Sex Difference in the Clinical Presentation of Primary Hyperparathyroidism: Influence of Menopausal Status

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Context: Female-to-male ratio in primary hyperparathyroidism (PHPT) is 3:1, but data on sex impact on the clinical presentation are limited.

Design: We evaluated, retrospectively, sex difference in biochemistry and clinical presentation at diagnosis in a monocentric series of 417 patients with PHPT: 93 men (58.6 ± 14.5 years), and 324 women (61.7 ± 12.8 years), of whom 54 were premenopausal (pre-F) and 270 postmenopausal (post-F).

Results: Men were significantly younger ($P = 0.046$) and more frequently symptomatic than women (62.3% vs 47%, $P = 0.016$). No sex difference was found in serum parathyroid hormone, calcium, creatinine, 25-hydroxy-vitamin D, and urinary calcium levels, whereas serum phosphate was higher in women. Nephrolithiasis (detected by imaging or history of passing stones) was more frequent in men (50.5% vs 33% in women, $P = 0.003$) and osteoporosis (T-score <–2.5 at any site) was more frequent in women (52.2% vs 35.5% in men, $P = 0.0066$). Symptomatic patients were 43.3%, 64.8%, and 62.3% in post-F women, pre-F women, and men, respectively. Kidney stones were less frequent and osteoporosis more frequent in post-F women than in pre-F women (28.1% vs 59.2% and 58.9% vs 18.5%, respectively). After combining symptomatic and asymptomatic patients meeting surgical criteria recommended by current guidelines, no sex difference was observed in the proportion of patients to be referred for surgery (84.6% in men vs 84.9% in women).

Conclusion: Biochemical activity of PHPT seems to be independent of sex, but clinical presentation is different, mostly due to menopausal state. However, surgical referral was indicated equally in men and women. (***J Clin Endocrinol Metab*** **102: 4148–4152, 2017)**

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder (1). Its clinical profile in Western countries has changed in recent years from a highly symptomatic disease, characterized by symptoms of hypercalcemia with kidney and bone involvement, to a largely asymptomatic disease (2).

Women worldwide are about three times more commonly affected by PHPT than men (3), and this sexual dimorphism in epidemiology seems to widen in patients over 50 years old (4). Therefore, the highest prevalence of PHPT is reported in women after menopause (5).

A limited number of studies (4, 6, 7) have focused on sex difference in the clinical presentation of PHPT, reporting a more severe derangement of biochemical indices of disease in males. Mazeh *et al.* (4) reported that kidney stones and osteoporosis were the most common symptom of PHPT in men and women, respectively.

To the best of our knowledge there are no published reports exploring the influence of menopause on the clinical presentation of PHPT.

We thus evaluated the sex differences in clinical presentation with a particular focus on the menopausal state.

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Abbreviations: 25OHD, 25-hydroxy-vitamin D; DXA, dual X-ray absorptiometry; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PHPT, primary hyperparathyroidism; post-F, post-menopausal female; pre-F, pre-menopausal female; PTH, parathyroid hormone; RIA, radioimmunoassay; SD, standard deviation; US, ultrasound.

The investigation took place in a large, single-center, unselected series of patients with PHPT.

Patients and Methods

Design

A retrospective survey was performed on medical records of all patients diagnosed with PHPT and attending our department from January 1998 to December 2016.

Patients

Patients had been referred by general practitioners, primary care clinics, and subspecialty clinics.

Diagnosis of PHPT had been established by the presence of hypercalcemia and concomitant inappropriately raised serum parathyroid hormone (PTH) levels on at least two separate occasions (reference range for calcium levels, 8.4 to 10.2 mg/dL, for PTH *vide infra*).

Patients diagnosed with multiple endocrine neoplasm, hyperparathyroidism-jaw tumor syndrome, and familial hypocalciuric hypercalcemia were excluded.

No patients had been taking calcium or vitamin D supplementations, supplemental estrogens or testosterone or elective estrogen receptor modulators, and bone-active medications for at least 6 months.

In agreement with the summary statement by Bilezikian *et al.* (8), patients were classified as asymptomatic PHPT according to the lack of radiologic signs of bone involvement, nephrolithiasis, and symptoms of hypercalcemia.

Regarding bone involvement, all patients had routinely undergone dual X-ray absorptiometry (DXA) and a radiographic evaluation of the skull and hands, looking for subtle signs of osteitis fibrosa cystica, such as subperiosteal resorption in fingers, salt and pepper mottling of the skull, or brown tumors.

As for kidney involvement, patients were classified as symptomatic either if they had a recorded positive history for renal stones [ultrasound (US) examination, urography, plain-film radiography, history of passing stones or their endoscopic or surgical removal] or if renal stones (or calcinosis) were diagnosed by routinely performed US in either asymptomatic or symptomatic patients at physical examination.

The criteria for surgery reported in the latest guidelines (8) were retrospectively applied to all patients.

Methods

Serum total calcium, phosphate, and creatinine levels were assayed by automated analysis using colorimetric and enzymatic methods, while ionized serum calcium was analyzed by a specific probe after correction for pH.

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (9), namely:

$$\text{eGFR} = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\,[\text{if female}] \times 1.159\,[\text{if black}],$$

where SCr represents serum creatinine (in mg/dL), k represents 0.7 for women and 0.9 for men, α represents –0.329 for women and –0.411 for men, min represents the minimum of SCr/k or 1, and max represents the maximum of SCr/k or 1.

Serum intact PTH concentrations were measured up to 2012 using a two-site immunochemiluminometric assay (Immulite 2000; DPC, Los Angeles, CA) with an inter- and intra-assay variation coefficient of 6.3% to 8.8% and 4.2% to 5.7%, respectively. Thereafter, serum intact PTH concentrations were measured using a new second-generation immunochemiluminometric assay (COBAS e411, ROCHE Diagnostics, Basel, Switzerland) with an inter- and intra-assay variation coefficient of 3.1% to 6.5% and 1.4% to 3.2%, respectively. Normal ranges are 20 to 65 pg/mL and 15 to 65 pg/mL, respectively.

Serum 25-hydroxy-vitamin D (25OHD) levels were measured by a radioimmunoassay (RIA) (DIAsource 25OH Vitamin D3, RIA CT Kit; DIAsource Immuno Assays, Nivelles, Belgium), with a detection limit of 0.6 ng/mL (1.5 nmol/L) and inter- and intra-assay variation coefficient of 5.3% and 4.7%, respectively. Our laboratory periodically performs a quality control of every kit used with material provided by the manufacturer. Our laboratory is a member of the External Quality Assessment Scheme for the estimation of 25OHD conducted by the QualiMedLab-CNR (Pisa, Italy), as a means of determining the accuracy of results. A level less than 20 ng/mL was considered as cutoff for deficiency.

Bone mineral density was measured at the lumbar spine (L2 to L4), proximal femur, and distal third of the nondominant radius using the same instrument (DXA QDR-4500; Hologic, Bedford, MA) throughout the entire study period. Minor upgrades, mostly in the reporting and duration of the procedure, did not significantly impact the results. Data were analyzed as absolute measurements (in grams per square centimeter) and reported as T-scores.

All patients underwent standard reno-vescical US performed by a 2- to 5-MHz-wide band convex transducer. For a definitive diagnosis of stones thereby enabling patients to be classified as positive or negative for nephrolithiasis, radiologists looked for hyperechogenic spots that were more than 2 mm in diameter with multiplanar evaluation of specific signs such as echogenicity, posterior acoustic shadowing, or a positive twinkle sign.

Statistical analysis

Variables were preliminarily tested for normal distribution with the Shapiro-Wilks W test, and data were expressed as mean ± standard deviation (SD), or median and interquartile range (IQR) as appropriate, depending on the results.

Continuous variables with non-normal and normal distribution were analyzed by analysis of variance for repeated measures followed by the Tukey test, completely randomized analysis of variance followed by the Games-Howell test, and Mann-Whitney *U* test and *t* test for unpaired samples, respectively, as appropriate.

Differences in categorical variables were analyzed by χ^2 or Fisher's exact test, as appropriate.

The level of statistical significance was set at $P \leq 0.05$ with Bonferroni correction.

Calculations were performed using SPSS version 21 (IBM SPSS Statistics).

Results

Table 1 summarizes the demographics and biochemical and clinical characteristics of the whole series of 417 patients with PHPT.

Table 1. Demographics and Biochemical and Clinical Characteristics of Patients

	Whole Series (N = 417)	Males (n = 93)	Females (n = 324)	*P*
Age (y)	61.0 ± 13.2	58.6 ± 14.5	61.7 ± 12.8	0.046
Body mass index (kg/m^2)	25.3 ± 5	25.7 ± 4.5	25.1 ± 5.2	0.31
Symptomatic (n, %)	210 (50.4%)	58 (62.3%)	152 (47%)	0.016
PTH (ng/L)	135.9 [134.5]	121 [148]	138 [130]	0.783
Total serum calcium (mg/dL)	11.2 ± 1.1	11.2 ± 1.2	11.2 ± 1.1	0.654
Ionized calcium (mmol/L)	1.45 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	0.337
25OHD (μg/L)	28.5 ± 19.4	27.9 ± 14.3	28.6 ± 20.5	0.758
Vitamin D deficiency (%)	36	29.8	37.5	0.53
Urinary calcium (mg/24 h)	257.4 ± 171.1	278.2 ± 195.3	250.3 ± 163.9	0.167
Serum phosphate (mg/dL)	2.61 ± 0.6	2.37 ± 0.5	2.68 ± 0.6	0.0001
eGFR (mL/min/1.73 m^2)	79.7 ± 22.2	82.9 ± 23.9	78.6 ± 21.6	0.099
Presence of kidney stones (n, %)	155 (37%)	47 (50.5%)	108 (33.3%)	0.003
Presence of osteitis fibrosa cystica (n, %)	87 (20.9%)	20 (21.5%)	67 (20.7%)	0.977
Distal third-radius T-score	−2.3 ± 1.6	−1.9 ± 1.4	−2.4 ± 1.7	0.001
Lumbar spine T-score	−2.4 ± 1.5	−1.7 ± 1.5	−2.6 ± 1.4	0.001
Femoral neck T-score	−2.0 ± 1.2	−1.8 ± 1.3	−2.1 ± 1.2	0.013
Osteoporosis at any site (n, %)	202 (48.4%)	33 (35.5%)	169 (52.2%)	0.0066
Positive presurgical localization (n, %)	298 (71.5%)	66 (71%)	232 (71.6%)	0.992

Data are expressed as mean ± SD when normally distributed, median and [IQR] when not normally distributed, and absolute number and percentage when categorical.

The female-to-male ratio was 3.5:1. Female patients were older at presentation than males and less symptomatic. No sex differences were observed in serum total and ionized calcium, PTH, 25OHD, eGFR, or urinary calcium levels, whereas serum phosphate levels were significantly lower in men.

The most common symptom in male patients was the presence of kidney stones, whereas osteoporosis at any site was significantly more frequent in female patients, with a lower T-score and mean bone mineral density (not reported) at any site.

Table 2 shows the comparison between male and female patients divided according to menopausal state [premenopausal female (pre-F) and post-menopausal female (post-F)]. Men were significantly older than pre-F and younger than post-F. Body mass index was lower in pre-F than in men and post-F. No difference was found in serum total and ionized calcium, PTH, 24h urinary-calcium, or 25OHD among the three groups. Serum phosphate levels were significantly lower in men and in pre-F than in post-F. Post-F were more commonly asymptomatic than men and pre-F. Post-F had lower eGFR levels than male and

Table 2. Comparison Between Men and Women (According to Menopausal State)

	Males (n = 93)	Pre-F (n = 54)	Post-F (n = 270)	*P*
Age (y)	58.6 ± 14.5[a,b]	40.5 ± 8[b]	65.9 ± 8.7	0.001
Body mass index (kg/m^2)	25.7 ± 4.5[a]	22.6 ± 5.7[b]	25.7 ± 4.9	0.0001
Symptomatic (n, %)	58 (62.3%)[b]	35 (64.8%)[b]	117 (43.3%)	0.0005
PTH (ng/L)	121 [148]	126.5 [96.8]	139 [137]	0.955
Total serum calcium (mg/dL)	11.2 ± 1.2	11.2 ± 1	11.2 ± 1.2	0.985
Ionized calcium (mmol/L)	1.5 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	0.639
25OHD (μg/L)	27.9 ± 14.3	31.8 ± 21.6	28.1 ± 20.3	0.560
Vitamin D deficiency (%)	29.8	30.5	38.9	0.27
Urinary calcium (mg/24 h)	278.2 ± 195.3	296 ± 175.4	241.3 ± 160.5	0.080
Serum phosphate (mg/dL)	2.37 ± 0.5[b]	2.54 ± 0.6[b]	2.71 ± 0.6	0.0001
eGFR (mL/min/1.73 m^2)	82.9 ± 23.9[b]	90.9 ± 22.7[b]	76.1 ± 20.5	0.0001
Presence of kidney stones (n, %)	47 (50.5%)[b]	32 (59.2%)[b]	76 (28.1%)	0.0001
Presence of osteitis fibrosa cystica (n, %)	20 (21.5%)	7 (12.9%)	60 (22.2%)	0.308
Distal third-radius T-score	−1.9 ± 1.4[a,b]	−1.1 ± 1.2[b]	−2.7 ± 1.6	0.0001
Lumbar spine T-score	−1.7 ± 1.5[b]	−1.7 ± 1.3[b]	−2.7 ± 1.4	0.0001
Femoral neck T-score	−1.8 ± 1.3[b]	−1.5 ± 1.2[b]	−2.2 ± 1.1	0.0001
Osteoporosis at any site (n, %)	33 (35.5%)[a,b]	10 (18.5%)[b]	159 (58.9%)	0.0004
Positive presurgical localization (n, %)	66 (71%)	42 (77.7%)	190 (70.4%)	0.544

Data are expressed as mean ± SD when normally distributed, median and [IQR] when not normally distributed, and absolute number and percentage when categorical.

[a]Significant vs pre-F.

[b]Significant vs post-F.

pre-F patients. Kidney stones occurred equally in men and pre-F but were less frequent in post-F. Osteoporosis prevalence at any site was intermediate in male patients compared with pre-F and post-F, whose values were respectively lower and higher than that in men. The bone site most affected by disease was the forearm in male patients and the lumbar spine in pre-F and post-F.

Finally, except for age, nephrolithiasis was the most common criterion for surgery in men and pre-F (50.5% and 59.2%, respectively) and osteoporosis at any site in post-F (58.9%). However, by combining symptomatic with asymptomatic patients meeting surgical criteria, surgery was indicated in the same high proportion among groups, namely 84.9% in male patients and 84.6% in female patients (98.1% and 81.9%, respectively, in pre-F and post-F).

Discussion

Our study highlights a sex difference in the clinical presentation of PHPT and the influence of menopausal state on this difference.

Male patients were more frequently symptomatic than females. Renal stones were significantly more frequent in men, and osteoporosis was significantly more frequent in women. Accordingly, regarding the surgical criteria recommended by current guidelines (8), nephrolithiasis and osteoporosis at any site were met most frequently in male and female patients, respectively; both groups, however, reached surgical indication in the same high proportion.

After splitting the females group according to menopausal state, the clinical presentation of PHPT was still different between men and post-F, whereas it was similar between men and pre-F.

Our data are in substantial agreement with the large surgical series reported by Mazeh *et al.* (4) regarding the greater prevalence of kidney stones in males and osteoporosis in female patients. Also in the general population, the risk of nephrolithiasis is higher in men than in women.

In the general population, the etiology for increased incidence of nephrolithiasis in men is attributed to the higher muscle mass and increased metabolic waste as well as possible obstruction of the bladder outflow as a result of prostate hypertrophy (10, 11).

In contrast with our data, Mazeh *et al.* (4) found that more male patients were asymptomatic than females, in spite of biochemical markers pointing to a more active disease and higher gland weight in men. Note that these authors did not detail the criteria for clinical classification. In addition, patients complaining of fatigue and neurocognitive symptoms, more frequently reported by female patients, were included in the symptomatic group.

In contrast with Mazeh *et al.* (4) and other studies performed in selected series of PHPT patients (6, 7), except for serum phosphate, we did not find any sex difference in the biochemical evaluated parameters, including 25OHD levels. This suggests that the sex differences in the clinical presentation of PHPT should be independent of the severity of the disease.

Our study, for the first time to our knowledge, underlines the influence of menopausal state on sex differences in the biochemical and clinical presentation of PHPT. In fact, the differences observed in comparing male patients with the whole group of females with PHPT disappear when men are compared with pre-F only. Serum phosphate levels were significantly lower in men and pre-F than in post-F. An influence of the gonadal hormones on the hypophosphatemic effect of PHPT can be hypothesized to explain this finding, as recently reported in an experimental hyperparathyroidism model (12).

Most patients in men and pre-F were symptomatic, with an identical rate of renal stones. Accordingly, in both these groups, other than age, the most frequently met surgical criterion was nephrolithiasis.

As for bone damage, no differences were found between men and pre-F with regard to the lumbar spine or hip T-score. In contrast, the forearm T-score was significantly lower and osteoporosis at any site was more frequent in male patients. It is likely that these differences could be accounted for by a longer disease duration in men, who were significantly older than the pre-F patients in our series.

The clear impact of menopausal state on the clinical expression of PHPT suggests a critical role of estrogen withdrawal. As in the general population (13), the estrogen withdrawal caused by the menopause plays a major role in the genesis of osteoporosis, which is the typical symptom of post-F with PHPT (14, 15). Consequently, osteoporosis at any site is the most frequent surgical criterion met in post-F with PHPT.

It is clear that the screening for osteoporosis in post-F contributes to the high prevalence of PHPT in this population (16, 17). It has also been suggested that an estrogen drop plays a role in parathyroid tumorigenesis (18, 19), thus contributing to the increased prevalence of PHPT in post-F. Hence, the clinical profile of PHPT in post-F results from the synergistic effect of PTH excess and estrogen withdrawal.

Our study has several limitations. Despite the large cohort studied, this is a retrospective, single-institution study, which may be affected by selection bias. These findings cannot therefore be generalized indiscriminately to patients with PHPT in other countries and ethnic groups. However, unlike previous studies, this study evaluated a consecutive series of patients, and thus it better reflects real-life clinical practice.

The putative impact of menopause on the clinical presentation of PHPT must be taken with caution, because the design of the study was cross-sectional and not longitudinal.

We acknowledge that we did not use the gold standard "liquid chromatography aligned to mass spectrometry" to assess 25OHD levels and also that our RIA may have slightly overestimated 25OHD levels (in line with several RIAs). However, all measurements were performed in the same laboratory, thereby ensuring a good quality of data.

The reasons why PHPT had been diagnosed also need to be taken into account. It is likely that the evaluation followed the onset of symptoms in most male and pre-F patients, whereas routine osteoporosis screening can often drive the diagnosis in post-F. Nevertheless, unlike previous studies, our patients underwent routine renal US and DXA at three sites, thus facilitating a comprehensive clinical evaluation, which revealed even silent damage. Furthermore, spine X-ray was not routinely performed, thus leading to a possible underestimation of morphometric fractures.

Finally, we applied the criteria for clinical classification suggested by the latest guidelines.

In conclusion, our study highlighted significant sex-dependent differences in the clinical presentation of PHPT. This was similar between men and pre-F, with most patients symptomatic, with a high prevalence of renal stones. Conversely, the predominant PHPT phenotype in post-F was asymptomatic, mostly associated with osteoporosis. Because the biochemical markers of PHPT severity were similar among groups, estrogen deficiency would seem to represent the main determinant influencing the clinical presentation of PHPT in post-F. In spite of the different clinical presentations, surgical indications appear to be met in very high proportion regardless of sex.

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