Clinical Study

Normocalcemic versus Hypercalcemic Primary Hyperparathyroidism: More Stone than Bone?

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Introduction. Normocalcemic primary hyperparathyroidism (NPHPT) is considered a variant of the more frequent form of the disease characterized by normal serum calcium levels with high PTH. The higher prevalence of renal stones in patients with HPTP and the well established association with bone disorders show the importance of studies on how to manage asymptomatic patients. *Objective*. To compare the clinical and laboratory data between the normocalcemic and mild hypercalcemic forms of PHPT. *Methods*. We retrospectively evaluated 70 patients with PHPT, 33 normocalcemic and 37 mild hypercalcemic. *Results*. The frequency of nephrolithiasis was 18.2% in normocalcemic patients and 18.9% in the hypercalcemic ones ($P = 0.937$). Fifteen percent of normocalcemic patients had a previous history of fractures compared to 10.8% of hypercalcemic patients, although there was no statistically significant difference ($P = 0.726$). *Conclusion*. Our data confirms a high prevalence of urolithiasis in normocalcemic primary hyperparathyroidism, but with the preservation of cortical bone. This finding supports the hypothesis that this disease is not an idle condition and needs treatment.

1. Introduction

Primary hyperparathyroidism (PHPT) is a disease characterized by elevated or inappropriately normal parathyroid hormone (PTH) levels due to excessive secretion by one or more parathyroid glands. The classical form of the disease is characterized by hypercalcemia, kidney stones, and severe bone disease [1]. The routine measurement of serum calcium as a screening tool has led to a sharp increase in the incidence of a new presentation of the disease, namely, asymptomatic PHPT, whose demonstration of bone involvement depends exclusively on the bone densitometry data [2–4].

The association with kidney disease, nephrocalcinosis, and nephrolithiasis is well established in the HPTP and has been reported in several studies. Suh et al. found a prevalence of 7% in 271 individuals with the disorder and 1.6% in 500 healthy patients evaluated by sonography. The risk of hospitalization due to urolithiasis is increased for patients with HPTP even ten years after parathyroidectomy [5, 6].

Currently a new phenotype has arisen, in which normocalcemia is observed, despite persistently high levels of PTH.

In this situation, a thorough search for causes of secondary hyperparathyroidism, particularly vitamin D deficiency, is imperative [7–9]. The demonstration of normocalcemic PHPT is even more difficult as there are no guidelines for routine PTH measurement, as HPTP is most frequently identified during the investigation of reduced bone density [9, 10].

2. Patients and Methods

We retrospectively reviewed the medical records of 70 patients with PHPT from our institution, who were divided into two groups: 33 patients with normal serum calcium levels and 37 with hypercalcemia (serum calcium $\geq$ 10.2 mg/dL).

The following clinical data were obtained: gender, age, weight, height, and BMI.

The diagnostic criteria for NPHPT were as follows: apart from normal serum calcium and high PTH levels, serum 25OHD levels above 30 ng/mL, absence of bisphosphonates,

TABLE 1: Baseline characteristics of study patients.

Variable	Normocalcemic	Hypercalcemic	Total	P value
Gender				
Male %	21.2	24.3	22.9	$P = 0.757$
Female %	78.8	75.7	77.1	
Age (years)	63.67 ± 13.83	61.68 ± 13.86	62.61 ± 13.78	$P = 0.550$
BMI (Kg/m^2)	25.78 ± 3.85	26.66 ± 4.25	26.25 ± 4.06	$P = 0.376$
Serum calcium (mg/dL)	9.58 ± 0.44	11.33 ± 0.90	10.51 ± 1.13	$P < 0.001$
Serum creatinine (mg/dL)	0.89 ± 0.20	0.85 ± 0.32	0.86 ± 0.29	$P = 0.676$
Serum 25OHD (ng/mL)	42.45 ± 12.94	30.91 ± 10.63	36.68 ± 13.11	$P < 0.001$
Serum PTH (pg/mL)	127.52 ± 114.41	226.18 ± 398.61	179.67 ± 302.38	$P = 0.175$
Serum CTX (pg/mL)	342.94 ± 207.16	492.13 ± 425.37	416.39 ± 338.75	$P = 0.080$
CrCL (mL/min/1,73)	80.08 ± 21.08	87.82 ± 34.17	84.17 ± 28.82	$P = 0.253$

Data expressed as mean $\pm$ SD.

thiazide diuretics, anticonvulsants or lithium use, glomerular filtration rate greater than 60 mL/min, using the formula *Modification of Diet in Renal Disease* (MDRD), and the absence of other metabolic bone diseases or gastrointestinal diseases associated with malabsorption or liver disease. All patients had a urinary Ca/Cr ratio of less than 240 mg/g Cr, demonstrating the absence of hypercalciuria.

Serum calcium was determined using the Johnson and Johnson VITROS 950 system (Rochester, NY, USA) with reference value 8.4 to 10.2 mg/dL, serum 25-hydroxyvitamin D using the DiaSorin LIAISON competitive chemiluminescent immunoassay (Stillwater, MN, USA) 10% coefficient of variation, with the following reference values: normal: 30 to 60 ng/mL), serum PTH using the chemiluminescence method, Immulite 2000 (SIEMENS, Llanberis, Gwynedd, UK), with intra- and interassay coefficients of variation of 4.2 to 5.7% and 6.3 to 6.8%, respectively, and serum C-telopeptide when using the electrochemiluminescence assay, Elecsys systems, Roche Diagnostics, Mannheim, Germany, reference value 50–450 pg/mL. Bone mineral density (BMD) and T-score were evaluated at the lumbar spine (L1–L4), femoral neck, and distal radius (Lunar Corporation Madison, Wisconsin, USA). The correction of serum calcium levels in relation to albumin was performed using the following formula: corrected calcium = calcium found + (4-serum albumin) $\times$ 0.8.

Patients who had clinical manifestations of nephrolithiasis were evaluated by ultrasound, and the results of the examinations were obtained from the medical records. Bone fractures were investigated by radiography.

The study was approved by the Ethics in Research Committee of Agamenon Magalhães Hospital.

3. Statistical Analysis

Pearson's chi-square test or Fisher's exact test and the Student's t-test with equal or unequal variances were used for comparisons. Verification of the hypothesis of equal variances was performed using Levene's F test, and the level of significance used in interpreting the statistical test was 5%.

4. Results

Baseline characteristics are shown in Table 1. The prevalence of nephrolithiasis in the normocalcemic group was 18.2% and 18.9% in the hypercalcemic group ($P = 0.937$). Fifteen percent of normocalcemic patients had a previous history of fractures compared to 10.8% of hypercalcemic patients, although there was no statistically significant difference ($P = 0.726$) Table 2.

In both groups, the bone mineral density in the lumbar spine was 0.95 ± 0.24 g/cm^2 (T score: -1.3), femoral neck 0.76 ± 0.15 g/cm^2 (T score: -1.75), and distal radius 0.54 ± 0.15 g/cm^2 (T score: -1.96). LS BMD was normocalcemic 0.95 ± 0.22 g/cm^2 versus hypercalcemic 0.95 ± 0.26 g/cm^2, $P = 0.885$ and FN BMD: normocalcemic 0.73 ± 0.15 g/cm^2 versus hypercalcemic 0.79 ± 0.19 g/cm^2, $P = 0.123$. Patients with normocalcemia had BMD values in the distal radius significantly higher than the hypercalcemic patients ($P = 0.046$), as shown in Table 3.

5. Discussion

In the present study we found a high prevalence of kidney stones in NPHPT, suggesting that the normocalcemia condition does not mean that the patient is without clinical manifestations. In relation to a history of fractures, we found a similar occurrence in the two groups with 15.2% in the normocalcemic and 10.8% in the hypercalcemic. We also observed that the bone mineral density in the distal radius was more preserved in the normocalcemic group than in the hypercalcemic group, although there were no significant differences in the lumbar spine and femoral neck.

Few studies have addressed the issue of NPHPT. Lundgren et al., in a sample of 109 patients, found that 17 (16%) had normal levels of calcium with elevated PTH characterizing NPHPT [11]. In our institution, Marques et al. found a prevalence of NPHPT of 8.9% in a population of 156 postmenopausal women with osteoporosis [8]. These data suggest that it is not a rare condition and therefore needs to be

TABLE 2: History of fracture and kidney stones in normocalcemic and hypercalcemic PHPT.

Variable	Normocalcemic		Hypercalcemic		Group total		P value
	N	%	N	%	N	%	
Total	33	100,0	37	100,0	70	100,0	
(i) Fracture							
Yes	5 1M/4F	15.2	4 0M/4F	10.8	9	12.9	$P^{(1)} = 0.726$
(ii) Kidney Stones							
Yes	6 0M/6F	18.2	7 3M/4F	18.9	13	18.6	$P^{(2)} = 0.937$

[1] Using Fisher's exact test. [2] Using Pearson's chi-square test.
M: male; F: female.

TABLE 3: Bone mineral density in normocalcemic and hypercalcemic PHPT.

BMD#	Normocalcemic	Hypercalcemic	Group total	P value
(i) Distal radius	0.54 ± 0.15	0.45 ± 0.18	0.50 ± 0.17	$P^{(1)} = 0.046$
(ii) Lumbar spine	0.95 ± 0.22	0.95 ± 0.26	0.95 ± 0.24	$P^{(1)} = 0.885$
(iii) Femoral neck	0.73 ± 0.15	0.79 ± 0.19	0.76 ± 0.17	$P^{(1)} = 0.123$

#BMD in g/m^2. Data expressed as mean ± SD.

investigated in all patients with reduced bone mineral density. In contrast, in a population-based survey conducted in Sweden, the prevalence of NPHPT, in postmenopausal women was 0.6% [11].

The incidence of kidney stones and fractures has also been documented in small studies. Lowe et al. [9], in a series of 37 normocalcemic patients, found a frequency of nephrolithiasis of 14%, which is comparable with our findings, and a history of fracture of 11% [9]. Marques et al. showed an occurrence of kidney stones of 28.6% in osteoporotic women with NPHPT in contrast to 0.7% in noncarriers. For clinical fractures they found a 21.4% prevalence in NPHPT compared with 16.2% in those not affected [8]. Our study showed a preservation of cortical bone in patients with the normocalcemic form of the disease, and this is in agreement with the findings of Lowe et al., who showed a deterioration, particularly in LS BMD [9].

Patients with NPHPT may present PTH resistance in target tissues. One study showed that after an oral calcium load, normocalcemic subjects had an inadequate suppression of PTH compared with hypercalcemic subjects. The high frequency of kidney stones and fractures in normocalcemic primary hyperparathyroidism could be explained by the possible lower renal and bone sensitivity to the biological effects of PTH, although this hypothesis needs further investigation [12]. Gomes et al. stated that another possibility could be the presence of non-1–84 PTH circulating molecules, such as a 7–84 PTH fragment, blocking the calcemic effect of 1–84 PTH and preventing hypercalcemia [13].

Our data suggests that NPHPT may not be an idle condition as it may progress to complication regardless of the development of hypercalcemia. Controversies regarding the suggestion that NPHPT should be treated, since the disease can lead to a deterioration in bone mineral density, fractures, and kidney stones. Thus, the routine determination of PTH could detect these individuals early on in an attempt to prevent an unfavorable clinical course.

There is no consensus about when to treat patients with HPTPN, but if there is progression to clinical complications such as urolithiasis, bone mass loss, or fractures, surgery is indicated [4].

Finally, a new phenotype of NPHPT was recently described in a population-based survey MrOS (Osteoporosis Fractures in Men). Using less rigid criteria for the diagnosis of NPHPT (GFR > 40 mL/min and serum 25OHD < 20 mg/mL), the authors found a 0.7% prevalence of the disease that was associated with a significantly higher LS BMD in comparison with the elderly men without NPHPT [14].

6. Conclusion

Our findings revealed a high prevalence of urolithiasis in normocalcemic primary hyperparathyroidism, but with preservation of the cortical bone, corroborating the belief that the disease is not an indolent condition and needs to be not only investigated but also treated when complications are diagnosed.

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