Symptoms of Primary Hyperparathyroidism in Men and Women: The Same but Different?

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Keywords

Primary hyperparathyroidism · Gender · Symptoms

Abstract

Introduction and Objective: Typical symptoms for primary hyperparathyroidism (pHPT) include osteoporosis, bone or joint pain, and nephrolithiasis, as well as fatigue, depression, gastritis, and cardiovascular disease. The female:male ratio was 3:1. The aim of this retrospective study was to evaluate the possible influence of gender-specific aspects of these symptoms. **Methods:** From February 2018 to November 2019, parathyroid surgery was performed in 125 patients with pHPT (age: 23–83 years); 95 (76%) were female, and 30 (24%) were male. Preoperatively, a standardized medical history including 7 typical symptoms of pHPT was used for routine clinical documentation according to the StuDoQ Thyroid and Parathyroid Registry. **Results:** For both groups (mean age: 60.4 years for females and 60.2 years for males), no sex differences were found in serum calcium or parathyroid hormone levels. For females, there was a tendency towards smaller hyperfunctioning parathyroid glands (16.8 vs. 20.5 mm) with less weight (1.14 vs. 1.52 g) and multiglandular disease. Nephrolithiasis was significantly more frequent in men than in women (36.7 vs. 16.8%, respectively; $p = 0.036$), but the difference in hypertension was not significant (60% in men vs. 47.4% in women, $p = 0.230$). Women reported significantly more often bone and joint pain (44.2% in women vs. 20% in men, $p = 0.053$) and depressive episodes (32.6% in women vs. 10% in men, $p = 0.016$). **Conclusion:** 91.2% of patients transferred for parathyroidectomy de-

scribed typical symptoms of pHPT. However, an unexpected high gender difference was found following the analysis of symptoms documented in the StuDoQ Registry.

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Introduction

Primary hyperparathyroidism (pHPT) is caused by an overproduction of parathyroid hormone (PTH) in relation to serum calcium levels either by a single parathyroid adenoma (85–90%) or multiple hyperfunctional parathyroid glands (10–15%), such as double adenomas or parathyroid hyperplasia.

The incidence/prevalence of pHPT amounts to 0.78–1.07% of the general population in Latin America, the United States, Canada, and Europe. In Canada, about 3.3% of women and 1.4% of men are diagnosed with pHPT [1].

The diagnosis of pHPT is proven biochemically by elevated serum calcium levels and correspondingly elevated or high normal PTH levels. Twenty-four-hour urinary calcium measurement is recommended to exclude familial hypocalciuric hypercalcemia. According to the guidelines of the American Association of Endocrine Surgeons (AAES) [2], a careful medical history should assess renal and skeletal manifestations.

From 1990 to 2014, several consensus conferences for the management of asymptomatic pHPT [3, 4] recommended parathyroid surgery only for patients with elevated serum calcium levels (>2.85 mmol/L) or increased

Table 1. Characteristics of 125 patients undergoing parathyroid surgery for pHPT: medians (ranges) and numbers (%)

	pHPT (total)	Female	Male
Patients, <i>n</i>	125	95	30
Age, years	60.4 (23–83)	60.4 (23–83)	60.2 (44–83)
Serum calcium (normal range 2.1–2.6), mmol/L	2.75 (2.26–3.53)	2.75 (2.4–3.53)	2.76 (2.26–3.21)
Parathyroid hormone (normal range 15–78), ng/L	162.7 (47.4–648.2)	163.2 (47.4–648.2)	161.1 (68.5–412.4)
Single gland adenoma, <i>n</i>	115 (92.0)	87 (91.6)	28 (93.3)
Double adenoma, <i>n</i>	5 (4.0)	4 (4.2)	1 (3.3)
Parathyroid hyperplasia, <i>n</i>	5 (4.0)	4 (4.2)	1 (3.3)
Additional goiter, <i>n</i>	34 (27.2)	30 (31.6)	4 (13.3)
Additional thyroid carcinoma, <i>n</i>	4 (3.2)	4 (4.2)	0 (0)
Minimally invasive parathyroidectomy, <i>n</i>	39 (31.2)	29 (30.5)	10 (33.3)
Size of the largest parathyroid gland, mm	17.7 (5–45)	16.8 (5–40)	20.5 (5–45)
Weight of the largest parathyroid gland, g	1.23 (0.1–8.5)	1.14 (0.1–8.5)	1.52 (0.3–8.0)
Patients cured, <i>n</i>	122 (97.6)	92 (96.8)	30 (100)

urinary calcium excretion (>10 mmol/day), osteoporosis, vertebral fractures, presence of nephrolithiasis, or nephrocalcinosis in patients aged <50 years. The 4th International Consensus Conference [3, 4] in 2014 stated that symptoms such as changes in cognition, depression, and reduced quality of life were “nonspecific” and should not be used to recommend parathyroidectomy.

In 2016, the AAES released the first evidence-based guidelines [2] for definitive management of pHPT and strongly recommended parathyroidectomy in patients with neurocognitive and neuropsychiatric symptoms attributable to pHPT.

Both guidelines confirmed that surgery is the only curative treatment for pHPT. High-volume surgeons and hospitals for thyroid and parathyroid surgery had lower complication rates, less reoperations, and better outcomes [5, 6].

Until now, gender-specific differences in pHPT were reported only in a limited number of studies [7–9]. The aim of this retrospective study was, therefore, to evaluate typical symptoms of pHPT using a standardized medical history as provided by the StuDoQ Thyroid and Parathyroid Registry of the German Society of General and Visceral Surgery (DGAV) with a special focus on gender-specific differences.

Patients and Methods

From February 2018 to November 2019, 125 patients with pHPT presented at the Division of Endocrine Surgery, Catholic Hospital, Mainz, Germany. pHPT was diagnosed by hypercalcemia (serum calcium above the normal range of 2.1–2.6 mmol/L) and elevated PTH (normal range 18.4–80.1 pg/mL) or PTH levels in the upper normal range with elevated serum calcium.

Basic clinical data were obtained from electronic patients' records. Symptoms at presentation were documented according to the German StuDoQ Thyroid and Parathyroid Registry on the patients' first visit of the outpatient clinic. The StuDoQ Registry de-

finied the following items as symptoms of pHPT: fatigue, depression, osteoporosis, bone or joint pain, gastritis, nephrolithiasis or nephrocalcinosis, and hypertension.

Statistical Analysis

To compare differences between gender outcomes, we used a Mann-Whitney U test. For all analyses, the level of statistical significance was set at $p \leq 0.05$. All statistical analyses were performed on WinSTAT® for Microsoft Excel.

Results

A total of 125 patients (95 females and 30 males) were included in the present study (Table 1). The mean age at the time of surgery was 60.4 years for females (23–83 years) and 60.2 years for males (44–83 years).

The mean serum calcium levels for female and male patients (2.75 and 2.76 mmol/L, respectively) as well as the PTH levels were distributed equally (163.2 pg/mL for females and 161.1 pg/mL for males). Only 24.8% (31/125) of the patients (21.1% females and 36.7% males) presented with calcium levels >0.25 mmol/L above the upper limit of normal (2.85 mmol/L), currently recommended by surgical and endocrinological guidelines [2, 3].

Parathyroid Surgery

All of the patients were subjected to parathyroid surgery. In 122 of 125 patients (97.6%), a parathyroid adenoma (92%) was successfully removed, and patients were cured. Five patients presented a double adenoma and 5 parathyroid hyperplasia intraoperatively, which were confirmed by histopathology. Three patients had persistent pHPT. In 2 of them, intraoperative and early postoperative (24 h after surgery) PTH declined from 128 to 31.4 pg/mL and from 267 to 31 pg/mL following removal of a parathyroid adenoma. Two weeks postoperatively, PTH was above the upper limit in both patients. In one of these

Table 2. Symptoms of pHPT in 95 female and 30 male patients

	pHPT total (<i>n</i> = 125) <i>n</i> (%)	Female (<i>n</i> = 95) <i>n</i> (%)	Male (<i>n</i> = 30) <i>n</i> (%)	<i>p</i> value
Symptomatic pHPT	114 (91.2)	85 (89.5)	29 (96.7)	
Asymptomatic pHPT	11 (8.8)	10 (10.5)	1 (3.3)	
Fatigue	60 (48.0)	47 (49.5)	13 (43.3)	0.559
Depression	34 (27.2)	31 (32.6)	3 (10.0)	0.016
Osteoporosis	50 (40.0)	40 (42.1)	10 (33.3)	0.394
Bone or joint pain	48 (38.4)	42 (44.2)	6 (20.0)	0.053
Nephrolithiasis/nephrocalcinosis	27 (21.6)	16 (16.8)	11 (36.7)	0.036
Hypertension	63 (50.4)	45 (47.4)	18 (60.0)	0.230
Gastritis	18 (14.4)	15 (15.8)	3 (10.0)	0.433

patients, a small (5 mm) double adenoma was successfully excised. In the second patient, a 59-year-old female, genetic testing detected a new heterogeneous mutation of the calcium-sensing receptor. A 68-year-old female with persistent pHPT refused to have any further testing or localization procedures.

In 30 of 95 females (31.6%) and 4 of 30 males (13.3%) with pHPT, a lobectomy or total thyroidectomy was performed for additional thyroid nodules. In 4 women, 3 papillary thyroid carcinomas and 1 Hurthle cell carcinoma were found intraoperatively.

Histopathologically, the mean size of the largest hyperfunctioning parathyroid removed was 16.8 mm (5–40 mm) in females and 20.5 mm (5–45 mm) in males. Compared to female parathyroid glands with a mean weight of 1.14 g (0.1–8.5 g), male parathyroid glands were heavier, with a mean weight of 1.52 g (0.3–8.0 g). No postoperative surgical complications such as recurrent nerve palsy or persistent hypoparathyroidism were seen.

Symptoms of pHPT in Female and Male Patients

Overall, 114 of 125 patients (91.2%) reported symptoms of pHPT according to the items defined in the StuDoQ Registry (Table 2). Men tended to be more symptomatic (96.7%) than women (89.5%).

Biochemically, symptomatic patients showed higher serum calcium levels (average: 2.77 mmol/L) than asymptomatic patients (2.60 mmol/L). PTH levels in symptomatic patients were also higher (mean PTH of 167.2 pg/mL) than in asymptomatic patients (116.8 pg/mL).

Overall, the most commonly reported symptoms of pHPT at initial presentation were hypertension (50.4%), fatigue (48%), and osteoporosis (40%).

Gender differences became evident especially for depression, muscular complaints, nephrolithiasis, and hypertension. Female patients reported 3 times more often depressive symptoms, and antidepressive medication was also prescribed more often than in male patients (32.6 vs. 10.0%, $p = 0.016$). Moreover, women complained twice as

Fig. 1. Hypertension in 95 females and 30 males with pHPT.

much about bone and joint pain than males (44.2 vs. 20.0%, $p = 0.053$).

On the other hand, 36.7% of male patients had a history of kidney stones or nephrocalcinosis, while only 16.8% of female patients showed a pathologic ultrasound of the kidneys ($p = 0.036$). Of note, abdominal ultrasound was not performed regularly. Hypertension was a frequent finding in females (47.4%) and even more frequent in males (60.0%), but the difference failed to reach statistical significance ($p = 0.230$). Regardless of age (Fig. 1), male patients showed a higher percentage of increased blood pressure when compared to females. At the age of 41–50 years, 3 of 6 men with pHPT (50%) had hypertension compared to 1 of 7 females (14.2%). At 51–60 and 61–70 years of age, hypertension was 8.7 and 16.7% higher in males, respectively, than in females. Hypertension was only diagnosed when the patients obtained anti-hypertensive medication.

Figures 2 and 3 compare the percentages of hypertension in our study to the prevalence rates of hypertension in Germany, published by the Robert-Koch-Institute [10]. In women, we found a higher percentage of hypertension, especially in younger females aged 30–44 years:

Fig. 2. Prevalence of hypertension in Germany and in 95 females with pHPT.

Fig. 3. Prevalence of hypertension in Germany and in 30 males with pHPT.

20% of our study patients compared to 9% in a representative sample of the German population. Since we had only 1 male patient in this age group, this finding was not comparable. In the group aged 45–64 years, 55% of males with pHPT were medically treated for hypertension compared to 38.3% in the German population.

In another 2 male patients, potential symptoms of pHPT were chronic pancreatitis and a rupture of the patellar tendon.

Discussion

According to the guidelines for the management of asymptomatic pHPT, published in 2014 by Bilezikian et al. [3], only 69.5% of our cohort patients (67.4% female and 76.6% males) would have been subjected to parathyroid surgery.

In contrast to these findings, the AAES guidelines of 2016 [2] would have recommended parathyroidectomy in 92.8% of our patients (91.6% of females and 96.7% of males). Interestingly, both guidelines presented a stronger indication to operate on male patients than females. The reason to do so is mainly caused by a quite restrictive definition of symptoms in the consensus guidelines of 2014 [3, 4], which were upgraded by the AAES guidelines for definite management of pHPT [2] with a successful approach to establish an evidence-based guideline. From our point of view, it was not only very important to state that pHPT remains underdiagnosed and undertreated, but also to refer to neurocognitive and psychiatric symptoms. In the present study, every third female patient was diagnosed with depression or was using antidepressant drugs, which was significantly less noticed in male patients (only 1 of 10 male patients).

In addition, in a German multicenter trial comparing anxiety, depression, and quality of life in pHPT patients

and a control group with benign thyroid nodules, our group [11] showed that women's preoperative anxiety scores exceeded those of men ($p = 0.05$) and were significantly improved at the 12-month follow-up ($p < 0.001$).

Blanchard et al. [12] performed a multicenter study including 116 patients with mild pHPT; using the SF-36 questionnaire, they found that men did not improve their mental component summary. Women with a preoperative mental component summary score <43.6 of 100 showed postoperative improvement.

In 1998, Pasiaka and Parsons [13] were one of the first endocrine surgeons bringing neuromuscular and psychiatric complaints such as fatigue, weakness, mood swings, and bone and joint pain into the focus of parathyroid research and developed a patient-based surgical outcome tool to examine these symptoms [14].

In a multicenter trial, Pasiaka et al. [14] described that the symptom “feeling tired easily” was reported by 45–60% pHPT patients treated at 3 endocrine centers in Canada, the United States, and Australia [14]. In a study by Roman et al. [15], fatigue was noted in 53% of 212 patients with pHPT. In our recent series, 48% of all patients with pHPT reported fatigue, which occurred slightly more often in women (49.5%) than men (43.3%).

Osteoporosis defined as T scores ≤ 2.5 at lumbar spine, total hip, or femoral neck by bone densitometry was recognized in 40% of all patients in our study. It was more prevalent in women (42.1%) than men (33.3%). Castellano et al. [8] found osteoporosis much more frequently in postmenopausal women (59.2%) than in premenopausal women (28.1%) with pHPT.

In a retrospective study, Vodopivec et al. [9] analyzed pre- and postoperative results of bone mineral density in 80 patients (56 women and 24 men) with pHPT undergoing parathyroid surgery. In this study, 25% of men and 33.9% of women had osteoporotic preoperative T scores.

One year after parathyroidectomy, men had a greater increase in bone mineral density in the femoral neck than women.

In a nested case-control study of the Danish National Data Patient Register [16], published in 2018, on prevalence and risk of vertebral fractures in pHPT patients, 588 patients (77% females and 23% males) were examined. Vertebral fractures were quite equally distributed in females and males (20.5 and 21.5%, respectively). After stratification by age, the prevalence differed significantly between sexes ($p < 0.01$). In patients <50 and between 50 and 59 years, the prevalence of vertebral fractures in men was almost 3 times, and twice as high in women, respectively. For both sexes, prevalence of vertebral fractures did not correlate with serum calcium or PTH levels.

Even though we did not perform a routine screening for kidney stones or nephrocalcinosis, 36.7% of our male patients and 16.8% of the females with pHPT presented with a history of nephrolithiasis or nephrocalcinosis. In 2000, a study on urolithiasis in Germany including a representative sample of 7,500 persons found a prevalence of 4.7%. In males 50–64 years old, 9.7% had urinary stones compared to 5.9% in females [17].

Reid et al. [18] described that younger age and male sex were the only independent predictors for nephrolithiasis in 611 patients with pHPT. A history of nephrolithiasis was present in 10% of the patients and was associated with higher serum calcium and PTH levels. In this cohort, at presentation, 8.5% of women and 16.7% of men had a history of renal stones.

In contrast to our findings which showed no difference in serum calcium levels in patients with or without kidney disease, Pappachan et al. [19] found that a higher peak calcium concentration was an independent predictor for acute kidney injury.

With respect to cardiovascular disease as an indication to perform parathyroid surgery, the current AAES guidelines [2] reported conflicting data for observational studies in mild pHPT. Therefore, they supported only a weak recommendation for offering parathyroidectomy to surgical candidates with mild pHPT and cardiovascular disease. In this study, we found a constantly higher percentage of hypertensive female and male patients with pHPT compared to a representative sample of 7,500 persons of the German population [10].

In 2012, even more striking results were published by Han et al. [7], who performed a retrospective case-control study. They compared patients with pHPT with an average age of 56 years to the general population of New Jersey. In the pHPT group, 48.6% of females and 57.4% of males had hypertension. In the New Jersey population, the percentage of hypertension was only 27.2% for females and 29% for males. In addition to these findings,

prevalence rates of obesity, hyperlipidemia, type 2 diabetes, and coronary artery disease were higher in pHPT patients than in the general New Jersey population and age-, sex-, and BMI-matched goiter patients. Compared to female patients with pHPT, prevalence rates of obesity, hypertension, and type 2 diabetes were 29.7, 15.3, and 52.6% higher in male patients, respectively.

In 2018, Pappachan et al. [19] summarized that male gender was a statistically significant predictor for patients receiving parathyroidectomy. Since male patients have larger and heavier adenomas, which can be detected more easily with localization procedures, more often present with kidney stones or nephrocalcinosis, and have higher blood pressure, parathyroid surgery might probably be offered more liberally to them than to women complaining of bone pain, depression, or mood swings, which are more difficult to explore.

The advantage of this study was that the StuDoQ Thyroid and Parathyroid Registry enabled participating hospitals to evaluate symptoms, laboratory tests, and operative strategies of pHPT according to gender and age to relate these results to our studies or current guidelines.

The limitations of our retrospective, single-center study are that kidney ultrasound, bone densitometry, and questionnaires for depression were not performed in all patients. Since patients were already referred to a department of endocrine surgery, the possibility of a selection bias must be addressed, and reported patients were more likely to present with advanced stages of the disease.

Conclusions

The results of our study suggest that symptoms of pHPT are different in women and men. While women suffer more often from osteoporosis, bone and joint pain, as well as depression, male patients presented higher rates of nephrolithiasis and hypertension. Current guidelines are focusing on both sexes, but maybe a more gender-specific approach to pHPT seems to be eligible.

Statement of Ethics

This retrospective study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All of the patients provided written informed consent to participate in the StuDoQ Thyroid and Parathyroid DGAV Registry, and agreed to data evaluation and publication. Ethics committee approval was not required since the study involved only retrospective data of our own patient cohort.

Disclosure Statement

T.W. received speakers' honoraria from Sanofi-Aventis, Germany, and Novo Nordisk, Germany, as well as expert testimonials from Sanofi-Aventis, Germany, and Shire Pharmaceutical, Germany. R.H. received a travel grant from Medtronic, Germany. A.H. and S.P. have no conflicts of interest to declare.

Author Contributions

T.W., S.P., and R.H.: data collection and analysis. A.H.: statistical analysis. T.W.: drafting of the manuscript. All of the authors approved the manuscript.

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