Introduction

Primary hyperparathyroidism (PHPT) is a common disorder of calcium, phosphate, and bone metabolism due to an increased release of parathyroid hormone (PTH) by the parathyroid glands, traditionally characterized by hypercalcemia and elevated levels of PTH [1]. PHPT may present as an isolated disease or can be a part of a familial syndrome, with specific germline mutations [2]. In western countries with serum calcium measurements routinely available, over 80% of patients with PHPT are asymptomatic or present with nonspecific symptoms and are usually stable for many years or a lifetime. Disease progression may occur and symptomatic subjects may present with symptoms of hypercalcemia – such as anorexia, nausea, constipation, polydipsia, and polyuria – and signs as bone loss and nephrolithiasis [1, 3]. Surgery may be performed when indicated and is the only definite therapy [4]. It improves the overall health-related quality of life with an improvement in bone density and neurocognition, and a reduction of fracture incidence and kidney stones [4, 5]. (Fig. 1–3)

Over the past ten years, a new clinical phenotype, the normocalcemic primary hyperparathyroidism (NPHPT), has emerged [6]. NPHPT is characterized by normal total and ionized serum calcium levels accompanied by elevated parathyroid hormone levels in the absence of secondary causes for hyperparathyroidism [7]. The exact prevalence of NPHPT is not known [8]. There are several hy-
hypotheses regarding its pathophysiology – such as a biphasic disease course for PHPT and resistance of the PTH receptor in bone and kidney to the action of PTH – however, the exact mechanism rest unclear [9–13]. The available studies report that subjects are frequently diagnosed with complications of PHP (nephrolithiasis, osteoporosis, and fragility fracture) [11, 14–17], but data are still limited and confounded by inconsistent case identification, difficulties in PTH measurements and the use of different diagnostic criteria, and exclusion criteria [6]. Most cohorts described in literature were small and consisted of symptomatic subjects that were diagnosed during an evaluation for an underlying metabolic bone disease or nephrolithiasis [18]. Evidence-based guidelines for the management of NHPHT are lacking [8].

Since these issues have not yet been completely elucidated, further studies, in accordance with the recommendations proceeding from the International Workshop on Asymptomatic PHPT to reduce patient heterogenicity, are necessary [19].

In our present study, we analyzed possible differences between normocalcemic and hypercalcemic subjects diagnosed with PHPT in a tertiary referral center (UZ Brussel). First, we aimed to compare clinical and biochemical parameters between normocalcemic and hypercalcemic PHPT and second, we aimed to evaluate the frequency of normocalcemic PHPT and the recommendations for the management recommendations of asymptomatic, normocalcemic PHPT.
Subjects and Methods

Subjects and study method

We retrospectively reviewed in a cross-sectional, observational design the medical records of 659 patients with PHPT and ‘hyperparathyroidism of undefined origin’ present in the electronic medical records registry system (KWS = software system used for the administration of the electronic medical records) of UZ Brussel. All patients who were known to have PHPT or ‘hyperparathyroidism of undefined origin’, registered under this diagnosis in the KWS at the UZ Brussel between January 1st 2007 and December 31st 2016, were selected irrespective of age or gender. A total of 528 subjects were excluded from further analysis because of the presence of an active malignity (15 subjects), insufficient data in the KWS (24 subjects), post-renal transplant patients (53 subjects), secondary hyperparathyroidism (432 subjects), and PHPT in the context of a MEN-1 or 2 (4 subjects).

For the analysis of the mean PTH concentrations, 29 hypercalcemic subjects were excluded because of an impaired renal function (eGFR < 60 ml/min). Subsequently, 131 patients were studied.

This cohort was divided in two groups based on their corrected total serum calcium concentration. Group 1 consisted of 25 subjects, who were classified as having normocalcemic PHPT, while Group 2 consisted of 106 subjects, who were identified as having hypercalcemic PHPT. We used the diagnostic criteria for PHPT and normocalcemic PHPT in our study as published in the proceedings from the Fourth International Workshop on asymptomatic PHPT [19]. The diagnosis of normocalcemic PHPT requires normal total corrected serum calcium concentrations and elevated plasma PTH levels in the absence of secondary causes of hyperparathyroidism, such as vitamin D deficiency (25-OH vitamin D < 20 ng/ml), impaired renal function (eGFR < 60 ml/min), medications influencing serum calcium levels (loop diuretics, thiazide diuretics, bisphosphonates, denosumab, and lithium), gastro-intestinal malabsorption disorders (coeliac disease, pancreatic, and biliary insufficiency) and hypercalciuria (urinary Ca/Cr ratio more than 240 mg/g Cr) [19]. The diagnosis of hypercalcemic PHPT requires elevated serum albumin-corrected calcium concentrations and an elevated or inappropriately normal PTH concentration. Serum calcium and plasma PTH were measured simultaneously on at least two subsequent evaluation moments in a period of 3–6 months [19].

For further analysis the following clinical data were obtained: age, gender, weight, height, and BMI. We reviewed the biochemical evaluation of all patients at the moment of their diagnosis, including total serum calcium, albumin, phosphorus, creatinine, plasma PTH, and 25-OH vitamin D. The results of urine calcium, phosphorus, and creatinine concentration were obtained. The glomerular filtration ratio (eGFR) was calculated using the CKD-EPI creatinine equation. Serum calcium was determined by colorimetric method (Vitros 4600 analyzer) with reference interval: 2.10–2.50 mmol/l. The correction of serum calcium levels in relation to albumin was performed using the following formula: albumin-corrected serum calcium = total serum calcium × (4-serum albumin) × 0.2. Ionized serum calcium levels were measured in only a few patients and these results were not included. Familial Hypocalciuric Hypercalcemia (FHH) can be distinguished from PHPT by a low urinary calcium excretion and Ca/Cr ratio clearance ratio <0.01 [2, 19]. The plasma PTH concentration and 25-OH vitamin D were both measured by electro chemiluminescence: PTH (Cobas e411–1 analyzer) with reference interval: 15.0–65.0 ng/l and 25-OH vitamin D (Cobas 6000 analyzer) with reference interval: 20–50 μg/l. Vitamin D deficiency is defined as a 25-OH vitamin D level <20 μg/l.

The presence of nephrolithiasis and bone fractures were obtained from the medical reports. The results of Bone Mineral Density (BMD) and T-score at the lumbar spine and left hip using Dual-energy X-ray Absorptiometry (DXA) were obtained from the medical records. The study was approved by the Commission Medical Ethics of UZ Brussel and VUB.

Statistical analysis

Microsoft Office Excel was used to collect our data and SPSS Statistics 23.0 and 24.0 software were used for the statistical analysis. First, we described the distribution of the several variables, including its central tendency and dispersion. We calculated the mean, maximum, minimum and the standard deviation of the different variables. After the descriptive statistics, we performed Pearson’s chi-square test and the Student’s t-test with equal or unequal variances to compare the normocalcemic subgroup with the hypercalcemic subgroup for respectively the qualitative variables and the quantitative variables. The level of significance used in interpreting the statistical test was 5 %.

Results

The baseline characteristics and biochemical data of the 131 study patients are shown in Table 1. We compared the data of 25 normocalcemic subjects and 106 hypercalcemic subjects. Data on the clinical manifestations and bone densitometry (DXA) are shown in Table 2. There were no statistical differences in prevalence of nephrolithiasis or fractures and bone densitometry between both groups.

Discussion

In our present study, we identified 25 subjects with normocalcemic PHPT out of 131 subjects diagnosed with PHPT or ‘hyperparathyroidism of undefined origin’ at UZ Brussel between 2007 and 2016 (relative prevalence of 19 %). Because serum ionized calcium concentration values were not available in most subjects, the corrected calcium concentration was used for diagnosis – as recommended. With the use of the corrected calcium concentrations instead of the ionized serum calcium concentrations, the reported frequency may overestimate the true prevalence of normocalcemic PHPT [8, 19].

The main purpose in the present study was to compare the clinical and biochemical data of normocalcemic and hypercalcemic PHPT in a hospital-based population. We observed a lower mean serum PTH concentration in the normocalcemic subjects compared to the hypercalcemic subjects after exclusion of subjects with an impaired renal function, as a lower glomerular filtration rate could induce a rise in PTH [11]. Maruani et al. [11] investigated the underlying pathophysiological mechanisms of normocalcemic PHPT and found a comparable result. In their study, the lower PTH levels in the normocalcemic group corresponded with a lower mean parathyroid tumor mass in normocalcemic subjects who underwent
Table 1 Baseline characteristics of the 131 study patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normocalcemic PHPT</th>
<th>Hypercalcemic PHPT</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>25</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 12</td>
<td>67 ± 14</td>
<td>0.087</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>6/19</td>
<td>32/74</td>
<td>0.630</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 ± 4.7</td>
<td>26.0 ± 5.4</td>
<td>0.206</td>
</tr>
<tr>
<td>Total corrected serum calcium (mmol/l)</td>
<td>2.34 ± 0.11</td>
<td>2.71 ± 0.20</td>
<td>0.000</td>
</tr>
<tr>
<td>Serum P (mmol/l)</td>
<td>0.98 ± 0.13</td>
<td>0.87 ± 0.19</td>
<td>0.006</td>
</tr>
<tr>
<td>Plasma 25-OH vitamin D (µg/l)</td>
<td>28 ± 9</td>
<td>20 ± 19</td>
<td>0.054</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>80.52 ± 15.50</td>
<td>71.13 ± 22.68</td>
<td>0.017</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.85 ± 0.17</td>
<td>0.99 ± 0.38</td>
<td>0.005</td>
</tr>
<tr>
<td>Urinary Ca (mmol/24h)</td>
<td>4.9 ± 2.23</td>
<td>6.8 ± 4.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Urine P (mmol/24h)</td>
<td>25.1 ± 9.9</td>
<td>24.5 ± 11.01</td>
<td>0.866</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD; P: Phosphate; eGFR: Estimated glomerular filtration ratio; Reference range for serum calcium: 2.10–2.50 mmol/l; serum phosphate: 0.81–1.45 mmol/l; 25-OH vitamin D: 20–50 µg/l; serum creatinine: 0.66–1.28 mg/dl (men), 0.52–1.04 mg/dl; urinary Ca: 2.5–7.5 mmol/col.; urinary P: 13–42 mmol/col.; Student’s t-test and Pearson’s chi-square test were used for statistical analysis of the quantitative variables and the qualitative variables, respectively. Level of significance: 5%.

Table 2 Clinical manifestations in normocalcemic and hypercalcemic PHPT.

<table>
<thead>
<tr>
<th></th>
<th>Normocalcemic PHPT</th>
<th>Hypercalcemic PHPT</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>9 (25)</td>
<td>25 (106)</td>
<td>0.371</td>
</tr>
<tr>
<td>Fractures LS</td>
<td>3 (25)</td>
<td>14 (106)</td>
<td>0.599</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>9 (16)</td>
<td>33 (77)</td>
<td>0.619</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>4 (16)</td>
<td>25 (77)</td>
<td>0.619</td>
</tr>
<tr>
<td>Bone disease</td>
<td>13 (16)</td>
<td>58 (77)</td>
<td>0.612</td>
</tr>
<tr>
<td>BMD LS (g/cm²)</td>
<td>0.95 ± 0.15</td>
<td>0.91 ± 0.19</td>
<td>0.398</td>
</tr>
<tr>
<td>T score LS</td>
<td>−0.92 ± 1.38</td>
<td>−1.38 ± 1.7</td>
<td>0.319</td>
</tr>
<tr>
<td>BMD LH (g/cm²)</td>
<td>0.80 ± 0.11</td>
<td>0.80 ± 0.17</td>
<td>0.991</td>
</tr>
<tr>
<td>T score LH</td>
<td>−1.26 ± 0.78</td>
<td>−1.40 ± 1.18</td>
<td>0.641</td>
</tr>
</tbody>
</table>

Data expressed as subjects (studied subjects in the group) or mean ± SD. The data for bone evaluation of 16 normocalcemic and 77 hypercalcemic subjects were studied; LS: Lumbar spine; LH: Left hip; Bone disease is the sum of osteopenia and osteoporosis. Student’s t-test and Pearson’s chi-square test were used for statistical analysis. Level of significance: 5%.

Parathyroidectomy compared to the hypercalcemic subjects. Normocalcemic PHPT may present an earlier form of PHPT than hypercalcemic PHPT, however, there is an overlap in PTH levels between the two groups and there is no significant difference in age at time of diagnosis in our study. In addition, Maruani et al. [11] suggested that normocalcemic subjects present with bone and kidney resistance to the biological actions of PTH and found lower fasting urine calcium excretion (UCa/UCr, corresponding with the net bone calcium release), lower renal tubular calcium reabsorption and higher values of renal phosphate threshold in the normocalcemic subjects. In our study, the 24-hour calcium excretion was significantly lower in the normocalcemic compared to the hypercalcemic group and these findings do not seem to be consistent with these hypothesis, however these findings need to be interpreted in the context of the significantly higher PTH levels in the hypercalcemic group and the exclusion of hypercalcuria in the normocalcemic subjects [19]. In addition, Diaz-Soto et al. evaluated the clinical effect of calcium sensing receptor (CaSR) and PTH polymorphism in PHPT. They found that CaSR A986S polymorphism probably act as a sort of resistance factor in normocalcemic, but not in asymptomatic hypercalcemic subjects [12, 13].

The kidney plays a key role in the calcium-phosphate metabolism and is the organ that is most likely to be affected in PHPT [20]. In addition to the classical renal manifestations of PHPT (nephrolithiasis and nephrocalcinosis), renal insufficiency may develop, although mild hypercalcemia is rarely associated with renal insufficiency [1]. In our study, we found significant higher serum creatinine levels and lower eGFR levels in the hypercalcemic subjects compared to the normocalcemic subjects with PHPT. An impaired renal function is an exclusion criteria for the diagnosis of normocalcemic PHPT [19] and may explain the significant difference, but we have to keep in mind that renal insufficiency may develop in patients with PHPT and is related to the degree and duration of the hypercalcemia [1].

In the normocalcemic PHPT subjects, we found a high prevalence of nephrolithiasis (36%), compression fractures of the lumbar spine (12%) and bone disease (81.3%) comparable with the hypercalcemic group. These observations are comparable with findings in other studies [10, 14–18, 21, 22] and demonstrate that normocalcemic PHPT is not an indolent disease state and that normocalcemic subjects may present with the classical features of PHPT. However, normocalcemic patients are often diagnosed during an evaluation for nephrolithiasis or metabolic bone disease and are already symptomatic at the time of diagnosis [18]. Since PTH screening is not routinely performed in hospitalized patients, we suggest that in a hospital-based population the clinical manifestations between the normocalcemic and the hypercalcemic group are comparable. Data on the further evolution of our subjects is lacking. Few studies have followed normocalcemic subjects with PHPT in time and described both persistence of normocalcemia and disease progression with development of hypercalcemia [11, 14]. These findings suggest that there is no uniform time course of the emergence of hypercalcemia in normocalcemic PHPT, and the normocalcemic state may persist for a lifetime in some patients.

Regarding to bone density measurements by DXA, there were no significant differences between both groups and they showed...
in both groups a high prevalence of deterioration of bone mass. Bone measurements at the highly cortical distal radius were not available. Classical PHPT typically present with a diffuse bone involvement with a preponderance for cortical bone [1], while previous studies described a preponderance for trabecular bone in normocalcemic subjects [17]. Further research addressing this issue with unselected, larger cohorts is necessary.

Management guidelines for the hypercalcemic form of PHPT are well known [4], but have not yet been established for the normocalcemic form of PHPT [8]. A recommended approach for normocalcemic subjects include monitoring for the asymptomatic, normocalcemic subjects and surgery for those who have or develop complications of PHPT, including fragility fractures, osteoporosis or nephrolithiasis. Experts recommend that the monitoring for disease progression is the same for both the hypercalcemic and normocalcemic form: annual clinical assessment, serum calcium (total and ionized) and plasma PTH measurements. In addition, BMD measurements every 1–2 years by DXA. Patients who develop subsequently hypercalcemia can be managed later by following the guidelines for mild, asymptomatic PHPT [4, 8].

Our study has several limitations. First, it is a small, retrospective study with only 25 subjects diagnosed with true normocalcemic PHPT, even though we started out with 659 patients diagnosed with PHPT or ‘hyperparathyroidism of undefined origin’. Our study may have insufficient power to determine differences between the two groups and our findings should be interpreted with caution. Second, ionized serum calcium level measurements were not available in most subjects and total corrected serum calcium levels were used for diagnosis. Third, we started out from a list of patients who were already diagnosed with PHP, during their hospitalization or during an evaluation for a metabolic bone disease or nephrolithiasis and that some asymptomatic, normocalcemic subjects might not be included in our study. Our study might be influenced by referral bias.

Further research is required to further elucidate the pathophysiology and natural course of the NPHPT. Larger study cohorts and consistent case identification using the recommended diagnostic criteria are needed. Population-based studies could reveal the real prevalence of this disorder and identify asymptomatic subjects, but population screening is not recommended.

Author Contributions

Prof. Dr. Bert Bravenboer: initial idea and review of the work. Prof. Dr. CE Andreescu, Prof. Dr. David Unuane, Dr. Marian Vanhoeij, and Prof. Dr. Brigitte Velkeniers: review of the work.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References


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Notice
This article was changed according to the Erratum on November 19th 2018.

Erratum
In the above article the list of authors was incomplete. The full list of authors is: Jan Pierreux¹, Bert Bravenboer¹, Brigitte Velkeniers¹, David Unuane¹, Corina E. Andreescu¹, Marian Vanhoeij²

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