Research Article

High Rate of Occult Urolithiasis in Normocalcemic Primary Hyperparathyroidism

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Keywords

Primary hyperparathyroidism · Normocalcemia · Nephrolithiasis

Abstract

Introduction: Normocalcemic primary hyperparathyroidism (NPHPT) is characterized by elevations in serum parathyroid hormone levels in the presence of normal serum calcium concentrations after exclusion of secondary hyperparathyroidism. We have previously demonstrated no differences in the prevalence of clinically active urolithiasis between NPHPT and hypercalcemic asymptomatic PHPT, and that it is significantly higher in postmenopausal osteoporotic women with NPHPT in comparison to women with normal serum PTH and calcium concentrations. Few studies have addressed the occurrence of silent or occult kidney stones in asymptomatic hypercalcemic PHPT, but no data are available for NPHPT. **Objective:** To determine the presence of occult urolithiasis in NPHPT patients using routine abdominal ultrasonography. **Methods and Results:** We studied 35 patients with NPHPT (mean age 63.2 ± 10.7 years, 96% women; serum PTH 116.5 ± 39.2 pg/mL, 25OHD 38.5 ± 6.82 ng/mL, total calcium 9.1 ± 0.56 mg/dL; albumin 4.02 ± 0.37 g/dL; BUN 34.35 ± 10.23 mg/dL; $p = 3.51 \pm 0.60$ mg/dL; estimated glomerular filtration rate 88.44 ± 32.45 mL/min/1.73 m², and 24-h urinary calcium excretion 140.6 ± 94.3 mg/24 h). The criteria for the diagnosis of NPHPT were as follows: serum PTH above the reference range (11–65 pg/mL), normal albumin-corrected serum calcium concentrations, normal 24-h urinary calcium excretion, serum 25OHD above 30 ng/mL, estimated GFR (MDRD) above 60 mL/min/1.73 m² (with the exclusion of medications such as thiazide diuretics, lithium, bisphosphonates, and denosumab), a history of clinical symptoms of urolithiasis, and a family history of kidney stones. Thirty-five patients were evaluated and 25 of them met the inclusion criteria. Five patients presented nephrolithiasis corresponding to 20% of the study

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population. There were no statistically significant differences in any of the clinical or laboratory variables studied between patients with or without urolithiasis, although mean serum PTH levels were higher in patients with stones (180.06 ± 126.48 vs. 100.72 ± 25.28 pg/mL, $p = 0.1$). The size of the stones ranged from 0.6 to 0.9 cm and all of the stones were located in the renal pelvis. **Conclusion:** We found a high prevalence of occult kidney stones in NPHPT patients, similar to what is observed in clinically manifested urolithiasis, in hypercalcemic PHPT.

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Introduction

Normocalcemic primary hyperparathyroidism (NPHPT) is characterized by elevated serum parathyroid hormone concentrations and normal levels of serum calcium. It is necessary to exclude secondary causes of PTH elevation, such as renal disease, hypovitaminosis D, malabsorption, and use of medications that alter calcium homeostasis, such as thiazide diuretics and lithium [1]. We have previously demonstrated no differences in the prevalence of clinically active urolithiasis between NPHPT and hypercalcemic asymptomatic PHPT, and that it is significantly higher in postmenopausal osteoporotic women with NPHPT than in women with normal serum PTH and calcium concentrations. Few studies have addressed the occurrence of silent or occult kidney stones in asymptomatic hypercalcemic PHPT, but no data are available for NPHPT [2].

Materials and Methods

Thirty-five patients with NPHPT were studied (mean age 63.2 ± 10.7 years, 96% women). The diagnosis of NPHPT was based on the following criteria: serum PTH above the reference range (normal: 10–65 pg/mL) and serum calcium in the normal range (8.8–10.5 mg/dL), estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m², serum 25OHD >30 ng/mL, and no treatment with thiazide diuretics, lithium, or antiresorptive agents. We excluded patients with a history of urolithiasis.

Patients who agreed to participate, after signing the informed consent form, answered a questionnaire and underwent a complete physical examination.

After an overnight fast, blood was drawn for laboratory tests, including serum PTH, 25OHD, total calcium, albumin, phosphorus, BUN, and creatinine, as well as 24-h urinary calcium. Measurement of PTH and 25OHD was done by electrochemoluminescent assay (Architect i2000 Abbott, USA) and 24-h urinary calcium was assessed by calorimetry. eGFR was calculated using the MDRD equation.

Urinary tract ultrasonogram (USG) was performed using transducers from 3 to 7 MHz (HD7 EX Phillips, The Netherlands) allowing evaluation of the entire kidney. The patient was positioned in left and right lateral decubitus, and renal length and echogenicity and the presence, number, and position of renal calculi were evaluated. Calculi smaller than 3 mm were not considered as they may not produce a posterior acoustic shadow as larger ones do and thus lead to difficulties in the diagnosis [3].

Statistical Analysis

Data were presented as absolute and percentage frequencies for categorical variables and as means and SD for numerical variables. The Mann-Whitney test was used to compare those with or without renal stones in relation to numerical variables and the choice of the test was based on the number of cases with complications.

Table 1. General characteristics of the study patients

Age, years	63.28±10.76
Serum PTH, pg/mL	116.58±39.20
Serum 25OHD, ng/mL	64.97±6.82
Serum calcium, mg/dL	9.11±0.56
Serum albumin, g/dL	4.02±0.37
Serum phosphorus, mg/dL	3.50±0.60
BUN, mg/dL	34.35±10.23
Serum creatinine, mg/dL	0.70±0.13
eGFR ^a , mL/min/1.73 m ²	88.44±32.65
Urinary pH	5.8±0.3
24-h urinary calcium excretion, mg	140.64±94.37

Data are presented as means ± SD. ^a Estimated using the MDRD formula.

Table 2. Differences between patients with or without stones

	Kidney stones		<i>p</i>
	yes	no	
Age, years	60.0±15.20	64.10±9.70	0.705
Weight, kg	66.42±13.26	63.18±11.62	0.660
Serum PTH, pg/mL	180.06±126.48	100.72±25.28	0.110
Serum 25OHD, ng/mL	36.68±2.61	39.84±7.43	0.629
Serum calcium, mg/dL	9.46±0.58	9.03±0.54	0.125
Serum albumin, g/dL	4.00±0.51	4.03±0.34	0.750
Serum phosphorus, mg/dL	3.28±0.19	3.56±0.66	0.471
BUN, mg/dL	32.8±12.62	34.74±9.90	0.497
Serum creatinine, mg/dL	0.68±0.08	0.70±0.15	0.723
eGFR ^a , mL/min/1.73 m ²	87.4±12.57	88.7±36.23	0.860
Urinary pH	5.7±0.2	5.9±0.3	0.758
24-h urinary calcium excretion, mg	155.8±65.09	136.85±101.4	0.371

Data are presented as means ± SD. ^a Estimated using the MDRD formula.

The statistical analysis was based on a 5% margin of error. Calculations encompassed the mean, SD, and application of the comparison of variables between the groups with and without nephrolithiasis. The data was entered into an Excel worksheet and the software used to obtain the statistical calculations was IBM – SPSS, version 23.

Results

Of the 36 patients with NPHPT who were recruited, 25 met the inclusion criteria and were included in the statistical analysis. Two patients were excluded because they presented an eGFR of less than 60 mL/min, 3 patients were excluded because they presented serum levels of 25OHD below 30 ng/mL, and the other patients were excluded owing to incomplete data or discontinuation of clinical follow-up.

Table 1 summarizes the characteristics of the study population. The mean age of the patients was 63.28 ± 10.76 years, with no difference between patients with and without renal calculi; 88% of the patients were going through menopause. Only 2 male patients were selected, and 1 of them was excluded because of renal dysfunction. The mean values were as

follows: serum PTH, 116.58 ± 39.20 pg/mL; 25OHD, 38.52 ng/mL; albumin-corrected serum calcium, 9.11 ± 0.56 mg/dL; and 24-h urinary calcium, 140.64 ± 94.37 mg/24 h.

There were no statistically significant differences regarding the mean age, weight, MDRD and laboratory tests, including urinary pH, between patients with and without renal calculi, as shown in Table 2.

Of the 25 patients studied, 5 presented a renal calculus identified in the USG of the urinary tract, corresponding to 20% of the cases described. Three patients had a single stone, ranging in size from 0.6 to 0.9 cm. Two patients had multiple renal stones, with the largest being 0.9 cm in both kidneys, but 1 of them also presented nephrocalcinosis.

Patients with nephrolithiasis had higher serum PTH and serum calcium values (180.06 ± 126.48 vs. 100.72 ± 25.28 pg/mL and 9.46 ± 0.58 vs. 9.03 ± 0.54 mg/dL), but these differences were not statistically significant.

There were no significant differences between the groups with and without stones regarding obesity or metabolic syndrome as additional risk factors for stone formation (BMI 27.6 ± 5.7 vs. 26.8 ± 6.2 ; $p = 0.2$, and WC 94.5 ± 3.2 vs. 95.2 ± 2.8 cm; $p = 0.3$).

Discussion

Nephrolithiasis is a common complication of hypercalcemic primary hyperparathyroidism [4]. This study identified the presence of a renal calculus in 20% of the patients with the normocalcemic form, similar to what has been reported in the literature when evaluating symptomatic nephrolithiasis in mild normocalcemic or hypercalcemic patients [5, 6].

With respect to the general population, data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2010 reported a prevalence of renal calculi in the USA of 10.6% in men and 7.1% in women [7]. In Europe, this prevalence is 5–9% [8] and in Brazil it is 6% [9]. In our study, in patients with NPHPT, the prevalence was 20%; this is much higher than in the general population, suggesting the impact of NPHPT on the increased risk of nephrolithiasis.

The incidence of primary hyperparathyroidism increases with age, with a higher prevalence in postmenopausal women [10]. About 88% of the study participants were postmenopausal women who were diagnosed with NPHPT during the investigation for osteoporosis. This data is consistent with findings in the literature regarding the diagnosis of NPHPT. Lowe et al. [11], in a study set out to characterize the population of normocalcemic hyperparathyroidism after ruling out the possibility of secondary causes. Thirty-seven patients were identified with this condition, with most of them being women. Of these, 5 (14%) had symptomatic nephrolithiasis and 21 (57%) had osteoporosis at at least 1 site and 11% had fragility fractures [11].

Ejlsmark-Svensson et al. [12], using computerized tomography, showed a 23% prevalence rate of renal calcifications with the same gender frequency in patients with hypercalcemic PHPT. Of these, 12% had common nephrolithiasis, 12% had nephrocalcinosis, and 1% had both nephrolithiasis and nephrocalcinosis. Impaired renal function was also common in PHPT, but it was not associated with renal calcifications [12].

In a cross-sectional analysis of 96 asymptomatic hypercalcemic PHPT patients, an increased incidence of occult urolithiasis was observed, representing 21% of the sample. Patients with stones had significantly higher serum 1,25OH₂D concentrations as well as higher 24-h urinary calcium levels compared to those without stones [13].

Tuna et al. [6] compared the complications of PTH in normocalcemic and hypercalcemic patients. The studied population consisted of 36 (12%) men and 271 (88%) women. Twenty-three of the patients were diagnosed with NPHPT and 284 were diagnosed with the hyper-

calcemic form. There were no significant differences in terms of age, sex, the prevalence of hypertension, low bone mineral density, and renal calculi between groups. Nephrolithiasis was found in 15.4% of the normocalcemic patients and 19.4% of the hypercalcemic ones [6].

At our institution, other studies have evaluated the presence of complications associated with primary normocalcemic hyperparathyroidism. Marques et al. [14] retrospectively evaluated the occurrence of hyperparathyroidism in 156 female patients with osteoporosis and found that 14% of the patients had primary normocalcemic hyperparathyroidism. Among these patients, the presence of symptomatic nephrolithiasis was 28.6%, in contrast to only 0.7% of non-NPHPT carriers [14]. Amaral et al. [2] compared clinical and laboratory data among patients with normal and hypercalcemic primary hyperparathyroidism. Seventy patients were studied (i.e., 33 normocalcemic and 37 hypercalcemic patients). The frequency of symptomatic nephrolithiasis was 18.2% in the normocalcemic patients and 18.9% in the hypercalcemic patients [2].

In our study, there were no significant statistical differences in the biochemical tests between the 2 groups; however, there was a trend toward higher serum PTH levels and calcium elevation in patients with nephrolithiasis. The 24-h urinary calcium was similar in the 2 groups, suggesting that renal stone formation in the patient with primary hyperparathyroidism may be associated with other factors, not only hypercalcemia and hypercalciuria [15, 16]. This is justified by the similarity in the prevalence of renal calculus among normocalcemic and hypercalcemic patients, as described in the study by Amaral et al. [2].

The higher rate of occult nephrolithiasis in patients with NPHPT suggests that renal complications associated with primary hyperparathyroidism may be an early event. This findings thus reinforce the importance of the diagnosis and follow-up of patients with NPHPT for the early identification of complications that were previously associated only with hypercalcemic PHPT [6].

Concerns regarding NPHPT arise from the increased prevalence of this condition over the years. Kontogeorgos et al. [17] showed that the prevalence of NPHPT was 2% in 1995 and 11% in 2008. With the increase in prevalence come an increase in the appearance of complications and resulting increased costs for health services.

In the present study USG of the urinary tract was performed like in most studies investigating renal stones in hypercalcemic PHPT [2]. In addition to being a low-cost examination, it does not expose the patient to radiation. Its sensitivity varies depending on the location and size of the calculi. Our study evaluated calculi that were found in the renal pelvis, which in most cases are asymptomatic. Migratory or localized calculi in the ureter are usually accompanied by signs and symptoms such as hematuria, dysuria, and abdominal pain. Renal calculi of less than 3 mm were not considered in this study. The USG is unable to identify stones smaller than 3 mm, which may be confused with artifacts or increased echogenicity of renal sinus fat. Computed tomography (CT) allows visualization of these calculi since this method also measures their density. However, CT should not be used routinely due to the risk of exposure to radiation, and it is reserved in cases with a high clinical suspicion of nephrolithiasis and normal USG and abdominal x-ray [3].

In conclusion, we found a high prevalence of occult kidney stones in NPHPT patients similar to what is observed, for clinically manifested urolithiasis, in hypercalcemic PHPT.

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Statement of Ethics

All of the patients in this study signed an informed consent form. This study was approved by the Research Ethics Committee of the Agamenon Magalhães Hospital.

Disclosure of Statement

The authors have no conflict of interests to declare.

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Author Contributions

Research design: A.L.P.L., S.R.L.A., L.L.H.P., L.C.B., and F.B. Data collection: A.L.P.L., S.R.L.A., L.L.H.P., P.M.C.T., E.B., and L.C.B. Data analysis: E.B., L.C.B. and, F.B. Article development: A.L.P.L., E.B., L.C.B., and F.B. Mentorship: F.B.

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