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ORIGINAL ARTICLES

PRIMARY HYPERPARATHYROIDISM – A CONTEMPORARY PICTURE BASED ON 100 PATIENTS FROM THE LAST DECADE

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Abstract. *Primary hyperparathyroidism (PHPT) is an endocrine disease, the clinical picture of which has slowly shifted to milder and asymptomatic forms during the last decades.* ***Objective:*** *to describe the clinical presentation and the main laboratory and imaging findings in a group of patients with PHPT diagnosed during the last 10 years.* ***Materials and Methods:*** *This was a retrospective cross-sectional study with data review from the database of a tertiary endocrine clinic from the last 10 years. Secondary causes for elevated PTH were excluded. The major clinical symptoms and signs of hypercalcemia/HPT were reviewed as well as concomitant diseases and medications. Serum calcium (total, albumin-corrected and ionized; sCa, corrCa, iCa^{+}), phosphates (P), magnesium, creatinine, alkaline phosphatase, beta-crosslinks were measured. The intact parathyroid hormone (iPTH) and 25(OH)-vitamin D were determined by electro-hemi-luminescence (Elecsys, Roche Diagnostics). 24-hour urinary probes for calcium and phosphate were collected. Neck ultrasound (US) was used as the localization study of choice. Almost half of the participants underwent fine-needle aspiration biopsy (FNAB) with cytology and needle-washouts for iPTH. One fourth of the patients were assessed by Single-Photon Emission Tomography (SPECT-CT). Data on bone density (from DXA), fractures and renal stones (from renal US) were collected.* ***Results:*** *One hundred patients met the study criteria – 95 were women. Most of them were in their 5th and 6th decades. The median corrected sCa was 2.73 mmol/l, iCa^{+} – 1.39 mmol/l, P – 0.88 mmol/l, iPTH – 14.5 pmol/l and 25(OH)D – 54.0 nmol/l. Normal sCa was registered in 20 participants (20%), while normal sP – in 67.0%. The neck US located single lesions (parathyroid adenoma) in 81% – behind or below the left inferior pole of the thyroid gland in 33 cases (33%) and contra-laterally in another 33%. FNAB of the suspicious lesion had been performed in 51% of the study subjects. The cytology confirmed the presence of parathyroid cells in 22 cases (43.1%), Bethesda II thyroid nodules in 21 cases (41.2%), Bethesda III nodules in 2 cases (3.9%) and insufficient samples (Bethesda I) in 5 cases (9.8%). SPECT-CT from 27 patients identified a suspicious left parathyroid in 11 cases, a right one – in 6 cases, as well as three ectopic locations. BMD data were available in 66 female patients and showed a higher prevalence of osteoporosis than in the general age-matched population; fractures, however, were not more frequent. Data from renal ultrasound were available in 77% and revealed chronic pyelonephritis without stones in 8 patients and renal stone disease – in 37 patients.* ***Conclusion:*** *To our knowledge, this study is the first of its kind in our country during the last two decades. Mild to moderate hypercalcemia was very common, although most patients were oligo- or asymptomatic.*

Renal and bone involvement were surprisingly frequent, with reduced eGFR and low bone mass being more prevalent than in the general population. The most typical location was a single parathyroid lesion within the lower glands. The use of SPECT-CT seems to decline and is replaced by US-guided FNAB with needle washout measurements of iPTH and cytological examination. Although the general picture of PHPT is shifting towards milder and asymptomatic (and probably earlier) forms of the disease, the classical clinical presentation can still be found in everyday practice.

Key words: *parathyroid glands, primary hyperparathyroidism, laboratory findings, localization studies, comorbidities*

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the endocrine diseases, the diagnosis of which had been made easier by recent advances in laboratory and imaging technologies. PHPT has been known for many decades as the disease of "stones, bones and moans" as described by F. Albright in the 1940's [1]. The improved measurements of serum calcium levels since the 1970's have led to the description of a milder, possibly earlier asymptomatic form of the disease. This asymptomatic form has widely replaced the classical musculoskeletal or renal form of PHPT and is now regarded as the predominant form [2, 3]. The introduction of sophisticated methods for measurement of serum intact parathyroid hormone (iPTH) around the millennium years has enabled the diagnosis of PHPT at a point when serum calcium is still not elevated – the so called "normocalcemic" form [4].

In addition, the wide spread screening for osteoporosis has led to a more active search for bone mineral abnormalities. The routine measurement of serum calcium and eventually iPTH have become part of the lab panel in the work-up of osteoporosis [5]. Around 1.0-1.5% of all postmenopausal women with osteoporosis are expected to have some form of PHPT [6]. On the other hand, imaging technologies and especially neck ultrasound are often the first investigation raising the suspicion for enlarged parathyroid glands [7].

The prevalence of PHPT in the general population is not negligible. Large analyses cited figures around 3-4/1000 [6, 8, 9]. In a representative Bulgarian population sample the prevalence of hyperparathyroidism (HPT) among 2032 individuals was 3.59%, and increased with age – from 1.9% in the younger groups to 6.8% among individuals > 60 years ($p < 0.05$) [10]. The authors identified the serum vitamin D levels /25(OH)D/ and the estimated glomerular filtration rate (eGFR) as major factors affecting the serum levels of PTH [10].

The objective of our study was to describe the clinical presentation and the main laboratory and imaging findings in a group of patients with diagnosed PHPT during the last decade.

MATERIALS AND METHODS

Design

The study design was retrospective cross-sectional. It was based on data extraction from an electronic database of a tertiary endocrine clinic. All patients had signed informed consent prior to hospitalization. The inpatients' hospital records for the last ten years were searched through with the keyword "primary hyperparathyroidism". One hundred sixty (160) possible patient records were identified. Fifty-five of the cases with hyperparathyroidism (HPT) were due to secondary causes and were labeled as secondary hyperparathyroidism (SHPT). Five cases had incomplete data and were not included in the analyses.

Primary hyperparathyroidism (PHPT) was defined as either a combination of high albumin-corrected or ionized serum calcium and high parathyroid hormone (PTH), or as inappropriately high PTH in the presence of high normal calcium levels [6,8]. Based on the available records other causes for elevated PTH were excluded including but not limited to: CKD grade 4 and 5, malabsorption syndromes, hypercalciuria due to other causes (loop diuretics, idiopathic, etc.), pseudohyperparathyroidism, severe hypothyroidism, recent application of high doses of denosumab or bisphosphonates [11].

Pre-hospitalization data

The medical history of the patients was reviewed and the clues leading to the suspicion/diagnosis of PHPT were identified: clinical complaints (renal stones or nephrocalcinosis, bone fractures, low bone mass or osteoporosis, gastro-intestinal complaints and others), laboratory measurements (serum calcium, phosphate or PTH) or imaging findings (ultrasound, nuclear imaging, etc.). The initial lab measurements of total/ionized serum calcium, phosphate, PTH and 25(OH)-vitamin D were identified.

Data collection

All data were part of the routinely performed investigations for PHPT. The major clinical symptoms and signs of hypercalcemia/HPT were reviewed: renal stones, nephrocalcinosis, renal failure, pyelonephritis etc.; low bone mass/osteoporosis and/or fractures; gastro-intestinal complaints or diseases.

The prior or current use of thiazide and loop diuretics, vitamin D and calcium supplements, antiresorptive bone agents (bisphosphonates, denosumab) was included in the analysis. Comorbidities with possible regard to calcium-phosphate metabolism were identified.

Laboratory and hormonal data

Total serum calcium was measured by a photometric assay and whenever possible by atomic absorptiometry – Ca-AAS (reference range 2.12-2.62 mmol/l). Albumin-corrected calcium was calculated by the formula:

Corrected calcium (mmol/l) = total serum calcium (mmol/l) + 0.8 x (mean albumin – patient's albumin in g/l), where mean albumin was 44 g/l (local lab reference range for albumin 35-52 g/l; and for corrected sCa: 2.10-2.60 mmol/l).

The calcium-phosphorus product was calculated. Ionized calcium (iCa^+) was measured by atomic absorptiometry (reference range 1.1-1.3 mmol/l).

Intact PTH (iPTH) was measured by a second generation assay (Elecsys, Roche Diagnostics, Switzerland) and expressed in pmol/l (reference range 1.59-6.89 pmol/l). External lab PTH values in pg/ml or ng/l were converted into SI units (pmol/l) by a factor of 9.43 (division). Serum levels of vitamin D were measured by electro-hemi-luminescent detection (ECLIA method) as 25(OH)D Total (Elecsys, Roche Diagnostics, Switzerland). Levels of 25(OH)D ≤ 25.0 nmol/l were interpreted as deficiency, levels between 25.0 and 50.0 nmol/l – as insufficiency, and above 50 nmol/l – as sufficiency. Optimal 25(OH)D levels were accepted for values above 75.0 nmol/l.

Serum creatinine was measured by a colorimetric method and the estimated glomerular filtration rate (eGFR) was calculated according to the MDRD-formula and expressed in ml/min/1.73 m^2. Urinary excretion of calcium and phosphate was measured from 24h urinary samples in mmol/24 hr. Total alkaline phosphatase in IU/l and serum Beta-crosslinks in ng/ml (Elecsys, Roche Diagnostics, Switzerland) were also measured.

Imaging

The localization studies included neck ultrasound of all patients (by a linear 9-12 MHz transducer, including Doppler imaging) and single-photon emission computed tomography (SPECT-CT) in selected cases. Conventional CT or MRI scans were available in a few patients. In cases of single parathyroid adenoma its volume was calculated by multiplying the three diameters (anterior-posterior, medial-lateral, proximal-distal) and dividing the product by a factor for ellipsoids of 0.48.

Additional localization studies included fine-needle biopsy (FNAB) of the suspected parathyroid lesion with cytological analysis of the specimen and/or measurements of iPTH in the needle washout.

Bone density measurements by dual-energy X-ray absorptiometry (DXA) had been recommended to all patients. BMD T-scores at the lumbar spine, total hip, femoral neck and/or proximal radius were included in the analyses where available. Data on previous fractures were also included.

Abdominal ultrasound had been performed routinely to check for renal stone disease, pyelonephritis or nephrocalcinosis.

Statistical analysis

All analyses were performed on an IBM SPSS 13.0 for Windows platform (SPSS Corp., Chicago, IL). Descriptive statistics and frequency analysis were performed. Missing data were not replaced. Data were checked for normal distribution. Most of the data were positively skewed, thus medians and quartile ranges were used. Statistical significance was set as $p \leq 0.05$.

RESULTS

One hundred (100) patients met the criteria for PHPT and had complete data. They included 95 female and 5 male participants. Their age distribution is shown in Fig. 1. Most patients with PHPT were in their sixth decade (almost half of all), followed by the fifth decade.

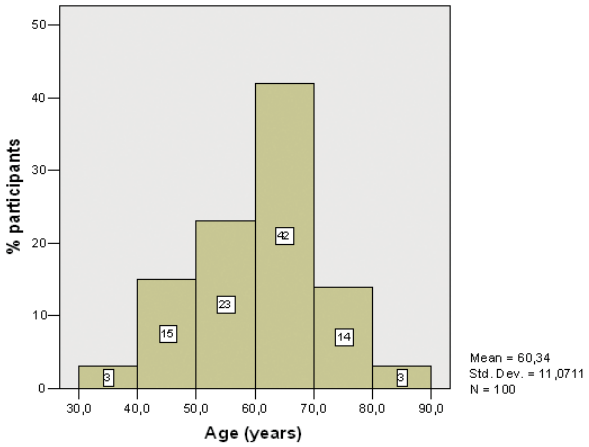


Fig. 1. Age distribution of the participants

Data available prior to the analyzed hospital stay

In most cases the disturbance of the calcium-phosphate metabolism had been diagnosed prior to the hospital stay for a median of 1.0 year, interquartile range (IQR) 0.5-3.0 years, with a minimum of 0.0 (newly diagnosed) and a maximum of 10 years. The most common causes rising suspicion for PHPT were a routine measurement of serum calcium (in 26%), followed by lab investigations for osteoporosis (in 20%) and neck ultrasound for thyroid disease (18%). The next most common diagnostic step had been measurement of PTH (in 40%) or serum calcium (in 24%).

The first available laboratory data prior to the hospital stay are presented in Table 1.

Biochemical and hormonal data

The biochemical and hormonal data of the patients as found during the analyzed hospital stay are presented in Table 2. The distributions of uncorrected and corrected total serum calcium values (sCa and corr. sCa), of serum 25(OH)D and eGFR are presented in Table 3.

Table 1. The laboratory data at the time of the first suspicion for PHPT, prior to the analyzed hospital stay

	Serum calcium (sCa, mmol/l)	Ionized calcium (Ca++, mmol/l)	Serum phosphate (sP, mmol/l)	Intact PTH (iPTH, pmol/l)	25(OH)D, nmol/l
% data available	83	37	64	83	55
Median	2.75	1.38	0.88	15.8	33.3
Minimum	2.14	0.82	0.57	7.2	7.5
25th percentile	2.61	1.30	0.77	12.1	24.3
75th percentile	2.88	1.46	1.02	25.0	55.0
Maximum	4.27	2.05	1.45	226.0	127.0

Table 2. The biochemical and hormonal data of the patients as found during the analyzed hospital stay

	Total sCa, mmol/l	iCa^{++}, mmol/l	Corr. sCa, mmol/l	sP, mmol/l	sMg, mmol/l	iPTH, pmol/l	25(OH)D, nmol/l	eGFR, ml/min/1.73 m^2	uCa, mmol/day	uP, mmol/day	ALP, IU/l
Median	2.71	1.39	2.73	0.88	0.84	14.5	54.0	59.9	5.57	16.96	100.5
25th percentile	2.57	1.31	2.56	0.78	0.77	12.0	31.0	48.9	2.70	12.20	69.0
75th percentile	2.97	1.50	3.18	1.00	0.87	23.7	77.3	78.2	8.18	22.95	129.5
Minimum	2.28	1.12	2.15	0.48	0.48	7.3	7.5	30.7	0.12	1.55	40.0
Maximum	4.69	2.44	4.70	1.38	1.91	225.4	190.0	132.0	22.23	77.76	1359.0

Table 3. The distributions of uncorrected and corrected total serum calcium values (sCa and corr. sCa), of serum 25(OH)D and eGFR are presented in percentages

	Total sCa, uncorrected, mmol/l (Ref. range 2.12-2.62)			
Cut-off values	≤ 2.62	2.63-3.00	3.01-3.50	> 3.50
% patients	36	44	13	7
	Albumin-corrected sCa, mmol/l (Ref. range 2.1-2.6)			
Cut-off values	≤ 2.60	2.61-3.00	3.01-3.50	> 3.50
% patients	29	38	18	15
	Serum 25(OH)D Total, nmol/l (Sufficiency ≥ 50 nmol/l)			
Cut-off values	< 25	25.0-49.9	50.0-74.9	≥ 75.0
% patients	16	30	24	31
	eGFR – MDRD, ml/min/1.73 m^2			
Cut-off values	30-44.9	45-59.9	60.0-89.9	≥ 90
% patients	16	31	44	9

Table 3 shows that less patients were assessed as normocalcaemic when albumin-corrected Ca was used instead of total serum values. Ionized calcium exceeded 1.30 mmol/l in 77.0% of the patients, and 1.32 mmol/l (local URR) – in 71.0%. Based on both corrected total and ionized calcium, only 20% of the participants had a normocalcaemic form of PHPT. Serum phosphate was ≤0.8 mmol/l in 33.0% of the patients while 67.0% were having normal serum phosphate levels. The calcium-phosphate product exceeded 4.4 $mmol^2/l^2$ in only 4 patients (4%). Serum magnesium was low ≤ 0.65 mmol/l in only 6.0% and ≤ 0.70 mmol/l – in 11.0%.

Intact PTH was above the reference range in all patients but ≤ 30.0 pmol/l in 84% of them. The serum alkaline phosphatase was elevated in only 16% of the patients.

Imaging (localization studies)

The neck ultrasound (US) located single lesions suspicious for parathyroid adenoma in 81 patients (81%). The suspected lesion was behind or below the left inferior pole of the thyroid gland in 33 cases (33%), behind the middle left portion – in 4%, at the upper left pole – in 3%, at the right upper pole – in 1%, behind the middle right lobe – in 6%, and behind or below the right inferior pole – in 33%. One lesion had an isthmic location. The localization could not be identified by US in 19 cases (19%). The median volume of the suspected parathyroid lesions was 0.7 cm3 (IQR 0.3-1.8 cm3). The US volume was below 1.0 cm^3 in 60% and below 2.0 cm^3 – in 77% of the cases, exceeding 5.0 cm^3 in only 11% (maximal volume 7.5 cm^3).

The neck US had revealed thyroid nodules in addition in 42 patients (42%) with half of them (21 cases, 50%) having a single nodule, and 21.4% – two nodules.

Fine-needle biopsy of the suspicious lesion had been performed in 51 cases (51% of the whole study sample). The cytology confirmed the presence of parathyroid cells in 22 cases (43.1%), while a suspicion for parathyroid carcinoma was raised in 1 case. Out of the remaining 29 cases the cytology revealed Bethesda II thyroid nodules in 21 cases (41.2%), Bethesda III nodules in 2 cases (3.9%), insufficient samples (Bethesda I) in 5 cases (9.8%) and suspicion for lymphoma or metastatic lesion – in 1 case (2.0%).

Needle washout measurements of iPTH were performed in 46 patients (46% of the study sample), with 24 patients (24%) providing washout samples from two different biopsies. The median value of iPTH in the washouts was 177.9 pmol/l. The iPTH from the needle washouts exceeded thrice the URR for serum iPTH (6.89 x 3 = 20.67 pmol/l) in 69.6% of the samples and those samples were regarded as truly positive. The second washout result was concordant with the first one in 20 out of 24 patients (83.3%), both washouts revealing positive results in 12 cases and negative results in 8 cases. In three cases the second washout was negative while the first had been positive, and vice versa in 1 case (first washout negative, second one – positive).

SPECT-CT had been performed in 27 patients. It identified a suspicious left parathyroid in 11 cases, a right one – in 6 cases, as well as three ectopic locations (1 retrotracheal, 1 retroesophageal and 1 mediastinal). All ectopic locations could not be accessed by US exam. In 7 cases SPECT-CT was unable to identify a parathyroid lesion. Both US and SPECT-CT findings were concordant in 18 of all 27 patients (66.7%), with US being positive and SPECT-CT negative in 5 cases (18.5%) and vice versa – in 4 cases (14.8%). Regular 3D-CT had been performed in 3 patients and MRI – in one patient, confirming possible ectopic location of the parathyroid tissue.

Metabolic bone disease

Dual-energy X-ray BMD data were available in 66 female patients: L1-L4 lumbar spine in 56, femoral neck BMD – in 42 and distal radius BMD – in 20 of them. The prevalence of normal, low BMD and osteoporosis based on the T-scores at the three measurement sites is presented in Figure 2.

Bone resorption markers (beta crosslinks) had been measured in half of the female participants. The median value of beta-crosslaps was 0.783 ng/ml (refer-

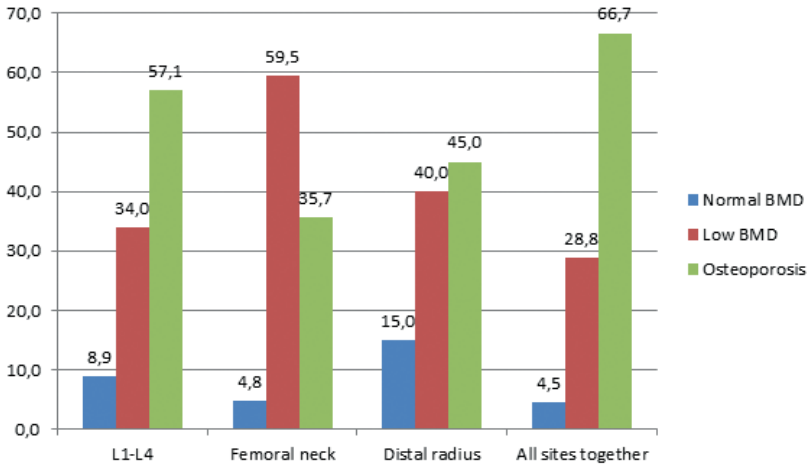


Fig. 2. The prevalence of normal, low BMD and osteoporosis at the different measurement sites is shown in percentages of all measurements

ence range for premenopausal women < 0.573 ng/ml) with interquartile values of 0.577 (25th percentile) and 1.160 (75th percentile), and a maximal value of 3.78 ng/ml. In fact, 30.2% of the values were above the upper reference range for postmenopausal women (1.05 ng/ml), a finding rarely seen in osteoporosis.

Seventy-five of all participants (75%) reported no previous bone fractures at all. Five participants had previous vertebral fractures (5%), and three – previous hip fractures (3%). Eight subjects reported wrist fractures (8%) and three – rib fractures (3%). One female patient reported to have been operated in the past for a brown tumor in the mandibular bone.

18 female patients with osteoporosis had been taking bisphosphonates prior to the hospitalization for PHPT (15 current and 3 past users), four patients were receiving denosumab. One patient reported previous use of strontrium ranelate and two patients – previous use of salmon calcitonin. One third of all patients reported previous short-term use of vitamin D supplements.

Renal involvement

Urinary calcium exceeded 6.5 mmol/l in 41% of the participants and 8.0 mmol/l (local URR) – in 29%. Very low values (uCa < 0.5 mmol/24 hrs) were found in 2 participants. Urinary phosphate exceeded 42 mmol/24 hrs in only 6 of the patients with PHPT.

Data from renal ultrasound were available in 77 participants (77%). In 32 of them (41.6%) the renal ultrasound had not found any pathology, however 6 of those patients with negative US had a positive history for renal stones in the past. The US showed suspicion for chronic pyelonephritis without stones in 8 patients and renal stone disease – in 37 patients. The exact data on the location and size of the renal stones are presented in Table 4. Four patients reported having previous lithotripsy and one – ureterotomy.

Table 4. Distribution, size and location of the diagnosed renal stones – data from renal US

Stone size, mm	Bilateral	Left kidney	Right kidney
≤ 5 mm	15 patients	4 patients	2 patients
6-10 mm	7	3	3
> 10 mm	1	1	1

Nephrocalcinosis was suspected in one patient, high-grade hydronephrosis was found in another one.

Concomitant diseases

Gastro-duodenal disease was reported by 9 participants: 5 with chronic gastritis/gastro-duodenitis, 2 with duodenal ulcers, 1 with gastro-esophageal reflux and 1 with a history of acute pancreatitis.

Anxiety/depression were reported by 7 participants (7%).

Autoimmune thyroid disease was present in 32 participants (32%) – 30 of them had autoimmune thyroiditis and two – Graves' disease. Seven patients (7%) had a history of thyroid surgery because of nodular disease. Five patients had a history of operations for PHPT (4 confirmed adenomas and one suspected parathyroid carcinoma).

Twelve participants (12%) reported data for malignant diseases: breast cancer (5 cases), colon carcinoma (2 cases), parotid cancer (1 case), lung carcinoma (1 case), prostatic carcinoma (1 case), malignant fibroma (1 case) and pharyngeal carcinoma (1 case).

Twenty-six participants (26%) were taking antihypertensive treatment; two had prior myocardial infarction and one – prior stroke. Four participants had known type 2 diabetes and another two – prediabetes.

DISCUSSION

We performed a study in a large sample of patients with PHPT. The most common finding leading to the diagnosis had been increased serum calcium further warranting measurements of serum PTH and possibly neck ultrasound. The proportion of normocalcaemic forms was rather low (20%), while reduced kidney function was a common finding (eGFR < 60 ml/min/1.73 m2 in 47.2%). Vitamin D insufficiency/deficiency rates were lower than reported previously in the general population [12]. iPTH was moderately increased in all but a few patients (≤ 30 pmol/l in 84%). Neck US located a possible parathyroid adenoma in 81% of the patients with 81% of the visible lesions being behind or below the lower portions of the thyroid lobes (inferior glans?). The use of FNA with cytological exams and needle washouts had been increasing (51% and 46%), partly replacing the need for SPECT-CT, the latter being used predominantly in cases with unclear US and FNA findings (SPECT-CT performed in 27%). The prevalence of low BMD and osteoporosis was much higher than previously reported in the general population; however the prevalence of low-trauma fractures was not increased in PHPT [13]. Renal stone disease was far more often diagnosed than expected (in 43 out of 77 cases – 55.8%).

The clinical and biochemical presentation of PHPT

The most recent study describing the clinical and biochemical picture of PHPT in Bulgarian patients is a 7-year retrospective analysis of 64 cases with HPT

(31 of them with PHPT) published in 2004 [14]. In the studied time period 1996-2002 nephrolithiasis followed by low bone mass/osteoporosis had been the leading cause for the diagnosis of PHPT. In our study sample high serum calcium found during routine annual check-ups or as part of the lab panel for osteoporosis was the most common finding. Serum calcium was also often found elevated after locating a suspicious lesion on thyroid ultrasound. The importance of measuring serum calcium has been well acknowledged for many years [15].

The proportion of normocalcaemic forms of PHPT in our sample was rather low (20%), compared to recent publications [4, 16]. This might be due to the rather high prevalence of chronic kidney disease grade III (in 47.2%) and grade II (in 44%) in combination with vitamin D deficiency (in 16.2%) or insufficiency (in 29.4%). In fact, only 8.8% of the patients had an eGFR ≥ 90 ml/min/1.73 m^2, and 30.9% – optimal vitamin D levels (≥ 75 nmol/l). However, the vitamin D levels of our patients with PHPT were higher than those reported in the general Bulgarian population [12]. The higher levels could be in part explained by vitamin D supplementation prior to the hospitalization in an attempt to control for possible secondary causes of HPT (as vitamin D deficiency).

Renal and skeletal involvement

A possible explanation for the markedly reduced eGFR in our study sample might be the high prevalence of kidney stone disease (55.8%). This percentage is higher than expected in asymptomatic PHPT [17] and rather close to that from the older seminal studies in PHPT [18, 19]. In addition, only two thirds of our patients with kidney stones had previous history or suggestive current symptoms. In the majority of cases the kidney stones were rather small (up to 5 mm) but located in both kidneys (bilateral disease). This proportion of patients with nephrolithiasis seems rather high if compared to data from the literature [20, 21]. Other explanations for the reduced eGFR might be the advanced age (most of the patients in the age subgroups > 60 yrs), the concomitant arterial hypertension (in 26% of the patients) and the toxic effects of oncology treatments (malignant disease present in 12% of the participants).

Osteoporosis was more common in our study sample than previously found in 1331 women form the National Osteoporosis Study in 2010 [13]. Osteoporosis and low BMD at the femoral neck were found in 35.7% and 59.5% of the patients with PHPT, while their proportions in the general populations were found to be 16.8% and 46.5%, respectively [13]. The lower BMD values in our study sample might be due to the skewed age distribution – most participants were women around and after the menopause. However, the prevalence of self-reported low-trauma fractures was similar in both samples – 23.3% (in the National Osteoporosis Study) versus 25% in PHPT. The difference in the BMD results might be partly due to the more advanced age of the patients with PHPT. Our data did not fit the hypothesis for predominant bone loss at the radius as a pure cortical site [22]. However, a few patients had BMD measured at all three sites (spine, hip and forearm); therefore we did not perform direct comparisons among the sites.

Parathyroid imaging

Our data confirmed the leading role of US as the localization study of first choice in PHPT. The proportion of positive US imaging is close to the upper sensitivity of this method as described elsewhere [23, 24]. However, the specificity of US is far below 100%, introducing the need for a second confirmatory localization method.

In our practice the FNA of the suspected parathyroid lesion followed by measurement of iPTH in the needle-washout and a cytological examination of the aspirate has replaced the previously widely used nuclear imaging methods. The US-guided FNA might be performed in one session as a natural appendix to the standard US exam [25, 26]. Our data bring two major difficulties with parathyroid FNA into consideration. First, the differentiation of parathyroid and thyroid cells can only be easily made by an experienced pathologist. Second, the needle path to the parathyroid lesion might very often cross the thyroid parenchyma, thus confounding the cytology report. This is why many centers are advocating the preferential use of washout measurements of iPTH and performing classical cytology in cases of negative washouts only.

Nuclear imaging of the parathyroids is nowadays represented mainly by SPECT-CT. The use of this procedure is declining due to the improving FNA technology. Our study was underpowered for a direct comparison of both US and nuclear imaging. SPECT-CT can be extremely useful in cases of absent US localization or ambiguous results from the FNA washout and cytology report [27].

Limitations

The first limitation of this study is its cross-sectional design. Longitudinal data were present for one third of all patients. Secondly, data from the recommended parathyroid surgery were present in a minority of patients (up to one fourth). Thirdly, the size of the study sample was underpowered for detailed comparisons, such as US versus SPECT-CT etc.

CONCLUSION

To our knowledge, our study is the first one performed in the last two decades in our country and including a relatively high number of patients. Mild to moderate hypercalcemia was very common, although the majority of the patients were oligo- or asymptomatic. Low serum phosphate was less common. Renal and bone involvement were frequently diagnosed, with reduced eGFR and low bone mass being more prevalent than in the general population. A single parathyroid lesion (presumably adenoma) was localized in practically all cases with the lower glands being the affected site in more than two thirds of the cases. The use of SPECT-CT seems to decline and is gradually replaced to US-guided FNA biopsy of the parathyroid lesions with needle washout measurements of iPTH and cytological examination of the aspirate. Although the general picture of PHPT is gradually shifting towards milder and asymptomatic (and probably earlier) forms of the disease, the classical clinical presentation might also be found in everyday practice.

Ethical considerations

All patients had given their informed consent for hospitalization and data handling.

Disclosure Summary: *The authors have nothing to disclose.*

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