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Age, gender, and BMI in presentation of primary hyperparathyroidism: a single-center experience

Katarina Mlekus Kozamernik [1, 2], ***Gaj Vidmar*** [2–4], ***Mojca Jensterle Sever*** [1, 2], ***Luka Lezaic*** [2, 5], ***Marko Hocevar*** [2, 6], ***Soncka Jazbinsek*** [2, 7], ***Katarina Remec*** [2, 8], ***Andrej Janez*** [1, 2], ***Tomaz Kocjan*** [1, 2]

[1]*Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center Ljubljana, Ljubljana, Slovenia*
[2]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[3]*University Rehabilitation Institute, Ljubljana, Slovenia*
[4]*FAMNIT, University of Primorska, Koper, Slovenia*
[5]*Department of Nuclear Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia*
[6]*Institute of Oncology Ljubljana, Ljubljana, Slovenia*
[7] *Department of Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, University Medical Center Ljubljana, Ljubljana, Slovenia*
[8]*Department of Vascular Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia*

Abstract

Background: Primary hyperparathyroidism (PHPT) is a relatively common disease with considerable heterogeneity. We aimed to assess the impact of age, gender, and body mass index (BMI) on the presentation of PHPT.

Material and methods: We retrospectively analyzed the baseline biochemical status, symptoms, renal manifestations, and bone mineral density (BMD) of patients diagnosed with PHPT at the national tertiary endocrine referral clinic from January 2004 to December 2016.

Results: We included 415 patients [333 women (41 premenopausal, 292 postmenopausal) and 82 men] with PHPT, aged 64 years on average [standard deviation (SD) 13, range 19–89 years], with an average BMI of 28.4 (SD 6.0, range 11.2–51.1 kg/m^2). Older age was statistically significantly associated with milder biochemical presentation — lower total and corrected calcium (standardized regression coefficient $\beta = -0.17$, $p < 0.001$ and $\beta = -0.12$, $p = 0.018$). In comparison with premenopausal women, postmenopausal women [estimated odds ratio (OR) = 8.6, 95% confidence interval (CI): 3.9–20.8; $p < 0.001$] and men (OR = 5.9, 95% CI: 2.5–15.6; $p < 0.001$) were more likely to suffer from skeletal manifestations of PHPT. Renal manifestations were less likely among postmenopausal than premenopausal women (OR = 0.4, 95% CI: 0.2–0.8; $p = 0.014$). BMI was negatively associated with skeletal and renal manifestations (OR = 0.94 per unit change, $p = 0.002$) and symptomatic presentation (OR = 0.96 per unit change, $p = 0.012$).

Conclusion: Older patients with PHPT presented with a biochemically less florid disease. Postmenopausal women and men with PHPT were more likely to suffer from skeletal manifestations of PHPT than premenopausal women. Patients with higher BMI had fewer skeletal and renal manifestations of PHPT and were less likely to be symptomatic. **(Endokrynol Pol 2025; 76 (4): 450–456)**

Keywords: *primary hyperparathyroidism; age; gender; BMI; hypercalcemia; osteoporosis*

Introduction

Primary hyperparathyroidism (PHPT) is a relatively common disease the incidence of which increases with age, especially among older women. Characteristic clinical manifestations are hypercalcemia, osteoporosis with fractures, nephrolithiasis, depression, and gastrointestinal problems. There is a substantial symptomatic and biochemical heterogeneity in patients diagnosed with PHPT. The geographical influence on the presentation of PHPT is well known, with a high prevalence of patients with non-classic symptoms or asymptomatic PHPT in Western countries and symptomatic PHPT in countries where screening biochemistries are not routinely used as part of the health care system [1].

An association between patients' age and PHPT presentation has been reported [2–4]. The differences in presentation are especially pronounced between the pediatric and adult populations [5, 6]. The data on differences among adults of different age groups are conflicting [3, 7–9]. The impact of gender on PHPT expression has been proposed. There seem to be no significant differences in the severity of biochemical presentation between women and men [10, 11]. The data regarding the symptomatic presentation between women and men are conflicting [10, 12–14]. There is little evidence of the impact of BMI on the clinical presentation of PHPT. Studies have analyzed the effect of body mass index (BMI) on calciuria, osteoporosis, symptomatic presentation, the size of parathyroid

Katarina Mlekuš Kozamernik, MD, Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center Ljubljana, Zaloska 7, SI-1525 Ljubljana, Slovenia, tel: +386 1 522 3114, fax: +386 1 522 2136; e-mail: katarina.mlekuskozamernik@kclj.si

adenomas, the risk for persistent or recurrent PHPT, and the incidence of multiglandular disease (MGD) [15–18]. We aimed to establish the presenting pattern in a sizeable cohort of PHPT patients, considering their age, gender, and BMI.

Materials and methods

Study design

A retrospective cross-sectional study was conducted from January 2004 to December 2016 at the national tertiary endocrine referral center. It was conducted according to the Declaration of Helsinki and approved by the National Medical Ethics Committee, ID 0120-353/2018/6. Due to the retrospective nature of the study, informed consent was waived.

Patients

Patients with confirmed PHPT (hypercalcemia > 2.6 mmol/L) with elevated or inappropriately normal intact parathyroid hormone (iPTH) level or normal calcium with persistently elevated iPTH level without a secondary cause (normocalcaemic hyperparathyroidism) over 18 years of age were eligible for enrolment. To exclude secondary causes of hyperparathyroidism, patients were supplemented with vitamin D as needed, and the estimated glomerular filtration rate (eGFR) was calculated. Interfering drugs were stopped when possible (e.g., thiazides, indapamide) or taken into account (e.g., bisphosphonates, denosumab) when interpreting the laboratory results. Demographic characteristics, including age, gender, and BMI, were collected from the study participants' medical records. We also analyzed their baseline clinical data, consisting of biochemical status, presenting symptoms (symptomatic hypercalcemia, renal colic, musculoskeletal pain, gastrointestinal symptoms, psychiatric problems), renal manifestations [nephrolithiasis, nephrocalcinosis, whereby 312 (75%) patients underwent an ultrasound of the urinary tract], and skeletal involvement [defined as osteoporosis as diagnosed by dual-energy X-ray absorptiometry (DXA) and/or clinical osteoporotic fractures]. All but four patients who did not meet the criteria for surgical treatment underwent parathyroid imaging with neck ultrasound. A further attempt to identify enlarged parathyroid gland(s) was made in 385 (93%) patients with technetium-99m (99m-Tc) sestamibi scintigraphy, while 69 (17%) patients also had ^{11}C-choline positron emission tomography/computed tomography (PET/CT). Treatment was surgical in 333 (80%) patients and medical in 29 (7%) asymptomatic patients who did not meet the criteria for surgery, as well as in 53 (13%) patients who did not agree to surgery or were not suitable candidates because of their comorbidities.

Biochemical analysis

In addition to routine biochemistry with total serum calcium, ionized calcium, and urinary creatinine and calcium, laboratory data gathered included baseline iPTH and 25-hydroxy vitamin D (25OH vitamin D). Albumin-adjusted calcium was calculated. Serum iPTH levels (reference range 12–65 ng/L) were determined with a second-generation chemiluminescent immunometric assay (Immulite 2000 Intact PTH test on an Immulite 2000 analyzer by Siemens Healthcare Diagnostics Products Ltd., United Kingdom). Serum 25OH vitamin D levels (reference range: deficient: < 50 nmol/L, insufficient: 50–74 nmol/L, sufficient: > 75 nmol/L) were determined with competitive chemiluminescent immunoassay (IDS-iSYS 25-Hydroxy Vitamin D^{S}") test on an iSYS analyzer by Immunodiagnostic Systems Ltd,, United Kingdom. eGFR was calculated from the CKD EPI equation using the eGFR calculator at www.kidney.org.

Dual-energy X-ray absorptiometry (DXA)

BMD measurements of the lumbar spine (LS), total hip (TH), femoral neck (FN), and distal third of the non-dominant radius (1/3R) were performed by dual-energy X-ray absorptiometry (DXA; Discovery, Hologic, Waltham, MA) at baseline. Osteoporosis was diagnosed according to the World Health Organization (WHO) criteria. This method's precision [coefficient of variation (CV)] at LS, TH, FN, and 1/3R was 0.6%, 1.1%, 1.3%, and 1.5%, respectively.

Statistical analysis

Descriptive statistics were tabulated for all the studied variables. The effects of gender, menopausal status, and age were assessed using regression models (linear for numeric outcomes, logistic with Firth bias correction for binary outcomes). Linear regression models were fitted using age and gender as predictors. Firth logistic regression models were fitted using group (coded via two indicator variables for both groups of women, i.e., men as the reference group) and BMI as predictors.

Results

Patient characteristics

We included 415 patients (333 women and 82 men) with PHPT, aged 64 years on average [standard deviation (SD) 13, range 19–89 years], with an average BMI of 28.4 (SD 6.0, range 11.2–51.1 kg/m^2). Forty-one (12%) women were premenopausal, and 292 (88%) were postmenopausal. The mean time since menopause had been 16 years (range 1 to 60 years). Table 1 summarizes baseline clinical characteristics, biochemical parameters, renal manifestations, and symptomatic presentation for the three studied groups (premenopausal women, postmenopausal women, and men). Table 2 summarizes baseline BMD with T-scores of the LS, TH, FN, and 1/3R, as well as the number and site of osteoporotic fractures for each studied group. The observed proportion of skeletal manifestations in premenopausal women was 20%, in postmenopausal women 68%, and in men 56%.

Biochemical measurements

After adjustment for gender, age was statistically significantly negatively associated with total calcium (standardized regression coefficient $\beta = -0.17$, $p < 0.001$), corrected calcium ($\beta = -0.12$, $p = 0.018$), urinary calcium ($\beta = -0.32$, $p < 0.001$), and eGFR ($\beta = -0.38$, $p < 0.001$) and positively associated with phosphate ($\beta = 0.15$, $p = 0.002$; Tab. 3). The negative association of age with total calcium and eGFR for both genders is illustrated in Figure 1.

Skeletal manifestations, renal manifestations, and symptomatic presentation

The results of the logistic regression models are summarized in Table 4. In comparison with premenopausal women, postmenopausal women (estimated odds ratio OR = 8.6, $p < 0.001$) and men (OR = 5.9, $p < 0.001$) were more likely to suffer from skeletal manifestations

Table 1. *Clinical characteristics and biochemical parameters of the patients by gender and menopausal status at baseline*

Characteristic*	Premenopausal women (n = 41)	Postmenopausal women (n = 292)	Men (n = 82)	Total sample (n = 415)
Age at diagnosis [years]	42.5 (8.7)	67.2 (9.6)	62.0 (15.5)	63.8 (13.2)
	43.8 [23, 58]	68.2 [39, 89]	67.3 [19, 84]	66.8 [19, 89]
BMI [kg/m^2]	27.4 (7.8)	28.5 (5.8)	28.4 (5.7)	28.4 (6.0)
	26.0 [16.3, 51.1]	27.8 [11.2, 50.6]	27.5 [16.8, 49.4]	27.6 [11.2, 51.1]
Total calcium	2.83 (0.33)	2.74 (0.26)	2.84 (0.27)	2.77 (0.27)
	2.74 [2.38, 3.86]	2.70 [2.34, 4.65]	2.78 [2.49, 3.60]	2.71 [2.34, 4.65]
Corrected calcium	2.75 (0.35)	2.68 (0.26)	2.78 (0.29)	2.70 (0.28)
	2.66 [2.33, 3.91]	2.63 [2.37, 4.53]	2.72 [2.31, 3.69]	2.66 [2.33, 4.53]
Urinary calcium	8.43 (4.90)	6.24 (4.34)	7.59 (4.91)	6.76 (4.58)
	7.65 [0.90, 22.40]	5.60 [0.10, 23.10]	6.68 [0.10, 17.50]	6.00 [0.10, 23.10]
eGFR	96.9 (24.0)	74.7 (21.0)	78.7 (26.2)	77.7 (23.3)
	107.5 [45, 128]	76.0 [19, 119]	75.5 [22, 130]	78.0 [19, 130]
25(OH) vitamin D	46.1 (22.6)	40.3 (22.2)	41.8 (18.7)	41.2 (21.6)
	42.0 [3, 96]	37.0 [7, 138]	40.6 [8, 83]	39.0 [3, 138]
iPTH	277 (480)	222 (302)	255 (322)	234 (327)
	139 [48, 2958]	147 [39, 3566]	152 [34, 2379]	148 [34, 3566]
Phosphate	0.77 (0.16)	0.85 (0.16)	0.73 (0.16)	0.82 (0.17)
	0.76 [0.45, 1.17]	0.87 [0.28, 1.36]	0.74 [0.32, 1.16]	0.82 [0.28, 1.36]
Renal manifestations	20 (49%)	81 (28%)	31 (38%)	132 (32%)
Symptomatic presentation	16 (39%)	148 (51%)	34 (41%)	198 (48%)

BMI — body mass index; eGFR — estimated glomerular filtration rate; iPTH — intact parathyroid hormone; *numerical variables are reported as mean (SD); median [minimum, maximum]

of PHPT. At the same time, they did not differ statistically significantly between each other (p = 0.196).

Renal manifestations were less likely among postmenopausal than premenopausal women (OR = 0.41, p = 0.014), while neither group differed statistically significantly from men (p = 0.353 for premenopausal women, p = 0.069 for postmenopausal women). The odds for symptomatic presentation (as opposed to asymptomatic) were not statistically significantly different between those three groups (p-values > 0.1).

BMI was negatively associated with skeletal manifestations (OR = 0.94 per unit change, p = 0.002), renal manifestations (OR = 0.94 per unit change, p = 0.002), and symptomatic presentation (OR = 0.96 per unit change, p = 0.012). Figure 2 depicts the observed difference in BMI distribution according to skeletal manifestations, renal manifestations, and symptomatic presentation, respectively, in the total sample.

Discussion

Older adults in the cohort had biochemically milder disease, which concurs with most studies. In the study of Oltmann et al., young patients had the highest serum and urinary calcium levels [7]. In contrast, Castellano et al. found no differences in the mean serum PTH, calcium, or vitamin D levels between younger and older patients [4]. However, urinary calcium levels were also significantly lower in older adults, and renal involvement was considerably less frequent [4]. Similarly, Mollerup et al. found younger patients had more stone episodes than older patients [8]. Arya et al. showed that in India, premenopausal women with PHPT generally had more severe clinical and biochemical variables than postmenopausal women [9].

This can be partly explained by increasing chronic kidney disease (CKD) prevalence with age, which was also evident in our group. CKD is associated with impaired renal biosynthesis of 1 ,25$(OH)_2$D. Furthermore, older age is associated with decreased levels of vitamin D receptor (VDR), 25-hydroxyvitamin D-1 -hydroxylase (CYP27B1), and 24-hydroxylase (CYP24A1), while the PTH levels in human parathyroid glands are increased [19]. It has been shown that 1,25$(OH)_2$D inhibits the synthesis and secretion of PTH and prevents the proliferation of parathyroid glands [20]. Our findings could also be explained by age-related decreases in expression of the PTH/PTHrP receptor type 1 (PTHR1)

Table 2. *Skeletal outcomes by gender and menopausal status at baseline*

Characteristic*	Premenopausal women (n = 41)	Postmenopausal women (n = 292)	Men (n = 82)	Total sample (n = 415)
Bone mineral density				
Lumbar spine	0.96 (0.15) 0.95 [0.59, 1.27]	0.83 (0.16) 0.81 [0.49, 1.24]	0.96 (0.18) 0.93 [0.68, 1.44]	0.87 (0.17) 0.85 [0.49, 1.44]
Lumbar spine (T-score)	–0.99 (1.27) –1.00 [–4.20, 1.90]	–2.06 (1.43) –2.20 [–5.10, 1.70]	–1.16 (1.61) –1.35 [–3.70, 3.20]	–1.76 (1.52) –1.90 [–5.10, 3.20]
Total hip	0.93 (0.14) 0.92 [0.63, 1.27]	0.79 (0.14) 0.79 [0.34, 1.23]	0.91 (0.17) 0.92 [0.17, 1.35]	0.83 (0.16) 0.83 [0.17, 1.35]
Total hip (T-score)	–0.13 (1.18) –0.15 [–2.60, 2.70]	–1.31 (1.15) –1.30 [–4.90, 2.40]	–0.74 (1.06) –0.70 [–3.00, 2.10]	–1.06 (1.20) –1.10 [–4.90, 2.70]
Femoral neck	0.76 (0.13) 0.75 [0.48, 1.00]	0.65 (0.11) 0.64 [0.38, 1.16]	0.73 (0.12) 0.72 [0.51, 1.11]	0.68 (0.13) 0.67 [0.38, 1.16]
Femoral neck (T-score)	–0.85 (1.13) –0.90 [–3.30, 1.40]	–1.85 (1.01) –1.90 [–4.30, 2.80]	–1.46 (0.87) –1.50 [–3.10, 1.30]	–1.66 (1.05) –1.70 [–4.30, 2.80]
Distal radius	0.65 (0.09) 0.66 [0.38, 0.80]	0.55 (0.09) 0.55 [0.31, 0.79]	0.70 (0.08) 0.70 [0.51, 0.95]	0.59 (0.11) 0.59 [0.31, 0.95]
Distal radius (T-score)	–0.78 (1.41) –0.50 [–5.20, 1.80]	–2.45 (1.46) –2.40 [–6.30, 1.60]	–2.30 (1.41) –2.30 [–5.80, 1.30]	–2.24 (1.52) –2.20 [–6.30, 1.80]
Skeletal manifestations**	8 (20%)	187 (68%)	44 (56%)	239 (61%)
Clinical vertebral fractures	0 (0%)	23 (8%)	2 (2%)	25 (6%)
Hip fractures	0 (0%)	29 (10%)	1 (1%)	30 (7%)
Nonvertebral fractures	1 (2%)	29 (10%)	2 (2%)	32 (8%)

*numerical variables are reported as mean (SD); median [minimum, maximum]; **osteoporosis as diagnosed by dual-energy X-ray absorptiometry (DXA) and/or clinical osteoporotic fractures

Table 3. *Summary of multiple linear regression models for numerical outcomes*

Outcome	Model		Age		Gender	
	p	$R^2_{adjusted}$	p	β*	p	$b/SD_{outcome}$**
Total calcium	< 0.001	0.04	< 0.001	–0.17	0.031	–0.27
Corrected calcium	0.003	0.03	0.018	–0.12	0.021	–0.29
Urinary calcium	< 0.001	0.11	< 0.001	–0.32	0.147	–0.18
eGFR	< 0.001	0.14	< 0.001	–0.38	0.479	0.08
Phosphate	< 0.001	0.08	0.002	0.15	< 0.001	0.58

eGFR — estimated glomerular filtration rate; *standardized regression coefficient (predicted outcome change in SD units if predictor increases by 1 SD); **estimated difference in outcome mean in SD units between women and men (positive value indicates higher average among women, negative value among men)

gene, PTH activation of cAMP response element binding protein (CREB), and PTH stabilization of -catenin [21]. The resorption of bones in PHPT is mediated through RANKL signaling [22]. We can assume that bone response to RANKL is age dependent because it has been shown that younger patients (who were still older than 50 years or postmenopausal) treated with denosumab have more significant bone loss after treatment discontinuation than their older counterparts [23]. Whether we can extrapolate this information to premenopausal women and men younger than 50 years is unknown.

Unsurprisingly, there was more severe skeletal impairment in our older patients. As numerous factors influence the development of osteoporosis, we assessed whether these differences were more significant in PHPT patients than in patients with primary osteoporosis. As can be seen from our results, the estimated odds ratio for osteoporosis in postmenopausal women *vs*. premenopausal women was 8.6, which is obviously

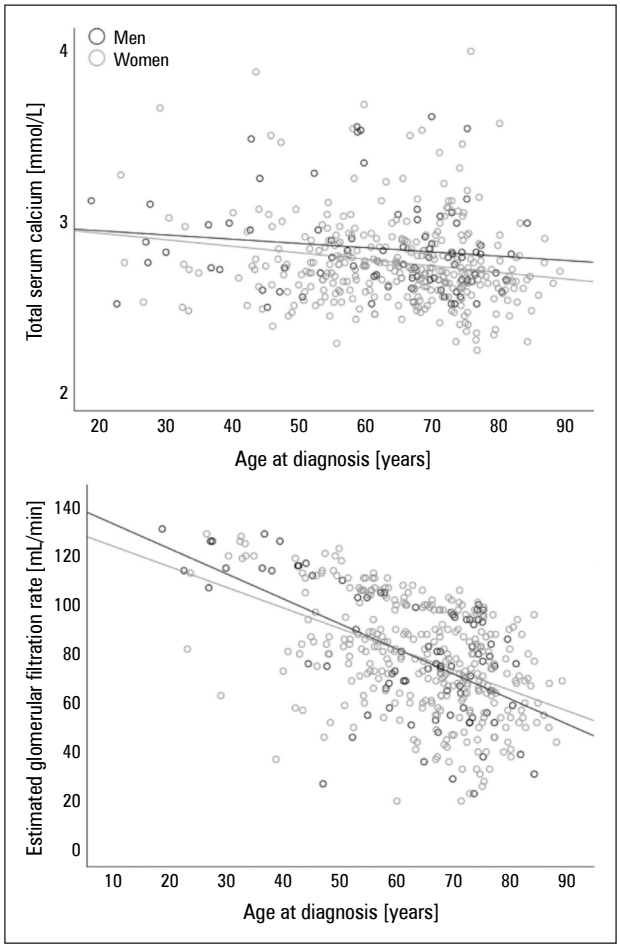

Figure 1. *Association of age with total calcium (top) and estimated glomerular filtration rate (eGFR) (bottom) for both sexes*

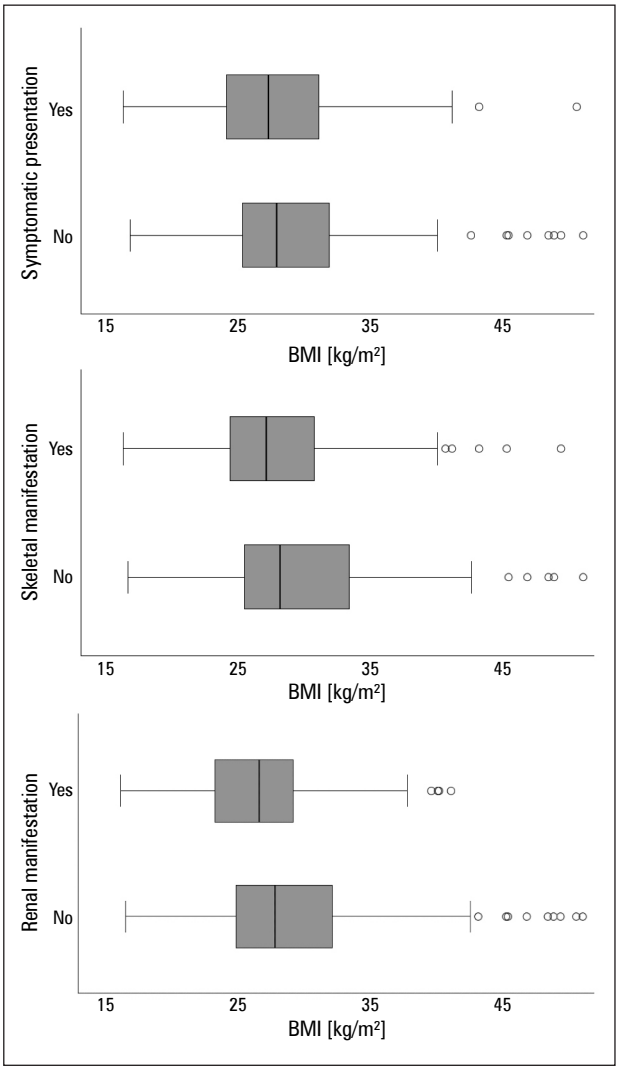

Figure 2. *Distribution of body mass index (BMI) among primary hyperparathyroidism (PHPT) patients with and without skeletal manifestations (top), among patients with and without renal manifestations (middle), and among symptomatic and asymptomatic patients (boxplots: vertical line — median, box — interquartile range, whiskers — non-outlier range, circles — outliers)*

higher than a reported odds ratio from the study of primary osteoporosis (in women with SOX6 rs29732 variant), in which the odds ratio was 1.48 (95% CI: 1.04–2.10) [24]. Therefore, the differences between premenopausal and postmenopausal women with PHPT appear to be larger than in women without PHPT.

Table 4. *Summary of Firth logistic regression models for binary outcomes*

Outcome	Model p*	Predictor	Post- *vs.* premenopausal women	Men *vs.* premenopausal women	Postmenopausal women *vs.* men	BMI [kg/m²]
Skeletal manifestations***	< 0.001	p	< 0.001	< 0.001	0.196	0.002
		OR (95% CI)**	8.56 (3.90, 20.78)	5.95 (2.47, 15.63)	1.44 (0.83, 2.48)	0.94 (0.90, 0.98)
Renal manifestations	< 0.001	p	0.014	0.353	0.069	0.002
		OR (95% CI)	0.41 (0.20, 0.83)	0.69 (0.31, 1.52)	0.60 (0.35, 1.04)	0.94 (0.90, 0.98)
Symptomatic presentation	0.025	p	0.146	0.715	0.172	0.012
		OR (95% CI)	1.67 (0.84, 3.41)	1.16 (0.52, 2.61)	1.44 (0.85, 2.44)	0.96 (0.92, 0.99)

BMI — body mass index; OR — odds ratio; CI — confidence interval; *from likelihood ratio test; **estimated odds ratio with 95% confidence interval (per unit change for BMI); ***osteoporosis as diagnosed by dual-energy X-ray absorptiometry (DXA) and/or clinical osteoporotic fractures

Presumably, a higher estrogen level means lower sensitivity of bones to PTH, which was already suggested in animal studies [25].

Our patients with higher BMI were less prone to skeletal manifestations of PHPT, which is in agreement with the study by Tran et al. [15]. This is also in accordance with the general population, in which obese people have a lower prevalence of osteoporosis [26]. The proposed mechanisms are higher estradiol levels and higher mechanical loads in obese people [27]. There seems to be a BMI-dependent response of osteoclasts to RANKL, as patients with lower BMI were shown to have a more significant bone loss after denosumab discontinuation [28, 29]. Similarly, bariatric procedures with the highest weight loss have been associated with the highest turnover bone loss and fracture risk [30]. Comparably to high estrogen status before menopause, a higher BMI could mean lower bone turnover and lower sensitivity of bones to PTH. In contrast, in a study by Tutaworn et al., higher BMI was associated with a more significant decrease in TH BMD upon denosumab discontinuation [31].

In our study, patients with higher BMI were shown to be less symptomatic, contrasting with the study by Adam et al., in which obesity was associated with a higher frequency of depression, musculoskeletal symptoms, weakness, gastroesophageal reflux disease, and higher PTH levels [16].

The odds for symptomatic presentation were not statistically significantly different between men and women. However, Castellano et al. found men to be more frequently symptomatic [10]. In contrast, in the study of Mazeh et al., men more often presented without symptoms [12]. Increased risk for pancreatitis in men with PHPT has been described [3, 8, 11]. Also, several data reveal that nephrolithiasis is more frequent in men than in women with PHPT [3, 8, 12, 14]. We used the term asymptomatic for patients who lacked apparent signs and symptoms, which could refer to a high calcium or parathyroid hormone level. We did not assess our patients with quality of life (QoL) questionnaires, so we could have missed more subtle signs and symptoms such as depression, cognitive impairment, easy fatigability, and weakness.

Men in our study had statistically significantly more skeletal manifestations than premenopausal women. This agrees with the study by Vodopivec et al., in which men had more severe bone disease at presentation [13]. This could be attributed to delayed PHPT diagnosis in men, who were shown to seek medical attention less often [32]. The effect of testosterone *vs*. estrogen on bones can also explain the differences in BMD. Both testosterone and estrogen improve bone formation, but only estrogen prevents resorption [33]. Therefore, estrogen might protect bones better from the effects of PHPT than testosterone.

The main limitation of our study is that it was retrospective; therefore, we had missing data, which may have led to selection bias. Also, we measured biochemical parameters at presentation, before targeted vitamin D replenishment, so we might not have achieved the maximal suppression point for PTH in all patients. However, the mean level of 25(OH) vitamin D was similar in all patient groups, so it did not significantly influence between-group comparisons. Another possible source of error might have been unrecognized morphometric vertebral fractures because we included solely DXA results and clinical osteoporotic fractures when considering skeletal manifestations. Furthermore, we did not routinely perform X-ray screening for osteitis fibrosa cystica, so we could have missed subperiosteal resorption in patients with more subtle clinical presentation.

The main strength of our study is that our results are based on a sizeable and well-defined cohort of PHPT patients who were managed in a standardized way. Furthermore, all laboratory diagnostics and DXA scans were performed at our center, reducing the variability of the measurements.

Conclusions

In a retrospective study, we observed that gender, age, and BMI influenced the clinical presentation of PHPT. In older adults, PHPT was biochemically milder but affected bones more severely. Men appeared to be more prone to skeletal manifestations than premenopausal women. Patients with increased BMI seemed to have asymptomatic PHPT more often with fewer skeletal and renal manifestations.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contributions

K.M.K. contributed to the conception and design, wrote the manuscript, contributed to the research data discussion, and critical review of the manuscript; G.V. analyzed the data and contributed to a critical review of the manuscript. M.J.S., L.L., M.H., and A.J. contributed to the research data discussion and critical review of the manuscript; S.J. and K.R. analyzed the data and contributed to a critical review of the manuscript. T.K. contributed to the conception and design, research data discussion, and critical manuscript review. All authors reviewed and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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