragility. In line with this report and several others [22, 23], the BMD values in our patients with HypoPT patients were significantly higher than in the normocalcemic control subjects.

Nevertheless, the fractures rate in the hypoparathyroid group was unexpectedly higher than anticipated, despite having higher bone density and the absence of parathyroid hormone (31% vs 21% in normocalcemic group). Yet, the difference did not reach a statistical significance. The annual fracture incidence was comparable in both groups, irrespective of whether specific treatment for osteoporosis was administered or not.

Similarly, to previous small studies [14, 15], patients with HypoPT in our study had a high rate of vertebral fractures (50% of all fractures), mostly nonclinical morphometric fractures. However, in contrast to the study of Underbjerg et al. [3], we found no difference in fracture rates in the upper extremity fractures (humerus, wrist) between patients with/without HypoPT after surgery.

Vertebral fractures are the most common osteoporotic fractures and are associated with a high risk of subsequent fractures [24]. Trabecular bone has a large surface exposed to the bone marrow and blood flow and a higher turnover than cortical bone. Hormones and medication may have different effects on different types of bones. Accordingly, the estrogen decrease in women after menopause is associated with a rapid loss of trabecular bone but not cortical bone [25]. Therefore, the population of the present study, which consisted mostly of postmenopausal women, can explain the relatively high incidence of vertebral fractures.

Notably, despite the significantly lower TSH level in the control patients, (caused by suppressive levothyroxine therapy) and therefore, theoretically, their higher risk of fracture, there was no between-group difference in the prevalence or annual incidence of fractures.

On Cox proportional hazards regression analysis, higher serum phosphorus level, especially more than 5 mg/dl, was the most significant predictor of fractures. This finding is in concordance with the findings in a Dutch study, which investigated the association of serum phosphate level and fracture risk [26].

Several possible pathways, underlying the relation between phosphate levels and bone metabolism, could be hypothesized, including direct effect of phosphorus on osteoblast apoptosis [27] as well as inhibition of bone resorption [28].

No association was found between the corrected Ca-P product and the occurrence of fractures. However, all our patients had corrected Ca-P product less than 55 mg^2/dl^2.

Our study has several strengths and limitations. A major strength is the availability of clinical, biochemical, and imaging data at diagnosis and throughout follow-up in a relatively large cohort of patients with HypoPT managed at a single large endocrine institute. Another strength of our study is the well-matched control group. The main limitation of our study is the retrospective design with its inherent risk of missing data. Incomplete radiological evaluation and exclusion of mild vertebral fractures limits an unbiased interpretation of the results, which likely underestimates the true prevalence of vertebral fractures. The finding that some patients received osteoporosis treatment at different periods of follow-up could confound the results obtained. However, no significant association was found between the osteoporosis treatment and fractures. Only a few patients were treated with PTH (1-34), so its impact on fracture prevention was unclear.

In conclusion, this study suggests that the relatively high BMD in patients with chronic HypoPT is not associated with a lower fracture risk. As clinically undiagnosed vertebral fractures are common, spinal imaging should be routinely performed in patients with HypoPT. Due to increased risk of fractures, early recognition and treatment consideration is prudent.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Research involving human participants and / or animals The study was performed in accordance with the ethical standards of the responsible committee on human experimentation at the Rabin Medical Center and Israel, and with the Helsinki declaration of 1964 and later versions.

Informed consent For this type of study formal consent was not required.

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