BONE TURNOVER MARKERS IN SPANISH POSTMENOPAUSAL WOMEN. THE CAMARGO COHORT STUDY.

Josefina Martínez[1], José M. Olmos[1], José L. Hernández[1], Gabriel Pinedo[2], Javier Llorca[3], Eduardo Obregón[2], Carmen Valero[1], Jesús González-Macías[1].

(1) Department of Internal Medicine, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria. RETICEF. Santander, Spain. (2) Centro de Salud "José Barros". Camargo. Universidad de Cantabria. Santander, Spain. (3) Epidemiology Unit, Medical School, Universidad de Cantabria. Santander, Spain.

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José M. Olmos
Departamento de Medicina Interna
Hospital Universitario Marqués de Valdecilla
Avda. Valdecilla s/n
39008-Santander
Spain
Fax: +34942201695
e-mail: miromj@humv.es

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ABSTRACT

BACKGROUND. This cross-sectional study was performed to determine the reference ranges for two bone turnover markers -aminoterminal propeptide of type I collagen (P1NP) and C-terminal telopeptide of type I collagen (β-CrossLaps, β-CTX)- in normal postmenopausal Spanish women as determined in serum by automated methods.

METHODS. A community-based population of 1080 healthy postmenopausal women was evaluated. Data regarding risk factors for osteoporosis and fractures were collected by means of a structured questionnaire. Fasting serum levels of P1NP, β-CTX, 25-Hydroxivitamin D (25OHD), and intact parathyroid hormone (iPTH) were measured on the Elecsys 2010 automated analyzer (Roche). BMD at lumbar spine, femoral neck and total hip was determined by DXA.

RESULTS. The mean age of subjects was 63±9. Logarithmic transformation of both markers was performed to allow for normal distributions. Mid-95% ranges for P1NP and β-CTX were 19-100 ng/ml and 0.112-1.018 ng/ml, respectively. Mean values of P1NP (47.7±19.9 ng/ml) were similar to those previously determined by the manufacturer of the assays, whereas β-CTX mean values (0.387± 0.197 ng/ml) were lower. Both markers were higher among osteoporotic women.

CONCLUSIONS. Values obtained from this well-characterized population study provide reference ranges for serum automated P1NP and β-CTX in normal Spanish postmenopausal women.

1. Introduction

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, which predisposes the patient to develop fractures [1]. It has been estimated that approximately one-third of all Caucasian women over the age of 50 will suffer a fracture of the spine, hip or wrist at some point in their life-time [2]. Osteoporosis-related bone fragility results from a combination of a decreased bone mass and deterioration in bone microarchitecture along with changes in bone tissue quality. Bone loss occurs in postmenopausal women as a result of an increase in the rate of bone turnover and an imbalance between the activity of the osteoclasts and osteoblasts [3]. Bone turnover markers (BTM) reflect whole body rates of bone resorption and bone formation, and provide a dynamic assessment of the skeleton which may complement the static information given by bone mass evaluation, usually carried out by means of bone mineral density (BMD) measurement. The intra-patient variability of most BTM, however, has been reported as too high to be recommended in general practice, particularly as far as urine measurements are concerned, and this fact has limited the spread of their use [4,5]. Nevertheless, sensitivity and specificity have improved with the development of assays that evaluate BTM in serum, and these new procedures are being incorporated into automated equipment which is increasingly being used [6].

Since these automated techniques are now becoming common, the need to know the values they provide in the general population, and in particular, the values they give in some specific types of people, such as postmenopausal women, is increasingly felt. Some publications addressing this issue have appeared [6], but values in different countries and regions have to be reported and compared. To our knowledge, there is no available information about normal values in Spanish postmenopausal women. The Elecsys 2010 (Roche Diagnostics, GmbH, Mannheim, Germany) equipment allows the determination not only of BTM but also of 25-hydroxyvitaminD3 (25OHD) and intact parathyroid hormone (iPTH), a knowledge of which is important for the interpretation of BTM results. Therefore, the aim of this study was: i) to evaluate these automated methods to measure the serum levels of two BTM, namely aminoterminal propeptide of type I collagen (P1NP) and C-terminal telopeptide of type I collagen (β-CrossLaps, β-CTX), in Spanish postmenopausal women,

and ii) to analyze their relationship with 25OHD and PTH serum concentrations provided by the same equipment. BMD measurements were also performed, and the relationship of their results with BTM, 25OHD and PTH analyzed.

2. Material and methods

2.1. Study design and participants

The study population was set up with postmenopausal women included in the Camargo Cohort Study, a community-based study designed to evaluate the prevalence of metabolic bone diseases and the prevalence of risk factors for osteoporosis and fragility fractures in postmenopausal women and men older than 50 attended at a primary care centre in Northern Spain. A total of 1350 consecutive postmenopausal women attending the clinic for whatever reason were initially included, after giving informed consent. All participants were white, as are more than 95% of people in our region (Cantabria). Some 100 premenopausal women aged 26-50 (mean± SD: 42±6 years), randomly recruited among healthy nonpregnant women from Camargo, were also studied at the same time for the sake of comparison with postmenopausal women. The local Ethic Committee approved the study protocol.

At the baseline visit, subjects were interviewed by investigators and all participants provided data regarding the risk factors of osteoporosis and fractures using a structured questionnaire which included age, race, weight, height, body mass index (BMI, defined as weight in kg. divided by squared height in meters), personal antecedents of fractures in adulthood (> 40 years), history of osteoporotic fractures among first-degree relatives, tobacco use, consumption of dairy products, alcohol consumption, physical exercise, the existence of sensory problems, the number of falls in the previous year, the presence of chronic diseases (hypertension, dyslipemia, diabetes mellitus, urolithiasis, hyperthyroidism, hyperparathyroidism, etc), and present or past consumption of medications.

Postmenopausal women in which the baseline assessment revealed the presence of diseases or treatments known to affect bone metabolism, such as osteoporosis, primary hyperparathyroidism, hyperthyroidism, serum creatinine >

151 μmol/L, or treatment with bisphosphonates, oestrogen, raloxifene, strontium ranelate, teriparatide, L-thyroxin or glucocorticoids, were excluded from the study. Therefore, those women previously diagnosed and treated for osteoporosis were left out. However, those women who were found to be osteoporotic as a result of our BMD study, were included and evaluated. None of premenopausal women had diseases or treatments that could interfere with bone metabolism

2.2. Biochemical tests

For each woman, fasting blood samples were collected between 09:00 and 10:30 h. Serum was divided into 0.5-ml aliquots and stored at -40ºC. Serum total calcium (TCa), phosphate, creatinine, albumin, and total alkaline phosphatase were measured by standard automated methods in a Technicon Dax autoanalyser (Technicon Instruments, CO. USA). TCa measurements were corrected for albumin concentration (cCa) following a previously published formula [7]. Serum concentrations of P1NP, β-CTX, 25OHD, and iPTH were determined by a fully automated Roche electrochemilluminiscence system (Elecsys 2010, Roche Diagnostics, GmbH, Mannheim, Germany). The P1NP limit of detection was 5 ng/ml (reference range between 20-76 ng/ml), and its intraassay and interassay coefficients of variation (CV) were 3.1% and 3.5%, respectively [8]. Intraassay and interassay CV for β-CTX were 4.2% and 4.7%, also respectively, and the detection limit was 0.01 ng/ml [6]. The detection limit of serum 25 OHD was 4 ng/ml, its intraassay CV 5%, and its interassay CV 8.5%. Regarding intact PTH, the detection limit was 6 pg/ml, with a normal range of 15-65 pg/ml. Intraassay and interassay CV were 5.4% and 5.9%, respectively [9].

2.3. DXA measurements

BMD was measured by DXA (Hologic QDR 4500, Bedford, MA, USA) at the lumbar spine, femoral neck, and total hip in all the 1080 women who finally entered the study (see below). *In vivo* precision was 0.4-0.5% at the different

measurement sites. Results were expressed as grams per square centimetre, T-score (defined as the number of standard deviations [SDs] below the mean value of young women), and Z-score (defined as the number of SDs below the mean of women of the same age). T and Z-scores were calculated using the NHANES III reference database for femur measurements [10]. Quality control was performed according to the usual standards [11].

2.4. Statistical analyses

Results were expressed as mean ± SD for quantitative variables and percentages for qualitative variables. As expected in postmenopausal women, serum β-CTX and P1NP were not normally distributed with a frequency distribution skewed to the left (Figure 1A and 1B). Thus, these variables underwent logarithmic transformation before statistical analyses. Chi-squared or Fisher's exact test were performed in order to identify differences in categorical variables between subgroups. Mann-Whitney U-Test was used to compare BTM between the groups of women distributed by serum levels of iPTH, vitamin D, or osteoporosis status. One-way ANOVA was undertaken to assess correlation between BTM and age strata. Bonferroni's test for multiple comparisons was performed when significant differences were found. Significance levels less than 5% were considered significant. All analyses were performed using SPSS for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Subjects

A total of 1350 postmenopausal women, aged 44-93, with no menses for at least 12 months were recruited. Some 270 were excluded because their baseline study revealed the presence of diseases or treatments known to affect bone metabolism, or even treatments addressed to bone metabolic diseases, including osteoporosis. The remaining 1080 women entered into the study, and their characteristics are listed in table 1.

3.2. Serum P1NP and β-CTX levels

Mean serum P1NP and β-CTX in postmenopausal women were 47.7 ng/ml (± 19.9) and 0.387 ng/ml (± 0.197) respectively (Table 2). Neither of them was distributed normally, but skewed toward the lowest values (Fig.1A, and 1B). After log- transformation, data in the two cases took on a normal, Gaussian distribution, and the geometric mean ± 2SD was used to determine the 95% range. The limits of this range were 19-100 ng/ml for P1NP, and 0.112-1.018 ng/ml for β-CTX (table 3). In premenopausal women, mean P1NP (41.1±18.5 ng/ml) and β-CTX (0.271±0.139 ng/ml) were significantly lower ($p<0.001$). In relation to these, postmenopausal levels were, respectively, 18% and 43% higher.

3.3. Changes in serum P1NP and β-CTX with age

Considering all postmenopausal women as a whole, no significant correlation between age and either P1NP or β–CTX concentrations was found. However, a U-shaped relationship was visually appreciated (Fig.1C, and 1D), so that both BTM serum levels decrease up till the age of 70-79 y. (*r* correlation coefficient between age and P1NP, -0.154 [$p<0.0001$]; between age and CTX, -0.114 [$p <0.0001$]), with a rise afterwards which reached a significant level for β–CTX ($p=0.01$, "t" test), and showed a trend for P1NP ($p=0.06$). Changes were somewhat more pronounced for β–CTX (about 30%) than for P1NP (20%).

3.4. Comparison of BTM between subgroups

Different subgroups were set up according to several criteria (presence or absence of densitometric osteoporosis; serum PTH above or below 65 pg/ml – the upper limit of normal -; and serum 25OHD above or below 30 ng/ml), and their corresponding P1NP and β–CTX values compared (Table 4). As expected, the two markers were higher in postmenopausal women with osteoporosis than in postmenopausal women without ($p<0.001$), the difference being 7.1% for P1NP and 14.6% for β–CTX. Regarding the differences between osteoporotic and premenopausal women, the respective differences amounted to 23% and

61%. Since the corresponding SD are in the range of 45% and 60% of premenopausal values, there is a marked overlap between both populations.

Women with PTH levels above the upper limit of normal also had higher levels of β–CTX ($p<0.05$), but not of P1NP. Regarding 25OHD, BTM tended to be higher in women with values above 30 ng/ml, although the difference was significant only for P1NP ($p<0.05$). This difference disappears however after adjusting for weight, a finding that was expected, since both 25OHD and BTM levels are inversely related to weight.

Finally, we did not find any relationship between smoking habits, alcohol consumption, physical activity, and the other characteristics of the population studied (Table 1) and bone mineral markers (data not shown).

3.5. BMD in postmenopausal women according to BTM values

The relationship between BTM and BMD was also analyzed categorizing women in quartiles according to bone marker levels, and comparing the BMD values. Women with P1NP and β-CTX levels in the lowest quartile had a lumbar spine BMD 4% and 7% greater than in the highest (P1NP: 0.934±0.129 g/cm^2 vs. 0.894±0.123 g/cm^2; $p<0.05$; β-CTX: 0.952±0.132 g/cm^2 vs. 0.883±0.123 g/cm^2; $p<0.05$). A similar pattern was seen at the femoral neck (P1NP: 0.748±0.118 g/cm^2 vs. 0.705±0.095 g/cm^2; $p<0.01$; βCTX: 0.761±0.121 g/cm^2 vs. 0.670±0.098 g/cm^2; $p<0.001$) and the total hip (P1NP: 0.888±0.120 g/cm^2 vs.0.836±0.106 g/cm^2; $p<0.01$; β-CTX: 0.913±0.122 g/cm^2 vs. 0.831±0.110 g/cm^2; $p<0.001$). BMD differences between the highest and lowest quartiles were greater when based on β-CTX than on P1NP.

4. Discussion

New automated techniques to determine bone markers are becoming increasingly common, and therefore their normal reference values must be established. The manufacturers have developed their own reference values [6], but normal levels for different countries, or even regions, must be defined and compared. We have studied the serum levels of P1NP and β-CTX determined

by the Elecsys 2010 equipment (Roche Diagnostics) in 1080 Spanish postmenopausal women in which mineral metabolic disorders, bone metabolic diseases (other than previously unknown osteoporosis) and treatments known to affect bone metabolism had been ruled out. The sample met the criteria for postmenopausal BTM reference individuals recommended by the Clinical and Laboratory Standards Institute (NCCLS) [12]: it was large enough, the participants were well-characterized, and all women provided data regarding their risk factors for osteoporosis and fractures. In addition, all samples were obtained at the same time of the day and in a fasting state, so that factors leading to biological variability could be controlled. Mean serum P1NP and β-CTX were 47.7 ng/ml (± 19.9) and 0.387 ng/ml (± 0.197). The ± 2SD range limits (after log-transformation) were 19-100 ng/ml for P1NP and 0.112-1.018 ng/ml for β-CTX.

The mean and reference values that we have found for P1NP in our postmenopausal women are similar to those described by the manufacturers in the OFELY cohort [6]. Moreover, mean values of P1NP in our osteoporotic women (50.5±18.6 ng/ml) were also similar to values reported recently by Garnero et al [8] in 238 postmenopausal osteoporotic women from the US using the same methodology**.** Therefore, P1NP values assessed by the Elecsys automated method appear to be similar in Caucasian women in different countries.

In contrast to P1NP, serum β-CTX determined by the automated assay appears to show some differences among various publications. The manufacturer reference values are those reported by Garnero et al in 429 French postmenopausal women (age range, from 45 to 80 or more years) from the OFELY cohort [6], and amount to 0.556±0.226 ng/ml. These values are in clear contrast to those of our own study, which were 0.387± 0.197 ng/ml. Similarly, they differ from the values reported by Boudou et al [13] in 30 normal French postmenopausal women, for which a range of 0.13-0.60 ng/ml was found (mean level not given). Trento et al [14], in 200 Italian recent postmenopausal women (54.6±6.1 years) attending a menopause centre found values of 0.45±0.10 and 0.47±0.12 ng/ml in women with normal or osteopenic BMD values respectively. In our sample, women of this age showed a mean

value of 0.405±0.200 ng/L. In a study performed by Lenora et al [15] in 75-year old women from Malmo, Sweden (the OPRA study), serum β-CTX levels were 0.312±0.186 ng/L. Again, in our sample, women of this age showed a similar value of 0.353±0.178 ng/ml. On the other hand, Chen et al [16] reported a value of 0.31 ng/ml (range 0.20-0.47) in frail elderly (older than 80) women from Sydney, Australia. At this age, in our sample β-CTX levels were 0.435±0.220 ng/ml.

Therefore, there seem to be wide differences regarding β-CTX results, which range from 0.556±0.226 ng/ml in normal postmenopausal women in the French OFELY cohort to 0.31 ng/ml (range 0.20-0.47) in frail elderly women from Australia (almost a 100% difference). These two extreme values are, respectively, about 47% higher and 28% lower than those of our own cohort. On the other hand, no such big differences are found between our results and those of the other publications. Thus, our values are just about 10% higher and 10% lower than those of Lenora et al [15] and Trento et al [14], respectively, and very close to those of Boudou et al. [13].

Some of these differences could be accounted for by the particular characteristics of women included in each study, such as age, weight, smoking habits, physical activity, etc. A higher proportion of women with osteoporosis, for instance, could result in higher β-CTX values. In this regard, OFELY cohort data [6] are of particular interest, since the serum β-CTX levels of this population, while considered the reference values by the ELECSYS 2010 manufacturer, are clearly above those of the rest of the studies.

All these uncertainties emphasize the importance –or even the necessity- of establishing reference values for different populations, and the interest of carrying out comparisons [17].

In conclusion, in our study we report the mean and reference ranges for BMT (P1NP and β-CTX) from a well characterized population of Spanish postmenopausal women, using a new automated technique. For serum P1NP, these values were similar to those previously reported by the equipment manufacturers, while for β-CTX they were lower. Although population differences always remain an explanation, we rather believe that manufacturer reference values for β-CTX may be overestimated. We trust that our reference

ranges can serve as useful standards for bone turnover in postmenopausal women in our country.

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No conflict of interest was declared

List of abbrevations

P1NP: Aminoterminal propeptide of type I collagen

β-CTX: C-terminal telopeptide of type I collagen

25OHD: 25-Hydroxivitamin D

iPTH: intact parathyroid hormone

BMD: Bone mineral density

LS: Lumbar spine

FN: Femoral neck

TH: Total hip

DXA: Dual X-ray absorptiometry

BMT: Bone turnover markers

SD: Standard deviation

BMI: Body mass index

TCa: serum total calcium

cCa : Albumin-corrected serum total calcium

CV: Coefficients of variation

NCCLS: Clinical and Laboratory Standards Institute

References

[1] NIH Consensus Conference: Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285: 785-795.

[2] Nguyen ND, Pongchaikayul C, Center JR, Eisman JA, Nguyen TV. Identification of high-risk individuals for hip fracture: A 14-year prospective study. J Bone Miner Res 2005; 20: 1921-1928.

[3] Khosla S, Riggs BL. Pathophysiology of age-related bone loss and osteoporosis. Endocrinol Metab Clin North Am 2005; 34: 1015-1030.

[4] Hannon RA, Bluhmson A, Naylor KE, Eastell R. Response of biochemical markers of bone turnover to hormone replacement therapy. J Bone Miner Res 1998; 13: 1124-1133.

[5] Garnero P, Hauser E, Chapuy MC, et al. Markers of bone resorption predict hip fracture in elderly women: The EPIDOS Prospective Study. J Bone Miner Res 1996; 11: 1531-1538.

[6] Garnero P, Borel O, Delmas PD. Evaluation of a fully automated serum assay for C-terminal cross-linking telopeptide of type I collagen in osteoporosis. Clin Chem 2001; 47: 694-702.

[7] Berry EM., Gupta MM, Turner SJ, Burns RR. Variations in plasma calcium with induced changes in plasma specific gravity, total protein, and albumin. Br Med J 1973; IV: 640-643.

[8] Garnero P, Vergnaud P, Hoyle N. Evaluation of a fully automated serum assay for total N-terminal propeptide of type I collagen in postmenopausal osteoporosis. Clin Chem 2008; 54: 188-196.

[9] Schmidt-Gayk H, Spanuth E, Kotting J, et al. Performance evaluation of automated assays for β-crossLaps, N-MID-Osteocalcin and intact parathyroid hormone (BIOROSE Multicenter Study). Clin Chem Lab Med 2004; 42: 90-95.

[10] Looker AC, Orwoll ES, Johnston CC, et al. Prevalence of low femoral bone density in oldr U.S. adults from NHANES III. J Bone Miner Res 1997; 12: 1761-1768.

[11] Riancho JA, Valero C, Hernández JL, et al. Biomechanical indices of the femoral neck estimated from the Standard DXA output: Age- and sex-related differences. J Clin Densitomet 2007; 10: 39-45.

[12] NCCLS. Application of biochemical markers of bone turnover in the assessment and monitoring of bone disease. Proposed Guidelines. NCCLS document C48-P, 2004.

[13] Boudou P, Ibrahim F, Cormier C, Sarfati E, Souberbielle JC. Potential utility of high preoperative levels of serum type I collagen markers in postmenopausal women with primary hyperparathyroidism with respect to their short-term variations after parathyroidectomy. J Bone Miner Res 2009; 27: 240-246.

[14] Trento LK, Pietriopolli A, Ticconi C, et al. Role of type I collagen C telopeptide, bone-specific alkaline phosphatase and osteocalcin in the assessment of bone status in postmenopausal women. J Obstet Gynecol Res 2009; 35: 152-159.

[15] Lenora J, Ivaska KK, Obrant KJ, Gerdhem P. Prediction of bone loss using biochemical markers of bone turnover. Osteoporos Int 2007; 18: 1297-1305.

[16] Chen JS, Camero IA, Cumming RG, et al. Effect of age-related chronic immobility on markers of bone turnover. J Bone Miner Res 2006; 21:324-331.

[17] Glover SJ, Gall M. Schoenborn-Kellenberg O, et al. Establishing a reference interval for bone turnover marker in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States. J Bone Miner Res 2009; 24: 389-397.

Figure 1. Frequency distribution of serum P1NP (A) and β-CTX (B) in postmenopausal women. Age-related changes in serum P1NP (C) and β-CTX (D) in postmenopausal women

Table 1. Basal characteristics of the population studied

	Mean± SD (n=1080)	Range
Age (years)	63 ± 9	44-93
Weight (Kg)	70 ± 12	43-120
Height (cm)	156 ± 6	138-175
BMI (Kg/m^2)	28.8 ± 4.8	16-49
Waist's perimeter (cm)	96 ± 13	60-148
Arm spam (cm)	158 ± 8	111-185
Age of menarche (ys)	13 ± 2	9-19
Age of menopause (ys)	49 ± 5	27-60
History of falls (last year) (%)	27	-
Any fracture > 40 ys (%)	16	-
Physical activity		
Sedentarism (%)	3	-
Moderate (%)	47	-
High (%)	50	-
Current smoking (%)	12	-
Current alcohol consumption (%)	12	-
Dairy calcium consumption (mg/day)	683 ± 331	0-2300
Calcium supplements (%)	8	-
Vitamin D supplements (%)	7	-
Dyslipemia (%)	29	-
Diabetes mellitus (%)	11	-
Urolithiasis (%)	12	-

Table 2. Biochemical parameters and bone mineral density (BMD) in postmenopausal women

	Mean ± SD (n=1080)	Range
Glucose (mmol/L)	5.27 ± 1.27	3.38-16.92
Creatinine (μmol/L)	83.98 ± 8.84	44.22-150.28
Calcium (mmol/L)	2.42 ± 0.1	2.07-2.57
Phosphate (mmol/L)	1.13 ± 0.16	0.35-1.64
Albumin (g/L)	45 ± 3	30-56
cCa (mmol/L)	2.30 ± 0.07	2.11-2.55
Alkaline phosphatase (U/L)	72± 19	29-171
25OHD (ng/ml)	23 ± 9	4-90
iPTH (pg/ml)	52 ± 16	9-98
P1NP (ng/ml)	47.7 ± 19.9	11.9-187.7
β-CTX (ng/ml)	0.387 ± 0.197	0.03-1.44
BMD, LS (g/cm^2)	0.924 ± 0.139	0.532-1.416
BMD, LS (T-score)	-1.40 ± 1.27	-4.97-3.06
BMD, LS (Z-score)	0.25 ± 1.35	-3.17-5.13
BMD, FN (g/cm^2)	0.729 ± 0.117	0.399-1.138
BMD, FN (T-score)	-1.09 ± 1.05	-4.13-2.60
BMD, FN (Z-score)	-0.09 ± 1.12	-2.57-4.87
BMD, TH (g/cm^2)	0.857 ± 0.122	0.493-1.264
BMD, TH (T-score)	-0.69 ± 1.00	-3.70-2.64
BMD, TH (Z-score)	0.44 ± 1.01	-2.76-3.79

cCa : Albumin-corrected serum total calcium; P1NP: Aminoterminal propeptide of type I collagen ; β-CTX: C-terminal telopeptide of type I collagen; 25OHD: 25-hydroxyvitamin D; iPTH intact parathyroid hormone. BMD, LS: Bone mineral density at the lumbar spine; BMD, FN: Bone mineral density at the femoral neck, BMD, TH: Bone mineral density at the total hip.

Table 3. Reference ranges and means for serum bone turnover markers (BMTs) in postmenopausal women

	Serum P1NP (ng/ml)	**Serum β-CTX** (ng/ml)
Study (N)	1080	1080
Ref. range	19-100	0.112-1.018
Mean	47.7	0.387
(SD)	(19.9)	(0.197)
Median	44.5	0.356
Manufacturer (N)	290	429
Ref. range	20-76	NA
Mean	45.1	0.556
(SD)	NA	0.226
Median	42.9	NA

P1NP: Aminoterminal propeptide of type I collagen ; β-CTX: C-terminal telopeptide of type I collagen. NA: Not available.

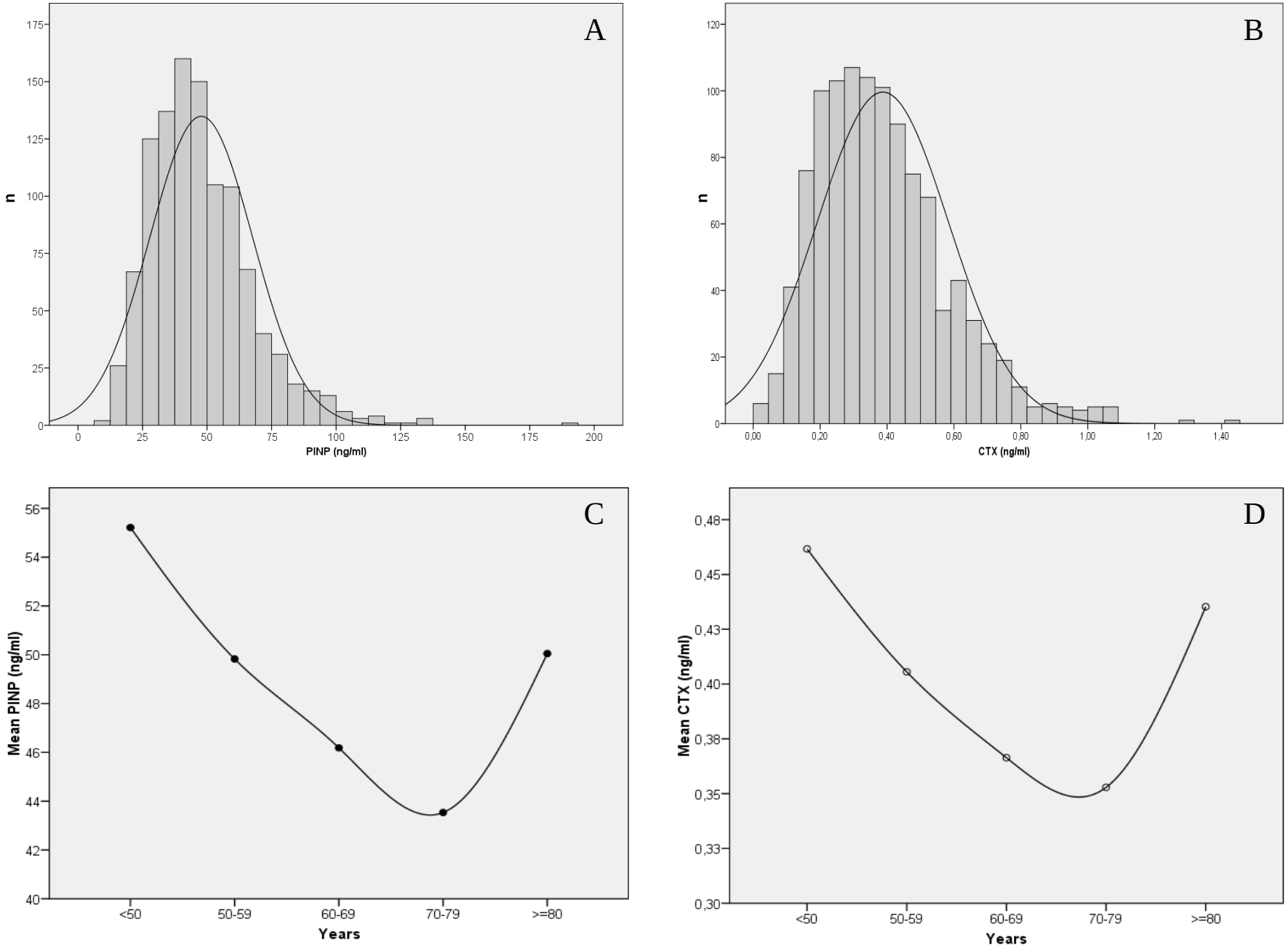
Table 4. Subgroup analysis of mean serum (±SD) P1NP and β-CTX among healthy postmenopausal women according to age, serum levels of 25OHD and PTH, and the presence or absence of osteoporosis

		N	Serum P1NP (ng/ml)	Serum β-CTX (ng/ml)
Age (years)		1080		
	<50	44	55.2±19.5	0.462±0.205
	50-59	444	49.8±19.2	0.405±0.200
	60-69	322	46.2±19.2	0.366±0.190
	70-79	212	43.5±16.5	0.353±0.178
	>80	58	50.0±24.9	0.435±0.220
25OHD		1080		
	<=30 ng/ml	874	47.2 ± 20.1	0.384 ± 0.197
	>30 ng/ml	206	50.2 ± 19.1*	0.400 ± 0.192
iPTH		1080		
	<=65 pg/ml	863	47.7 ± 20.1	0.378± 0.193
	>65 pg/ml	217	47.9 ± 19.6	0.426 ± 0.206**
Osteoporosis		1073		
	Yes	224	50.5 ± 18.6**	0.438 ± 0.187***
	No	849	46.9 ± 20.3	0.374 ± 0.197

*p<0.05; **p<0.01; ***p<0.0001

P1NP: Aminoterminal propeptide of type I collagen ; β-CTX: C-terminal telopeptide of type I collagen; 25OHD: 25-hydroxyvitamin D; iPTH intact parathyroid hormone

Figure(s)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