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ORIGINAL ARTICLE

# Role of serum FSH measurement on bone resorption in postmenopausal women

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**Abstract** In vitro and animals models have shown follicle-stimulating hormone (FSH) effects on osteoclastic function, and FSH levels seem to influence bone loss independently of estrogen concentrations in humans. Our aim was to evaluate the role of serum FSH measurement in the assessment of bone resorption in postmenopausal women. We conducted a cross-sectional study including 92 postmenopausal healthy women aged 56.2 (3.6) and 7.2 (4) years since menopause. Serum FSH, luteinizing hormone (LH), estradiol (E2) and bone turnover markers as osteocalcin (OC) and C-terminal telopeptide of type I collagen (CTX) were measured. We analyzed the relationship between serum levels of gonadotropins, E2, and bone turnover markers. Serum levels of OC and CTX were positively related to FSH ($r = 0.234$, $P = 0.047$ and $r = 0.384$, $P = 0.003$) and LH ($r = 0.319$, $P = 0.012$ and $r = 0.273$, $P = 0.038$). There was no relationship with E2 levels. When gonadotropins levels were divided into quartiles, we found significant differences in bone turnover markers between the first and the fourth quartile. OC levels were higher in the highest quartile of FSH ($P = 0.024$) and LH ($P = 0.001$). Serum CTX was also higher in the highest quartile of FSH ($P = 0.004$) and LH ($P = 0.039$). FSH levels could explain approximately 14.7% of the chances in CTX. In summary, gonadotropins were related to bone turnover in postmenopausal healthy women. Moreover, the rise in FSH appears to contribute to higher bone resorption. Our results suggest that the measurement of FSH could be usefulness to perform a more comprehensive assessment of bone loss in these women.

**Keywords** Gonadotropins · Bone turnover · Postmenopausal women

**Abbreviations**

| | |
|---|---|
| FSH | Follicle-stimulating hormone |
| BMD | Bone mineral density |
| LH | Luteinizing hormone |
| E2 | Estradiol |
| OC | Osteocalcin |
| CTX | C-terminal telopeptide of type I collagen |
| TSH | Thyroid stimulating hormone |
| BMI | Body mass index |
| SD | Standard deviation |
| Q | Quartile |
| NS | No significant |

## Introduction

The pathophysiology of menopausal bone loss involves an increase in osteoclastic activity and bone resorption,

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and estrogen deficiency has been widely known as the major determinant factor. In the perimenopausal period, a rapid decrease in bone mass occurs despite of no changes in estrogens levels that remain similar to premenopausal levels, and this fact raised the hypothesis that another hormonal factor may influence perimenopausal bone loss.

Thyroid-stimulating hormone (TSH) has direct effects on bone cells modulating bone turnover [1]. Recent studies suggest that other pituitary-derived hormones like follicle-stimulating hormone (FSH) may contribute to the late perimenopausal bone loss where estrogens levels are unaffected. In animal models, FSH regulates osteoclastic bone resorption and bone mass [2]. In humans, during the menopause transition, higher FSH concentrations are positively associated with greater bone turnover while no association was observed between estradiol (E2) and bone turnover [3]. Also, bone mineral density (BMD) loss was strongly related to changes in FSH across the menopause period but not to changes in E2 or androgens [4]. On the other hand, Guthrie et al. [5] found that endogenous E2 was the only hormone with effect on BMD during the menopausal transition although they did not analyzed the relationship with gonadotropins. According to those data it has been proposed that FSH levels can help to identify perimenopausal women at high risk of bone loss in whom antiresorptive treatment could be considered [6].

There are few data about luteinizing hormone (LH) effects on bone. Mice osteoblasts express LH receptor, and the ablation of the LH receptor resulted in a significant reduction in BMD [7]. In human males, serum FSH and LH were the major predictors of BMD changes [8]. Moreover, in Chinese healthy females both FSH and LH were negatively related to bone mass [9]. It has been postulated that the influence of FSH on bone turnover is 20 times higher compared to LH effects in Chinese adult women.

Previous reports evaluating the relationship between gonadotropins and bone turnover have been conducted in perimenopausal women [3, 4] or in postmenopausal non-Caucasian women [9, 10]. In this context, the objective of our study was to evaluate the role of serum FSH measurement in the assessment of bone resorption in postmenopausal women.

## Methods

### Study subjects

This study was carried out in 92 postmenopausal women aged between 45 and 65 years recruited in the Endocrinology and Nutrition Division of Hospital Universitario San Cecilio in Granada, Spain. This group was part of a cohort of 129 healthy participants enrolled in a program to evaluate the effects of a nutritional supplementation in postmenopausal women. From May 2007 to 2008, women were consecutively recruited. Menopausal status was defined by the absence of menses for more than 1 year a women over 45 years of age. All were white, ambulatory, in a good health and had no clinically significant abnormalities in laboratory values. Criteria for exclusion included cardiorespiratory, renal, hepatic, and gastrointestinal dysfunction; history of metabolic bone disease or secondary causes of osteoporosis and any drugs treatment known to might affect bone mass.

The study was cross sectional in design, approved by the ethical review board of our hospital and conformed to the ethics guidelines for research in humans. All the participants in the study provided written informed consent.

### Clinical and anthropometric evaluation

Anthropometric data collected was body mass index (BMI) calculated by the Quetelet formula (weight in kilograms divided by the square of height in meters).

### Biochemical measurements

Morning fasting samples of venous blood were taken. Serum was promptly separated and stored at −80°C until assay. Serum levels of FSH and LH were determined by Inmunoassay (Roche Elecsys 1010/2010). The Elecsys assay uses two specific antibodies and detects all currently described LH and FSH species with almost no cross reactivity with other hormones. Intra-assay and interassay variability <2% and <5%, respectively. FSH reference range postmenopausal women 25.8–134.8 mUI/ml and LH reference range postmenopausal women 7.7–58.5 mUI/ml. Serum levels E2 were also determined by Inmunoassay (Roche Elecsys 1010/2010). The reference range for postmenopausal women is <5.0–54.7 pg/ml, and intra-assay and interassay variability are 5.7 and 6.2%, respectively.

Serum total osteocalcin (OC) as a marker of bone formation was measured by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany; reference range, 6.5–42.3 ng/ml for women G55 y old and 5.4–59.1 ng/ml for women Q55 y old; intra-assay and interassay variability, 1.1–1.6% and 1.7–6.5%, respectively). Serum carboxyterminal cross-linked telopeptide of type I collagen (CTX) as a marker of bone resorption was measured by enzyme immunoassay (Elecsys [beta] CrossLaps; Roche Diagnostics SL, Barcelona, Spain; reference range postmenopausal women, 0.150–0.782 ng/ml; intra-assay and interassay variability of 4.2 and 5.1%, respectively).

### Statistical analysis

Data were expressed as mean (SD) and as percentage. Normality of the variables was analyzed using the Kolmogorov–Smirnov test. E2 and OC had a skewed distribution and were transformed to their natural logarithm for analyses (normal distribution was confirmed after transformation). Means and variances were back-transformed for presentation. Associations between continuous variables were described by the Pearson correlation coefficient. The entire cohort was divided into four equal groups according to levels of FSH and LH to obtain quartiles. Comparisons of quantitative variables among groups were performed using unpaired Student's $t$ test and one-way analysis of variance (ANOVA) with post-hoc analyses by Turkey's test. Linear regression model was performed to determine the associations between gonadotropins (FSH as dependent variable) and turnover markers (CTX) after adjustment for potential confounders (age, BMI, LH, and E2 concentrations). Statistical significance for all analyses was set at $P < 0.05$. Statistical analysis was performed with specific software, SPSS 15.0.

## Results

Clinical characteristics for the study group are shown in Table 1.

Serum levels of OC showed a positive correlation with FSH and LH concentrations ($r = 0.234$, $P = 0.04$ and $r = 0.319$, $P = 0.012$ respectively). Serum levels of CTX were positively related to FSH and LH concentrations ($r = 0.384$, $P = 0.003$ and $r = 0.273$, $P = 0.038$ respectively) (Fig. 1). There was no relationship between bone turnover markers and E2 (OC: $r = -0.145$, $P = 0.262$ and CTX: $r = -0.173$, $P = 0.194$).

**Table 1** Clinical characteristics of the study women ($n$ = 92)

| Characteristics ($n$ = 92) | Mean (SD) | Range |
|---|---|---|
| Age (years) | 56.2 (3.6) | 46–65 |
| Years since menopause (years) | 7.2 (4) | 2–18 |
| BMI (kg/m$^2$) | 28.4 (4.7) | 21.7–47.1 |
| FSH (mUI/ml) | 73.8 (28.3) | 26.1–200 |
| LH (mUI/ml) | 36.9 (13.2) | 17.4–96.1 |
| E2 (pg/ml) | 10.6 (10.1) | 5–53.9 |
| OC (ng/ml) | 15.8 (7.1) | 6.7–42 |
| CTX (ng/ml) | 0.483 (0.214) | 0.074–1.102 |

Data expressed as mean (SD)

*BMI* body mass index, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *E2* estradiol, *OC* osteocalcin, *CTX* C-terminal telopeptide of type I collagen

When FSH and LH levels were divided into quartiles, there were significant differences in bone turnovers markers between the first and the fourth quartile (Fig. 2). OC serum levels were higher in the highest quartile of FSH: 12.98 (5.49) versus 17.58 (6.37) ng/ml, $P = 0.024$ and LH: 11.89 (4.52) versus 18.64 (6.13) ng/ml, $P = 0.001$. Serum levels of CTX were also higher in the highest quartile of FSH: 0.352 (0.134) versus 0.599 (0.245) ng/ml, $P = 0.004$ and LH: 0.356 (0.196) versus 0.568 (0.268) ng/ml, $P = 0.039$. In contrast, when E2 levels were divided into quartiles, there were no significant differences in bone turnovers markers between the first and the fourth quartile (Fig. 3).

ANOVA showed significant differences between FSH quartiles for both serum OC ($P = 0.016$) and serum CTX ($P = 0.024$). After post-hoc analysis, differences remain significant between the first and the third quartile of OC ($P = 0.049$) and between the first and the fourth quartile of CTX ($P = 0.013$). Among LH quartiles only differences in serum OC remained statistically significant ($P = 0.002$) but not serum CTX ($P = 0.078$). After post-hoc analysis, differences remains significant between the first and the third quartile ($P = 0.006$) and between the first and the fourth quartile ($P = 0.021$) of OC (Fig. 2).

In multiple regression analysis adjusted for age, BMI, LH, and E2 concentrations, the relationship between FSH concentration (dependent variable) and serum CTX remained significant ($\beta = 0.328$, $P = 0.043$). FSH levels could explain approximately 14.7% of the changes in CTX.

## Discussion

In our study bone turnover markers were positively related to FSH and LH, while no relationship was observed with serum E2 concentrations. Higher levels of FSH and LH were associated with higher levels of OC and CTX. Moreover, FSH concentration was independently linked with serum CTX, a well established bone resorption marker, in multivariate analysis. Our results confirm previous data showing the influence of gonadotropins on bone turnover in postmenopausal women, as have been reported in perimenopausal women.

Several studies have proposed a paradigm shift in endocrine physiology. That is, the classic pituitary hormones as TSH also exert effects on non endocrine tissues as bone. In this way, acute TSH administration in postmenopausal women and men during thyroid cancer follow up was related to changes in bone turnover markers [11, 12]. Mazziotti et al. [13] also found that low-normal TSH values were associated with a high prevalence of vertebral fractures in women with postmenopausal osteoporosis or osteopenia, independently of thyroid hormones, age and

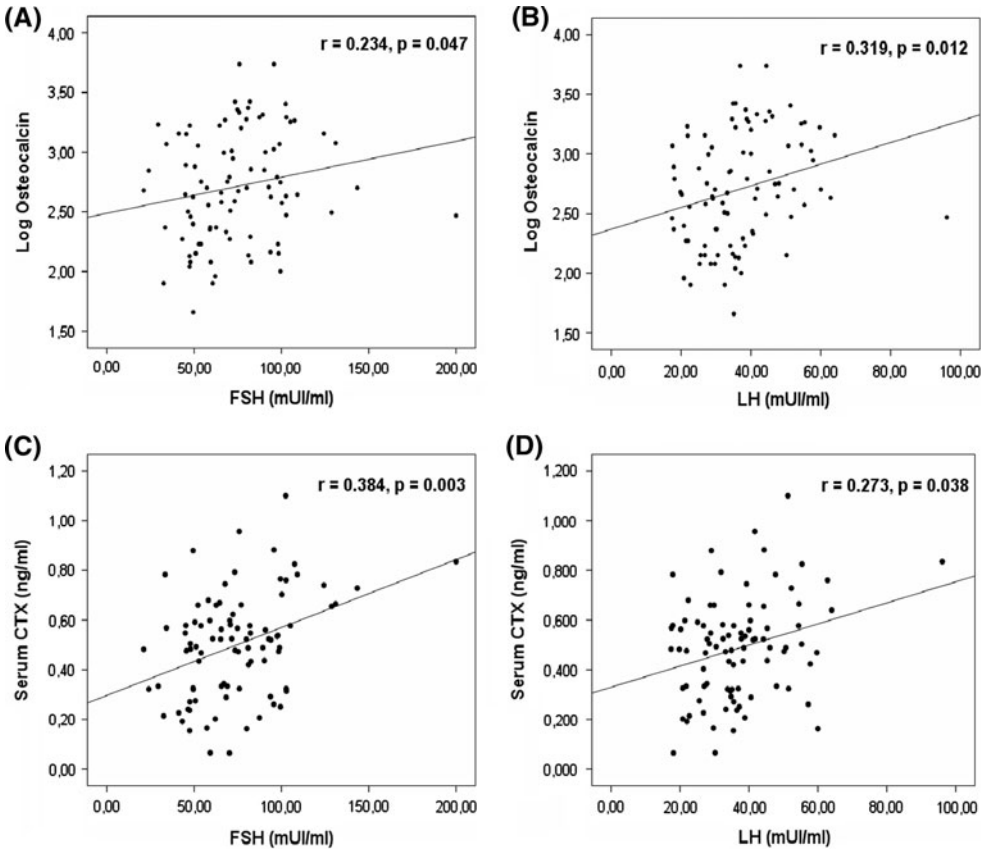


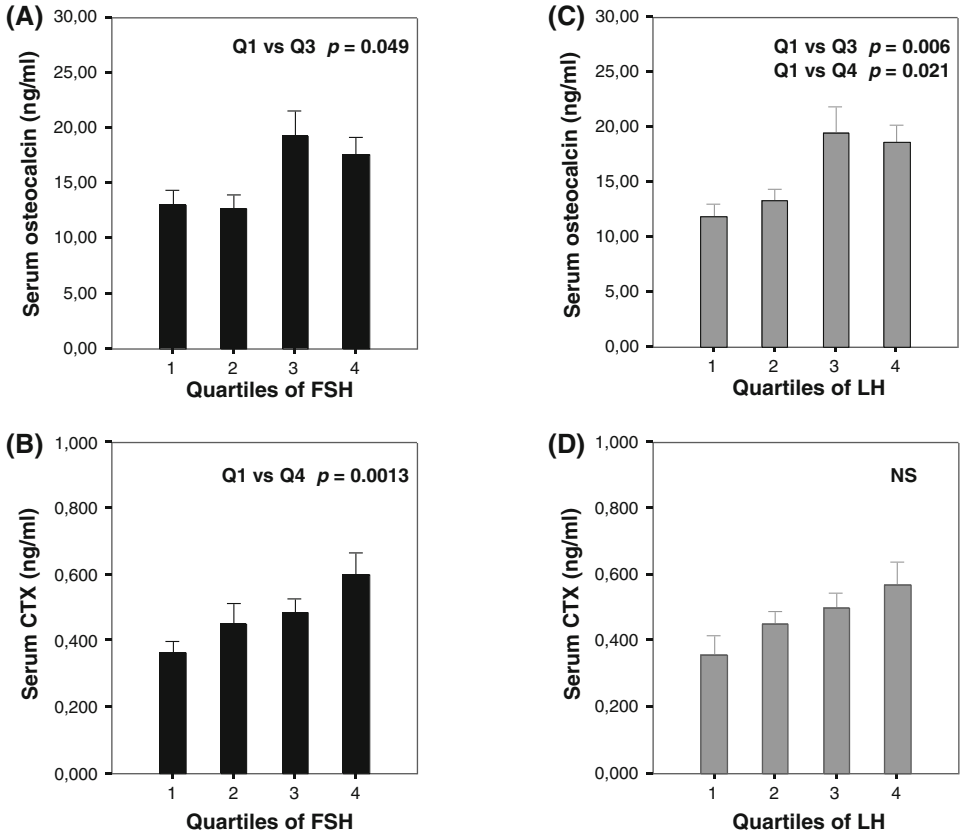

**Fig. 1** Scatter plot showing the correlation between bone turnover markers and gonadotropins (Pearson's bivariate test, $n = 92$). **a** OC and FSH. **b** OC and LH. **c** CTX and FSH. **d** CTX and LH. *OC* osteocalcin, *FSH* follicle-stimulating hormone, *CTX* C-terminal telopeptide of type I collagen, *LH* luteinizing hormone

BMD. Likewise, the bone loss of menopause can be attributed to elevated FSH levels.

Regarding FSH effects on bone, Sun et al. [2] suggested that FSH directly regulates bone mass in mice by stimulation of osteoclastic differentiation and function both in vitro and in vivo. A clinical study in postmenopausal women [14] evaluated the influence of FSH receptor polymorphisms gene and concluded that AArs6166 polymorphism increased the risk of low bone mass and high bone turnover in women. Previous reports in perimenopausal women had shown higher OC and NTX levels in women in the highest quartile of FSH while no relationship between bone turnover and E2 levels was found [3]. In addition, Gass et al. [15] showed changes in bone markers during the menstrual cycle with significantly higher serum CTX levels during the follicular phase than in the luteal phase. Our data in postmenopausal women are in agreement with those previous data, but to our knowledge no studies had been conducted in a postmenopausal Caucasian women-only cohort.

There have been reported less data about LH effects on bone turnover. LH levels were a determinant of bone turnover markers in multiple regression analysis in Saudi Arabian premenopausal women [16]. In healthy women, both FSH and LH were associated with BMD changes but bone turnover markers were not assessed [9]. Previous reports have shown a 20-times greater influence of FSH on bone turnover with respect to LH in Chinese women aged 20–80 years [10]. In our study, higher levels of LH were also related to greater levels of OC and CTX, and correlation between bone markers and FSH and LH were of similar magnitude. However, after multivariate analysis the relationship between LH and bone turnover markers did not remain significant. The discrepancy of our results with previous reports may be explained by ethnic and geographical differences in FSH levels and bone turnover markers that have been reported [17, 18].

In a recent study from Drake et al. [19], pharmacological suppression of FSH with gonadotropin-releasing hormone (GnRH) agonist treatment did not significantly reduce markers of bone resorption in postmenopausal women although a trend toward greater increases in CTX were observed in the GnRH group compared to control group. The authors claim that FSH does not regulate bone resorption in humans, and they suggest that the observed associations between FSH levels, bone turnover, and bone loss during menopause may be explained by association of FSH with inhibin levels. It has been suggested that the duration of the study, 3 months, may not be adequate to




| | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| FSH | 26.1-51.1 | 51.1-70.7 | 70.7-93.7 | 93.7-200 |
| OC | 12.98 (5.49) | 12.72 (4.32) | 19.23 (9.14) | 17.58 (6.37) |
| CTX | 0.352 (0.134) | 0.452 (0.226) | 0.485 (0.169) | 0.599 (0.245) |

| | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| LH | 17.4-27.5 | 27.5-35.3 | 35.3-44.4 | 44.4-96.1 |
| OC | 11.89 (4.52) | 13.34 (4.25) | 19.57 (9.36) | 18.64 (6.13) |
| CTX | 0.356 (0.196) | 0.449 (0.161) | 0.499 (0.177) | 0.568 (0.268) |

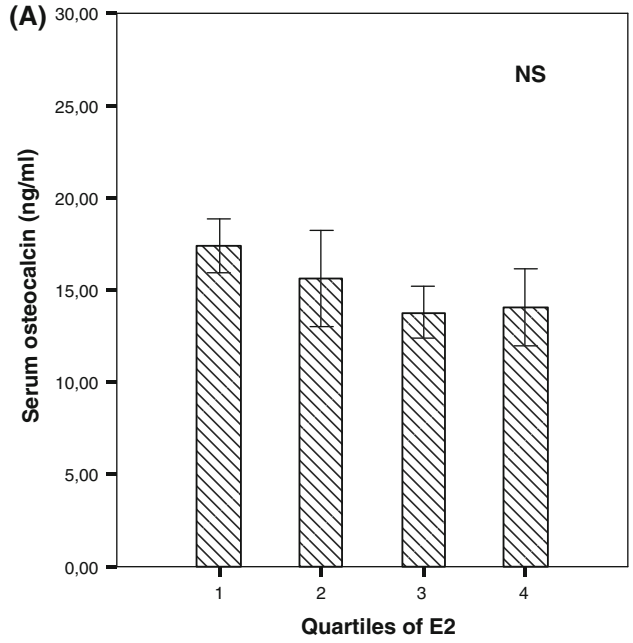
**Fig. 2** Serum levels of bone turnover markers by quartiles of gonadotropins (quartiles $n = 23$). Data expressed as mean (SD). *P* value reflects significant differences between quartiles corrected by post-hoc analysis. **a** OC and quartiles of FSH. **b** OC and quartiles of LH. **c** CTX and quartiles of FSH. **d** CTX and quartiles of LH. *OC* osteocalcin, *FSH* follicle-stimulating hormone, *CTX* C-terminal telopeptide of type I collagen, *LH* luteinizing hormone, *Q* quartile, *NS* no significant

evaluate the effects on bone formation markers and could explain in part the results [20].

In our opinion, the identification of risk factors of bone loss in postmenopausal women should be done earlier. We propose that elevated levels of FSH are indicative of increased bone resorption and according to this measurement a more extensive evaluation could be performed including bone turnover markers or BMD testing. A prospective study on bone loss during the menopausal transition among southern Chinese women supports our findings [21]. The authors found that subjects in the highest quartile of baseline FSH lost bone 1.3–2.3 times faster compared with those in the lowest quartile during a follow-up period of 4 years.

There are some limitations of our study. First, the size of the sample is not large. However, the correlation observed between gonadotropins and bone turnover in a relatively small sample increases the relevance of our findings. Second, the direction of our results from cross-sectional analyses cannot be determined with certainty. Furthermore, the lack of determination of inhibin levels, which have been proposed to be a mediator of FSH action on bone resorption. Strengths of our study are the inclusion of a postmenopausal women-only cohort what differs from previous reports that have included women in the perimenopausal period or women with a wide range of ages; the determination of LH, FSH and bone turnover markers, and the inclusion of Caucasian women what differs from previous studies conducted in other ethnic groups.

In summary, FSH and LH were related to bone turnover markers in postmenopausal healthy women.



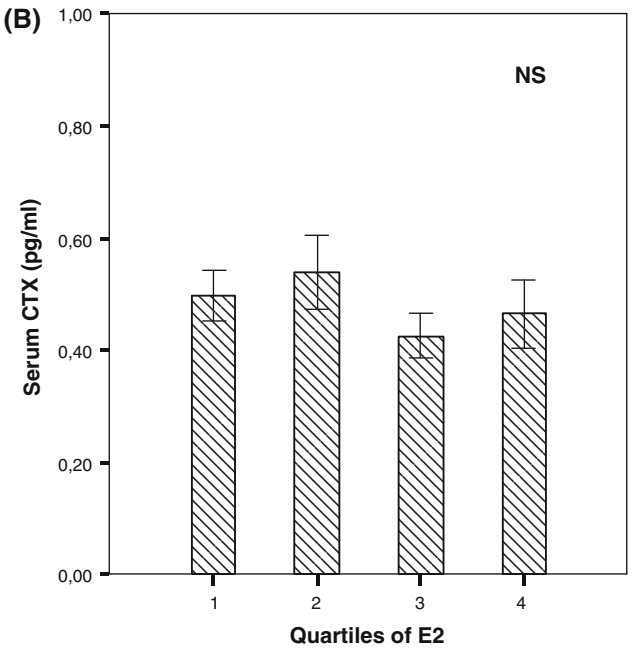




**Fig. 3** Serum levels of bone turnover markers by quartiles of E2 (quartiles $n = 23$). *P* value reflects significant differences between quartiles corrected by post-hoc analysis**.** Data expressed as mean (SD). *P* value reflects differences between the first and the fourth quartile. **a** OC and quartiles of E2. **b** CTX and quartiles of E2. *E2* estradiol, *OC* osteocalcin, *CTX* C-terminal telopeptide of type I collagen

| | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| **E2** | <5 | 5-6.86 | 6.86-10.68 | 10.68-53.9 |
| **OC** | 17.34 (7.98) | 15.22 (8.24) | 13.43 (7.18) | 14.06 (5.98) |
| **CTX** | 0.497 (0.234) | 0.552 (0.257) | 0.435 (0.177) | 0.465 (0.231) |

Moreover, the rise in FSH appears to contribute to higher bone resorption. Our hypothesis is that menopausal bone loss is explained in part by the rise in FSH levels, although if this effect occurs by direct actions on bone cells or is mediated by inhibins could not be established. Our results support the utility of serum FSH measurement to carry a more comprehensive assessment of bone loss in these women.

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

## References

1. E. Abe, R.C. Marians, W. Yu, X.B. Wu, T. Ando, Y. Li, J. Iqbal, L. Eldeiry, G. Rajendren, H.C. Blair, T.F. Davies, M. Zaidi, TSH is a negative regulator of skeletal remodeling. Cell **115**, 151–162 (2003)
2. L. Sun, Y. Peng, A.C. Sharrow, J. Iqbal, Z. Zhang, D.J. Papachristou, S. Zaidi, L.L. Zhu, B.B. Yaroslavskiy, H. Zhou, A. Zallone, M.R. Sairam, T.R. Kumar, W. Bo, J. Braun, L. Cardoso Landa, M.B. Schaffler, B.S. Moonga, H.C. Blair, M. Zaidi, FSH directly regulates bone mass. Cell **125**, 247–260 (2006)
3. M.R. Sowers, G.A. Greendale, I. Bondarenko, J.S. Finkelstein, J.A. Cauley, R.M. Neer, B. Ettinger, Endogenous hormones and bone turnover markers in pre- and perimenopausal women: SWAN. Osteoporos. Int. **14**, 191–197 (2003)
4. M.R. Sowers, M. Jannausch, D. McConnell, R. Little, G.A. Greendale, J.S. Finkelstein, R.M. Neer, J. Johnston, B. Ettinger, Hormone predictors of bone mineral density changes during the menopausal transition. J. Clin. Endocrinol. Metab. **91**, 1261–1267 (2006)
5. J.R. Guthrie, P. Lehert, L. Dennerstein, H.G. Burger, P.R. Ebeling, J.D. Wark, The relative effect of endogenous estradiol and androgens on menopausal bone loss: a longitudinal study. Osteoporos. Int. **15**, 881–886 (2004)
6. M. Zaidi, C.H. Turner, E. Canalis, R. Pacifici, L. Sun, J. Iqbal, X.E. Guo, S. Silverman, S. Epstein, C.J. Rosen, Bone loss or lost bone: rationale and recommendations for the diagnosis and treatment of early postmenopausal bone loss. Curr. Osteoporos. Rep. **7**, 118–126 (2009)
7. S.J. Yarram, M.J. Perry, T.J. Christopher, K. Westby, N.L. Brown, T. Lamminen, S.B. Rulli, F.P. Zhang, I. Huhtaniemi, J.R. Sandy, J. Mansell, Luteinizing hormone receptor knockout (LuRKO) mice and transgenic human chorionic gonadotropin (hCG)-overexpressing mice (hCG alphabeta+) have bone phenotypes. Endocrinology **144**, 3555–3564 (2003)
8. N. Karim, D. MacDonald, A.L. Dolan, I. Fogelman, A.S. Wierzbicki, G. Hampson, The relationship between gonadotrophins, gonadal hormones and bone mass in men. Clin. Endocrinol. (Oxf) **68**, 94–101 (2008)
9. Z.R. Xu, A.H. Wang, X.P. Wu, H. Zhang, Z.F. Sheng, X.Y. Wu, H. Xie, X.H. Luo, E.Y. Liao, Relationship of age-related concentrations of serum FSH and LH with bone mineral density, prevalence of osteoporosis in native Chinese women. Clin. Chim. Acta. **400**, 8–13 (2009)
10. X.Y. Wu, X.P. Wu, H. Xie, H. Zhang, Y.Q. Peng, L.Q. Yuan, X. Su, X.H. Luo, E.Y. Liao, Age-related changes in biochemical markers of bone turnover and gonadotropins levels and their relationship among Chinese adult women. Osteoporos. Int. **21**, 275–285 (2010)
11. G. Mazziotti, F. Sorvillo, M. Piscopo, M. Cioffi, P. Pilla, B. Biondi, S. Iorio, A. Giustina, G. Amato, C. Carella, Recombinant human TSH modulates in vivo C-telopeptides of type-1 collagen and bone alkaline phosphatase, but not osteoprotegerin production in postmenopausal women monitored for differentiated thyroid carcinoma. J. Bone Miner. Res. **20**, 480–486 (2004)
12. G. Martina, L. Gennari, De Paola, V., Pilli, T., Salvadori, S., Merlotti, D., Valleggi, F., Campagna, S., Franci, B., Avanzati, A., Nuti, R., Pacini, F.: The effects of recombinant TSH on bone turnover markers and serum osteoprotegerin and RANKL levels. Thyroid **18**, 455–460 (2008)
13. G. Mazziotti, T. Porcelli, I. Patelli, P.P. Vescovi, A. Giustina, Serum TSH values and risk of vertebral fractures in euthyroid postmenopausal women with low bone mineral density. Bone **46**, 747–751 (2010)
14. D. Rendina, F. Gianfrancesco, De Filippo, G., Merlotti, D., Esposito, T., Mingione, A., Nuti, R., Strazzullo, P., Mossetti, G., Gennari, L.: FSHR gene polymorphisms influence bone mineral density and bone turnover in postmenopausal women. Eur. J. Endocrinol. **163**, 165–172 (2010)
15. M.L. Gass, R. Kagan, J.D. Kohles, M.G. Garsten, Bone turnover marker profile in relation to the menstrual cycle of premenopausal healthy women. Menopause **15**, 667–675 (2008)
16. M.S. Ardawi, A.A. Maimani, T.A. Bahksh, A.A. Rouzi, M.H. Qari, R.M. Raddadi, Reference intervals of biochemical bone turnover markers for Saudi Arabian women: a cross-sectional study. Bone **47**, 804–814 (2010)
17. J.F. Randolph Jr, M. Sowers, E.B. Gold, B.A. Mohr, J. Luborsky, N. Santoro, D.S. McConnell, J.S. Finkelstein, S.G. Korenman, K.A. Matthews, B. Sternfeld, B.L. Lasley, Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J. Clin. Endocrinol. Metab. **88**, 1516–1522 (2003)
18. F.J. Cohen, S. Eckert, B.H. Mitlak, Geographic differences in bone turnover: data from a multinational study in healthy postmenopausal women. Calcif. Tissue Int. **63**, 277–282 (1998)
19. M.T. Drake, L.K. McCready, K.A. Hoey, E.J. Atkinson, S. Khosla, Effects of suppression of follicle-stimulating hormone secretion on bone resorption markers in postmenopausal women. J. Clin. Endocrinol. Metab. **95**, 5063–5068 (2010)
20. P.R. Ebeling, What is the missing hormonal factor controlling menopausal bone resorption? J. Clin. Endocrinol. Metab. **95**, 4864–4866 (2010)
21. E. Cheung, S. Tsang, C. Bow, C. Soong, S. Yeung, C. Loong, C.L. Cheung, A. Kan, S. Lo, S. Tam, G. Tang, A. Kung, Bone loss during menopausal transition among southern Chinese women. Maturitas **69**, 50–56 (2011)