Epidemiology and Clinical Forms of Primary Hyperparathyroidism: A Review

Epidemiología e formas clínicas do hiperparatireoidismo primário: uma revisão

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Abstract

Primary hyperparathyroidism (PHPT) is a disease caused by overactive parathyroid glands with consequent hypercalcemia. However, its presentation is variable, with patients demonstrating a range from normocalcemia to severe hypercalcemic PHPT. The present study aims to perform a literature review on the epidemiology and the clinical forms of PHPT using information published in the PubMed and Cochrane databases. It describes data about prevalence, etiology, diagnosis, classic and non-classic manifestations, providing updated information on classical hypercalcemic hyperthyroidism, in addition to its normocalcemic variant.

Resumo

O hiperparatireoidismo primário é uma doença causada pela hiperatividade das glândulas paratireóides, com consequente hipercalemia. No entanto, a apresentação clínica pode variar, desde um hiperparatireoidismo normocalcêmico até um hiperparatireoidismo hipercaleêmico grave. O presente estudo tem como objetivo realizar uma revisão bibliográfica sobre a epidemiologia e as formas clínicas do hiperparatireoidismo primário, utilizando informações publicadas nas bases de dados do PubMed e do Cochrane. Descrevemos dados atuais sobre prevalência, etiologia, diagnóstico, manifestações médicas e não médicas do hiperparatireoidismo primário hipercaleêmico clássico, além de sua variante normocalcêmica.

Introduction

Primary hyperparathyroidism (PHPT) is characterized by the hyperactivity of one or more of the parathyroid glands, causing increased levels of serum calcium associated with increased or inappropriately normal levels of the parathyroid hormone (PTH). Primary hyperparathyroidism is a common endocrine disorder, being the main cause of hypercalcemia found during an outpatient appointment. It is most commonly

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observed in female individuals over 50 years old, with a 3 to 4 times higher incidence in this population.³ The incidence rates among premenopausal men and women are similar.⁴

Primary hyperparathyroidism is sporadic in more than 90% of the cases, with a single adenoma as the main etiology (85 to 90% of the cases). Less frequently, there is multiglandular involvement, multiple adenomas or hyperplasia of all four glands (5–10% of the cases); and, more rarely (< 1% of the cases), parathyroid carcinoma.⁵

Primary hyperparathyroidism may also be a part of hereditary endocrine syndromes, including multiple endocrine neoplasia type 1 (MEN1), type 2A (MEN2A), type 4 (MEN4), hyperparathyroidism-jaw tumor syndrome, familial hypocalciuric hypercalcemia and severe neonatal hyperparathyroidism.⁶

Since 1970, when serum calcium screening tests increased, hyperparathyroidism (HPT) has become more routinely diagnosed at the asymptomatic stage.⁷ The clinical evolution of PHPT from symptomatic to asymptomatic occurred mainly in the United States and Europe, although other countries have appreciated this change more recently. The prevalence and clinical effects of PHPT can vary across countries and even within countries, according to the availability of screening tests and whether the source of information comes from reference centers or from the country’s demographic data.⁵ However, although the most common presentation of PHPT is called asymptomatic, the involvement of a microstructural disease in the skeleton and calcifications in the kidneys can be seen.⁸

The current discussion encompasses non-classical manifestations of PHPT, such as neurocognitive impairment⁹ and the cardiovascular system.¹⁰ Another phenotype of interest is normocalcemic primary hyperparathyroidism (NPHPT).¹¹

### Epidemiology

The prevalence of PHPT varies according to the screening methods, definitions, and populations studied.⁵,⁷ The risk of PHPT varies according to age and gender, being most commonly observed in women > 50 years old.³ The incidence rates between premenopausal men and women are similar.⁴

The prevalence of PHPT varies globally, but it has been better documented in Europe, the USA and Latin America (Table 1). In the United States, the prevalence is around 0.86%,¹² estimated at ~ 2 per 1,000 in women and at ~ 0.5 per 1,000 in men, and is approaching 10 per 1,000 individuals over the age of 40 years old and an even higher prevalence of 34 per 1,000 in postmenopausal women.¹³,¹⁴

In Europe, the prevalence of PHPT is ~ 1.07%.¹² A Danish study showed an increase in incidences between 1977 and 2010, with an annual rate of 16 per 100,000, with a higher incidence in women than in men, particularly in women > 50 years old.¹⁵ In the city of Tayside, Scotland, a population-based study showed that the incidence of PHPT was higher in women than in men and increased with age: in 2006, the overall prevalence was 6.72 per 1,000.⁷ Scotland has also recently detected an increase in the incidence of the disease, as studied between the years of 1986 and 2013.¹⁶ Epidemiological data on men are much less described, but a Swedish Osteoporotic Fractures in Men (MrOs, in the Swedish acronym) cohort study with 3,014 men aged between 69 and 81 years old identified a prevalence of PHPT of 0.73% in men.¹⁷

The prevalence of PHPT in Latin America is around 0.78%.¹² A cross-sectional study conducted in Brazil with 4,207 patients found a prevalence of PHPT of 7.8 per 1,000 individuals, with 81.8% of these patients being asymptomatic and 18.2%, symptomatic. In this study, the proportion of women/men affected was of 7.2 to 1, with 89.7% of postmenopausal women and a mean age of 61.12 years old.¹⁸

### Primary Causes of Hyperparathyroidism

Single parathyroid adenoma is the main cause of PHPT, and it is responsible for 85–90% of the cases.¹,⁹ Hyperplasia and multiple adenomas account for 15% of the cases.¹⁹,²⁰ Hyperfunction in multiple glands or parathyroid carcinoma are rarely seen (0.7% of the cases).¹

In children and young adults, PHPT is most commonly associated with its hereditary forms. In familial HPT syndromes, which account for 10% of the cases, the involvement of multiple glands is the most common.²⁰ Multiple endocrine neoplasia types 1 and 2 (MEN1/MEN2), HPT-jaw tumor syndrome, familial hypocalciuric hypercalcemia, familial hypercalcemia and isolated familial hyperparathyroidism are clinical conditions associated with primary familial HPT.⁵

When PHPT is detected in a young adult, the possibility of MEN1 should be investigated in the individual and in his or her first-degree relatives. Mutations in the MEN-1 gene are transmitted in an autosomal dominant manner, and multiple endocrine tumors involve the parathyroid, the pancreas, the anterior pituitary and/or the duodenal endocrine cells.²¹ Primary hyperparathyroidism is the first sign of MEN1 in most carriers between 20 and 30 years of age and is present in almost all patients > 50 years old.²² In MEN2, the clinical manifestations of most patients with PHPT are more discrete than in MEN1, and PHPT occurs in 20–30% of the cases of MEN2.²³

The rare diagnosis of HPT-mandible tumor syndrome (mutation in the CDC73 gene) is associated with tumors in the parathyroid, bone tumors of the mandible and/or maxilla, kidneys, and uterus.²¹ Parathyroid cancer is more frequent in this clinical condition than in isolated PHPT, occurring in more than 15% of the cases.¹⁹

The presence of mutations in the CDC73 gene, a gene that encodes the tumor suppressor protein parafibromin, has been recently related to the onset of PHPT and parathyroid carcinoma.²⁴

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**Table 1** Prevalence of primary hyperparathyroidism in the United States, Europe and Latin America

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
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<tr>
<td>United States</td>
<td>0.86%</td>
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<tr>
<td>Europe</td>
<td>1.07–9.95%</td>
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<tr>
<td>Latin America</td>
<td>0.78%</td>
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Some genes are involved in the development of parathyroid tumors, such as the cyclin D1/PRAD1 gene for sporadic tumors; and RET for familial tumors; and MEN1 or HRPT, both for sporadic and familial tumors. In addition, the vitamin D receptor (VDR) inactivates the onset of parathyroid adenomas, possibly due to the action of 1,25-dihydroxyvitamin D (25OHD), which inhibits the proliferation of parathyroid cells in a culture medium. The inactivation of the RVD gene does not appear to play a primary role in parathyroid gland tumorigenesis, but vitamin D deficiency may alter the phenotypic expression of parathyroid tumors.

In cases of isolated familial hyperparathyroidism, PHPT is diagnosed in close relatives in the absence of other endocrinopathies, and it may correspond to a phenotype of hidden syndromes such as MEN-1 and MEN-29.

In the presence of hypotonia and respiratory distress at birth associated with severe hypercalcemia, severe neonatal HPT should be suspected. This is a rare disease, which usually occurs due to the presence of an abnormal homozygous expression of the calcium receptor gene.9

Other conditions, such as a history of irradiation and defects in the Wnt/β-catenin signaling pathway, can be associated with the onset of PHPT. An example of irradiation are the workers at the Chernobyl nuclear power plant, exposed to a mean radiation dose between 0.3 and 8.7 Gy, with subsequent PHPT in 24.6% of the workers. In another study, an irradiation dose of 0.5 Gy showed an increased dose-dependent long-term risk for PHPT. Over six years of follow-up, isolated PHPT compared with PHPT with head and neck irradiation did not show any difference in clinical presentation, pathology or recurrence. In those exposed to radiation, however, concomitant thyroid tumors were seen.

Despite the data previously demonstrated, radioiodine therapy did not show a significant increase in the incidence of PHPT after a 21-year follow-up period.

**Classical Clinical Presentation**

The classical clinical presentation of PHPT, with intense bone involvement, cystic fibrosis and recurrent renal lithiasis (50% of the cases), was first described in 1930. The incidence of the asymptomatic presentation became more prevalent after the 1970s. In the 1960s, the prevalence of asymptomatic PHPT was 18%; at the present time, it corresponds to >80%.

Nephrolithiasis is seen in only 15% to 20% of the patients, and bone disease, in <5%. The latter, although less frequent, is the most severe form of the disease, probably due to vitamin D deficiency.

There is some evidence to suggest that vitamin D deficiency increases the likelihood of a more symptomatic disease, more severe bone disease, and higher PTH levels. This theory is supported by data indicating that the clinical and laboratory characteristics of PHTP are more severe in areas of the world where vitamin D deficiency is endemic.

Other studies suggest that changes in the clinical presentation of PHPT in the Western world from a symptomatic disease prior to the 1970s to a predominantly asymptomatic form over the past 40 years is due in part to higher levels of vitamin D resulting from the fortification of dairy products with this vitamin during this period, or even by the increase of its supplementation.

**Renal Involvement**

The most frequent clinical presentation of the renal disease in the patients with PHPT are kidneys calcifications. These complications are represented by nephrolithiasis and nephrocalcinosis, which can result in a decrease of the glomerular filtration in 20% of the patients and renal failure in that patients without appropriated clinical management. It is worth noting that these findings are quite infrequent at present, since the clinical pattern of the patients diagnosed with PHPT, who are mostly asymptomatic, has changed. When present, the tendency of the formation of kidney stones originates from an excess of calcium and phosphate absorbed at the level of the intestine or initiated in the bones and then excreted by the kidneys, leading to an overload in the concentration of these ions in the urine and, as a consequence, to the precipitation of crystals in the kidney.

The risk of nephrolithiasis appears to be higher in men and in individuals with onset of PHPT at younger ages, but it is not any greater in those who take oral calcium supplements, even having a lower prevalence in this subgroup. The incidence of asymptomatic nephrolithiasis was of 7% in individuals with PHPT, compared with 1.6% of the individuals of the same age who have undergone ultrasound of the urinary tract.

After parathyroidectomy, a risk of recurrence of renal stones of 20 to 50% is estimated after the first episode, setting a risk of recurrence equivalent to idiopathic renal stones. The risk of hospitalization for renal calculi is quite small, although it remains above the risk for the general population >10 years old.

**Skeletal Involvement**

Most patients with PHPT are generally identified during investigations of low bone mass. Bone involvement is directly proportional to the duration of the disease in PHPT and, even in cases of milder involvement, bone mineral density (BMD) evolves with a decrease. Typical bone involvement is represented by cortical involvement, best evidenced in the region of the distal third of the radius.

Bone pain, fragility fractures (fractures resulting from a fall or minor trauma), and muscle weakness are common features in symptomatic patients with PHPT. Bone tumors, called brown tumors, can be felt, especially along the long bone axis and at the extremities. Muscle weakness is often proximal and usually manifests as deep, hyperactive tendon reflexes. Cystic fibrosis osteitis, present in cases of advanced disease, is characterized by bone pain, skeletal deformities and pathological fractures, and there is no evidence of kidney stones in ~65% of these patients.

Other alterations present in PHPT are the loss of the hard blade of the teeth, and salt and pepper lesions in the skull. Subperiosteal bone erosions in the distal phalanges and on the lateral borders of the medial phalanges are also generally observed, such as numerous lytic lesions with irregular...
sclerotic margins, which are more common on the pelvis, on the long bones and on the shoulders. In symptomatic PHPT cases, the long bone cortical is extremely thin and, in some patients, almost absent.\textsuperscript{36,43}

**Bone Pathogenesis in Primary Hyperparathyroidism**

The excessive production of PTH found in PHPT leads to a decrease in BMD over time, mediated by the action of osteoclasts.\textsuperscript{36} In severe PHPT, osteoclastic absorption outweighs the osteoblastic ability to deposit new bone, leading to a disorganized and destroyed bone architecture, with bone radiographs revealing extensive decalcification and cystic areas in the skullcap, filled by osteoclasts (giant cell osteoclastic tumors).\textsuperscript{44}

High serum levels of PTH increase the expression and activation of the receptor activator of nuclear factor kappa-B ligand (RANKL) at the osteoblast level, which in turn stimulates osteoclastogenesis, raising the concentrations of calcium ions in the extracellular fluid. In addition, PTH has an inhibitory effect on the expression of osteoprotegerin, a natural inhibitor of RANKL, thus being an additional effect on osteoclastic differentiation.\textsuperscript{45} Although these changes may lead to significant bone pain, bone deformities and fragility fractures are uncommon findings in the age of densitometry and routine serum calcium and PTH dosages. The finding most frequently seen in asymptomatic patients is a decrease in BMD.\textsuperscript{44–46}

**Bone Density**

Bone densitometry and biopsy studies indicate that there is a predilection in PHPT for cortical bone involvement in contrast to an anabolic (protective) effect on spongy bones, so one would expect the finding of low BMD in areas with greater cortical bone constitution, as in the distal radius (almost 100% of the region consisting of cortical bone), as well as the protection of areas constituted preferably by trabecular bones, such as the vertebral column.\textsuperscript{44,46} However, more recent epidemiological studies have shown an increase in the risk of fracture at both cortical and trabecular sites. These discordant data suggest that PHPT leads to a structural weakness at both sites, which can be better investigated through a high resolution peripheral quantitative computed tomography (CT) that investigates not only the bone microarchitecture of the cortical and trabecular regions but also the volumetric density of the bones.\textsuperscript{47,48}

**Other Clinical Presentations**

**Gastrointestinal Involvement**

Peptic ulcer disease has been reported in patients with PHPT, as well as pancreatitis and gastrointestinal manifestations secondary to hypercalcemia (anorexia, constipation, nausea and vomiting). Although there are many reports of gastrointestinal symptoms isolated in patients with PHPT, a cause and effect relationship has not yet been established, and data on the association of gallstones\textsuperscript{49–51} and pancreatitis\textsuperscript{52,53} with PHPT are still conflicting.

A more recent study reported a higher prevalence of gastrointestinal symptoms in patients with symptomatic PHPT, without a significant difference between genders regarding gastrointestinal symptoms, except for the higher occurrence of gallstones in women, and of pancreatitis in men.\textsuperscript{54} In this study, the gastrointestinal symptoms were resolved within three months after parathyroidectomy in most patients.\textsuperscript{54} Chan et al\textsuperscript{55} also reported a significant reduction in symptom rates after parathyroidectomy.

Pancreatitis is almost never seen as a complication of modern PHPT due to its mild degree of hypercalcemia.\textsuperscript{56} A retrospective cohort study with 14 patients < 20 years old with symptomatic PHPT was evaluated. The predominant symptoms were bone disease and nephrolithiasis. Two patients had recurrent episodes of acute pancreatitis without any bone disease. These patients were followed for 44 months after parathyroidectomy, and it was found that the symptoms improved in all of them, and those with pancreatitis were cured without any recurrence of the disease during the follow-up period.\textsuperscript{57} In another retrospective cohort study, a group of nine patients with chronic PHPT-associated pancreatitis was compared with two other groups, one with chronic pancreatitis from alcoholism and one with idiopathic acute pancreatitis. Nephrolithiasis, bone disease, and psychiatric disorders (depression, psychosis) were significantly more common in the PHPT group. In this group, six patients underwent parathyroidectomy, and after 36 months of follow-up, there were no reports of recurrence of pancreatitis or renal colic episodes.\textsuperscript{58}

A retrospective study evaluated 84 patients with PHPT associated with Zollinger-Ellison Syndrome (SZE), the latter diagnosed based on gastrin levels fasting and after secretin stimulation. The patients underwent parathyroidectomy and, after an average of 7.2 years, 40% were free of the disease, 39% continued to have hypercalcemia, and 21% developed hypocalcemia. After the normalization of the calcium and PTH levels, gastrin levels fasting and after secretin stimulation returned to normal. In patients who did not achieve PHPT cure, SZE was not effectively controlled.\textsuperscript{59}

**Metabolic Involvement**

Patients with PHPT appear to have a higher weight than the age-matched controls. In a meta-analysis of 13 studies, individuals with PHPT, on average, weighed 3.3 kg more than the controls, and their body mass index (BMI) was 1.1 kg/m\textsuperscript{2} higher than that of the controls.\textsuperscript{60} Increased body weight may contribute to the association between PHPT and cardiovascular disease, hypertension and glucose intolerance.

An above-average frequency of altered glycemic levels and type 2 diabetes has been reported in some, but not all, PHPT studies.\textsuperscript{61–64}

Some studies have shown significant correlations between total calcium concentrations with fasting glycemia and insulin resistance.\textsuperscript{65,66} Tassone et al investigated the frequency of insulin resistance and glucose intolerance in 122 patients with PHPT compared with 61 healthy controls. The authors found a reduction in the markers of insulin sensitivity in patients with PHPT. This study showed for the first time that serum calcium levels contributed significantly and independently to decrease insulin sensitivity.\textsuperscript{67}
Yamaguchi et al examined patients with type 2 diabetes mellitus (DM) (271 men, 209 women), and analyzed the relationships between serum calcium concentrations, intact PTH, and diabetes-related variables. They suggest that serum calcium, not PTH, is potentially involved in worsening hyperglycemia and insulin resistance in type 2 diabetic patients.

As for the patients with NPHPT, there is little data on this issue. However, studies suggest that, in contrast to hypercalcemic PHPT, patients with NPHPT do not present insulin resistance and glucose intolerance.

In a prospective cohort study, 54 patients with PHPT associated with blood glucose changes were evaluated. Of these patients, 31 underwent parathyroidectomy and, after 6 months, and the results showed improvement in fasting glycemia and oral glucose tolerance tests in 96% of the patients, with a reduction of 50% in patients with diabetes, and a 33% reduction in glucose intolerance. In 35% of the patients, glycemia normalized. These results were maintained for 2.4 years of follow-up.

**Non-classic PHPT Manifestations**

Cardiovascular and neuropsychiatric diseases have been associated with PHPT, and characterize the involvement of organs that do not classically suffer damage in this disease, but the data are too conflicting to establish a causal relationship.

**Cardiovascular Involvement**

In PHPT, elevations in plasma PTH and calcium may have deleterious effects on the cardiovascular system, with increased cardiovascular morbidity and mortality. The cardiovascular pathophysiology of PHPT is still not well understood; however, some studies have demonstrated that PTH exerts a direct action on cardiac myocytes mediated by the activation of protein kinase C, promoting hypertrophy in the myocardiun. Both PTH and calcium promote endothelial dysfunction by the expression of pro-atherosclerotic and pro-inflammatory parameters such as interleukin 6 and receptor for advanced glycation and products (RAGE).

Several studies have demonstrated left ventricular hypertrophy and calcification of the aortic valve, demonstrating a positive correlation between PTH levels and valvular calcification area. In contrast, a control-case study showed that there were no changes in the cardiovascular risk of patients with PHPT undergoing parathyroidectomy when compared with the control group. Another study with 100 patients with PHPT with severe hypercalcemia (calcium: 11.8 mg/dL, PTH: 188 pg/dL) showed no alterations neither in the diastolic function nor in the cardiac structure; however, there was an alteration in the inversely proportional coronary flow reserve of the PTH levels (correlation coefficient \( r \): -0.3; \( p < 0.0004 \)). Regarding the cardiovascular risk factors, a randomized, controlled 2-year study showed that both observational (\( n = 54 \)) and surgical (\( n = 62 \)) groups were associated with lower blood pressure, lipoprotein, and apolipoprotein A levels. Several studies have demonstrated a reduction in blood pressure after parathyroidectomy, both short-term and over five years.

The main reasons given in the literature for the correlation between PHPT and cardiovascular risk are conflicting, because the pathophysiological mechanism is not completely elucidated. Moreover, there are few studies with a higher statistical value. This fact reinforces the need for greater cardiovascular surveillance in patients with PHPT.

**Neuropsychic Involvement**

Fatigue, weakness, memory loss, difficulty in concentration, irritability, depression and anxiety are all associated with PHPT. The studies are still inconsistent, so these have not yet entered as a criterion for parathyroidectomy.

Several studies correlate depression with PHPT, and report improvement in the symptoms after the surgical treatment. A prospective case-control study demonstrated that depression was present in PHPT, with parathyroidectomy benefit in these patients, as well as symptom improvement (169 patients, mean calcium = 10.6 mg/dL). A European epidemiological cohort study with 1,424 patients with asymptomatic PHPT demonstrated that individuals with associated comorbidities had a 4.25-fold higher risk (95% confidence interval [95%CI], 2.33–7.77) of having a psychiatric disease.

A prospective case-control study with 35 patients (mean calcium = 11.1 mg/dL) who underwent parathyroidectomy compared with 35 non-surgical PHPT control patients showed that the control subjects had greater difficulty in concentration, direct memory, verbal fluency, nonverbal learning and constructive visual skills. A cohort study with symptomatic and asymptomatic PHPT patients (mean calcium = 10.9 mg/dL; \( n = 39 \)) showed that nonverbal abstraction and some aspects of the verbal memory improved after the parathyroidectomy. An uncontrolled study with 212 symptomatic and asymptomatic PHPT patients (mean calcium = 10.8 mg/dL) reported an improvement in depression, anxiety, verbal memory and special memory. It is noted that specific components of cognition are variable in studies with PHPT, so it is difficult to draw definitive conclusions.

**Normocalcemic PHPT**

The concept of NPHPT was first mentioned ~ 50 years ago, but it has been increasingly recognized over the last decade after the measurement of PTH for the evaluation of secondary osteoporosis. These patients are diagnosed not only in the evaluation of secondary osteoporosis, but also in the evaluation of bone mass loss, fracture, or even during routine medical evaluations.

The definition of NPHPT is reported through persistently normal serum calcium levels and increased levels of PTH. According to Bilezikian et al, PTH must be kept above the upper limit in two subsequent measures over a period of 3 to 6 months. It is essential that serum calcium is corrected by albumin.

In addition to the diagnosis, secondary causes of hyperparathyroidism, such as vitamin D deficiency and renal failure, should be excluded. The levels of 25OHD must be > 20 ng/mL or 50 nmol/L, and the estimated glomerular filtration rate (eGFR) must be > 60 mL/min/1.73 m\(^2\). Some authors argue...
that levels of 25OHD > 30 ng/mL would be needed in some individuals to decrease the PTH levels;\textsuperscript{21} and others still report that normocalcemic patients could become hypercalcemic when 25OHD levels rise above 30 ng/mL.\textsuperscript{90}

Other secondary causes of elevated PTH should also be excluded, such as primary hyperparathyroidism, malabsorption syndromes, use of loop diuretics, bisphosphonate or denosumab therapy.\textsuperscript{3,11,90} Following the initiation of bisphosphonate or denosumab therapy, transient elevations of PTH may occur in healthy individuals due to the inhibition of bone resorption as a compensatory mechanism to maintain normal serum calcium levels. The PTH levels may rise above the normal range within 1 to 3 months after the initiation of the treatment, but usually normalize within 24 months with alendronate, and within 6 months with denosumab.\textsuperscript{91,92}

There are data in the literature showing that, over time, NPHPT can progress to the classic presentation of PHPT with its complications;\textsuperscript{11,12,93} however, this disorder seems to be associated with PHPT complications,\textsuperscript{94–97} including osteoporosis, even despite normal serum calcium levels.\textsuperscript{94,98}

Authors speculate that there may be two presentations of NPHPT, one asymptomatic and one symptomatic.\textsuperscript{11} What corroborates this is the presence of nephrolithiasis at the time of diagnosis of NPHPT as reported in some studies: 35% of nephrolithiasis prevalence in the study by Maruani et al,\textsuperscript{96} 9.4% in the study by Tordjman et al,\textsuperscript{98} 21.4% in the study by Marques et al\textsuperscript{99} and 18.9% in the study by Amaral et al\textsuperscript{94}. However, data from observational studies and an explicit lack of exclusion of secondary causes in some of these studies may interfere with the homogeneity of the data.

A longitudinal cohort study performed a follow-up of 37 patients with NPHPT (95% women, mean age = 58 years old, and mean serum calcium = 9.4 mg/dl) for 3 years. During this period, 18.91% of the patients developed hypercalcemia and presented higher levels of serum calcium and calcitriol at baseline than those who remained normocalcemic, but did not have higher PTH levels. In addition, 41% of the permanently normocalcemic patients developed complications (nephrolithiasis, hyperparathyroidism, reduction of bone mass, and fracture) or received indications for parathyroidectomy.\textsuperscript{99}

Although mild asymptomatic PHPT is not clearly associated with adverse cardiovascular effects, severe PHPT is associated with increased cardiovascular mortality.\textsuperscript{2} Because NPHPT is seen as a symptomatic disease, there has been a considerable interest in the potential metabolic and cardiovascular effects of the disease.

The data from the studies on glycemic changes are heterogeneous, with some studies finding an association with fasting glycemia\textsuperscript{100,101} and others not.\textsuperscript{98} Two case-control studies documented small increases in mean fasting glycemia, still within the normal range, but these same studies did not find differences in hemoglobin A1C levels.\textsuperscript{100,101} In the study by Cakir et al, there was no association with insulin resistance in individuals with NPHPT.\textsuperscript{98}

There appears to be an association with a worse lipid profile in individuals with NPHPT,\textsuperscript{101} as well as higher systolic and diastolic blood pressures in this population,\textsuperscript{102} but neither arterial stiffness nor complacency differed significantly in the PHPT and NPHPT groups compared with a control group adjusted for age, gender, BMI and other vascular risk factors.\textsuperscript{97} Longitudinal studies are needed to bring greater clarity to these outcomes.

**Conclusion**

Primary hyperparathyroidism is a common endocrine disease and its screening should be routinely performed, since the most common form of presentation would be asymptomatic. Its clinical manifestations involve not only bone and kidneys as already classically described, but also and possibly non-classical clinical manifestations, such as neurocognitive impairment and the cardiovascular system.

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