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LETTER TO THE EDITOR

Normocalcemic primary hyperparathyroidism: one-year follow-up in one hundred postmenopausal women

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Routine measurement of parathormone (PTH) has lead to the identification of high PTH levels without hypercalcemia. This situation, which is known as normocalcemic hyperparathyroidism [1], was defined by Wills in 1962 and is established after ruling out the main causes of secondary hyperparathyroidism. There are conflicting data about its bone effects and clinical course.

The aims of our study was to evaluate the frequency of normocalcemic hyperparathyroidism in postmenopausal, to analyse parameters related to bone metabolism, and to assess changes after one-year follow-up.

We conducted a prospective study conducted in a cohort of 100 healthy postmenopausal women. Clinical and biochemical data and bone mass by quantitative ultrasound (QUS) were determined at baseline and after 1 year. The study protocol was approved by the ethical review board of our hospital and was done conformed to the ethics guidelines for research in humans. All the participants in the study provided written informed consent.

Baseline characteristics of the study groups are shown in Table 1. 16 patients had high PTH levels, one woman with criteria of primary hyperparathyroidism (PTH 109 pg/ml and calcium 11.2 mg/dl) who was excluded from the study and 15 of them with normal calcium serum levels (PTH 78 ± 13 pg/ml and serum calcium 9.3 ± 0.3 mg/dl). In this group, six patients had high PTH with 25-OH vitamin D >30 ng/ml and were classified as normocalcemic primary hyperparathyroidism. There were no differences in biochemical and clinical variables between women with secondary hyperparathyroidism and normocalcemic hyperparathyroidism except for 25-OH vitamin D: 17.4 ± 10 versus 33.2 ± 2.6 ng/ml, $p < 0.001$ (Table 1).

There was a high percentage of women in both groups with low 25-OH vitamin levels: 72.6 % (61/84) in normal PTH group versus 57.2 % in women with secondary hyperparathyroidism (9/15) ($p = 0.32$). Women with secondary hyperparathyroidism and normocalcemic hyperparathyroidism have normal values of renal function, bone turnover markers and bone mass measured by QUS.

In the group consisting of secondary and normocalcemic hyperparathyroidism, PTH showed a negative correlation with QUS parameters: QUI: $r = -0.621$, $p = 0.013$; BMD $r = -0.554$, $p = 0.032$; *T*score $r = -0.571$, $p = 0.026$. No correlation was observed between PTH and bone mass in the group with normal PTH levels.

After one-year of follow-up, PTH remained high in 86.7 % (13/15) of women and in 13.3 % (2/15) PTH has dropped to normal values. In women with secondary hyperparathyroidism there were no significant changes in biochemical and clinical variables (Table 1). The six women with baseline criteria of normocalcemic hyperparathyroidism remained in this category after 1 year. No episodes of hypercalcemia or other relevant clinical events were observed in this group.

To our knowledge, no previous studies have evaluated the frequency of normocalcemic hyperparathyroidism in postmenopausal Spanish women. In the Canadian Multicentre Osteoporosis normocalcemic hyperparathyroidism was diagnosed in 16.7 % of subjects, but they considered 25-OH vitamin D <20 ng/ml as vitamin D deficiency which may have contributed to the higher prevalence observed. The evaluation of well known causes of secondary hyperparathyroidism in our sample (low vitamin D, renal disease, malnutrition) allowed us to exclude women

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Table 1 Baseline characteristics of study groups and 1 year parameters of normocalcemic hyperparathyroidism group

	NV	Normal PTH (*n*: 84)	Secondary HP baseline (*n*: 9)	Normocalcemic HP baseline (*n*: 6)	Secondary HP 1 year (*n*: 7)	Normocalcemic HP 1 year (*n*: 6)
Age (years)	–	55.6 ± 3.8	57.4 ± 3.7	56.3 ± 3.2	58.1 ± 1.6	57.2 ± 2.3
Years since menopause	–	7.2 ± 3.8	5.4 ± 2.6	5.7 ± 3.4	6.3 ± 3.1	6.2 ± 2.9
Smoking (yes/no)	–	15/69	1/9	1/6	1/7	1/6
Alcohol (yes/no)	–	21/63	1/9	1/6	0/7	1/6
Previous fracture (*n*-%)	–	2/2.4 %	0/0	0/0	0/0	0/0
Parent fracture (*n*-%)	–	8/9.5 %	1/6.7 %	1/6.7 %	1/7.7 %	1/7.7 %
Renal stones (*n*-%)	–	3/3.6 %	0/0 %	0/0 %	0/0 %	0/0 %
BMI (kg/m^2)	19–24	27.9 ± 4.2	29.8 ± 6.3	30.5 ± 5.8	30.1 ± 7	31.2 ± 5.9
Systolic BP (mm Hg)	<140	124 ± 17	130 ± 20	130 ± 21	135 ± 20	135 ± 18
Diastolic BP (mm Hg)	<90	78 ± 10	80 ± 14	82 ± 12	85 ± 10	86 ± 13
Total proteins (mg/dl)	6.5–8.7	7.4 ± 0.4	7.5 ± 0.6	7.5 ± 0.5	7.6 ± 0.5	7.5 ± 0.8
Albumin (mg/dl)	3.5–5	4.5 ± 0.2	4.5 ± 0.3	4.4 ± 0.2	4.4 ± 0.3	4.3 ± 0.4
Creatinine (mg/dl)	0.5–1.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Cr clearance (ml/min/1.73 m^2)	70–110	82.8 ± 11.9	79.8 ± 13.52	80.2 ± 13.45	80.8 ± 11.9	79.5 ± 14.76
Calcium (mg/dl)	8.5–11	9.3 ± 0.3	9.3 ± 0.4	9.2 ± 0.3	9.3 ± 0.2	9.4 ± 0.2
Corrected calcium	8.5–11	8.9 ± 0.3	8.8 ± 0.3	8.9 ± 0.2	9 ± 0.3	8.9 ± 0.2
Phosphate (mg/dl)	2.5–5	3.4 ± 0.4	3.2 ± 0.4	3.3 ± 0.4	3.2 ± 0.5	3.2 ± 0.4
PTH (pg/ml)	15–65	42 ± 10	79.1 ± 9.8	81.3 ± 10	73 ± 8	78 ± 10
25-OHD (ng/dl)	–	22.12 ± 10	17.4 ± 10	18.6 ± 9.6	33.2 ± 2.6	34.3 ± 3.5
BSAP (μg/ml)	7.57–33.74	14.47 ± 5.08	20.95 ± 9.79	23.02 ± 9.86	21.33 ± 8.37	23.24 ± 9.73
TRAP5β (U/l)	1.49–4.89	2.21 ± 0.81	2.08 ± 0.78	1.99 ± 0.76	2.06 ± 0.82	1.98 ± 0.97
SOS (m/s)	1,504–1,583	1,518 ± 39	1,715 ± 30	1,719 ± 26	1,714 ± 30	1,702 ± 32
BUA (dB/MHZ)	48.1–89	60.9 ± 16.2	64.5 ± 12.7	63.7 ± 11.6	61.9 ± 13.4	62.5 ± 12.4
QUI	66.8–111.9	76.2 ± 20.7	76.4 ± 13.8	77.5 ± 15.3	75.3 ± 14.6	76.5 ± 13.9
Estimated BMD (g/cm^2)	0.347–0.628	0.407 ± 0.132	0.41 ± 0.087	0.412 ± 0.076	0.398 ± 0.079	0.402 ± 0.086
T score	–	−1.56 ± 1.18	−1.46 ± 0.8	−1.48 ± 0.7	−1.53 ± 0.6	−1.5 ± 0.8

NV normal values, *HP* hyperparathyroidism, *BMI* body mass index, *BP* blood pressure, *PTH* parathyroid hormone, *Cr* creatinine, *25-OHD* 25-OH vitamin D, *BSAP* bone-specific alkaline phosphatase, *TRAP5β* tartrate-resistant acid phosphatase 5 *β*, *SOS* speed of sound, *BUA* broadband ultrasound attenuation

with secondary hyperparathyroidism and may explain the prevalence of normocalcemic hyperparathyroidism observed compared with previous reports.

Chronic increased PTH levels in primary hyperparathyroidism induce bone loss, and a recent prospective study has shown higher fracture risk and low bone mass in postmenopausal women with high PTH concentrations and normal calcium [2]. Our results confirm this previous data since only in women with high PTH there was an inverse correlation between PTH and QUS parameters.

In our study after 1 year no patients developed hypercalcemia, fractures or renal stones, and in two women PTH levels dropped to normal values. A shorter time of follow-up may explain the absence of clinical changes in our study. However, according to 2009 guidelines for the management of asymptomatic primary hyperparathyroidism [3], there is no enough evidence about the natural course of normocalcemic hyperparathyroidism to establish that progression of this disease will be high with a longer follow up.

In summary, our study shows that normocalcemic hyperparathyroidism is a frequent condition in postmenopausal women. After 1 year there were no relevant changes in clinical symptoms or biochemical variables, which indicate a slow progression. In addition, high PTH concentrations were inversely related to bone mass.

Conflicts of interest No potential conflicts of interest relevant to this article were reported.

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