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Diferencias en el metabolismo mineral óseo hiperparatiroidismo primario normocalcémico respecto al hiperparatiroidismo primario clásico

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Differences in bone mineral metabolism normocalcemic primary hyperparathyroidism with respect to classical primary hyperparathyroidism

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Summary

Objective: Normocalcemic primary hyperparathyroidism is a less known variety of classical primary hyperparathyroidism. In this paper, we present its clinical expression and data related to bone mineral metabolism, both analytically and densitometrically, comparing them with a group of patients with classic primary hyperparathyroidism, with hypercalcemia.

Material and methods: Study of cases and controls where we consider case of patients with normocalcemic primary hyperparathyroidism (n=25) and control (n=25) of patients with primary hyperpartyroidism with hypercalcemia (classical primary hyperparathyroidism). A complete clinical assessment was carried out with clinical data collection and 24h blood and urine analytical determinations were performed, as well as estimating bone mineral density and trabecular bone score by densitometry (dual x-ray absorptiometry, DXA) and ultrasound parameters in the calcaneus.

Results: In this clinical study, patients with classic primary hyperparathyroidism only show a higher prevalence of urolithiasis (OR: 9.333; 95% CI: 1.50-82.7) compared to patients suffering from a normocalcemic primary hyperparathyroidism. In all other clinical, analytical, densitometric and ultrasonographic parameters, there are no statistically significant differences between the two groups.

Conclusions: Apart from serum calcium levels and the prevalence of urolithiasis, normocalcemic hyperparathyroidism is indistinguishable from classical hyperparathyroidism.

Key words: hyperparathyroidism, primary, normocalcemic, densitometry, quantity, quality, bone.

Introduction

Primary hyperparathyroidism (HPT) is a very common bone mineral metabolic disease consisting of autonomous overproduction of parathyroid hormone (PTH), which leads to an increase in serum calcium[1]. It is the most frequent cause of hypercalcemia.

A lesser known clinical variant of HPT is the so-called "normocalcemic primary hyperparathyroidism" (NHPT), which has normal blood calcium levels and elevated parathyroid hormone (PTH) values, not knowing the mechanism by which this differential fact occurs[2-4]. These patients do not have clear causes that justify secondary elevations of PTH such as chronic renal damage[5], vitamin D deficiency (less than 30 ng/ml)[6], renal hypercalciuria or drugs[7]. Although NHPT was first formally recognized in the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008[8], all clinical features are not yet known, particularly with regard to its epidemiology, natural history, management and prognosis[9,10]. Therefore, this clinical variety of the disease is less studied[11] and there is less bibliography. All of which has motivated us to carry out this study.

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Material and methods

This is a case-control study, in which cases patients with primary normocalcemic hyperparathyroidism (PNPH) are considered, and controls those patients with a primary hyperparathyroidism that has attended with hypercalcemia and which we will call classical primary hyperparathyroidism (CHPT). The diagnosis of one or the other clinical picture was made following the criteria established by consensus[12]. All patients were given a questionnaire to collect clinical data, designed for this purpose.

Sample collection and laboratory techniques

Blood and urine samples were collected in the morning, between 8:00 and 9:00, after a fasting night. Blood was collected in the appropriate specific tubes for each determination, with the least possible venous compression, and centrifuged at 1,500 g for 10 minutes. The serum was separated into aliquots and stored within one hour of extraction at -20° C until the biochemical analyzes were carried out, although most of them were done on the same day as the extraction.

Glucose, urea, creatinine, calcium, inorganic phosphorus, total proteins, total cholesterol and its fractions and triglycerides were measured using standardized and automated colorimetric techniques in an auto-analyzer (Kodak Ektachem Clinical Chemistry Slides). The serum calcium was corrected according to total proteins by means of the following formula:

Corrected calcium = previous calcium (mg/dl)/[0.55 + total protein (g/l)/16].

Tartrate resistant acid phosphatase (TRAP) was determined by spectrophotometry. Glomerular filtration (GF) was calculated from the MDRD (Modification of Diet in Renal Disease) formula[13] and the existence of renal insufficiency with GF values below 60 ml/m/m^2 was considered[14].

Serum levels of 25(OH) vitamin D (25HCC) were measured by immunochemiluminescence, according to the Nichols method (Nichols Institute Diagnostics, San Clemente, California, USA). This method has an intra-assay coefficient variation of 3.0-4.5% and intersession of 7.1-10.0%. The values given by the laboratory as normal range between 10 and 68 ng/ml. Serum parathyroid hormone (PTH) concentrations for the intact molecule were determined by immunochemiluminescence, according to the Nichols Advantage method. The normal adult level ranges from 6 to 40 pg/ml, with an inter-assay variation coefficient of 7.0-9.2%. Propeptides of the amino-terminal fraction of collagen type I (P1NP) and blood beta-crosslaps were measured by previously described techniques[15-18]. The remaining biochemical parameters were determined by colorimetric techniques. Urine was collected for 24 hours and calcium, phosphorus and creatinine were measured by automated colorimetric methods.

In patients in the case group (NHPT) with 25HCC values below 30 ng/ml, 25,000 IU of cholecalciferol was prescribed every 15 days and analysis of PTH, calcium and 25HCC was repeated at 3 months, in order to carry out differential diagnosis with hyperparathyroidism secondary to vitamin D deficiency. Once this was ruled out, baseline analysis was considered for the study.

The diagnosis of depression was obtained after a thorough review of the clinical history of all patients, both hospital and primary care.

Ultrasound readings in the calcaneus

Ultrasound parameters were estimated in the calcaneus of the dominant foot, using a Sahara® Hologic® ultrasound (Bedford, Massachusetts, USA). This device measures both the ultrasonic broadband attenuation (BUA), and the speed of sound (SOS) in the region of interest of the calcaneus. The BUA and SOS values are combined into a single parameter called the Quantitative Ultrasound Index (QUI), also known as the consistency index, which is obtained through the formula: QUI = 0.41(SOS) + 0.41 (BUA) – 571. The T-score values were calculated from the values published as normal for the Spanish population[19].

Bone mineral density (BMD)

BMD was measured by dual x-ray absorptiometry (DXA), both in the lumbar spine (L2-L4) and in the proximal limb of the femur, with a Hologic Discovery® densitometer, (Hologic Inc. Waltham, USA). Its accuracy is 0.75-0.16%. The measurements were made by the same operator, so there was no inter-observer variation.

The T-score values were calculated from the values published as normal for the Canary Island population[20].

Trabecular bone score (TBS)

All TBS measurements were carried out using the TBS iNsight Software program, version 2.0.0.1 (Med-Imaps, Pessac, France). The software uses the image previously obtained by DXA in the same region of interest of the lumbar spine L2-L4. The T-score values were calculated from the reference values obtained for the Spanish population[21].

Ethics

The study was carried out following the norms of the Declaration of Helsinki[22] and was approved by the Ethics Committee of the Insular University Hospital. All patients were informed of the objectives of the work and their informed consent was requested.

Statistic analysis

To carry out the statistical study, the R program was used. Initially we analyzed the numerical variables, studying whether or not they followed a normal distribution. Later we carried out a descriptive study. Categorical variables were summarized by percentages, and numerical variables by means and typical deviations. To study the possible associations between categorical variables, the chi-square independence test was used, and as a measure of association the odds ratio (OR) with a 95% confidence interval (95% CI). In those cases where there were cells with less than 5 cases, the exact Fischer test was applied.

To assess the association between a quantitative variable and a categorical variable, Student's t test or ANOVA (if there were more than 2 categories) were used for normal distribution variables, or the non-parametric Mann-Whitney U test for the non-normal to study the degree of association or independence of 2 quantitative variables. We use correlation techniques to assess the strength of the association between the variables.

In all cases the level of significance was considered at 5% ($p<0.05$).

Results

Table 1 shows the baseline characteristics of the patients included in the study. Initially, 30 patients were included

in each group, but they completed the study and finally gave their informed consent 25 patients with HPTN and 25 patients with HPT. This table shows the continuous (numerical) variables. There were no statistically significant differences in any of the variables that we grouped as "baseline characteristics" in table 1, which were: age, height, body mass index (BMI) and size. Therefore, it was not necessary to adjust the remaining parameters studied in our work by any of these variables.

Table 2 presents the clinical characteristics and prevalence of some diseases in both groups of patients studied. Most of the patients were women, with only 4 men being collected in the 25 patients with HPT, which is 15.3%, and 2 men in the group of patients with PNHT, 8% of that group. These differences were not statistically significant (p=0.667). Nor did we obtain statistically significant differences in the prevalence of chronic renal failure, arthralgia, depressive syndrome, or in the prevalence of AHT between the two groups. The only clinical data that showed statistically significant differences between both groups was urolithiasis, which was more frequent in patients affected by the classic form of HPT.

Table 3 shows some biochemical parameters related to bone mineral metabolism. There were no statistically significant differences in renal function (urea, creatinine, uric acid) or in the biochemical markers of bone remodeling, both those of formation and bone resorption (type I procollagen, osteocalcin, tartrate-resistant acid phosphatase and beta-crosslaps), and also at serum levels of PTH and 25(OH) vitamin D.

Table 4 shows the values obtained by means of bone densitometry, both in the lumbar spine (L2-L4) and in the proximal limb of the femur in its different anatomical locations. In all cases the T-score was also calculated, obtained from the normal values of the Spanish population. This same table shows the values of the TBS technique, also calculating the corresponding T-score, based on the normal values of the Spanish population.

Table 5 shows the prevalence of osteoporosis, as well as fragility fractures. There were no statistically significant differences in either the prevalence of densitometric osteoporosis or that of fragility, total or hip fractures, nor in the number of falls between both groups of patients with primary hyperparathyroidism.

Discussion

The NHPT is a rare entity and has consequently received less study. The possible differences with respect to the other classic clinical form of HPTC are not known. In fact, the first recognition of classical HPT as a distinct entity was made at the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008[8].

Our objective was to try to identify possible differences between the two forms of clinical presentation of HPT, especially in aspects related to bone involvement: prevalence of osteoporosis, involvement of the amount of bone mass measured by bone densitometry (BMD), of bone quality, which we estimated by trabecular bone score (TBS), a relatively recent technique and using software makes an alternative assessment of lumbar spine densitometry, analyzing the quality of trabecular connections[23-26]. This is a complementary method to classical bone densitometry, since it allows the evaluation of

Table 1. Baseline characteristics of both groups studied, patients with normocalcemic HPT (NHPT) and classic primary hyperparathyroidism (CPHPT)

Variable	NHPT	CPHPT	P value
Number	25	25	
Age (years)	67.3 ± 10.2	63.4 ± 11.3	0.205
Height (cm)	160.2 ± 8.4	157.2 ± 9.7	0.244
Weight (kg)	75.7 ± 19.8	74.8 ± 12.5	0.850
BMI (kg/m^2)	30.2 ± 3.6	29.6 ± 8.2	0.758
Wingspan (cm)	158.5 ± 12.3	162.9 ± 8.1	0.143

Table 2. Distribution of sexes and comparison of the prevalence of some clinical data between both groups studied, patients with normocalcemic HPT (NHPT) and classic primary hyperparathyroidism (CPHPT)

Variable	CPHPT N=25	NHPT N=25	OR (IC 95%)	Chi-square	P value
Gender: men, n	4	2	2.190 (0.363-13.219)	0.758	0.667*
Presence of CRF, n	5	1	6.000 (0.647-55.6)	3,030	0.189*
Arthralgias, n	11	14	0.617 (0.202-1.886)	0.720	0.396
Depressive syndrome, n	14	12	1.279 (0.453-4.197)	0.3121	0.571
Urolithiasis, n	7	1	9.333 (1.50-82.7)	5.357	0.049*
AHT, n	19	16	1.781 (0.521-6.085)	0.857	0.355

*: Fischer's exact test was applied as there were cells with less than 5 cases; CRF: chronic renal failure; AHT: arterial hypertension.

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Table 3. Biochemical data obtained in both groups studied, patients with normocalcemic HPT (NHPT) and classic primary hyperparathyroidism (CHPT)

Variable	NHPT	CPHPT	P value
Urea (mg/dl)	40.2 ± 18	40.2 ± 16.9	0.989
Creatinine (mg/dl)	0.9 ± 0.3	1 ± 0.3	0.483
Calcium (mg/dl)	9.9 ± 0.4	11 ± 0.5	0.001
Phosphorus (mg/dl)	3.1 ± 0.4	2.7 ± 0.4	0.007
Total proteins (g/l)	7.1 ± 0.3	7.1 ± 0.4	0.728
Calcium corrected (mg/dl)	10 ± 0.5	11.1 ± 0.5	0.001
Uric acid (mg/dl)	5.1 ± 1.5	5.3 ± 1.5	0.662
Calciuria (mg/24h)	168.2 ± 114.2	235.3 ± 153.8	0.15
Phosphaturia /mg/24h)	635.7 ± 305.4	747.1 ± 279.1	0.13
Biochemical markers of bone remodeling and hormones			
P1NP* (mg/ml)	59.1 ± 33.8	77.2 ± 52.6	0.185
Osteocalcina (ng/ml)	33.5 ± 17.5	35.3 ± 15.6	0.711
Beta-crosslaps (ng/ml)	0.6 ± 0.3	0.8 ± 0.6	0.144
TRAP[§] (UI/l)	3.1 ± 0.9	3.1 ± 0.8	0.945
PTH[¥] (pg/ml)	119 ± 33	122 ± 20.7	0.701
Vitamin D (25HCC)[#] (ng/ml)	23.5 ± 9.7	21.9 ± 9	0.539

*: aminoterminal type I procollagen; [§]: tartrate-resistant acid phosphatase; [¥]: intact parathyroid hormone; [#]: 25 hydroxycholecalciferol.

Table 4. Densitometric values in lumbar spine and proximal limb of the femur, TBS and ultrasound in the calcaneus in both groups studied, patients with normocalcemic HPT (NPHPT) and classic primary hyperparathyroidism (PHPT). Ultrasound in the calcaneus

Variable	NHPT	CPHPT	P value
L2L4 (g/cm^2)	0.922 ± 0.200	0.929 ± 0.168	0.897
T-score L2L4	-1.1 ± 1.5	-1.0 ± 1.3	
Femoral neck (g/cm^2)	0.711 ± 0.114	0.728 ± 0.154	0.661
T-score femoral neck	-1.1 ± 0.9	-1 ± 1.2	
Total hip (g/cm^2)	0.843 ± 0.144	0.860 ± 0.156	0.693
T-score total hip	0.0 ± 1.0	-0.1 ± 1.1	
Trochanter (g/cm^2)	0.630 ± 0.120	0.644 ± 0.120	0.701
T-score trochanter	-0.1 ± 0.9	0.0 ± 0.9	
Intertrochanter (g/cm^2)	0.980 ± 0.171	1.010 ± 0.185	0.643
T-score intertrochanter	0.0 ± 1.0	0.0 ± 1.1	
TBS lumbar spine (g/cm^2)	1.288 ± 0.087	1.276 ± 0.105	0.747
T-score TBS	-1.9 ± 1	-2.1 ± 1.3	
Ultrasound in the calcaneus			
BUA (dB/MgHz)	66.9 ± 16.2	58.4 ± 14	0.148
SOS (m/s)	1,530.8 ± 33.4	1,518.3 ± 21.9	0.263
QUI	84 ± 19.7	75.4 ± 13.4	0.196

TBS: trabecular bone score. Bone trabecular score; BUA: broadband ultrasound attenuation. Ultrasonic Broadband Attenuation; SOS: speed of sound. Speed of sound; QUI: quantitative ultrasound Index. Quantitative Ultrasonic Index.

Table 5. Prevalence of osteoporosis, falls and fragility fractures in both groups studied, patients with normocalcemic HPT (HPTN) and classic primary hyperparathyroidism (CHPT)

	NHPT	CPHPT	OR (IC 95%)	Valor p
Densitometric osteoporosis, n (%)	5 (20%)	5 (20%)	1.000 (0.250 - 3.998)	1.000
Fragility fractures, n (%)	8 (32%)	6 (24%)	1.490 (0.429 - 5.172)	0.529
Falls in the last year, n (%)	6 (25%)	7 (28%)	0.857 (0.240 - 3.056)	0.812
Hip fracture, n (%)	0 (0%)	0 (0%)	Not applicable	Not applicable

aspects more related to bone architecture, being an indirect method of estimating bone quality[23,24,27]. Finally, we used ultrasound, a controversial method, which some authors recommend to measure bone quality[28,29].

We have not found statistically significant differences in the variables analyzed between both groups of patients with HPT, with the only exception of serum calcium values, the variable that distinguishes between one group and another. It is well known that HPT in its traditional form occurs more frequently in women and this same finding has been found in our study. Nor were differences observed in the prevalence of falls, chronic renal failure, the clinical presentation of arthralgia, depressive syndrome or high blood pressure (AHT). In contrast, patients who had CHPT presented a higher prevalence of kidney stones. Few studies analyze these clinical data in the literature. We found a series of cases published by Cusano et al. We included 9 patients who showed clinical and biochemical data very similar to those obtained in our work[3], while in another series we obtained conclusions precisely opposite to ours. In the series reported by Amaral et al. with 33 cases, an 18% prevalence of kidney stones was found, the same prevalence as the control group formed by patients with CHPT[30].

All these clinical manifestations (arthralgias, depression) or the association of other conditions such as high blood pressure or chronic renal failure can be observed in the HPT[1,31-36], although today, with the development of laboratory techniques and programs health prevention that include analytical determinations, HPT is usually diagnosed as an asymptomatic hypercalcemia, without any other symptoms[1,35,36]. Since precisely hypercalcemia is the guiding sign in the diagnosis of HPT, in the case of NHPT the diagnosis is more complicated and is reached by exclusion, after a more detailed study[2-4].

The results obtained on bone mineral metabolism indicate that bone remodeling does not differ in the two forms of HPT. Similar results to ours have been described in other studies[2-4,11,30].

We did detect statistically significant differences in PTH or vitamin D either. It should be noted that the average values of vitamin D, measured by its reserve metabolite, 25HCC[37], were low, in the range of vitamin D insufficiency, which is defined as serum values of 25HCC below 30 ng/ml[38,39]. This finding has been corroborated in other studies that coincide with our results[4,36,40,41].

Nor have we observed a different behavior of the bone in both groups of patients, since BMD values both in the lumbar spine (L2-L4) and in the proximal limb of the femur in all locations (femoral neck, total hip, trochanter and intertrochanter) were similar in both groups, thus affirming that in the normocalcemic primary HPT there are no differences in bone mineral density with respect to the HPTC. We have obtained the same finding when studying the TBS, which has been studied in patients with HPT and has shown lower values than the controls[24], and may indicate involvement of the trabecular structure and therefore of bone quality[23,25,26,41]. Regarding the existence of osteoporosis due to densitometry or the appearance of fragility fractures, we did not obtain statistically significant differences between both groups of patients with HPT. In fact, the existence of densitometric osteoporosis was observed the same number of patients in each group. No hip fracture event was observed. It does not appear, therefore, that there are clinical differences in bone involvement in patients with NHPT with respect to CHPT.

Our study's main limitation is the small sample size, due to the difficulty of detecting cases. It is noteworthy that NHPT is a condition whose incidence and actual prevalence are unknown. However, when reviewing the literature, we have verified that it is a very rare entity. The number of cases in the different reported series is also low[6,10-12,30,35].

Conflict of interests: Authors declare no conflict of interests.

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