Original Article

Association of Endogenous Hormones and Bone Mineral Density in Postmenopausal Women

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ABSTRACT

Aim: The aim of this study was to examine the association between endogenous hormones and bone mineral density (BMD) in postmenopausal women. **Materials and Methods:** This was a cross-sectional study of 798 postmenopausal women aged 47–85 years. Data were collected on age, age at menopause, years since menopause, smoking status, body mass index, adiposity, BMD, physical activity, and Vitamin D supplementation. Measured hormonal parameters were: follicle-stimulating hormone (FSH), estradiol, testosterone, dehydroepiandrosterone sulfate, Δ4-androstenedione, cortisol, insulin-like growth factor-1, 25-hydroxyvitamin D, and parathormone (PTH) levels. BMD was measured at the lumbar spine, femoral neck, and total hip using dual-energy X-ray absorptiometry. A directed acyclic graph was used to select potential confounding variables. **Results:** Multivariable analysis showed significant associations between cortisol and femoral neck BMD ($β$: −0.02, 95% confidence interval [CI]: −0.03–−0.00), and PTH with femoral neck BMD ($β$: −0.01, 95% CI: −0.02–−0.01) and total hip BMD ($β$: −0.01, 95% CI: −0.01–−0.00). Hormonal factors more likely associated with a higher risk of low BMD (osteopenia or osteoporosis) were FSH (odds ratio [OR]: 1.02, 95% CI: 1.01–1.03) and PTH (OR: 1.02, 95% CI: 1.01–1.04). **Conclusions:** Higher cortisol and PTH levels were inversely associated with BMD. Postmenopausal women with higher FSH or PTH levels were likely to have low BMD.

KEYWORDS: *Adrenal hormones, bone mineral density, directed acyclic graph, osteoporosis, ovarian steroids, Vitamin D*

INTRODUCTION

Aging is associated with a progressive decline of bone mineral density (BMD), contributing to the development of osteoporosis. The bone loss mass is accompanied by the microarchitectural deterioration of bone tissue, which produces an increase in bone fragility and predisposes to fracture. In addition to aging, other factors such as female gender, low body mass index (BMI), cigarette smoking, alcohol consumption, early menopause, and inadequate physical activity are associated with an increased risk of osteoporosis.[1]

With increasing life expectancy, it is a fact that the incidence of postmenopausal osteoporosis is increasing, causing an important public health and economic burden.[2] For the maintenance of bone properties, bone turnover is necessary, and when there is an imbalance between bone resorption and bone formation, osteoporosis develops. This process is influenced by sex steroids, Vitamin D, Parathormone (PTH), and plasma factors involved in cell growth.[3]

The decrease in plasma sex steroid levels during the menopause transition leads to a series of changes that affect body composition and BMD. In this period, BMD progressively decreases, with an accelerated rate of

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decline in density over the early postmenopausal years.[4] Whereas plasma estrogen deficiency plays an essential role in postmenopausal osteoporosis,[5] the action of other hormones on the bone mass is still not entirely clear. Some study suggests that high plasma follicle-stimulating hormone (FSH) levels cause hypogonadal bone loss,[6] instead others did not find this association.[7,8] The effect of testosterone on BMD in postmenopausal women is not well clarified.[9,10] In the same way, several studies have reported the relationship between dehydroepiandrosterone sulfate (DHEAS) and osteoporosis but with conflicting results.[11,12] Similarly, the reports regarding insulin-like growth factor-1 (IGF-1) and BMD are controversial.[13,14] The purpose of this study was to analyze the association between endogenous hormones and BMD applying a directed acyclic graph (DAG) to select potential confounding variables.[15]

MATERIALS AND METHODS

Study design

This cross-sectional study was approved by the Institutional Review Board and the University Hospital Ethics Committee (2022/13-GIN-DEX). It was performed from January 2021 to September 2022 at the Department of Obstetrics and Gynecology of the University Hospital. This analysis examines the impact of endogenous hormones on BMD as measured by dual-energy X-ray absorptiometry (DXA). Inclusion criteria: being naturally postmenopausal (amenorrhea of 1 year or more before the initiation of the study) and not physical disability. Women were excluded if (i) were using treatments that are known to influence bone mineralization (menopausal hormone therapy, corticosteroids, anticonvulsants, heparin, thiazide diuretics, and antiresorptive agents) or (ii) had cardiovascular, liver, or renal diseases and history of cancer. Finally, the results from 798 postmenopausal women aged 47–85 years were analyzed.

Bone mineral density measurements and laboratory parameters

BMD was measured at the lumbar spine (L1-L4), femoral neck, and total hip, by DXA using the Lunar iDXA system (GE healthCare. Chicago, IL, USA). Daily quality control of the scanner was performed by calibration with a spine phantom's density, and the coefficients of variation of DXA measurements ranged from 0.22% to 0.39%. The evaluation of BMD was performed using the raw data generated by the DXA. The values were expressed as grams of mineral content per square centimeters of bone area (g/cm^2) and *T*-scores. Women were categorized according to the WHO classification system on the lowest *T*-score

as follows: normal BMD with a *T*-score >-1 standard deviation (SD), osteopenia with *T*-scores ranging from -1 SD to -2.5 SD, and osteoporosis with a *T*-score ≤ -2.5 SD.[16] In our study, women with osteopenia or osteoporosis were categorized as low BMD.

Blood samples were collected after an overnight fast. Hormonal parameters (FSH, estradiol, testosterone, DHEAS, Δ4-androstenedione, cortisol, IGF-1, 25-hydroxyvitamin D, and parathormone plasma levels) were determined by electrochemiluminescence immunoassay by the use of Roche Elecsys reagents and were measured by an automated Cobas® 8000 Modular Analyzer System (Roche Diagnostics. Pleasanton, CA, USA). Laboratory performs daily quality control of each parameter, and the coefficients of variation ranged from 1.3% to 1.8% for FSH, 1.2% to 1.9% for estradiol, 1.3% to 1.9% for testosterone, 1.5% to 2.3% for DHEAS, 1.7% to 2.1% for Δ4-androstenedione, 1.5% to 1.7% for cortisol, 1.1% to 1.7% for IGF-1, 2.3% to 3.1% for 25-hydroxyvitamin D, and 1.4% to 1.7% for PTH. No women had hormonal plasma levels below the level of detection.

Confounding variables and directed acyclic graph

Data were collected on age, age at menopause, years since menopause, BMI, adiposity, current smoking status, physical activity, and Vitamin D supplementation. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Adiposity was assessed by bioelectrical impedance analysis equipment Omron BF306 monitor (Omron Healthcare Co. Ltd, Kyoto, Japan), and the results were expressed as a percentage of fat. Information on smoking status was recorded and classified as never or smoker. Physical activity was assessed using the Spanish version of the International Physical Activity Questionnaire-Short Form (IPAQ-SF). This instrument includes seven items that provide information about the average number of days per week and the average time per day that the individual spent in moderate and vigorous activities, walking, and sitting in the past 7 days. With the final score obtained, the physical activity was classified according to the official IPAQ as low, moderate, and high levels.[17]

A DAG representation [Figure 1] was used to distinguish the appropriate set of confounders for estimating the effect of endogenous hormones as the main exposure and BMD as the outcome.[15] The DAG represents each variable as a node, and the variables with a relationship are connected by an arrow. The arrowhead represents a direct effect of one variable over the other, but not the other way around. The absence of an arrow between two variables represents the assumption of no causal direct effect between those variables.[18] The following

variables, age, adiposity, BMI, smoking status, physical activity, and years since menopause, were considered in the regression model to assess the associations between endogenous hormones and BMD.

Statistical analysis

Continuous variables were calculated as mean and SD, whereas percentages and numbers were used for categorical variables The Student's *t*-test and Chi-square test were applied to compare continuous and categorical outcomes between women with normal BMD and women with low BMD. The Pearson correlation was used to estimate the relation between numeric parameters with the BMD. Multivariable linear regression models, adjusting for age, adiposity, BMI, smoking status, physical activity, and years since menopause according to DAG were applied to determine the associations between endogenous hormones and BMD. Finally, a multivariable logistic regression model was performed to analyze the association between endogenous hormones and the risk of low BMD adjusting for confounding factors. Results are reported as β-coefficients, odds ratios (OR), and 95% confidence interval (CI). All analyses were performed using the R software (R Core Team, 2019). The R package "dagitty" was used to design the DAG.[19] All the analyses were exploratory. No formal *a priori* sample size calculation was performed.

RESULTS

This study included 798 postmenopausal women with a mean age of 62.8 ± 6.4 years, mean age at menopause of 50.2 ± 2.8 years, and mean years since menopause of 12.6 ± 6.8. The mean whole BMI sample was 24.7 ± 3.7 kg/m², and the mean adiposity was 40.5%

Figure 1: Directed acyclic graph for estimating the effect of endogenous hormones on bone mineral density. The arrowhead represents a direct effect of one variable over the other. BMD: Bone mineral density, BMI: Body mass index

±4.7%. The mean values of the laboratory parameters, expressed as means ± SDs, are reported in Table 1. In accordance with the lowest *T*-score in any of the skeletal sites where BMD was calculated, 270 women had osteoporosis (33.8%), 408 had osteopenia (51.1%), and 120 had normal BMD values (15.1%). Regular physical activity and current smoking habits were respectively reported in 61.9% and 19.2% of the sample.

A comparison of the women with normal BMD and low BMD displayed that the low-BMD group was significantly older (OR: 1.10, 95% CI: 1.07–1.14). In women with low BMD, the mean years since menopause was significantly higher (OR: 1.10, 95% CI: 1.06–1.14), the mean BMI was significantly lower (OR: 0.89, 95% CI: 0.85–0.94), and had higher adiposity (OR: 1.14, 95% CI: 1.09–1.19) compared to women with normal BMD. There were no significant associations between BMD with either age at menopause, smoking status, degree of physical activity, and Vitamin D supplementation. Regarding the hormonal parameters, in the low-BMD group was significantly higher the mean plasma levels of FSH (OR: 1.01, 95% CI: 1.00–1.02) and PTH (OR: 1.02, 95% CI: 1.00–1.03) compared with the normal BMD group. Women with low BMD had significantly lower mean plasma levels of DHEAS (OR: 1.00, 95% CI: 0.99–1.00) and Δ 4-androstenedione (OR: 0.69, 95% CI: 0.54–0.90) with respect to normal BMD women. There was no statistically significant difference among the groups with regard to the other hormonal parameters. The results are summarized in Table 2.

The Pearson correlation coefficients (*r*) of the parameters pertaining to all the women are shown in Table 3. The present study observed that lumbar spine BMD was correlated to DHEAS (*r* = 0.10, *P* < 0.001). The femoral neck BMD was correlated with FSH (*r* = −0.08, *P* = 0.020), testosterone (*r* = 0.1, *P* = 0.010), DHEAS (*r* = 0.12, *P* < 0.001),
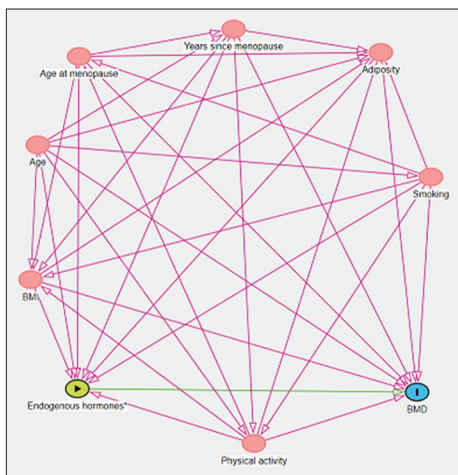
Table 1: Hormonal parameters reported as mean±standard deviation

Parameters	Estimate (*n*=798)	95% CI	Reference ranges
FSH	78.1±25.4	76.3–79.8	40–116 mU/mL
Estradiol	11.6±6.7	11.1–12.0	5–37 pg/mL
Testosterone	0.32±0.2	0.31–0.34	0.02–0.40 ng/mL
DHEAS	82.9±53.1	79.2–86.6	35–430 μg/dL
Δ4 androstenedione	0.86±0.6	0.82–0.91	0.49–1.31 ng/mL
Cortisol	14.1±4.9	13.8–14.4	4.3–22.4 μg/dL
IGF-1	127±41.3	124–129	44–241 ng/mL
Vitamin D	30.7±8.3	30.2–31.3	30–100 ng/mL
Parathormone	43.1±14.7	42.1–44.1	15–65 pg/mL

DHEAS: Dehydroepiandrosterone sulfate, FSH: Follicle-stimulating hormone, IGF-1: Insulin-like growth factor, CI: Confidence interval

Table 2: General characteristics of studied parameters reported as mean±standard deviation or *n* (%) in women with normal bone mineral density and low bone mineral density (osteopenia/osteoporosis)

Parameters	Normal BMD (*n*=120)	Low BMD (*n*=678)	OR (95% CI)	*P*
Age	59.7±6.2	63.4±6.2	1.10 (1.07–1.14)	<0.001
Age at menopause	50.2±2.6	50.2±2.7	1.01 (0.94–1.08)	0.835
Years since menopause	9.4±6.8	13.1±6.6	1.10 (1.06–1.14)	<0.001
Smoking				
Smoker	28 (23.3)	126 (18.6)	Reference	
Never	92 (76.7)	552 (81.4)	1.34 (0.38–2.11)	0.276
BMI (kg/m^2)	26.2±3.6	24.5±3.7	0.89 (0.85–0.94)	<0.001
Adiposity (% fat)	37.9±3.9	40.9±4.7	1.14 (1.09–1.19)	<0.001
FSH (mU/mL)	72.4±22.9	79.1±25.7	1.01 (1.00–1.02)	0.004
Estradiol (pg/mL)	11.6±6.9	11.6±6.6	1.00 (0.97–1.03)	0.980
Testosterone (ng mL)	0.35±0.2	0.32±0.2	0.57 (0.25–1.28)	0.157
DHEAS (µg/dL)	95.4±51.9	80.7±53.0	1.00 (0.99–1.00)	0.005
Δ4 androstenedione (ng/mL)	1.02±0.6	0.83±0.6	0.69 (0.54–0.90)	0.008
Cortisol (µg/dL)	13.8±4.7	14.2±4.9	1.02 (0.98–1.06)	0.442
IGF-1 (ng/mL)	133±42.3	125±41.1	1.00 (0.99–1.00)	0.083
Vitamin D (ng/mL)	29.5±10.0	31.0±8.0	1.02 (1.00–1.04)	0.145
Parathormone (pg/mL)	40.4±14.1	43.5±14.8	1.02 (1.00–1.03)	0.027
Physical activity				
Low	40 (33.4)	264 (38.9)	Reference	
Moderate/high	80 (66.6)	414 (61.1)	0.79 (0.52–1.18)	0.288
Vitamin D supplementation	44 (36.6)	249 (36.7)	0.99 (0.67–1.49)	0.998

BMD: Bone mineral density, CI: Confidence interval, DHEAS: Dehydroepiandrosterone sulfate, FSH: Follicle-stimulating hormone, IGF-1: Insulin-like growth factor, BMI: Body mass index, OR: Odds ratio

Table 3: The Pearson correlation between clinical and hormonal parameters and bone mineral density

Parameter	Lumbar spine BMD		Femoral neck BMD		Total hip BMD	
	r	*P*	*r*	*P*	*r*	*P*
Age	−0.12	<0.001	−0.15	<0.001	−0.08	0.030
Age at menopause	0.07	0.050	0.02	0.490	0.06	0.110
Years since menopause	−0.15	<0.001	−0.15	<0.001	−0.10	<0.001
BMI	0.27	<0.001	0.32	<0.001	0.36	<0.001
Adiposity	−0.20	<0.001	−0.06	0.080	−0.02	0.580
FSH	−0.03	0.430	−0.08	0.020	−0.08	0.020
Estradiol	−0.06	0.110	0.01	0.790	0.03	0.400
Testosterone	0.05	0.140	0.10	0.010	0.11	<0.001
DHEAS	0.10	<0.001	0.12	<0.001	0.12	<0.001
Δ4 androstenedione	0.06	0.070	0.09	0.020	0.10	0.010
Cortisol	−0.03	0.380	−0.12	<0.001	−0.08	0.030
IGF-1	0.05	0.180	0.05	0.200	0.04	0.290
Vitamin D	−0.04	0.240	−0.02	0.500	−0.05	0.180
Parathormona	−0.04	0.220	−0.14	<0.001	−0.07	0.040

BMD: Bone mineral density, DHEAS: Dehydroepiandrosterone sulfate, FSH: Follicle-stimulating hormone, IGF-1: Insulin-like growth factor, *r*: Pearson correlation, BMI: Body mass index

Δ4-androstenedione ($r = 0.09$, $P = 0.020$), cortisol ($r = −0.12$, $P < 0.001$), and PTH ($r = −0.14$, $P < 0.001$). We also observed that there were correlations between the total hip with FSH ($r = −0.08$, $P = 0.020$), testosterone ($r = 0.11$, $P < 0.001$), DHEAS ($r = 0.12$, $P < 0.001$), Δ4-androstenedione ($r = 0.10$, $P = 0.010$), cortisol ($r = −0.08$, $P = 0.030$), and PTH ($r = −0.07$, $P = 0.040$). Multivariable linear regression analysis was used to determine the association between endogenous hormones and BMD [Table 4]. After adjusting for confounding variables, a significant association was found between cortisol and femoral neck BMD (β: −0.02, 95% CI: −0.03–−0.00), and PTH with femoral neck BMD (β: −0.01, 95% CI: −0.02–−0.01) and total hip BMD (β: −0.01, 95% CI: −0.01–−0.00). Finally, a multivariable logistic regression adjusted

Table 4: Multivariable linear regression model to analyze the association between endogenous hormones and bone mineral density (g/cm²) adjusting for age, adiposity, body mass index, smoking status, physical activity, and years since menopause

	β (95% CI)		
	Lumbar spine BMD	**Femoral neck BMD**	**Total hip BMD**
FSH	0.00 (−0.00–0.00)	−0.00 (−0.00–0.00)	−0.00 (−0.00–0.00)
Estradiol	−0.01 (−0.02–0.00)	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)
Testosterone	−0.10 (−0.53–0.32)	0.17 (−0.15–0.49)	0.19 (−0.15–0.54)
DHEAS	0.00 (−0.00–0.00)	−0.00 (−0.00–0.00)	0.00 (−0.00–0.00)
Δ4 androstenedione	0.05 (−0.11–0.20)	0.09 (−0.02–0.21)	0.09 (−0.03–0.21)
Cortisol	0.01 (−0.01–0.03)	−0.02 (−0.03−−0.00)	−0.01 (−0.02–0.01)
IGF-1	0.00 (−0.00–0.00)	0.00 (−0.00–0.00)	0.00 (−0.00–0.00)
Vitamin D	−0.00 (−0.01–0.01)	−0.00 (−0.01–0.01)	−0.00 (−0.01–0.00)
Parathormona	−0.01 (−0.01–0.00)	−0.01 (−0.2−−0.01)	−0.01 (−0.01−−0.00)
R^2	0.22	0.22	0.21
Adjusted R^2	0.20	0.21	0.19

BMD: Bone mineral density, CI: Confidence interval, FSH: Follicle-stimulating hormone, DHEAS: Dehydroepiandrosterone sulfate, IGF-1: Insulin-like growth factor

for confounding variables was performed to analyze possible hormonal predictors of low BMD and showed that women with higher FSH levels (OR: 1.02, 95% CI: 1.01–1.03) or higher PTH levels (OR: 1.02, 95% CI: 1.01–1.04) were more likely to have low BMD [Table 5].

DISCUSSION

The present study showed in postmenopausal women that cortisol was associated with femoral neck BMD, and PTH with femoral neck BMD and total hip BMD. Hormonal factors more likely associated with a higher risk of low BMD were FSH and PTH. To the best of our knowledge, DAG has been rarely used in specific clinical issues of postmenopausal women.[20-22] We previously studied the association between handgrip strength and endogenous hormones in postmenopausal women using a DAG.[23] The present is the first study that analyzed the association between endogenous hormones and BMD in postmenopausal women using a DAG. This tool is a graphical structure connecting with arrows associated with variables dependence, may identify confounders, and avoids superfluous adjustments.[24,25]

During the menopausal transition, there is a progressive increase in circulating FSH levels, which remain high after menopause. This hormone activates osteoclastogenic pathways; hence, it has been postulated that high plasma FSH levels cause bone loss.[6] However, the possible direct effects of FSH on bone loss have generated controversy. Data from the Study of Women's Health Across the Nation showed that BMD loss during the menopause transition was related to plasma FSH levels, independent of plasma estradiol levels.[26] The AGES-Reykjavik

Table 5: Multivariable logistic regression to analyze the association between endogenous hormones and risk of presenting low bone mineral density, adjusted by age, adiposity, body mass index, smoking status, physical activity, and years since menopause

Hormonal parameters	Low-BMD (osteopenia/osteoporosis)	
	OR	**95% CI**
FSH	1.02	1.01–1.03
Estradiol	1.00	0.97–1.04
Testosterone	1.03	0.35–3.43
DHEAS	1.00	1.00–1.01
Δ4 androstenedione	0.71	0.48–1.04
Cortisol	0.99	0.94–1.03
IGF-1	1.00	0.99–1.00
Vitamin D	1.01	0.98–1.04
Parathormona	1.02	1.01–1.04

CI: Confidence interval, DHEAS: Dehydroepiandrosterone sulfate, FSH: Follicle-stimulating hormone, IGF-1: Insulin-like growth factor, OR: Odds ratio, BMD: Bone mineral density

Study reported a negative correlation between plasma FSH levels and BMD in older postmenopausal women.[27] On the contrary, Drake *et al*.[7] demonstrated that pharmacological suppression of FSH secretion is not associated with bone resorption markers in postmenopausal women, concluding that FSH does not regulate bone resorption. A cross-sectional study conducted in postmenopausal women aged 50–64 years found no significant association between FSH or bioavailable estradiol and BMD.[8] Our study finds a significant association between FSH and BMD, and higher FSH levels present a higher risk of low BMD, expressing the secondary adjustment of the global hypoestrogenism of postmenopause. Therefore, FSH levels are the expression of low estradiol levels in postmenopausal women in determining BMD.

The decline in estrogen levels in postmenopausal women was associated with low BMD[5,28] and increased risk of osteoporotic fractures.[29,30] However, not all women with estrogen deficiency develop osteoporosis. During the postmenopausal period, the effect of the serum levels of estradiol only explains a small percentage of bone loss. Other factors such as age, age at menopause, years since menopause, BMI, adiposity, smoking status, and physical activity may also affect the BMD.[31,32] Our study results confirm a lack of association between estradiol and BMD, and a possible explanation of these results would be that the low levels of estradiol during postmenopause do not have a relevant effect on BMD.

Previous studies reported that premenopausal women with high androgens levels are associated with increased BMD at the lumbar spine and the femoral neck.[33] In contrast, the effect of androgens on BMD in postmenopausal women is still controversial. The prospective study of Wu *et al*.[9] showed that testosterone correlates with the rate of change of bone density. Furthermore, endogenous testosterone levels were significantly associated with femoral neck BMD.[12] However, Crandall *et al*.[34] showed no significant associations between testosterone levels with rates of lumbar spine or femoral neck bone loss. Furthermore, during the menopausal transition, Guthrie *et al*.[10] demonstrated no significant effect of testosterone on BMD. In postmenopausal women, DHEAS is the dominant circulating androgen secreted by the adrenal glands and converted to estradiol or testosterone in the target organs. Its circulating levels decline with aging.[35] Several studies have examined the relationship between DHEAS and BMD but with a discrepancy in results. The longitudinal study of Ghebre *et al*.[36] demonstrated that high endogenous DHEAS levels at baseline were associated with reduced bone loss at the lumbar spine and the femoral neck, although this association decreases over time. Bácsi *et al*.[37] reported that plasma DHEAS levels correlate positively with BMD at the lumbar spine, and Park *et al*.[38] related a correlation with femur BMD but not at the lumbar spine. However, other studies found no association between DHEAS levels with BMD or with the rate of bone loss.[10,12,39] The positive effects of endogenous Δ 4-androstenedione on BMD have been reported, showing a positive association between Δ 4-androstenedione and femoral neck BMD.[12] The Women's Health in the Lund Area cohort study reported an increased fracture risk during follow-up in postmenopausal women with low serum Δ 4-androstenedione, suggesting that postmenopausal osteoporosis is influenced by lower levels of androgens.[40] Concerning the relationship between androgens and BMD, our multivariable analysis did not demonstrate the association between BMD and the studied androgens. In postmenopausal women, androgens are lower and possibly have less influence on BMD than in premenopausal women.

Corticosteroids are related to decreased BMD and increased fracture risk due to detrimental effects on osteoblast and osteocyte functions, prolonged osteoclast life span, decreased intestinal absorption of calcium, and stimulated PTH secretion.[41] In recent years, there has been a growing interest in the subtle cortisol excess because it is associated with an increased risk of complications, in particular osteoporosis and fragility fractures. On the other hand, the skeletal effect of cortisol excess may vary by ethnicity due to associating with polymorphism in the enzyme 11β-hydroxysteroid dehydrogenase type 1 and in the glucocorticoid receptor. Cortisol excess has a detrimental effect on the trabecular bone; however, the data on the effect on cortical bone are discordant.[42] Our results support the notion that endogenous plasma cortisol levels are associated with low BMD at the femoral neck, showing the detrimental effect of cortisol excess on the cortical bone.

The role of IGF-1 in the maintenance of BMD in postmenopausal women is controversial. Some studies found that higher plasma IGF-1 levels reduced BMD loss,[13,43] but not in others.[14,44] Some studies suggest gender-specific differences in relation to IGF-1 and BMD due to an association in men but not in women.[45] A recent meta-analysis in the Chinese population found that IGF-1 single-nucleotide polymorphism rs35767 TT genotype was associated with an increased risk of osteoporosis. However, this association needs to be evaluated in other ethnic groups.[46] Our present results were obtained in women of only Spanish ethnicity, and we observed no significant association between IGF-1 and BMD.

Vitamin D status influences calcium-phosphorus homeostasis and bone metabolism. Vitamin D deficiency is a risk factor associated with the development of osteoporosis. Several studies and systematic reviews have reported that more than 50% of the population has Vitamin D deficiency.[47] The threshold for Vitamin D deficiency of <12 ng/ml (30 nmol/L) is compatible with adverse effects on bone health.[48] Although Vitamin D deficiency coexists with low BMD, some studies found no correlation between serum Vitamin D levels and BMD.[49] In the present study, plasma 25-hydroxyvitamin D levels were not associated with BMD. However, this finding might be explained by the fact that in our study, there were no women with very low levels of Vitamin D. Therefore, this issue requires a future evaluation, including women with different Vitamin D levels.

Aging is associated with increased plasma PTH levels independent of Vitamin D, calcium, phosphorus, and renal function.[50] Hyperparathyroidism is usually asymptomatic and closely related to Vitamin D deficiency, particularly in the elderly.[51] High PTH levels cause osteoclasts hyperstimulation, BMD reduction, and increased fracture risk.[52] The results identified that PTH was associated with lower femoral neck and total hip BMD. Likewise, women with higher PTH levels had a higher risk of low BMD. In postmenopausal women, the effect of other endogenous factors on BMD is not completely understood. In this sense, the future use of DAGs to identify other risk factors of osteoporosis might facilitate future investigations.

Limitations and strengths

This study has certain limitations, including its cross-sectional design, and the longitudinal effect of the studied hormones on BMD could not be appropriately assessed. However, our study has several strengths. First, it includes a relatively large sample of postmenopausal women. Second, all BMD and measurements were conducted with the same densitometer and laboratory, with daily quality controls. Third, careful adjustments for confounders were performed in the regression model. Finally, we are not aware of a previous approach using DAGs to study BMD in postmenopausal women.

CONCLUSIONS

The present study showed that in studied postmenopausal women, (i) FSH is a secondary marker of low or nil estrogen ovarian production, rather than the direct cause of bone mineral alteration; (ii) high cortisol levels are associated with lower femoral neck BMD, showing the detrimental effect of cortisol excess on the cortical bone; (iii) higher PTH levels are associated with lower BMD in both the femoral neck and total hip; and (iv) high FSH and PTH levels are more likely associated with the risk of low BMD. Therefore, due to the clinical implications of osteoporosis, FSH, cortisol, and PTH measurements might be used in assessing BMD loss in postmenopausal women.

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Conflicts of interest

There are no conflicts of interest.

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