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NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM IS NOT INNOCENT AS IT SOUNDS

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Abstract

Objectives: Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia. A group of patients who were admitted with PHPT and had normal calcium levels with high parathyroid hormone (PTH) levels was defined as normocalcemic PHPT (NPHPT). The data of PHPT operated patients were retrospectively analyzed, and biochemical and clinical characteristics of hypercalcemic and normocalcemic patients were compared.

Materials and Methods: The data of patients diagnosed with PHPT between January 2012 and January 2019 were retrospectively evaluated. A total of 318 patients were divided into two subgroups, hypercalcemic and normocalcemic, according to their calcium level. The two groups were compared regarding clinical and biochemical properties.

Results: Female gender was dominant in both groups ($P = 0.072$). The mean age was similar in both groups ($P = 0.362$). As expected, serum corrected calcium (Ca), PTH levels, and urinary Ca excretion were higher in the hypercalcemia group ($P < 0.001$). There was no difference between the two groups in alkaline phosphatase, creatinine, and vitamin D levels. The percentage of localization with preoperative was similar. Also, there was no difference in adenoma features (echogenicity, cystic appearance) and localization on ultrasonography (US). The positive result obtained on neck MRI and MIBI scanning was similar. There was no difference between the two groups in terms of kidney stone and osteoporosis prevalence.

Conclusion: In our cohort, the NHPT phenotype was found to be like the hypercalcemic group. These findings suggest that the frequency of surgical indications is similar.

Keywords: Primary hyperparathyroidism, normocalcemic primary hyperparathyroidism, complications.

Introduction

Primary hyperparathyroidism (PHPT) is characterized by autonomous secretion of parathyroid hormone (PTH) from one or multiple parathyroid glands and involves a wide spectrum of clinical presentations, including symptomatic and sometimes life-threatening hypercalcemia on one side and mild asymptomatic hypercalcemia on the other side. [1]PHPT is one of the most common endocrine diseases after diabetes mellitus (DM) and thyroid disorders and the most common cause of hypercalcemia in outpatient clinics. [2]

Normocalcemic hyperparathyroidism (NPHPT) was first defined in 2009 at the Third International Workshop on Asymptomatic PHPT. It was defined as consistently elevated PTH with normal calcium (Ca) levels which should be confirmed with at least two consecutive measurements. [3] It is a diagnosis of exclusion and other possible etiologies that may increase PTH secretion, such as drugs (lithium), vitamin D deficiency, renal insufficiency, renal calcium loss, and malabsorptive bowel diseases (celiac disease, inflammatory bowel disease or previous bariatric surgery) should be excluded in the differential diagnosis. Prevalence of NPHPT in the literature varies in a wide range between 0.1- 8.9 %. [4]

It is not well known if NPHPT is a milder form of PHPT or if it has distinctive features, different courses, and natural history. Some studies suggest that it will progress into the hypercalcemic state eventually, whereas others oppose that.[4,5] The data on the disease course, biochemical progress and complications are scarce and difficult to draw any direct conclusion. Regarding the proceedings of the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism, NPHPT is not fully described, and its epidemiology, natural history, and management were not well defined.[6] We still do not clearly know how to diagnose, how many measurements we are supposed to make, how to manage, when to advise operation and how frequently we should see the patient during follow-up.

In this study, we compared the biochemical and clinical profiles of the patients with asymptomatic PHPT and NPHPT. All patients were previously operated and had histopathologically proven parathyroid adenoma. The operation criteria were determined according to the last version of the Endocrine Society guideline. Our primary aim was to evaluate the complications and prevalence of end-organ damage in NPHT. Secondary outcomes were to detect differences regarding biochemical features, preoperative imaging results and persistent/recurrent disease prevalence after the operation.

Materials and Methods

The patients who underwent parathyroid surgery for PHPT between January 2012 and January 2019 were retrospectively evaluated. Approval from the local ethics committee was provided before the data collection. A

total of 318 patients were enrolled. The patients were subdivided into two groups (NPHPT) and hypercalcemic PHPT. The diagnosis of NPHPT was made on persistently high serum PTH levels with normal serum total and ionized calcium levels. Ca was measured at least three times consecutively in a period of 3 to 6 months, and secondary causes that may lead to elevated serum PTH have been excluded. All patients who underwent operation had at least one indication for surgery were enrolled. Indications were determined according to the 'The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2014', which were as follows: Serum calcium exceeding 1 mg/dL above the normal range, a reduction in bone mineral density (BMD) at dual-energy x-ray absorptiometry (DEXA) that is significantly decreased over the baseline measurement and a T-score < -2.5 at that site, presence of a fragility fracture, the presence of nephrolithiasis, reduced GFR< 60 mL/min. [6] The decision of surgery was made by a multidisciplinary team including surgeons, endocrinologists, and nuclear medicine specialists. All patients had preoperative imaging tests, including Tc99m sestamibi scintigraphy and neck ultrasonography (US) with/without neck computed tomography (CT)/magnetic resonance imaging (MRI) or parathyroid hormone washout from the lesion.

The normal range of calcium, according to our hospital's assay was (8.8–10.2 mg/dL) (Roche Diagnostics, Manheim, Germany). Plasma intact PTH was measured using the Allegro immunoradiometric assay (Roche Diagnostics, Manheim, Germany). The detection limit of the assay was 1 pg/mL (normal range, 10–65 pg/mL), and the intra- and interassay coefficients of variation were 2% and 10%, respectively. In all individuals we calculated albumin-adjusted Ca by using the following equation (Ca+(4-serum albumin) x0.8). Vitamin D was measured by liquid chromatography coupled with tandem mass spectrometry (Schimadzu-API LC-MSMS API 3200, Canada). The lower and upper detection limits were 4 and 150 μg/L, respectively

Statistical analysis

All statistical analyses were performed with the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Descriptive analyses were presented using mean ± standard deviation (SD) for normally distributed variables, median and range (min-max) for non-normally distributed variables and as number of cases and (%) for nominal variables. The Chi-square test was used to investigate the difference between the groups regarding the categorical variables. The comparisons between groups were performed by the student's t-test for parametric variables and the Mann-Whitney U test for non-parametric variables to determine the best predictor(s). A p-value less than 0.05 was accepted as statistically significant.

Results

A total of 318 patients with PHPT who underwent surgery and histopathological proven parathyroid adenoma were enrolled in this study. Of all, 101(31.76%) had NPHPT, whereas 217 had hypercalcemic PHPT (68.24%). All patients were asymptomatic or had nonspecific symptoms that cannot be attributed to hypercalcemia alone. In the NPHPT group number and percentage of female/male patients were 93(92.07%)/8(7.93%), whereas it was 184(84.79%)/33(15.21%) in the hypercalcemic group. There wasn't any significant difference between the two groups. The mean age of the NPHPT and hypercalcemic PHPT groups were similar between the two groups. Mean serum Ca, median PTH and daily excretion of Ca in 24 hours urine collection were significantly higher in the NPHT group, whereas serum phosphorus (P) was significantly lower in the NPHT patients (Table 1). There was no significant difference between the two groups regarding serum 25 OH Vitamin D and alkaline phosphatase (ALP) levels (Table 1).

Table 1. Biochemical Parameters in Normocalcemic and Hypercalcemic PHPT Groups

Number of patients (n)	NPHPT 101	Hypercalcemic PHPT 217	p
Female/Male (number/percentage)	93 (92.07%)/8(7.93%)	184 (84.79%)/33(15.21)	0.072
Age (years)	54.08±10.37	55.41±12.82	0.362
Serum corrected Ca (mg/dl)	10.1± 0.33	11.4±0.92	<0.001
Serum P(mg/dl)	2.80±0.53	2.50±0.54	<0.001
PTH pg/ml (median; min-max)	123(90-260)	214 (70-1883)	<0.001
25 OH Vitamin D (µg/L)	25.9±6.32	27.4± 4.71	0.285
GFR (ml/min)	67.50± 6.53	72.5± 4.41	0.106
Creatine mg/dl	0.69±0.14	0.77±0.57	0.153
ALP (U/L)	99.8 ±6.50	115.75±12.70	0.061
24 hours urinary Ca (mg/day)	354 (80-770)	459(90-1216)	0.005
Mean Largest diameter of PA (mm)	14.73 ±7.82	17.75± 8.84	0.006
Volume of PAs (ml) (median)	0.87 (0.04-10.32)	1.9(0.03-31.63)	0.008

(GFR: Glomerular Filtration Rate, ALP: Alkaline Phosphatase, PA: Parathyroid adenoma)

When the preoperative imaging test results were evaluated, the rate of lesion detection with US was similar between the two groups. (Table 2). The rate of lesion detection with MIBI scintigraphy was also similar between the two groups (Table 2). Among 101 patients in the normocalcemic group, neck MRI was performed only in 11 patients, and it correctly localized the lesion in 4 patients. In the hypercalcemic group, MRI was performed in 58 patients, and a lesion was detected in 24 (Table 2). In the NPHPT group, 70 of the lesions that were suspicious for parathyroid adenoma were hypoechoic, whereas the rest had mixed echogenicity. In the hypercalcemic group, 141 of the lesions were hypoechoic, and the rest had mixed echogenicity (Table 2). The largest diameter of the adenoma and volume were measured significantly higher in the hypercalcemic group (Table 2).

The presence of nephrolithiasis was evaluated with US in 95 of 101 patients in the NPHPT group, and 22 had kidney stones. Renal US was performed in 212 of 217 hypercalcemic PHPT patients, and 58 were detected to have kidney stones. Prevalence of nephrolithiasis and estimated glomerular filtration rate (GFR) were similar between the two groups (Table 1 and 3).

BMD was evaluated with DEXA in all patients with PHPT. In the NPHPT group, 40 had osteoporosis (T score <-2.5 in one of three areas), 32 had osteopenia (T score between -1 and -2.5), and the rest had normal scores. In the hypercalcemic group, 102 patients had osteoporosis, 73 patients had osteopenia, and the rest had normal scores. There was not any significant difference between the two groups in the prevalence of osteoporosis (Table 3).

Table 2. Rate of Lesion Detection with US, MIBI Scintigraphy and MRI

	Total	Positive	Negative
NPHPT			
US*	101	92	9
MIBI**	98	56	32
MRI***	11	4	7
Hypercalcemic PHPT			
US*	217	208	9
MIBI**	210	129	81
MRI***	58	24	34

* p-value for the correct lesion localization of the lesion with US was 0.11
** p-value for the correct lesion localization of the lesion with MIBI was 0.570
*** p-value for the correct lesion localization of the lesion with MRI 0.062

Table 3. Rate of Complications of Hyperparathyroidism in Normocalcemic and Hypercalcemic Patients

	NPHPT n: 101(100%)	Hypercalcemic n: 217(100%)
DEXAs	101 (100%)	217(100%)
patients with a normal T score	29 (28.71%)	42 (19.35%)
patients with osteoporosis*	40 (39.60%)	102 (47.01%)
patients with osteopenia	32 (31.68%)	73 (33.64%)
Renal US	95(94.05%)	212(97.69%)
patients with kidney Stones**	22 (21.78%)	58 (26.72%)
patients without kidney stones	73 (72.27%)	154(70.96%)

* NPHPT vs hypercalcemic PHPT;p=0.082
** NPHPT vs hypercalcemic PHPT;p=0.721

Discussion

PHPT may present in different clinical subtypes, including obviously symptomatic type, which has been seen less frequently in the last decade, as well as the one with mild or nonspecific symptoms and asymptomatic subtypes.[7-9]The recently defined normocalcemic variant became a focus of interest among endocrinologists and surgeons with expertise in parathyroid diseases and surgery.

NPHPT is diagnosed by elevated serum PTH levels together with normal total corrected calcium and ionized serum Ca, after possible etiologies that may increase PTH are excluded.[9]Previous studies reported that NPHPT is a rare disorder. However, the prevalence is variable, probably due to different selection criteria used to define NPHPT patients. [2] The serum Ca level can fluctuate with time and may exceed the upper limit of the normal range and eventually become classical PHPT with hypercalcemia. Some authors recommend that the least significant change (LSC) of albumin-corrected calcium should be used to define and follow NPHPT. LSC shows if the quantitative change in the measured parameter is significant or not during the follow-up. [5,10]

The faith of the disease is unknown, and there is scarce data about the progression. In one study, it was suggested that the disease has a biphasic course and eventually will evolve to hypercalcemia.[11] In another study, 151 patients (81%) remained normocalcemic, and 36 (19%) became hypercalcemic; 24 (67%) had increased Ca to high levels within two years, 10 (28%) within 2 to 4 years, and 2 (5%) after more than four years.[12]

In our study, the clinical and biochemical profiles of 318 PHPT patients who underwent operation were evaluated retrospectively. In our cohort, almost one-third of the patients who had an indication for surgery were normocalcemic at the time of diagnosis. The localization of the parathyroid adenoma was not more difficult in normocalcemic patients despite the smaller lesion size and the volume measured with ultrasonography. Urinary calcium excretion was lower in the NPHPT group compared to hypercalcemic PHPT patients. In contrast to our study, in the reports by Díaz-Soto et al. and Kiriakopoulos et al., no significant difference in urinary calcium excretion between NHPT and PHPT was detected. [13,14]

NPHPT is characterized by several medical complications.[15] The first and major one is osteoporosis and consequent bone fractures. There is no study evaluating the incidence of fractures distinctively in patients with NPHPT. In our cohort, there weren't any reported femur or radius fractures. Since vertebral fracture assessment (VFA) was not routinely performed during DEXA and X-ray or CT/MRI was not ordered unless the patient had overt symptoms, we could not detect the exact prevalence of vertebral fractures. Among operated patients, the prevalence of osteopenia and osteoporosis was similar between NPHPT and PHPT groups in our study. In the previous reports from tertiary reference centers, NPHPT patients had decreased BMD compared

to controls and were classified either as osteopenia or osteoporosis.[16] As a result, all patients in those studies had decreased BMD. In our cohort, the prevalence of osteopenia and osteoporosis in the NPHPT group was like the hypercalcemic group. In the light of those findings, it may be suggested that increased serum PTH results in bone loss even if the serum calcium is normal and there is a lack of any other etiology explaining the elevated hormone levels. In addition to that, NPHPT patients with decreased bone mineral density may experience a further decrease in their BMD with time. The most well-organized and detailed study of NHPT was reported by Palermo et al., which was cross-sectional and prospective. [17] In that study, three groups were compared with each other which were PHPT (41 patients), NPHPT (47 patients) and age and gender-matched healthy controls (39 patients). BMD values at the lumbar spine, femur and distal radius in the NPHPT patients were detected to be between those in the PHPT and healthy controls. There wasn't any statistically significant difference between NPHPT and control groups, whereas it was lower at all sites in PHPT patients compared to controls. No statistical differences were found between BMD in NHPT and PHPT, except for a lower BMD value at the one-third distal radius in PHPT. Vertebral fractures detected by VFA were significantly more common in patients with PHPT (60%) compared to NPHPT (28%) or controls (23%). Bone turnover markers (serum carboxy-terminal [CTx]-telopeptide of type 1 collagen and procollagen type 1 N-terminal propeptide [P1NP]) were significantly higher than controls in both patient groups and significantly higher in PHPT than NPHPT. The authors concluded that NPHPT might be considered a milder form of classical PHPT and controls regarding biochemical parameters, but not associated with increased bone complications, reduced BMD, vertebral fractures, or increased bone turnover markers.

In the study of Palermo et al. that was prospective and cross-sectional, the presence of nephrolithiasis was evaluated from the medical database of medical records and patient notes.[17]They found that the prevalence of nephrolithiasis was 13% in NPHPT patients while it was 10% in patients with PHPT, and there wasn't a significant difference between the two groups. Controls had a kidney stone prevalence of 3%, although that might have been underestimated since subjects were not screened in detail with US or CT. Those findings suggest that nephrolithiasis prevalence is similar between NPHPT and PHPT; however, they couldn't demonstrate the pathophysiology of kidney stones in hyperparathyroidism. Our study confirms those findings. A study from Brazil reported that 20% of patients with NPHPT undergoing abdominal ultrasound imaging had kidney stones.[18]This prevalence is higher than that reported in the general population of approximately 10.6% in the United States but might be affected by selection bias, for example, caused by previous kidney stones.[19]

Our study has limitations. The most important one is including patients who underwent surgery alone. That might cause a selection bias since operated patients have more severe diseases. In addition to that, we can't discuss and compare the rate of indications for surgery in NPHPT and PHPT groups. The other limitations were retrospective nature, lack of follow-up data and bone fracture prevalence.

In conclusion rate of the patients with NPHPT was one-third of all hyperparathyroidism patients, which means being normocalcemic does not indicate the lack of need for surgery as a permanent treatment. End organ damage, defined as osteoporosis and kidney stones, is as prevalent as hypercalcemic PHPT in NPHPT patients. It should not be accepted as a milder form of the disease and should be followed like PHPT patients as advised in the guidelines for asymptomatic disease.

Ethical Considerations: Ethical approval was obtained from the clinical research ethics committee of Yıldırım Beyazıt University (date: 17.03.2021, decision number: 32).

Conflict of Interest: The authors declare no conflict of interest.

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