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Screening and biochemical characterization of primary hyperparathyroidism in Guayaquil (Ecuador)

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Summary

Objectives: To determine the prevalence of primary hyperparathyroidism (HPTP) using PTH and Ionic calcium screening in a population sample of Guayaquil (Ecuador).

Materials and methods: Prospective, cross-sectional study carried out between January 1, 2009 and November 30, 2014 of 13,860 people who attended routine control tests. All were tested in serum parathyroid hormone (PTH), ionic calcium, serum creatinine and the 25 (OH) total vitamin D (total VD). The diagnosis of HPTP was confirmed if PTH or Ionic calcium levels remained high at least in two different occasions. We excluded patients with raised serum creatinine, vitamin D insufficiency, malabsorption, chronic liver disease, or those receiving treatments that alter phosphocalcic metabolism.

Results: 61 cases were found with raised PTH on at least two different occasions. Among these, 34 presented vitamin D insufficiency and were excluded from the analysis. In 27 cases (4 men and 23 women) the diagnosis of HPTP was confirmed. The average age for women was 64.5±15.4 years and men of 71.3±12.8 years; average PTH values were 115±24.2 pg/ml; Ionic calcium, 5.15±0.4 mg/dl; total VD, 47.1±20.2 ng/ml; and serum creatinine 0.84±0.2 mg/ml; prevalence of HPTP corresponds to 2 cases per thousand adults (95% CI: 1.71-2.18). The greatest increase in prevalence occurred in women aged 60 years.

Conclusion: PTH prevalence in this sample is low compared to that reported in international series, being higher in advanced ages and in women. With the proposed screening for PTH and ionic calcium, we detected the normocalcemic form of HPTP in most cases.

Key words: primary hyperparathyroidism, screening, ionic calcium, prevalence, normocalcemia, epidemiology, vitamin D.

Introduction

Primary hyperparathyroidism (HPTP) is a relatively common endocrine disorder. Among endocrine diseases, it ranks third in frequency of diagnosis¹. HPTP is usually diagnosed in the sixth decade of life and is more common in women¹. Its clinical presentation has changed in recent decades, evolving from a classical form with significant bone and renal involvement², to the asymptomatic form that we are currently seeing³.

The epidemiology of HPTP has been difficult to establish, since the international literature contains different figures on incidence and prevalence in different populations.

The prevalence of HPTP depends on the populations studied and the detection methods used. In studies of Caucasian populations, it ranges from 1 to 7 per 1,000 adults⁴⁻⁶. A biochemical screening study has established a prevalence of 1 to 21 per 1,000 adults⁷⁻⁹. Incidence also varies according to the sources. Incidence studies with PTH and total calcium determinations have been described, in which both high and low rates are reported^{5,7,9-15}.

In Latin America, there are few studies on the epidemiology of the disease, with the exception of Eufrazino et al.¹⁶ in Recife (Brazil), Mautalen et al. in Argentina¹⁷, and in Chile by López et al.¹⁸. In Ecuador, PTH prevalence of 7.1% was found in a selected sample of postmenopausal women with low bone mass¹⁹.

The present study would be the first of its kind to evaluate HPTP prevalence in the city of Guayaquil (Ecuador), applying a uniform biochemical screening, by means of the simultaneous measurement of parathyroid hormone (PTH) and serum ionic calcium, and compare our results with those reported in the literature.

Material and methods

This descriptive, prospective and cross-sectional epidemiological study aims to determine the prevalence of PTH during the period between January 1, 2009 and November 30, 2014 in two reference centers in the city of Guayaquil. According to data from the last Population and Housing Census of 2010, provided by the National Institute of Statistics and Censuses of Ecuador (INEC)²⁰, the population of Guayaquil grew from 2,440,553 to 2,560,505 inhabitants from 2010 to 2014 (Table 1).

The study was approved by the Ethics and Research Committee at the Guayaquil National Police Teaching Hospital N° 2.

The diagnosis of PTHP was defined when PTH levels >72 pg/ml (normal values: 12-72 pg/ml) and/or ionic calcium >5.6 mg/dl (normal values: 4.5-5.6 mg/dl) remained elevated on at least two or more different occasions. Serum creatinine, total 25 (OH) vitamin D (D2+D3), and a basic biochemical study (complete blood count, glycemia, liver enzymes, serum lipids, and nitrogen products) were also measured in serum.

Biochemical screening with serum PTH and ionic calcium measurement was carried out in

13,860 people living in the city of Guayaquil (Figure 1), who underwent routine check-ups at the hospitals participating in the study. Patients were treated in primary care units, where they underwent screening tests. Those who returned for routine monitoring and presented serum PTH and/or calcium levels higher than the reference ranges were required to perform an additional assessment of PTH and serum calcium levels.

Serum ionic calcium was measured after 12 hours of fasting and without tourniquet use, under anaerobic conditions (taking the sample in a vacuum tube and uncovering the tube just before the test), and was reported without correction for pH, by direct measurement with selective ion electrode (NOVA-8 equipment), with reference values of 4.5 to 5.6 mg/dl.

Serum PTH (intact molecule) was measured with SIEMENS Immulite 2000 equipment (enzyme-labeled, two-site solid-phase chemiluminescent immunometric assay), with reference values ranging from 12 to 72 pg/ml. The intra-assay precision presented a coefficient of variation of 5.7, 4.3 and 4.2% for concentrations of 72, 258 and 662 pg/ml, respectively, and an interassay coefficient of variation of 6.3 and 8.8% for concentrations of 54 and 387 pg/ml, respectively. The limit of detection was 3.0 pg/ml and linearity up to 500,000 without Hook effect. PTH levels were considered inadequately "normal" when they were above the 75th percentile of the reference value (PTH ≤57 pg/ml) in the presence of hypercalcemia on 2 different occasions.

Serum level of 25 (OH) total vitamin D (total VD=D3+D2) was measured by chemiluminescence, with normal values: 30-70 ng/ml (Centauro kit; competitive 1-step assay with anti-Fluorecein). Total precision presented a coefficient of variation of 11.1, 9.6, 9.8, 8.2, 7.8, 4.8% for concentrations of 11.7, 18.0, 32.4, 49, 9, 55.8, 132.1 ng/ml, respectively, with detection limit of 3.2 and linearity up to 150 ng/ml. values ≥30 ng/ml were considered sufficient; mild insufficiency, between 20-29 ng/ml; moderate insufficiency, between 10-19 ng/ml; and severe deficiency, <10 ng/ml^{21,22}.

Renal function integrity was documented in all cases by measuring serum creatinine levels and calculating endogenous creatinine clearance expressed in ml/min (formula corrected for age, sex, weight and serum creatinine:

$$[140 - \text{age (years)} \times \text{weight (kg)}] / [72 \times \text{creatinine Serum (mg/dl)}] \times 0.85 \text{ (correction factor alone in women).}$$

Cases with a high level of calcium and/or PTH on one occasion were considered spurious and excluded. Cases with raised serum creatinine, malabsorption, chronic liver disease, vitamin D insufficiency or those receiving treatment that could alter phosphocalcic metabolism and/or PTH levels (glucocorticoids, estrogens, bisphosphonates, thiazides, lithium, calcium). All biochemical measurements were carried out in a single reference laboratory. All women and men aged 20 years or older were included in the screening sample. Ages ran-

Table 1. Projection of the Ecuadorian population by calendar years, according to cantons

Code	Name of the canton	2010	2014
901	Guayaquil	2,440,553	2,560,505

Source: Population and housing census of the year 2010. National Institute of Statistics and Censuses of Ecuador (INEC)²¹.

ged from 20 to 89 years. We stratified the cases by sex and age groups: 24-50, 51-60, 61-70 and 71-89 (Figure 2). Data are expressed as mean and standard deviations with the corresponding confidence intervals, 95% confidence level. For the comparison of groups, we used Student's t-test for independent means. A value of $p < 0.05$ was considered statistically significant. Prevalence of the disease was calculated as the number of existing cases divided by the population screened and expressed as a proportion of each population of 1,000 adults. Epidat 3.1 software was used to analyze the data.

Results

Of the 13,860 people evaluated in the screening period, HPTP was found in 27 cases. Patients ($n=13,378$) with elevated serum creatinine and/or receiving treatments affecting phosphocalcic metabolism (estrogens, bisphosphonates, lithium, calcium, thiazides) were excluded. Patients with normal and untreated serum creatinine but who had normal levels of ionic calcium and serum PTH were also excluded. In 482 cases PTH was elevated on at least one occasion of several successive ones; 61 cases had elevated PTH on two or more occasions, but 34 of them had total VD values in the range of insufficiency and were excluded. In the remaining 27 cases, the biochemical diagnosis of PTH was confirmed by raised PTH on two or more occasions (95% CI: 105.01-124.18), preserved renal function (95% CI: 0.765-0.915), and sufficiency of total RV (≥ 30 ng/ml) (95% CI: 39.12-55.09). In 25 cases (93%), the ionic calcium was in normal ranges (95% CI: 5.0-5.29) and only 2 (women) had minimally elevated values (5.89 and 5.95 mg/dl, respectively).

HPTP was diagnosed more frequently in women than in men (4 men and 23 women), with a 6:1 ratio; the majority of women (87%) were menopausal ($n=20$).

Table 2 presents the results of the biochemical variables of all patients with confirmed diagnosis of PTHP.

In our series, PTHP was diagnosed more frequently from the sixth decade of life in women, with a mean age of cases around 65 years (95% CI: 57.82-71.12; Range between 24 and 88) and a little later in men, at age 71 (95% CI: 50.95-91.55).

PTH levels far exceeded the upper limit of normal and were similar between women and men ($p=ns$). In spite of the large increase in PTH levels,

in almost all cases serum calcium levels were in the normal range or were slightly higher (range 4.52 to 5.95), and were not different between Men and women ($p=ns$). Serum levels of total vitamin D were found in the normal range (>30 ng/ml) in 27 cases, and were not different between males and females ($p=ns$).

In 34 cases vitamin D was in the insufficiency range 21.62 ± 4.7 ng/ml (95% CI: 19.98-23.26) and were excluded from the analysis. In these cases, vitamin D replacement was not performed.

Serum creatinine was within the normal ranges in all cases (95% CI: 0.76-0.91), as well as the endogenous creatinine clearance calculated by the corrected formula.

HPTP prevalence in this sample of the population of Guayaquil corresponds to 2 cases per thousand adults (95% CI: 1.714-2.182). The highest increase in the prevalence of PPH was seen in women ≥ 60 years and in men ≥ 70 years (Figure 2).

Discussion

Prevalence studies of HPTP have been carried out mostly in Caucasian populations^{4,6,7,10}, so that there is no exhaustive information available in other ethnicities and races of our Latin America. Only recently, Yeh MW et al. reported an age-adjusted prevalence of 169.4 and 54.8 per 100,000 women and men in a sub-group of Hispanic race, respectively¹¹. The population of Ecuador is multiethnic and the mestizo group is the majority, with an estimated 72% of the total population²⁰.

Data from epidemiological studies show that, in certain populations at risk, for example, in postmenopausal women and with decreased bone mass, the prevalence ranges from 2.1 to 11.5%^{19,23-25}.

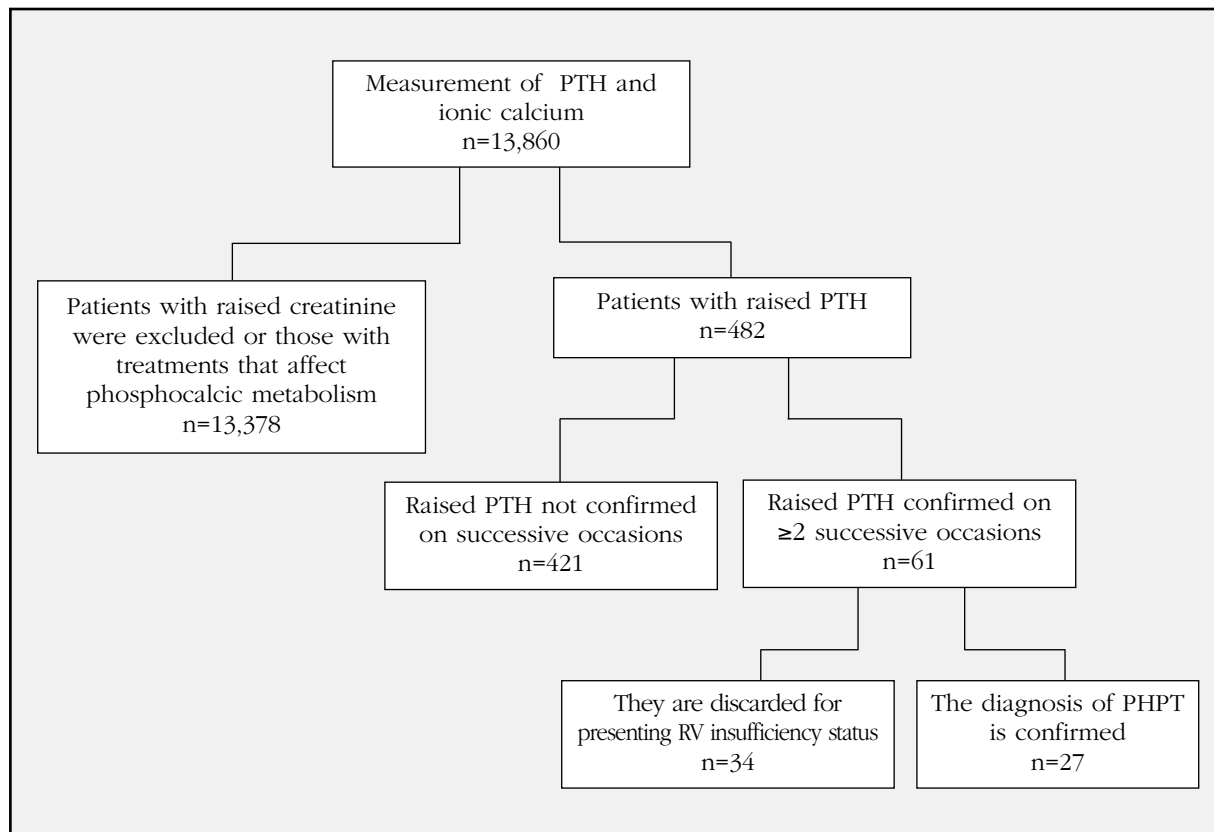
HPTP is much more common among women, with a ratio of women to men over the age of 60 in the range of 5 to 7:1^{1,17}, which is in agreement with our results.

PTHP is recognized as the most common cause of hypercalcemia in outpatient care²⁶, and in its classic form it has raised levels of PTH, renal lithiasis, and severe bone involvement^{1,9,27}. This classic form is still frequently found in developing countries, probably due to the time of delay in diagnosis and the lack of accessibility to measurements of calciotropic hormones and ionic calcium²⁷.

Another form of presentation of PTHP was identified formally in 2008, identified as normocalcemic HPTP²⁸, but its description is still incomplete, particularly with respect to its epidemiology, natural history and treatment. Patients with this condition lack the classic HPTP characteristics, and have high levels of PTH with normal serum calcium, which are considered an early sign of the disease^{29,30}. The diagnosis should focus on the exclusion of all causes of secondary hyperparathyroidism, particularly vitamin D deficiency (<30 ng/ml) and decreased renal function (endogenous creatinine clearance <60 ml/min)³⁰.

Normocalcemic HPTP prevalence varies from 0.7 to 16.7%³¹⁻³³ according to the design of the stu-

Figure 1. Design of PHPT screening in Guayaquil (Ecuador)



HPTP: primary hyperparathyroidism; PTH: parathyroid hormone; VD: vitamin D.

dies, populations studied, age, sex and methods used. In our series, most cases (93%) had high levels of PTH with ionic calcium in the range of normal or minimally elevated. This would show that the detection was carried out in the early stages of the disease³⁴ and/or that the predominant form of HPTP presentation in our population is normocalcemic.

The detection of HPTP cases in epidemiological studies has been carried out using a combination of biochemical, histopathological, radiological and clinical data sources^{5,6,13,14,35}. However, it should be noted that all data sources have a considerable bias in the results. Taking this into account, our study reveals some findings that are worth highlighting.

Although some controversy persists regarding the usefulness of serum ionic calcium determination, this is a method that reliably allows the diagnostic approach in HPTP. The total calcium concentration does not reliably reflect the predicted increase in the free fraction, especially in cases with minimal or no increase in the total serum calcium level^{29,36,37}.

Population screening with the simultaneous measurement of serum PTH and ionic calcium at least twice allows us to effectively and safely identify cases. Measuring vitamin D levels and assessing the integrity of renal function allows us to separate the secondary causes of parathyroid hyperfunction. In general terms, the use of our

biochemical screening of HPTP would solve the possible research bias obtained in the results of other studies. For example, if only histopathological data were used, there would be a higher detection rate for the minority of patients who are treated surgically. Another bias may also be found in patients with thyroidectomies, where parathyroid adenomas may be found coincidentally in normocalcemic individuals, but these patients cannot be considered cases of PTH³⁸. As for radiological studies, they are not an appropriate method for HPTP screening because of their reduced sensitivity and specificity³⁹.

Among the weaknesses of our study, we pointed out that we did not measure calcium in urine, so we recognize that in our series, the presence of cases with idiopathic hypercalciuria or familial hypocalciuric hypercalcemia cannot be ruled out, although the latter is a rare disease with an estimated prevalence in 1 out of 78,000 people⁴⁰. We also note the inherent limitations of the formula used to calculate endogenous creatinine clearance.

In conclusion, we have characterized the largest series of patients with PHPT described to date in our country and documented the prevalence of HPTP for the first time in our population. Compared to the international series, the prevalence of HPTP is low in this sample and is higher in women and in advanced ages. The biochemical presentation corresponds mostly to the normocalcemic form of the disease.

Figure 2. Cases of primary hyperparathyroidism stratified by age and sex

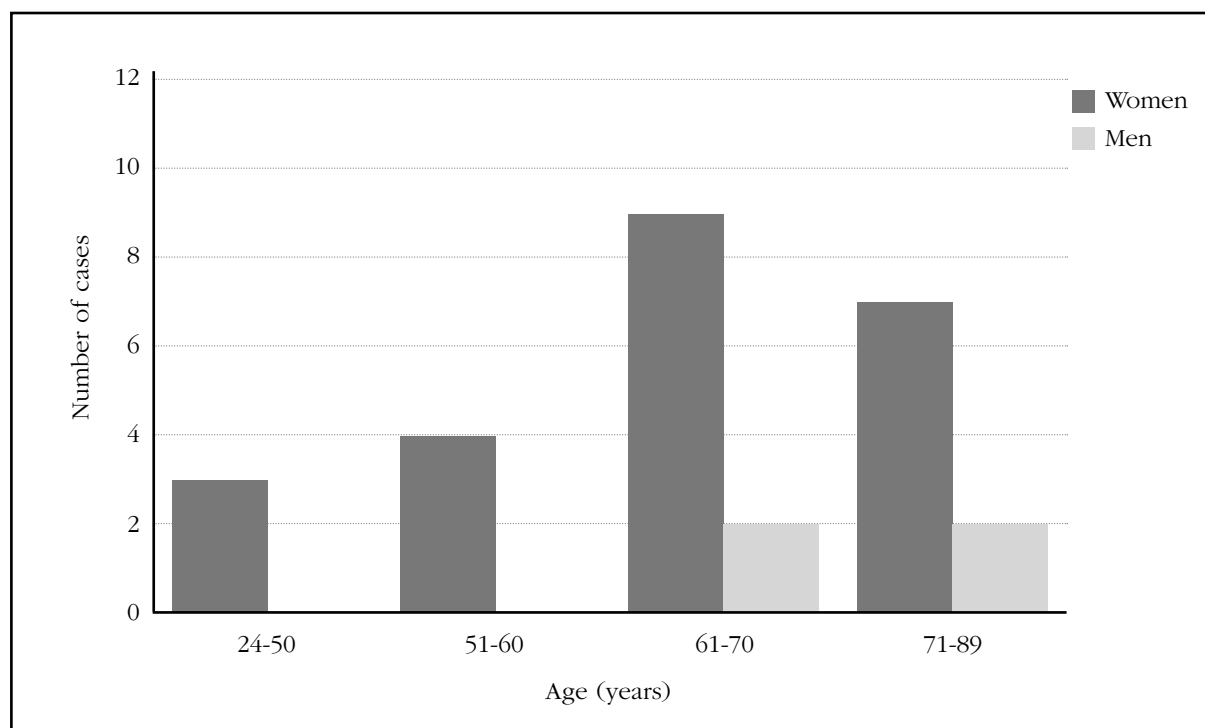


Table 2. Biochemical characteristics of cases with diagnosis of confirmed primary hyperparathyroidism

	Men (n=4)	Women (n=23)	Total (n=27)
Age, years	71.25 ± 12.76	64.2 ± 15.4	65 ± 15
PTH, pg/ml	113 ± 15.12	114.9 ± 25.8	114.6 ± 24.2
Ionic calcium, mg/dl	5.15 ± 0.36	5.15 ± 0.38	5.15 ± 0.37
Total vitamin D, ng/ml	44.2 ± 6.85	47.6 ± 21.8	47.3 ± 20.18
Serum creatinine, mg/ml	0.85 ± 0.16	0.84 ± 0.19	0.84 ± 0.19

PTH: parathyroid hormone. Values are expressed as mean ± standard deviation.

Our data may help health authorities develop effective strategies for prevention and treatment of skeletal (and non-skeletal) complications of HPTP in our population.

Conflict of interest: The authors declare that they have no conflicts of interest in relation to this work.

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