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Original Article

Ovarian volume is associated with adiposity measures and bone mineral density in postmenopausal women

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Abstract

Introduction: The present study aimed to assess the association between ovarian volume and demographic and anthropometric parameters, as well as sex hormones and bone mineral density (BMD) in postmenopausal women. **Methods:** 161 healthy postmenopausal women participated in this cross-sectional study. Fasting venous blood samples were obtained for biochemical/hormonal assessment. Anthropometric parameters included body mass index (BMI) and waist-to-hip ratio (WHR). Ultrasonography was used to estimate the average ovarian volume for each participant. BMD was measured in the femoral neck (FN) and the lumbar spine (LS) using DXA. **Results:** Mean ovarian volume increased linearly with increasing quartiles of BMI (Q1:0.985±0.25, Q2: 1.11±0.29, Q3: 1.07±0.28, Q4: 1.19±0.38, p-value for linear trend 0.013). Ovarian volume correlated positively with BMI (r=0.128, p-value=0.038), FN BMD (r=0.233, p-value=0.003), FN T-score (r=0.223, p-value=0.004) and FN Z-score (r=0.171, p-value=0.027). Multivariate analysis showed that ovarian volume was predicted by WHR (b-coefficient=0.157, p-value=0.047) and SHBG (b-coefficient= -0.160, p-value=0.042), independently of age and BMI. Finally, FN BMD was predicted by ovarian volume, independently of age, menopausal age and BMI. **Conclusion:** Ovarian volume was positively and independently associated with adiposity indexes and femoral BMD in postmenopausal women. Lower SHBG levels were associated with higher ovarian volume. Insulin resistance may mediate these results. The significance of these findings should be assessed in larger prospective studies.

Keywords: Ovarian Volume, Waist-to-hip-ratio, Bone Mineral Density, Postmenopausal Women

Introduction

Menopause consists of the cessation of the menstrual cycle caused by ovarian failure and leads to estrogen deficiency. The consequent hormonal imbalance is linked to short-term disturbances like the climacteric symptoms but also to long-term consequences as osteoporosis, cardiovascular disease as well as central body fat accumulation, metabolic alterations and urogenital atrophy[1].

The ovarian size declines after the menopausal transition[2]. A validated normative model describing changes of ovarian volume throughout life indicated that age is the principal determinant of ovarian volume, accounting for 69% of the variance throughout life[2]. Ovarian volume increases from 0.7 mL at 2 years of age up to 7.7 mL at 20 years of age, and subsequently decreases to about 2.8 mL at the time of the menopausal transition[2]. The morphological characteristics of the ovaries have been associated with adiposity measures as well as with lifestyle parameters in mixed populations of pre-, peri- and postmenopausal women[3-5]. Ovarian volume has furthermore been linked with insulin resistance[6] and with bone mineral density[7] in women with the polycystic ovary

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syndrome (PCOS). Factors, however, which may have an association with ovarian volume in postmenopausal women have not been adequately explored.

The objective of the present study was to assess ovarian volume in healthy postmenopausal women and to investigate possible associations with demographic-anthropometric and hormonal parameters, as well as with bone mineral density.

Materials and methods

Subjects

This cross-sectional study included a total of 161 informed-consenting postmenopausal women, recruited from the outpatient Menopause Clinic of the 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieio Hospital. This Clinic, active since 1998, provides information about menopause and offers screening and risk assessment for major morbidities of midlife and beyond, serving both asymptomatic and symptomatic middle-aged women. All postmenopausal women presenting for their first evaluation between January 2016 and December 2016 who fulfilled the inclusion criteria were asked to participate in this study. The menopausal status was defined as absence of menses for 12 consecutive months, serum follicle stimulating hormone >25 mIU/mL and serum estradiol levels <50 pg/mL. Inclusion criteria were: confirmed menopausal status and absence of previous hysterectomy, ovarian surgery, known diagnosis of polycystic ovarian syndrome, hormonal use currently or during the past 6 months and a personal history of gynecological malignancy. Women with a known history of polycystic ovarian syndrome were excluded, because the presence of the syndrome is associated with higher ovarian volume, acting therefore as potential confounder[8]. All women signed an informed consent and the study was approved by the hospital's Ethics Committee.

Protocol study procedures

A detailed electronic file was built for each informed-consenting woman containing life-style, anthropometric and demographic parameters. Weight and height were measured in the morning and in light clothing in order to estimate the Body Mass Index (BMI). Weight was measured on an electronic scale and height was measured in a stadiometer in the upright position. BMI was calculated using the equation BMI= body weight (kg) / height^2 (m^2). Fasting blood samples were drawn for biochemical evaluation, centrifuged and the serum was stored at -80 degrees Celsius until assessment.

Transvaginal ultrasound measurements

Transvaginal ultrasound evaluation was performed immediately thereafter, by a single observer (L.A.), blinded to the medical history of the patient, using a Toshiba Nemio 21 Ultrasound machine. Ovarian volume was calculated using the maximum longitudinal (*D1*), anteroposterior (*D2*) and transversal (*D3*) diameters: *D1* x *D2* x *D3* x 0,523 (12). **The mean ovarian volume was calculated in all cases, apart from women in whom both ovaries had the same volume**. When only one ovary could be measured by ultrasound, this was considered to be the patient's ovarian volume.

Biochemical and hormone assays

The plasma levels of FSH, LH, and E2 were measured on an Architect i1000 analyzer (Abbott Ireland, Diagnostics Division, Lisnamuck, Longford, Ireland), with an analytical sensitivity of 0.05 mIU/mL, 0.07 mIU/mL, and 10 pg/mL, respectively. The total CV% ranged from 3.2% to 4.6% for FSH, from 2.9% to 4.1% for LH, and from 1.9% to 7.1%, for E2. Total testosterone was measured with the Abbott Architect i1000 analyzer. The total CV% ranged from 3.1% to 8.0%, and analytical sensitivity was 0.08 ng/mL. Sex hormone-binding globulin concentrations were measured with electrochemiluminescence immunoassay on a Cobas e-411 analyzer (Roche Diagnostis, Mannheim, Germany). The total CV% ranged from 2.6% to 5.6%, and the analytical sensitivity of the assay was 0.35 nmol/L. Insulin was measured on an Abbott Architect i1000 analyzer. The total CV% ranged from 1.9% to 5.2%, and the analytical sensitivity was 1 μU/mL. Serum glucose was assessed enzymatically by an autoanalyzer (ARCHITECT-ci8200, Abbott Diagnostics Laboratories, Abbott Park, IL; Abbott 65205, Wiesbaden, Germany). Commercially available methodologies were used to estimate serum levels of total calcium, 25-hydroxyvitamin D (25-OH-VitD) and parathormone levels. Free estrogen index (FEI) and free androgen index (FAI) were calculated using total E2 and total testosterone, respectively, as well as SHBG values by the following equations: FEI=E2 (picograms per milliliter) · 0.367/SHBG (nanomoles per liter); FAI= testosterone (nanograms per milliliter) · 347 /SHBG (nanomoles per liter).

Bone densitometry

BMD was measured in two sites, lumbar spine (LS) and femoral neck (FN), using Dual Energy X-ray Absorptiometry (DXA) with a Norland-Excell Plus-XR-36 Densitometer (Norland Medical Systems, Inc., Fort Atkinson, WI). Within-subject coefficient of variation was 1.1% at the LS and 1.85% at the FN.

Statistical analysis

Data analysis was performed by Statistical Package for the Social Sciences version 20.0 (SPSS Inc, Chicago IL, USA). Normally distributed data are presented as mean±SD, while non-normally distributed parameters are presented as median and interquartile range. The Kolmogorov-Smirnov test was utilized to test for normality in distribution of quantitative measurements. Due to deviations from normality with normality in the distribution of several variables, non-parametric tests were preferred

Table 1. Demographic/anthropometric parameters, gynecological indices, markers of bone density and hormonal indices for the 161 postmenopausal women of the study.

Demographic/anthropometric parameters	*Mean±SD*	*Median*	*IQR*	*Range*
Age (years)	59.7±6.1			45-78
YSM (years)		8.0	5.0 – 13.0	1-37
Weight (kg)		67.0	59.4 – 74.2	48-117
BMI (kg/m^2)		26.1	23.9 – 29.0	19.7-47.5
Waist (cm)		85.0	79.0 – 94.0	66-119
Hip (cm)		105.0	100.0 – 109.0	91-150
WHR		0.82	0.77 – 0.86	0.66-1.03
SBP (mmHg)		117.5	103.5 – 130.0	80-185
DBP (mmHg)		70.0	60.0 – 80.0	50-110
Gynecological indices				
Mean ovarian volume (cc^3)		1.05	1.05 – 1.12	0.31-1.94
Endometrial thickness (mm)		3.5	2.5 – 4.8	0.60-8.9
Bone density parameters				
LS BMD (g/cm^3)	0.95±0.15			0.71-1.44
LS T-score	-1.47±1.07			-3.50 - 2.20
LS Z-score	-0.44±1.04			-2.60 - 3.4
FN BMD (g/cm^3)	0.78±0.11			0.59-1.14
FN T-score	-1.63±0.84			-3.01 – 0.60
FN Z-score	-0.29±0.73			-1.60 – 1.74
Biochemical and Hormonal indices				
FSH (mIU/mL)		63.7	51.4 – 80.3	29.2-147
LH (mIU/mL)		26.1	21.3 – 37.0	10.2-68.6
Estradiol (pg/mL)		10.0	10.0 – 13.5	8.0-35.0
Testosterone (ng/mL)		0.34	0.23 – 0.49	0.07-1.09
SHBG (nmol/L)		66.2	46.9 – 99.1	18.0-146.0
FEI		0.06	0.04 – 0.09	0.02-0.36
FAI		1.65	1.08 – 3.00	0.20-8.64
Calcium (mg/dL)		9.6	9.4 – 9.8	8.8-11.5
25hydroxyvitamin D (ng/mL)		28.1	19.2 – 33.9	4.0-64.6
Parathyroid hormone, PTH (pg/mL)		43.5	29.8 – 55.6	11.8-158.0

YSM=years since menopause; BMI=body mass index; WHR=waist to hip ratio; SBP=systolic blood pressure; DBP=diastolic blood pressure; LS=lumbar spine; FN=femoral neck; BMD=bone mass density; FSH=follicle stimulating hormone; LH=luteinising hormone; SHBG=sex hormone binding globulin; FEI=free estrogen index; FAI=free androgen index; IQR=Interquartile range.

for univariate analysis; the non-parametric Kruskal-Wallis and Wilcoxon-Mann-Whitney tests for independent samples were used for comparisons of quantitative measurements, accordingly. Spearman's correlation coefficient was used for bivariate associations between ovarian volume and all other quantitative parameters, while Kendall's tau was used, instead, for categorical parameters. The association between ovarian volume and anthropometric indices was performed linearly as well as according to quartiles of waist, WHR and BMI. Multiple linear regression was applied to further investigate possibly significant associations of parameters with logarithmically transformed mean ovarian volume a priori adjusting for age, years since menopause and BMI, all being possible confounders. A p value <0.05 was considered as statistically significant.

Results

Table 1 presents the mean values of demographic/anthropometric data, hormonal parameters and values of bone density for the overall sample, as well as mean values of ovarian volume. Table 2 presents the results of the correlation analysis between mean values of ovarian volume and anthropometric data, indices of bone density as well as levels of sex hormones. With respect to demographic/anthropometric indices, mean ovarian volume correlated positively with BMI (r=0.128, p-value=0.038). Significant correlations were observed between ovarian volume and indices of bone density in the femoral neck (FN BMD, FN T-score, FN Z-score: r=0.233, p-value=0.003; r=0.223, p-values=0.004 and r=0.171, p-value=0.027,

Table 2. Correlation analysis between patient's characteristics and ovarian volume for the 161 women of the study.

Anthropometric/ demographic parameters	*Ovarian volume*	
	r-coefficient	*p-value*
Age (years)	-0.037	0.524
YSM (years)	-0.054	0.355
BMI (kg/m^2)	**0.128**	**0.038**
Waist (cm)	0.088	0.144
WHR	0.079	0.184
Bone density		
LS BMD (g/cm^2)	0.086	0.349
LS T-score	0.073	0.420
LS Z-score	0.128	0.163
FN BMD (g/cm^2)	**0.233**	**0.003**
FN T-score	**0.223**	**0.004**
FN Z-score	**0.171**	**0.027**
Sex hormone levels		
FSH (mIU/mL)	-0.020	0.755
LH (mIU/mL)	-0.007	0.948
Estradiol (pg/mL)	**0.156**	**0.028**
Testosterone (ng/mL)	0.151	0.062
SHBG (nmol/L)	**-0.204**	**0.012**
FEI	**0.240**	**0.003**
FAI	**0.221**	**0.007**

LS=Lumbar spine; FN=femoral neck; BMD=bone mass density; YSM=years since menopause; BMI=body mass index; WHR=waist to hip ratio; FSH=follicle stimulating hormone; LH=luteinising hormone; SHBG=sex hormone binding globulin; FEI=free estrogen index; FAI=free androgen index. Bold indicates statistical significance which was set at the level of p-value<0.05.

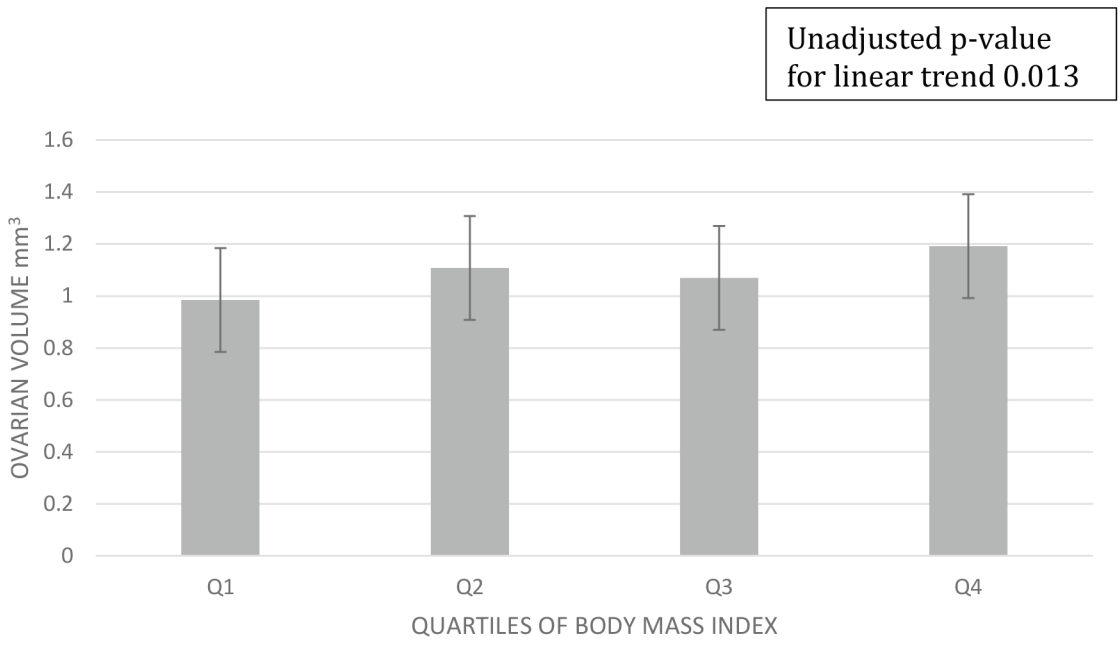

Figure 1. Mean ovarian volume values according to quartiles of body mass index, adjusted for age and menopausal age for the 161 women of this sample.

Table 3. Stepwise linear multivariate regression analysis including ovarian volume as dependent variable and potential risk factors as independent variables.

*Ovarian volume**	*b-coefficient*	*95% CI*	*P-value*
MODEL 1			
Age (years)	-0.024	-0.389 to 0.901	0.769
BMI (kg/m^2)	0.100	0.089 to 0.378	0.220
WHR	**0.157**	**0.013 to 1.655**	**0.047**
FAI	-0.002	-0.147 to 0.289	0.978
MODEL 2			
Age (years)	-0.024	-0.145 to 0.367	0.769
BMI (kg/m^2)	0.100	0.056 to 0.561	0.220
WHR	**0.157**	**0.013 to 1.655**	**0.047**
FEI	0.076	0.031 to 0.790	0.347
MODEL 3			
Age (years)	0.016	-0.258 to 0.512	0.841
BMI (kg/m^2)	0.097	-0.149 to 0.316	0.235
WHR	0.128	0.094 to 0.475	0.110
SHBG (nmol/L)	**-0.160**	**-0.315 to 0.214**	**0.042**

*BMI=body mass index; WHR=waist to hip ratio; FEI=free estrogen index; FAI=free androgen index; SHBG=Sex Hormone Binding Globulin. *Logarithmically transformed values. Bold indicates statistical significance which was set at the level of p-value<0.05.*

respectively). With respect to sex hormone levels, a direct positive correlation was observed between ovarian volume and estradiol (r=0.156, p-value=0.028), FEI (r=0.240, p-value=0.003) and FAI (r=0.221, p-value=0.007). A negative correlation was observed between ovarian volume and SHBG (r=-0.204, p-value=0.012). The reported correlations were all low but statistically significant. **Levels of SHBG did not differ between younger and older postmenopausal women**. Finally, an almost significant correlation was observed between mean ovarian volume and testosterone levels (r=0.151, p-value=0.062). Moreover, 25hydroxyvitamin D or parathyroid hormone levels did not correlate with ovarian volume or with indices of bone density.

We proceed evaluating the association between ovarian volume and anthropometric indices, namely BMI, waist and WHR in quartiles. Mean values of ovarian volume increase linearly with increasing quartiles of BMI (Q1, Q2, Q3 vs Q4: 0.985±0.25 vs 1.11±0.29 vs 1.07±0.28 vs 1.19±0.38) p-value for linear trend 0.013 (Figure 1). Ovarian volume did not differ according to quartiles of waist circumference or quartiles of WHR (data not shown).

Aiming to further evaluate the association of demographic, anthropometric and hormonal parameters with ovarian volume, we used a model of stepwise multivariate regression analysis. The model included ovarian volume as a dependent characteristic and the following parameters as independent characteristics: age, BMI, WHR and sex hormones (FEI or FAI or SHBG). Ovarian volume was predicted independently by WHR (b-coefficient=0.157, p-value=0.047) or by levels of SHBG (b-coefficient= -0.160, p-value=0.042, Table 3).

The potential association between ovarian volume and BMD was evaluated using models of linear regression analysis, which included each of the assessed indices of bone density as a dependent characteristic, while ovarian volume served as an independent characteristic, adjusted for age, menopausal age and BMI (Table 4). FN BMD was predicted by ovarian volume (Model R^2=13.8%, b-coefficient=0.285, p-value=0.012), independently of age, YSM and BMI. Similarly, FN T-score was predicted by ovarian volume (Model R^2=16.6%, b-coefficient=0.271, p-value=0.014), independently of age, YSM and BMI. Moreover, FN Z-score was also predicted by ovarian volume (Model R^2=14.0%, b-coefficient=0.276, p-value=0.014), independently of age, YSM and BMI. On the other hand, no associations were observed between ovarian volume and indices of bone density in the lumbar spine.

Discussion

This study evaluated the association of ovarian volume after the menopause with demographic, anthropometric and hormonal parameters as well as with bone mineral density. The main findings of this study are that ovarian volume is positively associated with WHR and BMI as well as with femoral neck bone mineral density, and inversely with levels of SHBG independently of confounders, such as age or sex hormone levels.

The association between obesity and ovarian volume after the menopause has been explored by a limited number of studies. Most studies have evaluated either mixed or premenopausal populations, reporting both positive[3,9] and negative associations[4,5], while studies focusing on strictly

Table 4. Linear multiple regression analysis including bone density markers as dependent parameters and ovarian volume as well as other significant risk factors of bone metabolism as independent parameters for the 161 women of the sample.

FN BMD	*Model R2*	*b-coefficient*	*95% CI*	*p-value*
Age (years)	13.8%	-0.187	-0.210 to 0.002	0.229
YSM (years)		0.028	-0.005 to 0.062	0.858
BMI (kg/m^2)		0.194	-0.001 to 0.301	0.081
Ovarian volume (cc)		**0.285**	**0.026 to 0.482**	**0.012**
FN T-score				
Age (years)	16.6%	-0.210	-0.076 to 0.340	0.168
YSM (years)		0.007	-0.040 to 0.040	0.999
BMI (kg/m^2)		0.226	0.002 to 0.439	0.039
Ovarian volume (cc)		**0.271**	**0.174 to 0.742**	**0.014**
FN Z-score				
Age (years)	14.0%	0.230	-0.010 to 0.390	0.138
YSM (years)		0.121	-0.021 to 0.380	0.435
BMI (kg/m^2)		0.069	-0.025 to 0.049	0.531
Ovarian volume (cc)		**0.276**	**0.155 to 0.352**	**0.014**
LS BMD				
Age (years)	3.3%	-0.083	-0.289 to 0.178	0.494
YSM (years)		-0.044	-0.210 to 0.123	0.714
BMI (kg/m^2)		**0.213**	**0.189 to 0.305**	**0.008**
Ovarian volume (cc)		0.042	-0.178 to 0.090	0.590
LS T-score				
Age (years)	0.6%	-0.106	-0.389 to -0.099	0.391
YSM (years)		0.012	-0.121 to 0.289	0.925
BMI (kg/m^2)		0.148	0.048 to 0.304	0.067
Ovarian volume (cc)		0.039	-0.078 to 0.182	0.628
LS Z-score				
Age (years)	2.8%	0.214	0.190 to 0.317	0.080
YSM (years)		-0.116	-0.310 to -0.038	0.340
BMI (kg/m^2)		0.146	0.039 to 0.209	0.067
Ovarian volume (cc)		0.051	0.004 to 0.290	0.517

YSM=years since menopause; BMI=body mass index; FN=femoral neck; LS=lumbar spine. Bold indicates statistical significance, which was set at the level of p-value<0.05.

postmenopausal women are sparse. The results of this study further support a direct independent association between central obesity and ovarian volume, even following adjustment for age, menopausal age, BMI and sex hormones. A growing body of evidence indicates that WHR is a better predictor of metabolic health compared to BMI after the menopause[10]. Postmenopausal women have an up to 5-fold higher risk of central adiposity compared to premenopausal women, independently of BMI[11]. Moreover, central fat accumulation contributes to insulin resistance[12], while insulin resistance and hyperinsulinemia affect directly the ovary[13]. In our study, the association between WHR and ovarian volume was rendered non-significant when SHBG, a marker of insulin resistance[14] was entered in the model. Insulin resistance and the associated hyperinsulinemia has been repeatedly associated with ovarian volume in premenopausal women with the PCOS, independently of the degree of obesity[15-17]. Our results indicate that the independent association of insulin resistance with ovarian volume may also pertain in postmenopausal women.

Our study showed an inverse association between SHBG and ovarian volume. Representing a major carrier of androgens in the circulation, SHBG levels fluctuate throughout the adult lifespan. A U-shape trajectory has been described between serum levels of SHBG and aging, which were shown to decline in women of reproductive age up until the 6th decade of life and subsequently start to increase[18,19]. In fact, levels of SHBG are mainly determined by metabolic factors. Following the menopausal transition, markers of adiposity like BMI and WHR are inversely related with serum levels of SHBG[20,21]. Furthermore, intraabdominal obesity has been inversely associated with SHBG levels[22], while on the other hand circulating SHBG increases following bariatric surgery[23]. Finally, SHBG has

been proposed as a marker of insulin resistance in women across the menopausal transition[24] The observed inverse association, therefore, between SHBG and ovarian volume demonstrated in our study could represent an effect of insulin resistance.

Our study demonstrated an independent positive association of ovarian volume with bone density at the femoral neck, potentially mediated by circulating SHBG. SHBG levels have been inversely associated with bone mineral density[25,26]. Furthermore, high SHBG levels predict the occurrence of fractures, mainly in the femur[26]. In addition, significant differences in values of hip but not spinal BMD in association with polymorphisms of the SHBG gene have been described in studies of postmenopausal women[27]. According to our findings, women with larger ovaries have higher WHR and evidence of insulin resistance compared to non-obese women[28]. This association seems rational considering that obesity and insulin resistance result into lower SHBG levels[20,29]. Insulin resistance and higher levels of circulating insulin[20,29] might exhibit a trophic effect on the ovaries, further increasing their volume. It is possible, therefore, that the observed association between ovarian volume and femoral bone mineral density is mediated by insulin resistance and levels of SHBG.

Limitations of the present study include the cross-sectional design, which does not permit the detection of causality. Secondly, we did not assess the potential association between ovarian volume and other steroids, like estrone or androstendione. However, this study included a carefully selected sample of purely postmenopausal women, excluding thus the effect of menopausal transition on ovarian volume.

The results of this study imply the significance of SHBG as a determinant of ovarian volume and possibly bone metabolism in women after the menopausal transition. As ovarian volume was negatively associated with BMD values and SHBG, this protein may therefore be used as a biomarker of bone health and ovarian tissue reserve in the postmenopausal population.

In conclusion, ovarian volume is positively associated with adiposity measures and bone mineral density at the femoral neck. Furthermore, lower levels of SHBG were associated with larger ovaries. Insulin resistance and hyperinsulinemia may mediate this association. Larger prospective studies on solely postmenopausal populations are required to elucidate the significance of these findings.

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