Normocalcemic Primary Hyperparathyroidism in Adults Without a History of Nephrolithiasis or Fractures: A Prospective Study

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Key words
primary hyperparathyroidism, normocalcemic, secondary hyperparathyroidism, diagnosis, prevalence

received 06.08.2018
accepted 11.02.2019

Bibliography
DOI https://doi.org/10.1055/a-0859-1020
Published online: 6.3.2019
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0018-5043

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ABSTRACT
The prevalence and the diagnostic criterion of “normocalcemic” primary hyperparathyroidism (NPHPT) are still uncertain and there is no consensual definition. This prospective study evaluated the prevalence of NPHPT in 676 adults without a history of fractures or nephrolithiasis and who would be submitted to thyroidectomy, the impact of adopting different cut-off values for 25-hydroxyvitamin D and estimated glomerular filtration rate (eGFR), and the agreement between biochemical diagnosis and the surgical finding of altered parathyroid glands. NPHPT was diagnosed in patients with normal total and ionized calcium and elevated PTH (in 2 measurements) and without a known cause of secondary HPT, including eGFR < 40 ml/min/1.73 m² and 25-hydroxyvitamin D < 20 ng/dl. The 4 parathyroid glands were fully explored in these patients. Forty-six patients (6.8%) had a laboratory diagnosis of NPHPT. Altered parathyroid glands were detected in only 4 patients, corresponding to 0.6% of all patients and to 8.7% of those with a biochemical diagnosis of NPHPT. The latter was confirmed in 0/174 men, 1/252 premenopausal women, and 3/250 postmenopausal women. Among the 42 patients with elevated PTH and without altered parathyroid glands, 25 had 25-hydroxyvitamin D between 20 and 30 ng/dl, 7 had eGFR between 40 and 60 ml/min/1.73 m², and 9 had both. The prevalence of NPHPT was 0.74% in this adult population without a history of nephrolithiasis or fractures. The diagnostic criterion using eGFR > 60 ml/min/1.73 m² and 25-hydroxyvitamin D > 30 ng/dl was more appropriate considering the agreement with the surgical finding of altered parathyroid glands.

Introduction
Classical and “symptomatic” primary hyperparathyroidism (PHPT) manifests with nephrolithiasis, fractures, or symptoms of hypercalcemia. Nowadays, most patients are “asymptomatic” at the time of diagnosis despite elevated serum calcium. Finally, some patients have normal calcium concentrations, which do not rule out bone or renal complications. The prevalence and even the diagnostic criterion of “normocalcemic” PHPT (NPHPT) are still uncertain and there is no consensual definition. In general, the diagnosis of NPHPT is made based on the finding of (i) normocalcemia, including ionized calcium, (ii) associated with elevated parathyroid hormone (PHT), and both should be confirmed (iii) after the exclusion of known causes of secondary HPT (SHPT) [1–5]. Surgery is not likely indicated in patients with NPHPT [6]. Thus, imaging methods for the detection of altered parathyroid glands initially are also not recommended [1, 3, 4, 7]. The underlying parathyroid pathology (hyperplasia or adenoma) is therefore unknown at the time of diagnosis of NPHPT. Curiously, many patients first diagnosed with NPHPT do not progress to hypercalcemia or PTH elevation and spontaneous normalization of this hormone is even observed [8–10]. It is possible that some patients with a laboratory diagnosis of NPHPT actually do not have the condition and may correspond to the small percentage of normal individuals whose PTH is outside the reference range or to patients with inapparent or subclinical causes of SHPT. Finally, controversy exists regarding the exclusion of the 2 main causes of SHPT (chronic kidney disease and vitamin D insuff-
Parathyroidectomy

Trained surgeons performed the surgery of all patients included in the study. The surgeon was aware of the screening results and the team of surgeons was the same throughout the study. The 4 parathyroid glands were fully explored in patients with elevated PTH. The exploration was considered complete when either the 4 glands had been seen or when at least one enlarged and one normal parathyroid gland had been identified [16, 18]. Parathyroid glands were examined based on their macroscopic appearance. We removed only the grossly abnormal parathyroid glands, that is, enlarged. Histology of the removed parathyroid glands was always obtained.

Methods

Total calcium [corrected for low albumin (<4 mg/dl) using the formula: (4 – albumin) × 0.8 + Ca] (reference range: 8.4–10.4 mg/dl) and urinary calcium were measured by a colorimetric method. Ionized calcium (reference range: 1.12–1.32 mmol/l) was measured with a selective electrode and automatic correction for pH variation. Serum PTH was measured with a chemiluminescent assay (Immule 2000, Diagnostic Products Corporation, Los Angeles, CA, USA), with reference values of 12–65 pg/ml. Chemiluminescence assay was used to measure 25-hydroxyvitamin D. Creatinine was measured by a kinetic colorimetric method. The eGFR was calculated using the Modification of Diet in Renal Disease Study equation. Tissue anti-transglutaminase IgA antibodies were measured by enzyme immunoassay. All measurements were obtained in the morning after fasting for approximately 10 h, and the samples were processed and analyzed immediately after collection. Of note, there was no change in laboratory methods during the study.

Results

After the exclusion of 6 patients with hypercalcemic PHPT [16] and 176 with known causes of SHPT, 46 patients (6.8 %) had normal total and ionized calcium and elevated PTH in 2 measurements, in the absence of conditions associated with SHPT (see Methods). Hence, these patients could have a laboratory diagnosis of NPHPT. During surgical exploration, altered parathyroid glands were only detected in 4 patients, corresponding to 0.6 % of all patients and to 8.7 % of those with a laboratory diagnosis of NPHPT. In these patients, the histological diagnosis was adenoma of the parathyroid.
The 5 patients with NPHTP were compared with the 41 patients with elevated PTH without altered parathyroid glands and who had vitamin D insufficiency and/or stage 3 CKD (group B). The 25 patients with vitamin D insufficiency received supplements and were followed up every 8 weeks for dose adjustment to achieve concentrations > 30 ng/dl. After 6 months, the 20 patients who achieved these concentrations in all 3 measurements had normal PTH without hypercalcemia.

**Discussion**

This was a prospective study that used predefined and uniformly followed selection criteria of the patients, laboratory assessment, and surgical approach [16]. In the present series, the prevalence of NPHTP was also evaluated in men and in premenopausal women, who were not included in some of the previous studies [8, 12, 15]. Regarding laboratory assessment, we emphasize that total and ionized calcium was measured and that normocalcemia and elevated PTH were confirmed for the diagnosis of NPHTP. Ionized calcium was not obtained [8–10, 12, 14] and PTH elevation was not confirmed [9, 10, 12, 14] at diagnosis in many previous series that ana-
lyzed the prevalence of NPHPT. In those population studies, hypercalciuria was not excluded as a cause of elevated PTH [8–10, 12, 14]. With respect to the eGFR and vitamin D cut-offs for the exclusion of SHPT, each study adopted a different criterion. In contrast, hypercalciuria and the 4 possible combinations of eGFR and vitamin D concentration were evaluated in the present study. We also point out that, in contrast to the previous studies [8–10, 12, 14], all participants in our series were submitted to surgical exploration of the parathyroid glands, which permitted to correlate the laboratory diagnosis of NPHPT with the confirmation of altered glands.

Using the more rigorous diagnostic criterion (eGFR > 60 ml/min/1.73 m² and 25-hydroxyvitamin D > 30 ng/dl), we found NPHPT (confirmed during surgery) in 1.2% of 250 postmenopausal women without a history of nephrolithiasis or fractures. Also in Brazil, another study found NPHPT in 8% of 179 postmenopausal women, but all of them had been referred to a specialty center for the investigation of osteoporosis [12]. In Spain, NPHPT was diagnosed in 6% of 100 postmenopausal women but this diagnosis was confirmed in only 4% (4%) when reevaluated after 1 year [8]. As mentioned earlier, NPHPT might be overestimated in these series since ionized calcium was not obtained [8, 12], elevated PTH was not confirmed at diagnosis [12], hypercalciuria was not excluded as a cause of this finding [8, 12], SHPT was only considered in the presence of eGFR < 40 ml/min/1.73 m² [12], and there was no confirmation of the underlying parathyroid pathology [8, 12]. With opposite results, the frequency of NPHPT was only 1.5% in a large Swedish study, but only patients with calcium ≥ 10.2 mg/dl were investigated [15], and no case of NPHPT was detected among 157 postmenopausal women in an Italian series [14].

To the best of our knowledge, only 3 previous studies have evaluated the prevalence of NPHPT in men and in women before menopause [9, 10, 14]. In the first, the prevalence was only 0.4% in men > 65 years, 0.67% in men between 18 and 65 years, and 0.35% in women between 18 and 65 years. Nevertheless, these prevalence rates might be overestimated since elevated PTH was not confirmed, hypercalciuria was not investigated for the exclusion of SHPT, and only individuals with 25-hydroxivitamin D < 20 ng/ml were excluded [9]. Corroborating the possibility of an initial misdiagnosis of NPHPT, during long-term follow-up, the criterion of PHT persisted in only 22% of the patients and spontaneous normalization of PTH was observed in 45% [9]. In the second study, no case was diagnosed in adult women and the prevalence was 1% in men, but again elevated PTH was not confirmed and hypercalciuria was not excluded [14]. In the present study in which elevated PTH was confirmed, hypercalciuria was excluded and 25-hydroxivitamin D > 30 ng/ml was considered for diagnosis, NPHPT was found in only 0.57% of 174 men (patient without altered parathyroid gland during surgery) and in 0.4% of 252 premenopausal women.

Another result of the present study was the implication of different eGFR and 25-hydroxyvitamin D cut-offs for the diagnosis of NPHPT. The prevalence of NPHPT was 6.8% considering eGFR > 40 ml/min/1.73 m² and 25-hydroxyvitamin D > 20 ng/dl and only 0.74% using eGFR > 60 ml/min/1.73 m² and 25-hydroxyvitamin D > 30 ng/dl. Whereas altered parathyroid glands were confirmed during surgery in only 8.7% of the patients with a diagnosis of NPHPT using the first criterion, the same was observed in 80% of patients diagnosed using the second criterion. Thus, the criterion of eGFR > 60 ml/min/1.73 m² and 25-hydroxyvitamin D > 30 ng/dl seems to be more appropriate to avoid an excessive number of false-positive results. Since patients with NPHPT can have eGFR < 60 ml/min/1.73 m² and 25-hydroxyvitamin D < 30 ng/dl, to ensure that these cases will also be diagnosed, replacement therapy would be useful when vitamin D is between 20–30 ng/dl, maintaining persistent levels > 30 ng/dl and observing if there is normalization of PTH (SHPT) or even the development of hypercalcinia (PHPT). In the case of eGFR < 60 ml/min/1.73 m², considering the irreversibility of this situation, follow-up verifying the evolution of calcium, PTH and correlation of eGFR with PTH may be helpful in the differential diagnosis.

Our study has limitations. Imaging methods directed at the parathyroid glands were not performed before surgery. However, these methods were found to be limited in patients with NPHPT [19], and surgical exploration by an experienced surgeon is known to be more sensitive for the identification of altered parathyroid glands. Another limitation was the lack of information about the follow-up of patients with elevated PTH and eGFR 40–60 ml/min/1.73 m² in the absence of altered parathyroid glands during surgery. However, with this negative finding, we believe that they in fact had SHPT.

In conclusion, the prevalence of NPHPT was 0.74% in an adult population without history of nephrolithiasis or fractures. The diagnostic criterion using eGFR > 60 ml/min/1.73 m² and 25-hydroxivitamin D > 30 ng/dl was more appropriate considering the agreement with the surgical finding of altered parathyroid glands.

Funding
This work was supported by the National Council for Scientific and Technological Development (CNPq).

Conflict of Interest
The authors declare no conflict of interest.

References


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