Is Normocalcemic Primary Hyperparathyroidism Harmful or Harmless?

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Context: Primary hyperparathyroidism (PHPT) is reported to be associated with an increased frequency of hypertension, however, information in this regard is sparse in relation to normocalcemic primary hyperparathyroidism (NPHPT).

Objective: The aim of this study was to determine the association between NPHPT and blood pressure.

Design, Setting, and Patients: We retrospectively enrolled 940 patients who visited the Fujian Provincial Hospital between September 2010 and December 2013 with a measured serum parathyroid hormone (PTH) and calcium level. Among them, 11 patients were diagnosed with NPHPT, while 296 cases with normal PTH and albumin-adjusted serum calcium.

Main Outcomes Measures: Systolic blood pressure (SBP), diastolic blood pressure (DBP), intact serum PTH, and serum calcium were recorded.

Results: There were no significant differences between subjects identified with NPHPT and those with normal PTH in terms of age, sex, body mass index, serum calcium, 25-Hydroxyvitamin D, serum creatinine, fasting plasma glucose, triglycerides, total cholesterol, high density lipoprotein, and low density lipoprotein. The subjects with a diagnosis of NPHPT had higher levels of SBP (141.9 ± 20.2 vs 131.2 ± 16.5, P = .041) and DBP (85.2 ± 12.4 vs 76.8 ± 10.3, P = .026) than the subjects in the cohort with normal PTH. After adjustment for all potential confounders, risks (odds ratios and 95% confidence interval) of SBP and DBP in NPHPT patients were 1.035 (1.000, 1.071) and 1.063 (1.004, 1.125), respectively (P < .05).

Conclusions: The NPHPT had higher risk of high blood pressure than subjects with normal PTH. It is worth considering the necessity of more aggressive therapeutic intervention aimed to normalize PTH even if patients with NPHPT continue to be normocalcemic. (J Clin Endocrinol Metab 100: 2420–2424, 2015)
should include consistently normal albumin-adjusted total serum calcium and normal ionized calcium. Additionally, secondary causes of an elevated PTH level must be ruled out, such as renal disease, vitamin D deficiency, renal hypercalciuria, gastrointestinal (GI) disorders associated with calcium malabsorption or the use of thiazide diuretics and lithium (3). Nowadays, with the widespread availability of PTH assays, NPHPT has gained increased scientific interest.

Hypertension is one of the most important cardiovascular risk factors. Several studies have confirmed that both calcium and PTH were associated directly or indirectly with increased incidence of cardiovascular diseases (4–6). PHPT is reported to be associated with an increased frequency of hypertension, dyslipidemia, overweight, impaired glucose tolerance, diabetes mellitus, and increased incidence of cardiovascular morbidity and mortality (7–9). In this regard, information is sparse in relation to NPHPT and only in one of the studies performed does some degree of relationship seem to exist (10). This study compared the prevalence of cardiovascular risk factors in patients with NPHPT, in those with hypercalcemic hyperparathyroidism, as well as in a control group, and the authors reported similar rates of cardiovascular risk factors in the three groups. However, as almost all evidence has been obtained from Western countries, there are no available data in Chinese patients. The aim of this study was to determine the association between NPHPT and blood pressure (BP) in Chinese patients, and to compare it with normal PTH group.

Materials and Methods

Study design and subjects

We retrospectively enrolled patients who visited at Fujian Provincial Hospital for examination or treatment between September 2010 and December 2013. In these patients, 940 cases had a measured serum PTH and calcium level. None of them were undergoing surgery at the time. Eleven subjects with normal serum calcium and inappropriately high serum PTH were identified, while 296 subjects with normal serum calcium and PTH. The remaining subjects with abnormal serum calcium or low serum PTH were not incorporated into our analysis. In addition, the causes of secondary hyperparathyroidism such as the use of thiazide diuretics and lithium, vitamin D deficiency, chronic kidney disease, hypercalciuria, and malabsorption syndrome had been excluded. As this is a retrospective study, subjects were not required to provide written informed consent, but the study protocol was approved by the Ethics Committee of Fujian Provincial Hospital.

Anthropometric and biochemical measurements

In this study, demographic characteristics were self-reported. Blood pressure was measured in the first 72 hours (one measurement every 8 h) after admission while the participants were in the supine position using a standard mercury sphygmomanometer according to a standard protocol. The mean of multiple recordings was finally used for analysis. The first and fifth Korotkoff sounds were recorded as systolic BP (SBP) and diastolic BP (DBP), respectively. Body mass index (BMI) was calculated as body weight (kilograms) divided by height (meters) squared. Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), and serum creatinine (Cr) were measured using chemiluminescence methods with an autoanalyzer. Serum calcium was also measured by automated techniques, with a normal range of 2.2–2.7 nmol/L. Intact serum PTH (normal range 1.5–65 ng/L) and 25-Hydroxyvitamin D (25-OH VitD) was measured with an electrochemiluminescence immunoassay (Roche Diagnostics). All biochemical values were measured in the minimum 8 h overnight fasting state and within the first 24 h after admission. The patients had not used any medicine at the time to make sure that we can rule out the false-negative results.

Definitions and diagnostic criteria

NPHPT was defined as serum PTH greater than the upper limit of the assay with normal albumin-adjusted serum calcium, and excluding disorders associated with secondary hyperparathyroidism, including renal insufficiency [estimated glomerular filtration rate (GFR) <60 mL/min], vitamin D deficiency (25-OH VitD ≤20 ng/mL), and the use of thiazide diuretics and lithium. Besides, other reasons lead to elevated PTH also should be excluded, such as renal hypercalciuria, GI disorders associated with calcium malabsorption, and so on. Serum calcium was adjusted for hypoalbuminemia by the following formula: albumin-corrected calcium (mg/dL) = serum calcium (mg/dL) + [0.8 × (4 – serum albumin)].

Statistical analysis

SPSS 19.0 statistical software package (SPSS) was used for data analysis. All P values were based on two-sided tests, with statistical significance defined as \( P < 0.05 \). All normally distributed continuous or categorical variables were presented as mean ± standard deviation (SD) or percentage, respectively. Differences between categories were tested by one-way ANOVA, \( \chi^2 \), and nonparametric tests as appropriate. In order to further detect the differences of BP between NPHPT and normal PTH, logistic regression models were applied to adjust for potential confounders. The first model was unadjusted. The second model was adjusted for age, sex, and BMI, and model 3 included the covariate in model 2 and also FPG, TG, TC, HDL, and LDL for adjustment. Next, further adjustment of other confounding variables were considered in model 4, including serum calcium, 25-OH VitD, and serum Cr. Results are presented as odds ratios (ORs) with 95% confidence interval (CI).

Results

In the present study, a total of 940 cases were included in the analysis. We identified 69 cases with elevated PTH and normal albumin-adjusted serum calcium. All common secondary causes of hyperparathyroidism were excluded: renal insufficiency (34 excluded), vitamin D deficiency (23...
excluded), and thiazide diuretic use (1 excluded), besides, none of them have hypercalciuria and malabsorption syndrome. Finally, 11 cases remained in whom the presence of NPHPT was established as defined. The laboratory tests of these 11 subjects were as follows: PTH 96.74 ± 38.80 (normal range 15–65 ng/L), serum calcium 2.38 ± 0.14 (normal range 2.2–2.7 mmol/L), creatinine 84.27 ± 27.11 (normal range 60–135 umol/L), 25-OH VitD 26.49 ± 6.69 (normal range 20–32 ng/mL), urine calcium 190.55 ± 48.64 (normal range: female <230 mg/24 h, male <300 mg/24 h). As the control, we identified 296 subjects with normal PTH and albumin-adjusted serum calcium, and the renal insufficiency and vitamin D deficiency had also been excluded.

Baseline characteristics and comparisons are shown in Table 1. There were no significant differences between subjects identified with NPHPT and those with normal PTH in terms of age, sex, BMI, serum calcium, 25-OH VitD, serum Cr, FPG, TG, TC, HDL, and LDL. The subjects with a diagnosis of NPHPT had higher levels of SBP and DBP (141.9 ± 20.2 vs 131.2 ± 16.5, P = .041) and DBP (85.2 ± 12.4 vs 76.8 ± 10.3, P = .026) than the subjects in the cohort with normal PTH.

Odds ratios of SBP and DBP between NPHPT and normal PTH are shown in Table 2. In all four models, the subjects with NPHPT had higher levels of SBP than the subjects in the cohort with normal PTH. After adjustment for all potential confounders, the difference was still statistically significant.

Discussion

In the present study, we investigated the association between NPHPT and BP. The results showed that the subjects with NPHPT had higher levels of BP than the subjects in the cohort with normal PTH. After adjustment for all potential confounders, the difference was still statistically significant.

PTH plays an important role in elevating BP. It is reported that infusion to normal subjects results in hypertension and increased levels of serum calcium. PTH can release bone calcium into the blood by increasing bone resorption, and enhance the synthesis of 1,25-dihydroxyvitamin D3 in renal, which can increasing the intestinal absorption of calcium, leading to elevated serum calcium. The increased serum calcium induce vascular contraction and raise BP. PTH receptors are expressed in the vessel wall and myocardium and may be involved in the pathological process of cardiovascular disease, leading to vascular stiffness and left ventricular (LV) hypertrophy. A previous study have shown that impaired endothelium dependent vasodilation and endothelial dysfunction in patients with PHPT were reversed after successful parathyroidectomy, may suggest that hypertension in PHPT patients might be attributable to endothelial damage. Other mechanisms of PTH induced hypertension include activation of the renin-aldosterone system, secretion of cortisol from the adrenal cortex, and sympathetic activity. Hypertension is associated with obligatory urinary calcium loss, leading to a negative calcium balance for bone remodeling. In addition, the loss of calcium in the urine is associated with an increase.

Table 1. Baseline Characteristics of NPHPT and Normal PTH

<table>
<thead>
<tr>
<th></th>
<th>NPHPT</th>
<th>Normal PTH</th>
<th>P Value</th>
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<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>296</td>
<td>.798</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.3 ± 18.5</td>
<td>61.2 ± 14.2</td>
<td>.224</td>
</tr>
<tr>
<td>Male (%)</td>
<td>54.5</td>
<td>36.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 3.2</td>
<td>24.4 ± 4.1</td>
<td>.492</td>
</tr>
<tr>
<td>PTH (ng/L)</td>
<td>96.74 ± 38.8</td>
<td>31.06 ± 12.20</td>
<td>.483</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.38 ± 0.14</td>
<td>2.41 ± 0.13</td>
<td>.483</td>
</tr>
<tr>
<td>25-OH VitD (ng/mL)</td>
<td>26.49 ± 6.69</td>
<td>28.53 ± 7.06</td>
<td>.248</td>
</tr>
<tr>
<td>Creatinine (umol/L)</td>
<td>84.27 ± 27.11</td>
<td>68.42 ± 17.85</td>
<td>.057</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>6.77 ± 2.91</td>
<td>6.24 ± 2.53</td>
<td>.477</td>
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<tr>
<td>TG (mmol/L)</td>
<td>1.34 ± 0.62</td>
<td>1.48 ± 0.86</td>
<td>.738</td>
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<tr>
<td>TC (mmol/L)</td>
<td>4.54 ± 1.03</td>
<td>5.02 ± 1.12</td>
<td>.166</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.11 ± 0.41</td>
<td>1.32 ± 0.44</td>
<td>.054</td>
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<tr>
<td>LDL (mmol/L)</td>
<td>2.92 ± 0.77</td>
<td>3.15 ± 0.93</td>
<td>.410</td>
</tr>
<tr>
<td>SBP (mm/Hg)</td>
<td>141.9 ± 20.2</td>
<td>131.2 ± 16.5</td>
<td>.041</td>
</tr>
<tr>
<td>DBP (mm/Hg)</td>
<td>85.2 ± 12.4</td>
<td>76.8 ± 10.3</td>
<td>.026</td>
</tr>
</tbody>
</table>

Table 2. Multivariate Adjusted ORs (95% CI) of Blood Pressure Between NPHPT and Normal PTH

<table>
<thead>
<tr>
<th></th>
<th>NPHPT</th>
<th>Normal PTH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mg/Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1a</td>
<td>1.032 (1.001, 1.064)</td>
<td>1</td>
<td>.043</td>
</tr>
<tr>
<td>Model 2b</td>
<td>1.035 (1.003, 1.069)</td>
<td>1</td>
<td>.034</td>
</tr>
<tr>
<td>Model 3c</td>
<td>1.034 (1.001, 1.068)</td>
<td>1</td>
<td>.044</td>
</tr>
<tr>
<td>Model 4d</td>
<td>1.035 (1.000, 1.071)</td>
<td>1</td>
<td>.047</td>
</tr>
<tr>
<td>DBP (mg/Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.072 (1.016, 1.132)</td>
<td>1</td>
<td>.011</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.071 (1.014, 1.131)</td>
<td>1</td>
<td>.015</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.066 (1.008, 1.126)</td>
<td>1</td>
<td>.024</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.063 (1.004, 1.125)</td>
<td>1</td>
<td>.035</td>
</tr>
</tbody>
</table>

a Model 1 was unadjusted.
b Model 2 included age, sex, and BMI for adjustment.
c Model 3 included the covariate in model 2 plus FPG, TG, TC, HDL, and LDL for adjustment.
d Model 4 included the covariate in model 3 plus serum calcium, 25-OH VitD, and serum creatinine for adjustment.
in the secretion of PTH, which may enhance the incidence of hypertension (4, 19).

NPHPT was first formally recognized at the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2009 (20, 21). In addition, guidelines for the management of Asymptomatic PHPT have been revised in the Fourth International Workshop (22). However, there are as of yet, no guidelines for the management of NPHPT. In our impression, most clinicians choose to follow up patients with NPHPT. We monitor subjects with NPHPT in the same way we monitor those with asymptomatic hypercalcemic PHPT. Annual serum calcium, PTH and bone mineral density (BMD) determinations seem reasonable (23). Some patients with NPHPT may progress to a hypercalcemic state or develop the classic conditions requiring surgical intervention such as fractures and kidney stones. In these conditions, it is recommend to follow the treatment guidelines of PHPT. As not all patients have a progression to a hypercalcemic hyperparathyroidism state, and no marks of disease progression are yet available, the decision regarding aggressive treatment vs follow-up must be individualized (9).

Surgery is an attractive option, however, it is also recognized that medical treatment may also be a reasonable option in a substantial number of individuals who present with contraindications for surgery or are unable or unwilling to proceed with parathyroidectomy (24). In this case, the aim of medical treatment would be to protect possible NPHPT-induced complications and not to attain normalization of PTH levels (9). The current medical treatment includes bisphosphonates, hormone replacement therapy, selective estrogen receptor modulators, and calcimimetics. Bisphosphonates, hormone replacement therapy and selective estrogen receptor modulators could be used in the treatment of NPHPT to protect the skeleton because of potential BMD increase and fracture risk reduction (24). Calcimimetics (such as cinacalcet) can modulate the calcium sensing receptor. Studies have shown that cinacalcet is effective in reducing or normalizing serum calcium levels in several groups of patients with PHPT with slight reduction of PTH levels and no effects on BMD (9, 24–26). However, there are no data as to whether long-term treatment can prevent the progression of NPHPT until now.

Since hypertension is one of the most important cardiovascular risk factors, and our study suggested that the subjects with NPHPT had higher risk of high BP than subjects with normal PTH, it seems reasonable to suppose that therapeutic intervention aimed to normalize PTH may have benefits in the short and long term in these patients, and it is worth considering the necessity of more aggressive treatment to reduce the PTH levels even if patients with NPHPT continue to be normocalcemic.

The present study has several limitations. First, some factors affecting BP, like smoking, alcohol consumption, physical activity, diets, etc., were not surveyed in this investigation. Second, there are some different etiologies for high PTH levels, such as PTH or calcium-sensing receptor mutations, which could not be excluded. Finally, this is a retrospective study with a small sample size in a single center, which would be a significant flaw. The findings should be interpreted with some caution as the study size was quite limited. Large, long-term prospective studies are required to confirm our findings.

**Conclusions**

In summary, our results provide evidence that the subjects with NPHPT had higher risk of high BP than subjects with normal PTH. It is reasonable to suppose that therapeutic intervention aimed to normalize PTH may have benefits in the short and long term in these patients, and it is worth considering the necessity of more aggressive treatment to reduce the PTH levels even if patients with NPHPT continue to be normocalcemic.

**Acknowledgments**

We thank all subjects for participating in this study.

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This study was supported by grants from National Natural Science Foundation of China (81270874), Natural Science Foundation of Fujian Province (2011J06012, 2012J01322), Provincial Health and Family Planning Commission of Fujian Province (2013-ZQN-ZD-3). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure Summary: The authors have nothing to disclose.

**References**


