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ORIGINAL ARTICLE

The influence of anthropometric parameters on the concentration of globulin that binds sex hormones during the menopausal transition

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ABSTRACT

Aim To determine the effect of body mass index (BMI) and waist-hip ratio (WHR) on the concentration of circulating sex hormone-binding globulin (SHBG) throughout the menopausal transition.

Methods This cross-sectional study included 150 women divided into three groups: premenopausal (n=50), perimenopausal (n=50), and postmenopausal (n=50). The processing of the test women consisted of three phases: interview, blood sampling and determination of BMI and WHR. The SHBG concentration was determined from the blood, and BMI and WHR were measured.

Results The BMI and WHR of the postmenopausal women were significantly higher comparing to the other two groups, while the postmenopausal SHBG was significantly lower compared to the premenopausal concentration. In all three groups, a significant negative correlation was found between SHBG and BMI (Rho= -0.385; $p<0.05$), and between SHBG and WHR (Rho= -0.411; $p<0.05$). By the univariate regression analysis model, it was determined that BMI (β= -0.594; $p<0.001$) and WHR (β= -0.407; p=0.003) were independently negative predictors of SHBG in postmenopausal women, while in the multivariate regression analysis model only BMI as an independently negative predictor of SHBG in postmenopausal women was found (β= -0.263; p=0.024).

Conclusion The value of SHBG during the menopausal transition decreases and women with higher BMI and WHR have lower values of SHBG regardless of the duration of menopause.

Considering the connection between SHBG and anthropometric parameters, and the drop in its values upon entering and passing through the menopausal transition as such it can be used as a predictor for an increased risk of cardiovascular diseases and metabolic syndrome in a selected group of women.

Keywords: body mass index, menopause, obesity, SHBG, waist-hip ratio

INTRODUCTION

Menopause is a discrete event characterized by the permanent cessation of the ovarian function, which is diagnosed after 12 months of amenorrhea. The change between reproductive and non-reproductive status, which usually lasts between 4 and 10 years, is the transition to menopause, also called perimenopause because it surrounds the last menstrual period (1).

Thus, three consecutive periods until menopause are connected: pre-menopause, perimenopause and postmenopause. The first period is defined as the phase before the last menstruation in which menstrual irregularity increases and decreases in the age range of about 45-49 years. Perimenopause begins with the onset of changes in the menstrual cycle, when the first clinical, biological, endocrine and psycho emotional features of the approach of the last menstruation begin to appear, as well as one to two years after menopause. Post-menopause is defined by the World Health Organization as the period of life after

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the last menstruation, regardless of whether the menopause is natural or artificially induced. Gradual or sudden cessation of estradiol and progesterone production in the ovaries manifests itself in various vasomotor, psychological, somatic and atrophic changes, which are expressed by very unique, well-known, climacteric symptoms (2).

Menopausal transition with accompanying changes in the hypothalamic-pituitary-ovarian axis may be an underappreciated factor that contributes to the risk of obesity in women. Although gains in body fat percentage and body weight have been observed among middle-aged women, previous studies have attributed this primarily to chronological aging rather than the menopausal transition; however, there are limitations to studies that conclude this (3).

The mechanisms between visceral obesity and sex hormones are not fully elucidated. Menopause in women leads to many physiological changes in the body and obesity itself is one of the commonest causes of postmenopausal diabetic women (4). In addition to changes in adipose tissue endocrinology, increased obesity in women of various ages has been associated with higher circulating concentrations of total or bioavailable testosterone in cross-sectional or prospective studies, along with decreased serum sex-hormone binding globulin concentrations (5).

Waist-hip ratio (WHR) can be used as a screening tool to identify postmenopausal women at increased cardiovascular risk. Both BMI and WHR are strong predictors of biological and clinical indicators associated with cardiovascular disease including elevated blood pressure and lipid levels (6).

Menopause is characterized by large changes in the concentration of sex steroids in the blood, and a particularly significant decrease in the concentration of estradiol (7). A low level of SHBG is consistent with a parallel decrease in estradiol concentrations during menopause. A lower level of SHBG was recorded in women between 45 and 65 years of age, and a higher level after 65 years. The underlying mechanism of the increase in SHBG after age 65 remains to be elucidated, but it is speculated that the relative higher androgens during the menopausal transition can partially explain the U-shaped SHBG trend (8). Low SHBG correlates with risk for metabolic syndrome, including diabetes, obesity, and cardiovascular events. However, the basic molecular mechanism that connects SHBG and metabolic syndrome remains unknown. SHBG suppresses inflammation and lipid accumulation in macrophages and adipocytes, which could be among the mechanisms underlying the protective effect of SHBG, i.e. its actions that reduce the frequency of metabolic syndrome (9).

SHBG concentration is also related to body mass. In general, SHBG decreases with increasing body mass. People with anorexia have high concentrations of SHBG, while people who are obese usually have low concentrations of SHBG (10).

A recent study showed that plasma SHBG concentration is associated with some components of the metabolic syndrome, and that there is a significant relationship between SHBG and WHR. However, they suggest that SHBG is not a sufficiently powerful factor that could be used as a predictor of the metabolic syndrome itself, and that there is no association between plasma SHBG levels and the development of metabolic syndrome components, except for the fact that a lower SHBG level may contribute to a change in the lipid profile (11).

The aim of this study was to investigate the relationship between the anthropometric parameters BMI, WHR and the level of globulin that binds sex hormones in the plasma through the menopausal transition.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study included 150 women attended to the Clinic for Gynaecology and Obstetrics and the Polyclinic for Laboratory Diagnostics of the University Hospital Tuzla in the period between April and July 2022. Women were divided into three groups: premenopausal (n=50), perimenopausal (n=50), and postmenopausal (n=50). The first group was aged between 45-50 years, the second between 50-55 years, and the third >55 years. Inclusion criteria were: not taking hormone replacement therapy or anticonvulsants, medications that could affect the lipid profile, suffering from hyperthyroidism, hypogonadism, liver disease, and myxedema. Exclusion criteria were women using hormone replacement therapy or medication that affect lipid profile and iatrogenic induced menopause. All women signed an informed consent. The Ethic Committee of the University Clinical Centre Tuzla approved the study.

Methods

All women were interviewed, BMI and WHR values were calculated, and a blood sample was taken for laboratory analysis. A special question-form was created and the interview was conducted.

The BMI was calculated according to the formula: BMI = body weight/body height (kg/m^2). The WHR was calculated as the ratio of waist circumference and hip circumference. Blood for laboratory analysis was taken by venipuncture from the cubital vein in the early morning hours on an empty stomach.

The concentration of SHBG was determined by chemiluminescent immunochemical tests, using the CMIA (Chemiluminescent micro particle immunoassay) method at the Clinic for Radiology and Nuclear Medicine of the University Clinical Centre in Tuzla using the Lenity i-series immunochemical analyser (Abbott diagnostics, Abbott Laboratories representative, Sarajevo, Bosnia and Herzegovina). Lenity and SHBG rgt 200t were used as reagents for this method. Reference values using this method for women are 19.8-155.2 nmol/L.

Statistical analysis

Results are expressed as absolute numbers (No), and percentage values (%), as mean ($\overline{X}$) and standard error of the arithmetic mean (SEM), and as median and interquartile range (IQ) (25-75 percentile). To test significance of the difference in the deviation from the normal distribution, the Kolmogorov–Smirnov or Shapiro-Wilk test was used. Independent numerical variables were analysed by ANOVA test and t-test for those that meet the conditions for application, i.e., by appropriate nonparametric tests (Kruskal-Wallis test and Mann-Whitney U test) for variables with an irregular distribution. The $\chi2$ test was used to analyse categorical variables. The degree of correlation was determined by the Spearman method (Rho Spearman's correlation coefficient). Multivariate regression analysis showed the dependence of (SHBG) on several independent variables. Univariate and multivariate regression analysis models were used in order to examine the independent association of parameters with SHBG. A $p<0.05$ was taken as statistically significant.

RESULTS

The median age of premenopausal women was 47.0 (45.0-48.9), perimenopausal 52.0 (49.0-55.0), and postmenopausal 59.0 (57.0-61.0) years ($p<0.001$). Menarche in the premenopausal group was at 13.0 (13.0-14.0) years, perimenopausal at 14.0 (13.0-14.25) years, and postmenopausal at 14.0 (13.0-15) years ($p=0.371$).

BMI in premenopausal women was 25.59 (23.94-28.74) kg/m2, in perimenopausal 25.37 (23.65-28.10) kg/m^2, while 27.72 (25. 47-31.22) kg/m2 in postmenopausal women. The BMI of postmenopausal women was significantly higher than that of premenopausal ($p=0.025$) and that of perimenopausal ($p=0.010$). The waist-hip ratio in premenopausal women was 0.80±0.05, in perimenopausal women 0 .80±0.05 and in postmenopausal 0.85±0.08. The ratio of the waist-hip circumference of postmenopausal women was significantly higher than the ratio of the waist-hip circumference of premenopausal women ($p<0.001$), as well as that of perimenopausal women ($p<0.001$).

The median concentration of SHBG in the premenopause group was 79.23 (55.90-103.60) nmol/L, in the perimenopause 77.50 (50.77-101.02) nmol/L, while in the postmenopause 59.60 (37 .80-80.0) nmol/L. SHBG concentration in postmenopause was significantly lower compared to SHBG concentration in premenopause ($p=0.002$) and perimenopause ($p=0.015$), while no significant difference was found between premenopause and perimenopause groups ($p=0.578$) (Table 1).

Table 1. Sex hormone binding globulin (SHBG) concentration in three groups of women

Group of women	SHBG median (min. = max.)	p
Premenopausal (N=50)	79.23 (55.90-103.60)	
Perimenopausal (N=50)	77.50 (50.77-101.02)	*p=0.578
Postmenopausal (N=50)	59.60 (37.80-80.0)	*p=0.002; †p=0.015

*in relation to the premenopausal group; †in relation to the perimenopausal group

In the group of premenopausal women, a significant negative correlation was found between SHBG and BMI (Rho= -0.385; $p<0.05$), and between SHBG and WHR (Rho= -0.411; $p<0.05$). A significant negative correlation was found between SHBG and BMI and between SHBG and WHR in premenopausal women (Rho= -0.385; $p<0.05$) (Table 2).

Table 2. Correlation of sex hormone binding globulin (SHBG) and anthropometric parameters in pre-, peri-, and post-menopausal women

Group of women	Parameter	Rho	p
Premenopausal (N=50)	BMI (kg/m^2)	-0.385	0.005
	WHR	-0.411	0.003
Perimenopausal (N=5050)	BMI (kg/m^2)	-0.667	<0.001
	WHR	-0.320	0.024
Postmenopausal (N=5050)	BMI (kg/m^2)	-0.594	0.001
	WHR	-0.407	0.003

Rho, Spearman correlation coefficient; SHBG, sex hormone binding globulin; BMI, body mass index; WHR, waist-hip ratio

In the group of perimenopausal women, a significant negative correlation was found between SHBG and BMI (Rho= -0.667; $p<0.01$), and between SHBG and WHR (Rho= -0.320; $p<0.05$).

In the univariate regression analysis model, it was determined that BMI (β= -0.667; $p<0.001$) and WHR (β= -0.320; $p=0.024$) were independent negative predictors of SHBG in the women of the perimenopause group, while in the multivariate non-regression analysis model it was determined that only BMI was a significant predictor of SHBG in women of the perimenopause group (β= -0.532; $p<0.001$) (Table 3).

In the group of postmenopausal women, a significant negative correlation was found between SHBG and BMI (Rho= -0.594; $p<0.01$), and between SHBG and WHR (Rho= -0.407; $p<0.05$). In the univariate regression analysis model, it was determined that BMI (β= -0.594; $p<0.001$) and WHR (β= -0.407; $p=0.003$) were independent negative predictors of SHBG in postmenopausal women, while in the multivariate regression analysis model it was determined that only BMI is an independent negative predictor of SHBG in postmenopausal women (β= -0.263; $p=0.024$) (Table 3).

Table 3. Non-dependent predictors of sex hormone binding globulin (SHBG) in peri– and postmenopausal women

Reproductive status of women	Variable	Univariate regression analysis		Multivariate regression analysis	
		Coefficient β	p	Coefficient β	p
Perimenopausal	BMI (kg/m^2)	-0.667	<0.001	-0.532	<0.001
	WHR	-0.320	0.024	-0.095	0.454
Postmenopausal	BMI (kg/m^2)	-0.594	<0.001	-0.296	0.046
	WHR	-0.407	0.003	-0.263	0.075

Dependent variable: SHBG

DISCUSSION

The results of our research showed that the BMI of postmenopausal women was significantly higher than the BMI of premenopausal women, as well as that of perimenopausal women. The ratio of the waist-hip circumference of postmenopausal women was also significantly higher than the ratio of the waist-hip circumference of premenopausal women, as well as that of perimenopausal women.

It was shown that the average BMI of postmenopausal women was higher than that of premenopausal women, even if they had better eating habits (12), which is in accordance with our results. An important result of some studies showed that the mean anthropometric values of waist circumference, WHR and BMI were significantly higher in postmenopausal women (13,14).

Some authors believe menopause is not associated with weight gain but leads to an increase in total body fat and a redistribution of body fat from the periphery to the trunk, resulting in visceral adiposity (15). In a study by Ahmed (16), significant changes were observed in postmenopausal women. Significant weight increase, BMI and waist-hip ratio were found in postmenopausal women. It may be due to the complex relationship between BMI and hypothalamic-pituitary axis function. In a study conducted by Hummadi et al., a significant increase in BMI and WC was found in postmenopausal women compared to the premenopausal group. It is commonly assumed that the volume of fat mass increases with age and results in a higher BMI recorded during aging (4).

While BMI is a widely applicable measure of general overweight and obesity in epidemiologic research, waist circumference and WHR generally serve as measures of abdominal fat distribution and hip circumference of gluteofemoral fat distribution. However, the dilemma remains whether these measures are related to SHBG values independently of total body mass. (17). In humans, liver fat, but not visceral fat or total body fat, has been shown to be an independent predictor of SHBG plasma values. Importantly, during lifestyle changes with dietary modification and increased physical activity, increases in SHBG are more strongly associated with decreases in liver fat compared to visceral fat or total body fat. Also, morbidly obese subjects who underwent bariatric surgery showed an increase in plasma SHBG concentration that was closely related to weight loss. (18). In our study, the concentration of SHBG during post-menopause was significantly lower than before a woman entered menopause, while in the study of Soares et al. (19), SHBG decreased slightly until the fourth year of post-menopause and increased thereafter. In the study by Franik et al. (20) and in our study, a higher WHR value resulted in a lower SHBG concentration.

In our study, anthropometric parameters, BMI and WHR were significantly higher in postmenopausal women comparing to premenopausal and perimenopausal groups, and a significant negative correlation of SHBG and anthropometric parameters was found in all three examined groups.

In conclusion, considering that our result showed the value of SHBG decreasing from pre-menopause towards menopause, regardless of the duration of menopause, it can be used in a certain population of women as a predictor of cardiovascular diseases and metabolic syndrome associated with obesity itself.

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TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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