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Clinical phenotypes of primary hyperparathyroidism in hospitalized patients who underwent parathyroidectomy

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ABSTRACT

Objective. The aim of our study was to investigate the distribution of the PHPT clinical manifestations and biochemical features in patients who underwent parathyroidectomy.

Materials and methods. Medical records of 449 patients from three Medical Centers (Saint-Petersburg, Russia), hospitalized during a period from 2011 to 2018, were reviewed. History and anthropometric data, laboratory results (iPTH, total and iCa, phosphorus, ALP, 24-h urinary calcium, 25(OH)D) and imaging data (ultrasonography, scintigraphy, CT/MRI scan, DXA) were analyzed.

Results. Three hundred ninety-four patients were included in the final analysis. Median age was 60 years with 94.2 % being women. Symptomatic disease was evident in 222 (56.4%) patients, asymptomatic in 172 (43.6%). Skeletal involvement was more common for women, while frequency of other manifestations did not differ in both genders. There was no difference between symptomatic and asymptomatic patients in age. Serum iPTH level was higher in symptomatic patients (202.9& 181.0 pg/ml, p=0.022). Serum 25(OH)D level was estimated in few patients and negatively correlated with PTH (r= -0.294, p=0.005), iCa (r= -0.268, p=0.010) and total Ca (r= -0.284, p=0.014) levels. Manifestations of CVD were observed in 67.7% of cases and affected equally both symptomatic and asymptomatic patients (70.7% & 63.4%, p=0.076). Both age and BMI were higher in patients with CVD, whether or not they were symptomatic (62 & 53 years, p <0.0001; 30.4 vs 26.0 kg/m^2, p<0.0001, respectively).

Conclusions. This experience illustrates that symptomatic phenotype is still the most common form of PHPT.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disease characterized by excessive synthesis and secretion of parathyroid hormone (PTH) from one or more of the 4 parathyroid glands [1]. Most patients present with hypercalcemia though normocalcemic PHPT is now recognized as a frequent phenotype of the disease [2].

The incidence of PHPT varies from 1 to 21 cases per 1,000 individuals [3], with aging associated with greater incidence [4]. The disease more commonly affects women, and the F:M ratio is 3:1 in North American and Western European population, but PHPT prevalence does not differ by gender under the age of 45 [5-8].

Since the 1970s, the clinical presentation of PHPT has gradually changed in many countries from being a symptomatic disorder to an asymptomatic one [1]. The reason for this change in presentation among individuals in those countries is the common use of biochemical screening tests that include the serum calcium measurement routinely. As a result, most patients diagnosed with PHPT do not have overt signs of kidney or bone disease, and are thus, termed asymptomatic [9]. This change in clinical presentation is relevant for Europe and North America where most published studies describe the asymptomatic form of the disease as the most common [1, 3, 6-10]. Since the 2000s, yet another PHPT presentation is recognized, namely normal total and ionized calcium concentration with high PTH in the absence of any secondary causes for the elevated PTH level [2, 10-13]. The characterization of these 3 groups of patients with PHPT was acknowledged and defined by the last workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2014 [11].

Much less is known about the PHPT presentations in Eastern European, former Soviet countries, and in Russia. To the extent that data are available, reports continue to demonstrate that symptomatic PHPT is the more common form of the disease in Russia, accounting for about

two-thirds of cases [5, 12]. This study was conducted to determine whether the prevalence of this disease with regard to clinical presentations in Russia has changed since earlier reports.

The aim of this study was to identify the distribution of the major clinical phenotypes of PHPT and their associated biochemical features by retrospectively collecting data for patients, admitted to three medical centers in Saint-Petersburg, Russia.

MATERIALS AND METHODS

Patients.

We reviewed medical records of 449 PHPT patients 18 years and older living in different regions of Russia and admitted to three Medical Centers in endocrinology and endocrine surgery departments in Saint-Petersburg, Russia between 2011 - 2018. All subjects were in-patients. Seventy-five patients (70 females and 5 males) from the endocrine department of Almazov National Medical Research Centre (Almazov Centre), 35 patients (33 females and 2 males) from the endocrine and the endocrine surgery departments of First Pavlov State Medical University (Medical University) and 339 patients (315 females and 24 males) from the endocrine surgery department of Saint-Petersburg State University N.I. Pirogov Clinic of High Medical Technologies (Pirogov Clinic). We collected all data from the patients records without having direct contact with them during their hospitalization. Patients with secondary and tertiary hyperparathyroidism were not included.

We analyzed anamnesis of the disease, anthropometric data (weight, height, body mass index). Analyzing the history, we tried to determine the duration of the disease. The checkpoint was the earliest (i) imaging data where the formation was found, (ii) the first recorded increase of the serum ionized or total calcium level, (iii) the first case of the fragility fracture, (iiii) the first renal colic associated with urolithiasis. The duration was calculated until the last surgery related visit. PHPT was diagnosed by laboratory tests (elevated iPTH, high or normal level of serum total or ionized calcium levels) [5, 13, 15]. Patients who had skeletal manifestations

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(osteitis fibrosa cystica and fragility fractures), nephrolithiasis or nephrocalcinosis, cholelithiasis, peptic ulcer disease (PUD), pancreatic calcification and erosive lesions of upper gastrointestinal (GI) tract were considered to be symptomatic. Patient without those clinical manifestation were considered to be asymptomatic [13, 15].

Out of 449 patients 18 had multiple endocrine neoplasia (MEN), and one had parathyroid carcinoma. These patients were excluded from the final analysis. In addition, 37 patients had normal serum calcium level, one of them had MEN. Serum 25(OH)D level, available only for 4 patients out of 37, was in the median range of 22.2 ng/ml (19.6-25.6). That being said, we could not rule out secondary PHPT in these patients due to lack of data, so we excluded them as well. Hence, 394 patients were included in the final analysis.

The Ethics Committee of Almazov National Medical Research Centre, St. Petersburg, Russia approved the study and all procedures were carried out in accordance with the Declaration of Helsinki. Patients provided their consent upon hospitalization for the use of their data in research purposes.

Laboratory and instrumental tests.

Laboratory methods were different depending on the Center. The biochemical parameters (alkaline phosphatase (ALP) (<105 UI/L), 24h-urinary calcium (2.5-8.0 mmol/day), creatinine (53.0-97.0 μmol/L), ionized (iCa) and total calcium (Ca) (2.15-2.65 mmol/L and 1.11-1.32 mmol/L respectively), and phosphorus (0.81-1.45 mmol/L) levels in Almazov Centre and Medical University were measured by autoanalyzer Architect c8000 (Abbott Laboratories, Chicago, IL, USA). In Pirogov Clinic biochemical parameters were measured by AU 5800 (Beckman Coulter Inc., CA, USA). Intact PTH (iPTH, 15.0-65.0 pg/mL) was assessed in Almazov Centre and in Medical University using immunochemiluminescent assay (Architect i2000SR, Abbott Laboratories, Chicago, IL, USA and Elycsys 2010, Roche-Diagnostics GmbH, Mannheim, Germany). In Pirogov Clinic the iPTH was determined by

chemiluminescence method (Liaison (Diasorin, Saluggia, VC, Italy and Unicel DXI 800 Access, Beckman Coulter Inc., CA, USA). To convert pmol/L to pg/ml we divided the value in pmol/L by 0.105. Serum 25(OH)D level (30-100 ng/mL) was measured by immunochemiluminescent assay (Architect i2000SR, Abbott Laboratories, Chicago, IL, USA) in all Centers. The calcium-phosphate product was calculated (<4.44 $mmol^2/L^2$). The glomerular filtration rate (GFR) was calculated by MDRD formula. It is noted that not all patients underwent complete biochemical evaluation according to the AAES guideline [13]: serum 25(OH)D level was identified only in 92 cases and 24-h urinary calcium level is known only in 64 cases.

Imaging data (neck ultrasonography, sestamibi parathyroid scintigraphy, CT/MRI scan, abdominal ultrasound, dual-energy X-ray absorptiometry (DXA)) available in medical records were analyzed.

Statistical analysis.

Statistical analysis was performed with STATISTICA 10.0 software (StatSoft, Tulsa, OK, USA). Most characteristics demonstrated non-normal distribution, therefore, non-parametric criteria were used. Continuous characteristics of the subgroups were described by medians [Me] and quartiles [25;75]. For paired comparisons of quantitative characteristics, the Mann-Whitney test was used. When comparing more than two groups, the Kruskal-Wallis test with post-hoc multiple comparisons was used. Discrete characteristics were compared using the chi-square test (Fisher's exact test was used for binary characteristics).

RESULTS

The majority of PHPT patients were women (94.2%). Ranging from 23 to 87 years, the median age was 60 years, with 69.5% of patients over 55 years old. The age of males and females did not differ (55 vs 60, p = 0.08). General characteristics of PHPT patients are presented in the Table 1.

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Clinical manifestation of PHPT included fragility fractures or osteitis fibrosa cystica, nephrolithiasis or nephrocalcinosis and other associations such as gallstones, peptic ulcer disease (PUD), erosive gastritis and erosive reflux esophagitis (Table 1).

Eighty-nine percent of patients underwent ultrasonography and in 94 % of cases the parathyroid adenoma was found. The sestamibi parathyroid scan was positive in 90 % of the 279 patients. Neck CT used less frequently, in only 134 (34.1 %) patients and was positive in 95.5% of cases. Neck MRI performed only in 14 patients, and was positive in 81.8% of cases.

Three hundred ninety-three patients (99.7%) had at least one criterion for surgery according to the guideline [13]: serum total calcium level more than 0.25 mmol/L above normal range, GRF less than 60 ml/min/1.73m^2, nephrocalcinosis/nephrolithiasis, DXA T-score less than -2.5SD, evidence of fragility fractures and age younger 50.

A total of 387 patients underwent parathyroidectomy. The vast majority had removal of a single adenoma (360 patients; 93.0%). Multiple adenomas were identified in 20 (5.2%) cases and only 7 patients (1.8%) had hyperplasia of parathyroid glands. Seven patients did not undergo parathyroid surgery: four patients refused, two of them had severe concomitant diseases and one did not have indication for surgical intervention.

Based upon the current guidelines [13, 15], patients were divided into two groups; symptomatic patients demonstrated one or more of these clinical manifestations and constituted 56.4 % (222 subjects) of the sample size. Asymptomatic patients had none of these clinical manifestations and constituted 43.6 % of the sample size (Table 2).

The median age of the symptomatic and asymptomatic PHPT patients did not differ (60 & 59 years, respectively, p=0.36). Also, the time between the first clinical or laboratory symptoms and diagnosis was the same in groups.

About half of the patients had low bone mineral density (BMD) and we did not find differences in DXA-based BMD at all three sites in symptomatic and asymptomatic patients

(Table 2). However, osteoporosis was more frequent among symptomatic ones (56.8% & 37.0%, p=0.0001).

We did not find the difference in adenoma size and 25(OH)D level between the groups, but the symptomatic patients demonstrated higher iPTH level (202.9 & 181.0 pg/ml, p=0.022). It should be noted that the subgroup who had 25(OH)D measurements represented only about 23% of the entire group. Serum 25(OH)D level was negatively correlated with PTH (r= -0.294, p=0.005), iCa (r= -0.268, p=0.010) and total Ca (r= -0.284, p=0.014) levels. All patients with known 25(OH)D level received vitamin D supplementation, but the vitamin D deficiency was compensated only in two patients before surgery.

Expected relationships between laboratory characteristics were noted between PTH and iCa (r= +0.450, p<0.0001); total Ca (r= +0.377, p<0.0001); phosphorus level (r= -0.308, <0.0001); and the ALP (r= +0.377, p=0.006). The 24-h urinary calcium excretion was negatively associated with age (r= -0.561, p<0.0001), creatinine level (r= -0.314, p=0.022) and positively associated with GRF (r= +0.488, p=0.0002). Negative correlations between PTH and BMD values were found in lumbar spine (r= -0.291, p=0.011) and distal radius (r= -0.472, p=0.006). There was no significant correlation between PTH and T-score in proximal femur (p=0.17).

Patients with symptomatic PHPT were subclassified into several groups depending on their clinical presentation (Table 3). More than a half of patients (50.9%) had renal manifestations (nephrolithiasis or nephrocalcinosis); a smaller number but nevertheless noteworthy 26.1% had disorders of the gastrointestinal tract (GI) only (cholelithiasis – 29 cases, peptic ulcer disease – 22 cases, erosive gastritis and esophagitis – 16 cases). Approximately 13% of patient had predominantly skeletal manifestations (fragility fractures or osteitis fibrosa cystica). The combination of skeletal, renal and GI involvement was seen in 9.5% of cases.

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Results of analysis showed that patients with predominantly renal manifestations were younger than those with GI and skeletal manifestations (59 & 62 & 64 years respectively). In addition, we found differences in iPTH level (265.8 & 187.1 pg/ml respectively) between skeletal and GI subgroup patients.

Interestingly, manifestations of CVD were observed in a large number of patients constituting 67.7% (267) of the entire cohort. Among cardiovascular diseases we observed arterial hypertension in 252 cases, angina pectoris in 41 cases, history of myocardial infarction in 15 cases, silent myocardial ischemia in 6 cases, cardiac conduction disturbances in 16 cases, cardiac rhythm disturbances in 37 cases, heart failure in 41 cases, acquired heart valve disease in 12 cases, and congenital heart valve disease in 6 cases. Seven patients underwent percutaneous transluminal coronary angioplasty, seven had a history of stroke and another two had a history of pulmonary embolism. Involvement of the cardiovascular system did not differ in symptomatic and asymptomatic subjects (70.7% vs 63.4%, p=0.076). Both age and BMI were higher in patients with CVD, whether or not they were symptomatic (62 & 53 years, p <0.0001; 30.4 vs 26.0 kg/m^2, p<0.0001, respectively), compared with patients with PHPT and no CVD.

When it comes to surgery, we found that focused parathyroidectomy was performed in 289 cases, unilateral neck exploration was performed in 6 cases and bilateral neck exploration in 47 cases. Six patients underwent parathyroidectomy plus thyroidectomy and in 36 cases there were parathyroidectomy was accompanied by hemithyroidectomy. In three cases videothoracoscopy was performed. Analysis of the postoperative period revealed hypocalcemia, which required urgent use of calcium supplements and active form of vitamin D, in 5.6% of patients. But in most cases hypocalcemia was transient. We did not find association between serum calcium level and the type of surgical approach. Of 90 interviewed patients who underwent parathyroidectomy, only four patients had permanent postoperative hypoparathyroidism, requiring constant intake of calcium and vitamin D supplementation.

Three of these patients underwent bilateral neck exploration and in one case parathyroidectomy plus hemithyroidectomy was performed.

DISCUSSION

In this report, we provide new information from a large cohort of 394 PHPT patients from three major medical Centers in Saint-Petersburg, Russia covering the period from 2011 to 2018. Because of the large cohort size, our experience has enabled a demographic analysis and comparison of the different clinical presentations. Of interest, since virtually all of these patients met at least one criterion for surgery, whether they were symptomatic or not, the data are specifically relevant for patients meeting surgical guidelines.

In our study females predominated to a greater extent in contrast to other studies [5, 13, 15]. Of note, based on the current Russian PHPT register, from a total of 1,914 patients there are only 178 men (9.3%) with a F:M ratio close to 9,8:1. But for patients around the age of 50 years the F:M ratio was 16:1, which is consistent with our research [16]. This could be explained by the general demographic features in the country from one hand, and the passive attitude of men when it comes to seeking medical care from the other hand. The average age of the patient population was 60 years, consistent with most observations that this disease surfaces most commonly in the first decade after menopause [5, 15]. As the study results showed, symptomatic PHPT remains the dominant form in Russia and other developing countries, where measuring of serum calcium level is not included in routine screening. S.K Bhadada and colleagues reported 95% symptomatic subjects among a cohort of 464 patients [17]. While V. J. Mallikarjuna and colleagues reported only 38% of asymptomatic subjects of their 54 patients [18]. More than 55% of patients in our study had symptomatic PHPT with classical skeletal and renal manifestations. Consequently, skeletal involvement was more common in females while the frequency of other manifestations was the same independently of gender. L. Meng and colleagues compared patients from USA and China and found that female

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PHPT patients might be more sensitive to bone loss and that male patients might be more likely to develop renal disease [19]. Osteitis cystica fibrosa is a rare skeletal PHPT manifestations nowadays. It is found in 2-3% of PHPT patients [20, 21]. Brown tumors commonly affect pelvic bones, femur, tibia, ribs or clavicles. In our study only six patients (1.5%) had brown tumors with the most frequent localization in pelvic bones, and all of them had renal or gastrointestinal disorders.

Gastrointestinal manifestation is not so common as skeletal or renal disturbances [22]. It includes peptic ulcer disease, pancreatitis, gallstone disease, erosive lesions of upper GI tract. But most of patients have any common GI complains, such as abdominal pain, nausea, constipation, heartburn or loss of appetite. Gallstone disease is more common in women compared to men, and the risk of its occurrence increases with age. The prevalence of cholelithiasis varies near 10-30% of population [23]. In our study 17.1% of patients had gall stones and there was no difference between men and women. But the frequency of gall stones was higher in patients older than 55 years compared to younger ones (14.8% & 2.3%, p=0.007) as it is in common population.

Pancreatitis is not uncommon complication of PHPT, however, in few countries, such as India, where symptomatic form is more common, pancreatitis is reported in 10-20% of PHPT patients [23]. In our study 57 patients had sings of chronic pancreatitis in their medical records and 12.8% of them were symptomatic, which is consistent with the data in other [24]. However, we exclude the possibility that pancreatitis was a comorbid disease in these patients and just in one case (young woman) we have confirmation that pancreatic calculi were associated with PHPT.

Of great interest is the widespread prevalence of CVD manifestations among our symptomatic and asymptomatic subjects. Approximately 65% of patients in both groups had one or more cardiovascular diseases. Mechanisms to account for these observations continue

to be speculative, including direct effects of PTH on the vascular endothelium and cardiomyocytes [25-27]. Vitamin D deficiency may also be etiologic in these patients who demonstrate CV involvement [28]. There are some studies that demonstrated the relationship of cardiovascular morbidity with iPTH level [29, 30]. D. Han et al [31] identified the prevalence of CV risk factors in patients with PHPT, especially in men, compared to the general population in New Jersey. It is known that male gender is a risk factor for CAD. In general, Russian population men are affected with CAD in three times more than women. According to Russian statistic agency the incidence of CAD in 2018 was 308.7 per 100,000 and mortality from CAD in men was much higher than in women (322.5 & 296.8 per 100,000 respectively) [30]. In our study of 28 men five subjects (17.9%) had CAD and there was no difference between females and males.

This experience adds an important dimension to the international demographics of PHPT, emphasizing how the clinical presentations of this disease will vary according to the referral patterns, standard evaluation procedures, and the prevalence of vitamin D deficiency.

Limitations

The limitations of this study are its retrospective nature and absence of a direct contact with patients. All data were collected only from medical histories, including the diagnoses and results of molecular-genetic tests. Infrequent assessment of both serum 25(OH)D level and the need of vitamin D deficiency compensation before surgery, does not allow us to finally rule out secondary PHPT in all cases. Infrequent measurement of 24-h urinary calcium and lack of determination of calcium-creatinine ratio in urine does not allow us to rule out familial hypocalciuric hypercalcemia. Also, infrequent measurement of both total and ionized calcium, phosphorus, alkaline phosphatase, lack of the DXA results in some medical histories, lack of the results of the abdominal ultrasound did not allow us to fully describe the differences between the clinical forms of the disease.

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Declaration of interest

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

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Table 1. General characteristics of patients with PHPT

Parameters	Values Median [25; 75 quartile], %	Normal range
Age, years	60 [53; 67]	N/A
Age over 55 years, n (%)	273 (69.3 %)	N/A
Gender: Female, n (%) Male, n (%)	371 (94.2%) 23 (5.8 %)	N/A
BMI, kg/m2	28.4 [25.6; 33.6]	18.5 - 24.9
Known duration of PHPT*, years	1.0 [1.0; 3.0]	N/A
Osteoporosis, n (%)	190 (48.2%)	N/A
Fractures, n (%)	46 (11.7%)	N/A
Osteitis fibrosa cystica, n (%)	7 (1.8%)	N/A
Nephrolithiasis/ nephrocalcinosis, n (%)	135 (34.3%)	N/A
Gallstone disease, n (%)	68 (17.1%)	N/A
Peptic ulcer disease, n (%)	43 (10.9%)	N/A
Erosive gastritis and erosive reflux esophagitis, n (%)	33 (8.4%)	N/A
Cardiovascular disease, n (%)	267 (67.8%)	N/A
Diabetes mellitus, n (%)	48 (12.2%)	N/A
Adenoma size, cm	1.6 [1.3; 2.5]	N/A
iPTH, pg/ml (n=394)	190.5 [133.3; 308.6]	15.0 - 65.0
Serum total Ca, mmol/l (n=205)	2.79 [2.69; 2.92]	2.15 - 2.65
Serum iCa, mmol/l (n=370)	1.49 [1.41; 1.58]	1.11 - 1.32
Serum P, mmol/l (n=161)	0.92 [0.81; 1.09]	0.81 - 1.45
ALP, IU/l (n=54)	96.6 [71.0; 127.2]	<105.0
24-h calciuria, mmol/24h (n=64)	8.6 [3.9; 10.8]	2.5 - 8.0
Creatinine, mcmol/l (n=394)	75.5 [65.6; 89.0]	50.0 – 97.0
GFR**, ml/min/1.73m2 (n=394)	79 [63; 91]	>90
25(OH)D, ng/ml (n=91)	14.8 [9.4; 19.8]	30.0 - 100.0

*Known duration of PHPT is a time between the first signs of PTPH and the surgery
BMI – body mass index; total Ca – total calcium; iCa – ionized calcium; P – phosphorus; CPP – calcium-phosphorus product; ALP – alkaline phosphatase; GFR – glomerular filtration rate (**was calculated by MDRD formula); iPTH – intact PTH; 25(OH)D – 25-hydroxyvitamin D.

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Table 2. Characteristics of symptomatic and asymptomatic PHPT patients

Parameters	Symptomatic PHPT n=222	Asymptomatic PHPT n=172	p
Age, years	60 [53; 67]	59 [53; 66]	0.36
Gender: Female, n (%) Male, n (%)	208 (93.7%) 13 (6.3%)	162 (94.2%) 10 (5.8%)	0.56
BMI, kg/m2	29.1 [25.7; 35.0]	27.9 [25.1; 33.4]	0.50
CVD, n (%)	157 (70.7%)	109 (63.4%)	0.076
Diabetes mellitus, n (%)	31 (13.6%)	16 (9.3%)	0.16
T-score, SD: L1-L4 Femoral Neck 1/3 Radius	-2.5 [-3.2; -1.4] n=43 -2.0 [-2.4; -1.3] n=42 -3.9 [-4.2; -1.8] n=17	-2.2 [-2.8; -1.2] n=32 -1.5 [-2.7; -0.8] n=30 -2.5 [-3.6; -1.5] n=16	0.23 0.47 0.12
Adenoma size, cm	1.7 [1.2; 2.5]	1.6 [1.4; 2.2]	0.96
Serum total Ca, mmol/l	2.81 [2.67; 2.96], n=117	2.79 [2.70; 2.90], n=88	0.55
Serum iCa, mmol/l	1.49 [1.42; 1.58], n=214	1.49 [1.40;1.58], n=156	0.59
Serum P, mmol/l	0.90 [0.81; 1.07], n=89	0.96 [0.79; 1.09], n=72	0.74
ALP, IU/l	87.2 [70.2; 132.0], n=32	99.3 [79.6; 127.2], n=22	0.73
24-h urinary calcium, mmol/24h	8.6 [4.0; 10.8], n=37	8.6 [3.2; 9.8], n=27	0.73
GFR, ml/min/1.73m2	78 [58; 91], n=222	81 [67; 91], n=172	0.56
iPTH, pg/ml	202.9 [140.1; 352.9] n=222	181.0 [127.6; 246.7] n=172	0.022
25(OH)D, ng/ml	13.3 [9.2; 16.9], n=52	15.4 [10.9; 20.3], n=39	0.13

BMI – body mass index; CVD – cardiovascular disease; total Ca – total calcium; iCa – ionized calcium; P – phosphorus; CPP – calcium-phosphorus product; ALP – alkaline phosphatase; GFR – glomerular filtration rate; iPTH – intact PTH; 25(OH)D – 25-hydroxyvitamin D.

Table 3. Comparative characteristics of patients with symptomatic form of PHPT (n=201)

Parameter	Skeletal manifestation, n=30 1	Renal manifestation (nephrolithiasis/ nephrocalcinosis), n=113 2	Gastrointestinal manifestation, n=58 3	p
Age, years	64 [54; 69]	59 [51; 66]	62 [56; 69]	0.06 $p_{\#1-2}$ 0.14; $p_{\#1-3}$ 0.96; $p_{\#2-3}$ 0.029
Gender: Female, n (%) Male, n (%)	30 (100%) 0	102 (90.3%) 11 (9.7%)	57 (98.3%) 1 (1.7%)	0.037
BMI, kg/m2	27.6 [24.4; 30.8]	28.7 [25.6; 33.4]	32.5 [26.1; 39.5]	0.15
CVD, n (%)	22 (73.3%)	74 (64.6%)	47 (81.0%)	0.078 $p_{\#1-2}$ 0.28; $p_{\#1-3}$ 0.28; $p_{\#2-3}$ 0.05
Diabetes mellitus, n (%)	5 (16.7%)	15 (13.3%)	7 (12.1%)	0.89
T-score, SD L1-L4 Neck 1/3 Radius	-2.9 [-3.9; -1.9] n=7 -2.1[-2.8; -1.6] n=7 -4.5[-4.5; -4.5] n=2	-2.5 [-3.3; -1,6] n=22 -2.3 [-2.7; -1.9] n=18 -4.0[-4.8; -1.8] n=8	-1.9 [-2.6; -0.9] n=7 -1.5[-1.8; -1.08] n=9 -3.0 [N/A] n=1	0.34 0.026 $p_{\#1-2}$ 1.0; $p_{\#1-3}$ 0.026; $p_{\#2-3}$ 0.014 0.45
Adenoma size, cm	1.5 [1.3; 2.1]	1.8 [1.2; 2.5]	1.6 [1.2; 2.0]	0.69
Serum total Ca, mmol/l	2.78 [2.66; 2.92] n=20	2.88 [2.70; 3.01] n=55	2.77 [2.67; 2.82] n=27	0.08 $p_{\#1-2}$ 0.15; $p_{\#1-3}$ 0.88; $p_{\#2-3}$ 0.043
Serum iCa, mmol/l	1.48 [1.41; 1.55] n=29	1.52 [1.43; 1.61] n=108	1.49 [1.41; 1.59] n=57	0.21
Serum P, mmol/l	0.92 [0.87; 1.04] n=14	0.90 [0.80; 1.08] n=44	0.88 [0.76; 0.98] n=20	0.69
ALP, IU/l	132.0 [87.9; 249.2] n=5	87.2 [70.4; 109.3] n=13	82.2 [61.0; 134] n=7	0.43
24-h calciuria, mmol/24h	6.2 [2.7; 9.0], n=3	8.8 [4.6; 10.8], n=19	9.2 [8.1; 11.9], n=8	0.21
GFR, ml/min/1.73m^2	95 [66; 111], n=29	78 [58; 91], n=113	75 [46; 91], n=58	0.25
iPTH, pg/ml	265.8 [176.2; 443.8], n=29	205.9 [146.7; 364.0], n=113	187.1 [125.7; 259.0], n=21	0.031 $p_{\#1-2}$ 0.10; $p_{\#1-3}$ 0.010; $p_{\#2-3}$ 0.11
25(OH)D, ng/ml	11.1 [9.2; 16.3] n=10	14.9 [10.2; 27.2] n=22	12.8 [8.0; 16.7] n=14	0.38

p - Kruskal-Wallis test; $p_{\#}$ - Mann-Whitney test; $p_{\#1-2}$ comparison "predominantly skeletal manifestation" group and "predominantly renal manifestation" group; $p_{\#1-3}$ comparison "predominantly skeletal manifestation" group and "gastrointestinal manifestation" group; $p_{\#2-3}$ comparison "predominantly renal manifestation" group and "gastrointestinal manifestation" group; BMI – body mass index; CVD – cardiovascular disease; total Ca – total calcium; iCa – ionized calcium; P – phosphorus; CPP – calcium-phosphorus product; ALP – alkaline phosphatase; GFR – glomerular filtration rate; iPTH – intact PTH; 25(OH)D – 25-hydroxyvitamin D.