Biochemistry in Symptomatic and Asymptomatic Primary Hyperparathyroidism: A Cross-Sectional Study

Bioquímica en hiperparatiroidismo primario sintomático y asintomático: estudio transversal

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ABSTRACT

Background: PHPT can be symptomatic or asymptomatic, according to the presence of classic symptoms (skeletal or renal involvement), without conclusive evidence of its relation to biochemical parameters. **Objective:** The objective of the study was to characterize clinical and biochemical profiles in symptomatic and asymptomatic PHPT. **Methods:** A cross-sectional study in patients with parathyroidectomy at a private hospital. Clinical and biochemical reports of 61 cases were collected from 2010 to 2018. **Results:** Median age was 59 ± 13 years and 72% were women. Of the total sample, 42 were symptomatic and 19 asymptomatic (68.8% vs. 32.2%). Neurocognitive and cardiovascular syndromes had a higher proportion in symptomatic cases ($p = 0.02$ and $p = 0.01$, respectively). **Conclusions:** Serum calcium and PTH levels are not related to target organ injury in the pre-operative setting, but statistically higher postoperative serum calcium levels were found in the symptomatic group. Further research is needed to elucidate the relation of biochemical parameters and symptoms in PHPT progression.

Key words: Hyperparathyroidism. Primary hyperparathyroidism. Hypercalcemia. Symptomatic primary hyperparathyroidism. Asymptomatic primary hyperparathyroidism.

RESUMEN

Antecedentes: El HPTP es sintomático o asintomático, según las complicaciones esqueléticas o renales, sin evidencia concluyente de su relación con parámetros bioquímicos. **Objetivo:** Caracterizar perfiles clínicos y bioquímicos en HPTP sintomático y asintomático. **Métodos:** Estudio transversal en pacientes con HPTP y paratiroidectomía en un hospital privado de la Ciudad de México. Se recolectaron datos clínicos y bioquímicos de 61 casos de 2010 a 2018. **Resultados:** La mediana de edad fue 59 ± 13 años y el 72% eran mujeres. Del total, 42 fueron sintomáticos y 19 asintomáticos (68.8 vs. 32.2%). Los síndromes neurocognitivos y cardiovasculares tuvieron mayor proporción en sintomáticos ($p = 0.02$ y $p = 0.01$, respectivamente). **Conclusiones:** Los niveles de calcio y PTH no están relacionados con lesión a órgano diana en el preoperatorio, pero se encontraron niveles de calcio postoperatorios estadísticamente más altos en el grupo sintomático. Se necesitan más estudios para aclarar la relación entre parámetros bioquímicos y síntomas en HPTP.

Palabras clave: Hiperparatiroidismo. Hiperparatiroidismo primario. Hipercalcemia. Hiperparatiroidismo primario sintomático. Hiperparatiroidismo primario asintomático.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a calcium metabolism disorder due to excessive parathyroid hormone (PTH) production, being parathyroidectomy the only definitive treatment¹⁻³. PHPT is the third most common endocrine pathology, with 100,000 new cases annually worldwide^{4,5}. Its prevalence is around 0.2-0.5% and increases after 65 years and in postmenopausal women^{6,7}. Latin American PHPT prevalence reports vary from 4 to 8 cases per 1000 inhabitants, with no defined prevalence in Mexico⁸⁻¹⁰. PHPT diagnosis is made by high serum calcium levels and elevated, or inappropriately normal, PTH and commonly diagnosed in the past by skeletal and/or renal complications, defined as classic symptoms¹¹⁻¹³. In the past decades, classical PHPT has been replaced by an asymptomatic phenotype, detected incidentally through routine biochemical testing without target organ complications, but only non-classic symptoms^{14,15}. Prevalence of symptomatic and asymptomatic PHPT has not been well defined in low- and middle-income countries^{15,16}. Both symptomatic and asymptomatic cases can display non-classic manifestations which can be grouped into cardiovascular conditions, with an increased risk of hypertension in 40-65% of the cases; gastrointestinal manifestations such as peptic ulcer and pancreatitis in mild hypercalcemia; and neuropsychiatric syndrome with high prevalence of depression, anxiety, mental weariness, and weakness¹⁷⁻²¹. Thyroid disease is diagnosed in coincidence of PHPT in an increasing number of middle-aged people, in approximately 17-84% of PHPT patients in the form of nodules, thyroid cancer, or impaired thyroid hormone secretion²². Nonetheless, the relationship of PHPT biochemical parameters with the presence of non-classic symptoms has not been well established^{23,24}. In relation to the above, the aim of this study is to characterize the clinical and biochemical profiles in symptomatic and asymptomatic Mexican patients with PHPT in a private hospital.

METHODS

This was a cross-sectional, retrospective study with a simple non-probabilistic sampling made in the Ángeles Pedregal private hospital in Mexico City.

PATIENTS

PHPT cases were recovered from the hospital's pathology database from January 2010 to December 2018. After obtaining pathology reports that confirmed parathyroid disease (adenoma, hyperplasia, carcinoma, adenoma and hyperplasia, and double adenoma), clinical records were obtained to collect biochemical and clinical parameters of each case. Inclusion criteria were PHPT diagnosis by hypercalcemia (corrected calcium 1 mg/dL above the reference range in asymptomatic patients and only above normal range in symptomatic patients) and high or inappropriately normal PTH levels according to the Fourth International Consensus on the Management of Asymptomatic PHPT²³. Exclusion criteria included previous non-curative surgery, secondary or tertiary hyperparathyroidism, incomplete medical records, and negative histopathological report for parathyroid disease. As a private hospital, suspicious cases of PHPT are arbitrarily referred to endocrine, oncological, head and neck, and general surgeons through personal or hospital networking, therefore, diagnosis and therapeutic approach may differ between surgeons' medical criteria and is not necessarily based on national or international guidelines.

CLINICAL ASSESSMENT

Blood samples were taken at hospitalization the same day before surgery, with previous indication of 8 h fasting and no recent vitamin supplementations. Only a few cases had recent blood analysis (less than a week) from different laboratories before hospitalization, with the same indications. Fasting pre-operative serum calcium, recent blood albumin (3 months or less before surgery), intact PTH (before surgery), post-operative calcium levels, and post-operative PTH (intraoperative or within the first 24 h after removing parathyroid glands and before hospital discharge) for symptomatic and asymptomatic cases were examined. Fasting serum calcium and albumin levels were assessed with Abbott's ARCHITECT c8000

biochemistry analyzer and PTH levels with Abbott's ARCHITECT i2000SR immunoassay analyzer, with population-based reference values of 8.4-10.2 mg/dl for calcium and 31.4-90 pg/mL for PTH. Since no ionized calcium was available for all patients, corrected calcium was used to detect hypercalcemia, with the formula measured total calcium (mg/dL) + 0.8 (4.0 - serum albumin [g/dL]). Non-anesthesia influenced BP was collected in 30 individuals (pre-operative and discharge reports) from nurse's vital sign report sheet in medical records. Philips Efficia CM100 electronic monitor was used for fasting pre-operative BP (accuracy - Maximum SD $\leq$ 8 mmHg - Maximum ME: $\pm$ 5 mmHg) before the administration of anesthetics, while discharge BP values were obtained with the Welch Allyn® BP monitor, during no special physical conditions by nursing staff, according to the NOM 030. Patients were classified into two groups: the symptomatic group had classical symptoms, with skeletal and/or renal complications (history of osteoporosis/osteopenia treatment, fractures, and/or kidney stones reported in medical records), described in international guidelines²⁵, and the asymptomatic group refers to patients with unequivocal biochemical PHPT but without the classical symptoms (skeletal or renal complications), and only non-classical manifestations classified into cardiovascular (ischemic cardiopathy, systemic hypertension, hypertensive cardiopathy, stroke, and arrhythmia) and neuropsychiatric (depression, anxiety, muscle weakness, and dementia), according to Nilsson²⁰. Other symptoms not necessarily related to PHPT but to hypercalcemia (peptic ulcer disease, pancreatitis, and other abdominal pain causes) or in coincidence with the disease such as thyroid disease (nodules, adenoma, hypothyroidism, and papillary carcinoma) were also collected and reported. For this study were only considered the non-classical symptoms, specifically neuropsychiatric ones, reported in clinical records, and no standardized assessment tool was used for its evaluation previous and after surgery by the specialist.

Statistical analysis

Microsoft Office Excel was used for data collection and Stata 14.0 software (StataCorp, College Station, USA) for statistical analysis. Normality was evaluated

in quantitative variables by graphical (Kernel density) and statistical methods (Shapiro-Wilk test). Group comparison was performed with Student's t-test or Mann-Whitney U-test according to the data distribution. Categorical variables were analyzed using the Chi-squared test. The analysis considered $p \leq 0.05$ as a statistically significant difference.

Ethics

The study was approved by the hospital's ethics committee, and the audit and research department of the institution. The authors declare no conflicts of interest.

RESULTS

An initial sample of 88 PHPT confirmed cases by histopathology reports was examined. Only 61 patients completed eligibility criteria, had confirmed PHPT diagnosis, and were included in the analysis. The patients were then classified into symptomatic or asymptomatic PHPT according to the presence or absence of target organ complications, respectively (Fig. 1). The sample was distributed into 42 (68.8%) symptomatic patients and 19 (31.2%) asymptomatic cases. Associated symptomatology to PHPT was described individually and grouped into four syndromes: renal, skeletal, neurocognitive, and cardiovascular; each syndrome was determined by the presence of one or more of related signs or symptoms reported on clinical records (Table 1). Gastrointestinal symptoms and thyroid disease in coincidence to PHPT were also registered for each group into different conditions (Table 2). The most common manifestations were hypertension (49.1%) and nephrolithiasis (42.6%) followed by bone fractures (26.2%) and ischemic cardiopathy (19.6%). Regarding frequency, all manifestations had a higher proportion in the symptomatic group compared to the asymptomatic group, except for pancreatitis which was present in 1 asymptomatic patient (1.6%). Syndrome proportion was the following: cardiovascular syndrome was the most frequent (54.1%), followed by renal (45.9%), skeletal

Figure 1. Flowchart of sample selection in PHPT Mexican patients. An initial sample of 88 PHPT confirmed cases by histopathology reports was examined. Only 61 patients completed eligibility criteria and were confirmed with PHPT diagnosis. The patients were then classified into symptomatic or asymptomatic PHPT according to the presence or absence of nephrolithiasis and/or bone fractures. *MEN 2A: Multiple Endocrine Neoplasia Type 2A.

(39.3%), neuropsychiatric (27.8%), thyroid (27.9%), and gastrointestinal syndromes (14.8%) (Tables 1 and 2). Patients' median age was 59 years $\pm$ 11. Only 13 cases were younger than 50 years (21.3%), most of them symptomatic ($n = 10$) and of this group only one had parathyroid hyperplasia as one case from the asymptomatic group, the rest of them had parathyroid adenoma in pathology report. Women represented 72% of the sample; this proportion was maintained in the group analysis, with no statistical difference (symptomatic 73.7% vs. asymptomatic 71.4%, $p = 0.85$) (Table 3). Neurocognitive syndrome was present in 29.5% of the sample, with a significantly higher proportion in symptomatic individuals than in asymptomatic individuals (38% vs. 10.5%, $p = 0.02$). More than half of the total sample was found to have cardiovascular syndrome, which was significantly higher in symptomatic patients compared to asymptomatic (64.3% vs. 31.6%, $p = 0.01$). Thyroid disease was reported in 27.9% of the sample, with similar percentages in both groups (symptomatic 28.6% vs. asymptomatic 26.3% $p = 0.85$). Only 14.8% of the sample had gastrointestinal symptoms, without significant differences between groups (symptomatic 15.8% vs.

asymptomatic 14.3%, $p = 0.85$) (Table 3). Since not all records were available for blood pressure measurements, only half of the total cases were included for this variable. Pre-operative systolic blood pressure (SBP) mean had no statistical difference between groups ($p = 0.40$), just like diastolic blood pressure (DBP) mean between groups ($p = 0.11$). Discharge SBP mean for symptomatic and asymptomatic groups had no statistical significance ($p = 0.31$), similarly as DBP mean ($p = 0.41$). Concerning biochemical measures, albumin average of the sample was 3.4 mg/dl $\pm$ 0.5 without difference between groups ($p = 0.46$). The median intact PTH was 183.5 pg/dl (129.4-257 pg/dl) with no statistical difference in groups ($p = 0.94$). The same results were found in pre-operative calcium ($p = 0.93$) and corrected calcium ($p = 0.58$) medians between symptomatic and asymptomatic cases (Table 4). However, for post-operative biochemical measures, the total sample calcium median was 8.9 (8.6-9.4) mg/dl, and for total sample, corrected calcium median was 9.4 (9.1-9.8) mg/dl, with significant statistical difference between groups in both variables ($p = 0.04$). Post-operative PTH had a median of 37.8 (22.3-55.2) pg/dl in the total sample, with no statistical difference between symptomatic and asymptomatic groups ($p = 0.73$) (Table 4). In terms of pathology reports, a predominance of parathyroid adenoma was found in 78% ($n = 48$), followed by parathyroid hyperplasia with 16% ($n = 10$), 3.2% ($n = 2$) of adenoma and hyperplasia, and 1.6% ($n = 1$) of carcinoma. A higher parathyroid weight was found in the asymptomatic group versus symptomatic group, without statistical difference ($p = 0.26$). Most of the procedures were performed by an endocrine surgeon (67.2%), followed by general surgeons (21.3%), oncology and head-and-neck surgeons (5% each), and only one surgical procedure performed by a neurosurgeon (1.6%). There were no differences between the type of surgical specialist (endocrine and non-endocrine) between the two groups (68% vs. 66.7%, $p = 0.86$) (Table 3).

DISCUSSION

Symptomatic PHPT in postmenopausal women is still the most common form of presentation in the

Table 1. Frequency of manifestations and related syndromes

Syndrome	Manifestation	Total (n = 61) (%)	Asymptomatic (n = 19) (%)	Symptomatic (n = 42) (%)
Renal		45.9	-	66.7
	Nephrolithiasis	42.6	-	61.9
	Nephrocalcinosis	3.3	-	4.8
Skeletal		39.3	-	-
	Bone fractures	26.2	-	38.1
	Osteopenia	3.3	-	4.8
	Osteoporosis	9.8	-	14.3
Cardiovascular		54.1	31.6	64.3
	Ischemic cardiopathy	19.6	36.3	16.7
	Systemic hypertension	49.1	36.8	54.8
	Hypertensive cardiopathy	3.3	5.3	2.4
	Stroke	3.3	5.3	2.4
	Arrhythmia	8.2	10.5	7.1
Neuropsychiatric		27.8	10.5	38
	Depression	6.5	-	6.6
	Anxiety	8.2	3.2	4.9
	Weakness	11.5	-	16.7
	Dementia	3.3	-	4.8

Table 2. Symptoms and diseases in coincidence to PHPT

Syndrome	Manifestation	Total (n = 61) (%)	Asymptomatic (n = 19) (%)	Symptomatic (n = 42) (%)
Gastrointestinal		14.8	15.8	14.3
	GERD	4.9	3.2	2.4
	IBD	1.6	-	2.4
	Peptic ulcer disease	4.9	-	7.1
	Pancreatitis	1.6	5.3	-
	Mesenteric ischemia	1.6	-	2.4
Thyroid disease		27.9	26.3	28.6
	Hypothyroidism	9.8	21	4.8
	Thyroid nodule	13.1	-	19
	Adenoma	1.6	-	2.4
	Papillary carcinoma	4.9	5.3	2.4

GERD: gastroesophageal reflux disease, IBDL: inflammatory bowel disease.

private hospital, which is concordant with a systematic review in developing countries¹⁰. International guidelines as well as Western and European studies describe similar proportions⁶. Still, other Latin American study reported higher frequencies in asymptomatic patients (81.8%) in a Brazilian population (n = 33) studied by Eufrazino et al., in which

27 patients were asymptomatic¹⁵. In the asymptomatic group, although the main criteria for surgery were corrected calcium 1 mg/dL above range, only a small proportion was younger than 50 years old; the rest of asymptomatic patients, who did not meet the previous criteria for surgical intervention and did not have bone or renal decline, preferred

Table 3. Clinical characteristics of symptomatic and asymptomatic PHPT cases

Characteristics	n	Total (n = 61)	Asymptomatic (n = 19)	Symptomatic (n = 42)	p
Age (years)	61	59 ± 13	59 ± 11	59 ± 13	0.84
<50 years	61	21.3% (13)	15.8% (3)	23.8% (10)	NA
Gender (female vs. male)	61	27.9%	26.3% (5)	28.6% (12)	0.85
Pre-operative SBP (mmHg)	30	124 ± 14	121 ± 15	125 ± 14	0.4
Pre-operative DBP (mmHg)	30	70 ± 12	66 ± 9	73 ± 12	0.11
Discharge SBP (mmHg)	31	111 ± 13	108 ± 13	113 ± 13	0.31
Discharge DBP (mmHg)	31	71 ± 9	69 ± 8	72 ± 9	0.41
Nephrolithiasis	61	45.9% (28)	-	66.7% (28)	<0.001
Fractures	61	39.3% (24)	-	57.1% (24)	<0.001
Neuropsychiatric syndrome	61	29.5% (18)	10.5% (2)	38% (16)	0.02
Cardiovascular syndrome	61	54.1% (33)	31.6% (6)	64.3% (27)	0.01
Thyroid pathology	61	27.9% (17)	26.3% (5)	28.6% (12)	0.85
Gastrointestinal syndrome	61	14.8% (9)	15.8% (3)	14.3% (6)	0.87
Histopathological report Parathyroid volume (cm ³)	51	0.6 (0.4-2)	0.5 (0.4-1.2)	0.7 (0.3-2.6)	0.69
Parathyroid weight (mg)	51	600 (208-1100)	710 (450-1085)	493.5 (132.5-1645)	0.25
Adenoma	61	78% (n = 48)	89.4% (n = 17)	73.8% (n = 31)	NA
Hyperplasia	61	16% (n = 10)	10.6% (n = 2)	19% (n = 8)	NA
Carcinoma	61	1.6% (n = 1)	-	2.4% (n = 1)	NA
Adenoma and hyperplasia	61	3.2% (n = 2)	-	4.8% (n = 2)	NA
Surgeon specialty					
Non-endocrine versus endocrine	61	67.2% (41)	68% (13)	66.7% (28)	0.89

PHPT: primary hyperparathyroidism. SBP: systolic blood pressure. DBP: diastolic blood pressure. Student's t-test, mean ± SD. Mann-Whitney's U-test, median [p25-p75] and % (n).

Table 4. Biochemical characteristics of PHPT symptomatic and asymptomatic cases

Characteristics	n	Total (n = 61)	Asymptomatic (n = 19)	Symptomatic (n = 42)	p
Biochemical					
Albumin (g/dl)	61	3.4 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	0.46
Intact PTH (pg/dl)	58	183.5 (129.4-257)	186 (116-245)	183.5 (129.9-260.6)	0.94
Pre-operative calcium (mg/dl)	61	11.1 (10.6-11.6)	11 (10.6-11.4)	11.2 (10.6-11.7)	0.93
Pre-operative corrected calcium (mg/dl)	61	11.5 (10.9-12)	11.5 (10.8-12.2)	11.6 (10.9-12)	0.58
Post-operative PTH (pg/dl)	61	37.8 (22.3-55.2)	44.4 (32-52.9)	33.3 (19.4-57.4)	0.73
Post-operative calcium (mg/dl)	58	8.9 (8.6-9.4)	8.8 (8.1-9.3)	9.1 (8.7-9.5)	0.04
Post-operative corrected calcium (mg/dl)	58	9.4 (9.1-9.8)	9.3 (8.9-9.6)	9.6 (9.2-9.9)	0.04

PTH: parathyroid hormone. Student's t-test, mean ± SD. Mann-Whitney's U-test, median [p25-p75] and % (n).

surgery over long-term monitoring. The higher proportion of neuropsychiatric and cardiovascular syndromes found in symptomatic patients ($p = 0.02$ and $p = 0.01$, respectively), do not relate with other

Latin American studies ($p = 0.563$ and $p = 0.643$, respectively, between groups)¹⁵. This could be attributed to design limitations of cross-sectional studies and the absence of applicable clinical tools of

proper identification pre- and post-operative for description of neuropsychiatric ailments in our study. Cardiovascular manifestations were present in 54.1% of cases, agreeing with a prospective study with 11 cases out of 34 total cases (32.3%)²⁶. These results could be due to hypercalcemia and persistently high levels of PTH¹⁹. Thyroid disease was present in 22.9% of the sample, while Scerrino et al. described the coexistence of PHPT and thyroid disease in 17-84%²². Due to the wide range of prevalence reported in the previous studies, more evidence is needed. Digestive ailments were present in both symptomatic and asymptomatic cases which are concordant with Eufrazino et al. who found no differences between groups ($p = 1$)¹⁵. Pancreatitis in one "asymptomatic" patient was found, presumably from hypercalcemia; however, this patient never presented classical symptoms (skeletal and/or renal complications), therefore was assorted into asymptomatic group, although this matter is debatable. Histopathological reports in our study relate to international bibliography, reporting a higher frequency of parathyroid adenoma, followed by hyperplasia, and rarely carcinoma and adenoma with hyperplasia³.

Pre-operative calcium and PTH levels are similar to the ones found by Odvina et al., with non-significant differences in both variables between groups (stone formers and non-stone formers)²¹. The above could be explained by the role of hypercalciuria (not collected in our study), and not hypercalcemia, in kidney stone development in PHPT patients⁹. Finally, we observed significantly higher post-operative calcium levels in symptomatic cases ($p = 0.04$), which is comparable to the results reported by Yu et al. for post-operative ionized calcium in symptomatic patients ($p \leq 0.0001$), though not clinically relevant. However, in the same study, post-operative PTH was lower in symptomatic patients ($p = 0.031$), not related to our results between groups (intact PTH, $p = 0.94$, and post-operative PTH, $p = 0.73$)²⁷. Our study contributes to PHPT clinical and biochemical parameters description in Mexico, helping further establishment of study designs and hypotheses in this matter. It also highlights the importance of screening for onset diagnosis in asymptomatic patients.

Limitations

First, result interpretation needs to consider differences between the target population and the sample involved in the study, which is small and may have insufficient power to determine differences between groups. Second, this is a retrospective descriptive study of one center that may be influenced by referral bias, having patients the proper income to cover private surgery independently of PHPT surgical indications for parathyroidectomy. Third, current national guidelines do not recommend routine screening for PHPT, this can explain the heterogeneity between groups and higher proportion of symptomatic cases in our study. Fourth, symptom development pre and postoperatively could not be correctly measured due to the lack of standardized measurement tools during hospitalization, especially for neuropsychiatric symptoms, therefore, they were only collected from medical records and not intentionally explored at admission. For this same retrospective nature, Vitamin D repletion levels for diagnosis were neither measured nor registered in all cases, therefore, they could not be collected for this study. Last, information in clinical records about the exact reason why asymptomatic patients were studied for PHPT in the first place was not available in all cases (e.g., neuropsychiatric symptoms), although most of clinical history reports mention incidental findings (hypercalcemia) in routine laboratory test.

CONCLUSIONS

There is a higher proportion of symptomatic PHPT patients compared to asymptomatic PHPT patients in the private hospital. The presence of cardiovascular and neurocognitive syndromes was also more frequent in the symptomatic group. Serum levels of PTH and calcium are not related to target organ injury in the pre-operative setting, but statistically higher post-operative calcium levels were found in the symptomatic group. Population-based studies could reveal the real prevalence of PHPT and identify non-complicated presentations of the disease, since the lack of national report and screening

strategies can result in a misdiagnosis of PHPT in our country. However, this study sets a baseline for future hypotheses and study designs with a higher level of evidence in Mexican population.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and / or subjects referred to in the article.

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