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Uric acid independently correlates with sex-hormone binding globuline in postmenopausal women

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Summary. *Background/Aim:* Low sex-hormone binding globuline (SHBG) and high uric acid level are shown to be the independent predictors of many cardiometabolic diseases. However, it is unknown whether this two biomarkers are interrelated, and if so, whether this relationship is independent or it is mediated by some whether these factors. Therefore, the aim of the current study was to examine the potential relationship between serum SHBG and uric acid levels in the cohort of postmenopausal women. *Methods:* A total of 150 postmenopausal women encompassed this cross-sectional study. Biochemical and anthropometric data were obtained. *Results:* In univariate ordinal regression analysis, uric acid (Odds ratio (OR)=0.983, 95% Confidence Interval (CI) 0.978-0.989, p<0.001), high-density lipoprotein cholesterol (OR=4.135, 95% CI 2.004-9.291, p<0.001), high sensitivity C-reactive protein (OR=0.656, 95% CI 0.530-0.811, p<0.001), retinol-binding protein 4 (OR=0.962, 95% CI 0.931-0.995, p=0.023), and cystatin C (OR=0.004, 95% CI 0.000-0.079, p<0.001), were shown to be associated with SHBG level. However, multivariate ordinal regression analysis showed that only uric acid was independently associated with SHBG level in postmenopausal women (OR=0.990, 95% CI 0.983-0.988, p=0.018). Rise in uric acid concentration by 1 μmol/L decreased the probability of higher SHBG concentration by 1%. Nagelkerke R^2 for the Model was 0.464 which indicated that 46.4% of variation in SHBG concentration could be explained with this Model. *Conclusion:* Uric acid is independently associated with SHBG in postmenopausal women.

Key words: obesity, postmenopausal, sex-hormone binding globuline, uric acid

Introduction

Postmenopausal women experience increased risk of cardiometabolic disorders compared with premenopausal ones (1). Hormonal changes characterized with decreased estradiol levels, as well as increased androgenicity which occur during menopause are assumed as one of the main reasons for such disturbances (2).

Additionally, the increased prevalence of obesity, especially central obesity, and metabolic syndrome in postmenopause and its concomitant worsening insulin resistance, higher level of inflammation, dyslipidemia, and increased cardiovascular risk burden further aggravate already existed complex pathophysiological milleu in this vulnerable period (3).

Sex-hormone binding globuline (SHBG) is protein synthesized in liver whose function is not merely the transport of sex steroids in circulation (4). Previous reports have shown the relationship between low SHBG and obesity (5), metabolic syndrome (6), diabetes mellitus type 2 (7), as well as cardiovascular diseases (8). However, although an independent role of sex hormones on cardiovascular events (9) has been confirmed by some large studies, there are still conflicting data on this relationship (10).

In addition, postmenopausal women experience increased risk for hyperuricemia compared with women in reproductive age (11). One of the proposed explanation for such finding is the lack of uricosuric effect of estrogen due to its decrease (11), as well as increased

abdominal fat accumulation with concomitant insulin resistance in postmenopause (12). Since high uric acid level was also shown to be the independent predictor for many cardiometabolic diseases (11, 13), just like low SHBG (5-8), it is unknown whether these two biomarkers are interrelated, and if so, whether this relationship is independent or it is mediated by some other factors. Especially considering the fact that studies examining its relationship are scarce.

Therefore, the aim of the current study was to examine the potential relationship between serum SHBG and uric acid levels in the cohort of postmenopausal women.

Materials and Methods

Study population

This study with cross-sectional design resulted from previous investigations of cardiometabolic risk factors in postmenopausal women (2, 14).

A total of 150 postmenopausal women were enrolled in the examination, after their recruitment by the gynecologist in the Primary Health Care Center in Podgorica, Montenegro. The study was conducted in a period from October 2012 to May 2013.

Women were eligible to enter the research if they were postmenopausal (i.e., the absence of menstrual bleeding for more than one year), with preserved kidney function, with no signs of acute inflammatory disease, and without any medicament therapy usage in the last six months.

Postmenopausal women were excluded from the study if they had: gout, high sensitivity C-reactive protein (hsCRP) higher than 10 mg/L, estimated glomerular filtration rate (eGFR) lower than 90 mL/min/1.73 m^2, liver diseases, hypothyroidism or hyperthyroidism, cardiovascular diseases, malignant diseases, cigarette smoking, and any medications usage in the last six months. Women with diabetes were also excluded from the research. Criteria for diabetes were described elsewhere (15).

Ethical Committee of Primary Health Care Center in Podgorica, Montenegro gave the approval for the research protocol. All postmenopausal women provided written informed consent. The survey was conducted in compliance with the Declaration of Helsinki.

Anthropometric measurements

Each participant underwent for basic anthropometric measurements. Women were considered to be normal weight with body mass index (BMI) < 25 kg/m^2 and waist circumference (WC) < 80 cm, whereas those with BMI ≥ 25 kg/m^2 and WC ≥ 80 cm, were regarded to be with overweight/obesity (14).

Biochemical analyses

Serum levels of uric acid, lipid parameters (i.e., total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides (TG)), glucose, bilirubin, creatinine, as well as the activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), were determined spectrophotometrically (Roche Cobas 400, Mannheim, Germany).

Levels of cystatin C, retinol-binding protein 4 (RBP4), and hsCRP were measured using an immunonephelometric assay (Behring Nephelometer Analyzer, BN II, Marburg, Germany). Sex hormones, SHBG and insulin levels were measured by chemiluminescent assay (Immulite 2000, Siemens, Muenchen, Germany). HOMA-IR was calculated, as described elsewhere (2).
Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained, and glomerular filtration rate was estimated, using Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) (1), as previously reported.

Statistical analysis

Data distributions were tested with Shapiro-Wilk test. Normally and *log*-normally distributed data were presented as arithmetic mean±standard deviation and geometrical mean (95% confidence interval-CI), respectively and compared by one-way analysis of variance with *post-hoc* Tukey test. Asymmetric data were presented as median (interquartile range) and compared by Kruskal-Wallis and Mann-Whitney test depending on the number of the groups. Categorical variables were given as absolute frequencies and compared by Chi-square test for contingency tables. Correlations of SHBG and clinical markers were evaluated by bivariate Spearman's correlation analysis and presented as correlation coefficient (ϱ). To assess the associations and predictions of clinical markers on SHBG concentration (ordinal dependent variable)

in postmenopausal women univariate and multivariate ordinal regression analysis was employed. Independent variables were those which significantly correlated with SHBG in Spearman's correlation analysis and had the identical effect at each cumulative split of the ordinal dependent variable (i.e., SHBG concentration). Also, in multivariate ordinal regression analysis, beside the assumption of proportional odds, independent variables were tested for multicollinearity. For internal validation of the models the bootstrap method with 10000 permutations was used. Data from those analyses are presented as odds ratios (ORs) and 95% CI. The explained variation in SHBG concentration in postmenopausal women was given by Nagelkerke R^2 value. Statistical analyses were performed using IBM® SPSS® Statistics version 22 software (Chicago, IL, USA). P values less than 0.05 were considered as statistically significant.

Results

General characteristics of postmenopausal women were given for SHBG tertile groups and were listed in Table 1. Postmenopausal women in the first SHBG tertile group had the highest BMI, WC, SBP and DBP than postmenopausal women in the second and the third SHBG tertile group. Women in all three groups were of the same age and had similar menopausal duration. There was unequal distribution of obese women in tested SHBG tertile groups. The highest percentage of obese women was in the lowest SHBG tertile group (Table 1).

There were significant differences in HDL-c, TG, glucose, ALT, GGT, uric acid, hsCRP, fibrinogen, RBP4, cystatin C, insulin levels and HOMA-IR across SHBG tertile groups (p<0.001, p=0.001, p=0.001, p<0.001, p=0.001, p<0.001, p<0.001, p=0.001, p=0.047, p=0.001, p<0.001, p<0.001, respectively). Postmenopausal women in the first/lowest SHBG tertile group had higher TG, glucose, ALT, GGT and uric acid levels and the lowest HDL-c, than those in the second and the third SHBG tertile group (Table 2). Also, the highest hsCRP levels, insulin concentrations and HOMA-IR were found among women in the first/lowest SHBG tertile group and their lowest concentrations were among women in the third/highest SHBG tertile group. The fibrinogen concentration was the lowest in the third/highest SHBG tertile group. Women in the third/highest tertile group had lower RBP4 and cystatin C levels than women in the first SHBG tertile group (Table 2).

Significant negative correlations were established between SHBG concentration and BMI, WC, SBP, DBP, LDL-c, TG, glucose, ALT, GGT, creatinine, uric

Table 1. General data of postmenopausal women according to SHBG tertile values

	First SHBG tertile group (≤52.11 nmol/L)	Second SHBG tertile group (52.12-69.65 nmol/L)	Third SHBG tertile group (≥69.66 nmol/L)	p
N	49	51	50	
Age, years	57±5	57±4	56±5	0.259
BMI, kg/m^2	30.3±3.5	25.4±3.4^{a*}	23.7±3.1^{a*,b**}	<0.001
WC, cm	99±9	86±11^{a*}	81±8^{a*,b**}	<0.001
SBP, mmHg$^+$	150 (130-160)	130 (112-148)^{c**}	120 (95-130)^{c**,d**}	<0.001
DBP, mmHg$^+$	90 (85-96)	86 (73-95)^{c**}	76 (65-86)^{c**,d**}	<0.001
Obesity status, (No/Yes)	0/49	22/29	28/22	<0.001
Menopause duration, years$^+$	5 (3-10)	5 (2-9)	3 (1-9)	0.395

Data are presented as arithmetic mean±standard deviation and compared by one-way ANOVA.
$^+$Skewed distributed data are presented as median (interquartile range) and compared by Kruskal-Wallis test.
Categorical variables are presented as absolute frequencies and compared by Chi-square test for contingency tables.
a - significantly different from the first SHBG tertile group using *post-hoc* Tukey test
b - significantly different from the second SHBG tertile group using *post-hoc* Tukey test
c - significantly different from the first SHBG tertile group using Mann-Whitney test
d - significantly different from the second SHBG tertile group using Mann-Whitney test
*p<0.01 **p<0.05

acid, hsCRP, fibrinogen, RBP4, cystatin C, insulin and HOMA-IR. Significant positive correlations were determined between SHBG concentration and HDL-c (Table 3).

In univariate ordinal regression analysis, uric acid, HDL-c, hsCRP, RBP4 and cystatin C were showed to be associated with SHBG concentration. This analysis indicated that as uric acid level rose for 1 μmol/L, the probability for higher SHBG concentration decreased for 1.7% (OR=0.983, 95% CI 0.978-0.989, p<0.001). As HDL-c rose for 1 mmol/L, the probability for higher SHBG concentration increased 4.315 times (OR=4.135, 95% CI 2.004-9.291, p<0.001). As well, an increase in hsCRP (OR=0.656, 95% CI 0.530-0.811, p<0.001), RBP4 (OR=0.962, 95% CI 0.931-0.995, p=0.023), and cystatin C (OR=0.004, 95% CI 0.000-0.079, p<0.001), decreased the probability for higher SHBG concentration by 34.4%, 3.8% and 99.6%, respectively (Table 4). Nagelkerke R^2 for the uric acid was 0.267 which means that 26.7% variation in SHBG concentration could be explained by uric acid level.

Independent variables which correlated significantly with SHBG (Table 3) and were proportional across the different SHBG tertiles showing no multicollinearity were included in multivariate ordinal regression analysis. This statistical analysis showed independent associations and predictions of uric acid on SHBG concentration in postmenopausal women (Table 4). Ad-

Table 2. Clinical markers of postmenopausal women according to SHBG tertile groups

	First SHBG tertile group (≤52.11 nmol/L)	Second SHBG tertile group (52.12-69.65 nmol/L)	Third SHBG tertile group (≥69.66 nmol/L)	p
TC, mmol/L	6.54±0.97	6.40±1.10	6.47±1.10	0.789
HDL-c, mmol/L	1.49±0.36	1.76±0.41[a*]	1.82±0.41[a*]	<0.001
LDL-c, mmol/L	4.51±0.93	4.25±1.07	4.18±1.05	0.250
TG, mmol/L[+]	1.56 (1.39-1.76)	1.21 (1.06-1.37)[a**]	1.15(1.02-1.30)[a*]	0.001
Glucose, mmol/L	5.57±0.61	5.30±0.45[a**]	5.19±0.41[a*]	0.001
AST, U/L[++]	18 (15-21)	18 (16-21)	18(17-20)	0.497
ALT, U/L[++]	22 (17-28)	18 (14-21)[c**]	15 (13-21)[c**]	<0.001
GGT, U/L[++]	14 (12-19)	11 (9-14)[c**]	10 (9-13)[c**]	0.001
Total bilirubin, μmol/L[++]	7.60 (6.77-9.72)	7.20 (6.10-10.95)	7.75 (6.20-10.20)	0.818
Creatinine, μmol/L[++]	56.07 (53.92-58.32)	54.00 (52.33-55.73)	54.21 (52.38-56.11)	0.252
Uric acid, μmol/L	305.82±63.38	253.78±57.20[a**]	227.58±47.55[a**]	<0.001
hsCRP, mg/L[+]	1.70 (1.33-2.16)	1.02 (0.79-1.33)[a*]	0.55 (0.42-0.73)[a**,b**]	<0.001
Fibrinogen, g/L	3.98 (3.81-4.17)	3.94 (3.78-4.11)	3.54 (3.36-3.73)[a**,b**]	0.001
RBP4, g/L	43.73±8.17	41.08±9.70	38.48±8.82[a**]	0.047
Cystatin C, mg/L	0.80±0.10	0.77±0.10	0.73±0.09[a*]	0.001
Estradiol, pmol/L[+]	56.10 (51.93-60.60)	49.78 (45.95-53.94)	56.49 (51.36-62.14)	0.060
Testosterone, nmol/L[+]	1.04 (0.95-1.14)	0.99 (0.91-1.07)	0.92 (0.83-1.02)	0.196
Insulin, μIU/L[++]	9.99 (7.86-14.00)	5.99 (4.76-7.89)[c**]	4.71 (3.69-5.20)[c**,d**]	<0.001
HOMA-IR[++]	2.55 (1.93-3.58)	1.46 (1.07-1.80)[c**]	1.04 (0.82-1.22)[c**,d**]	<0.001

Data are presented as arithmetic mean ± SD and compared by one-way ANOVA.

[+] *Log*-normal distributed data are presented as geometric mean (95% CI) and compared by one-way ANOVA after logarithmic transformation.

[++]Skewed distributed data are presented as median (interquartile range) and compared by Kruskal-Wallis test.

a - significantly different from the first SHBG tertile group using *post-hoc* Tukey test

b - significantly different from the second SHBG tertile group using *post-hoc* Tukey test

c - significantly different from the first SHBG tertile group using Mann-Whitney test

d - significantly different from the second SHBG tertile group using Mann-Whitney test

*p<0.01; **p<0.05

Table 3. Bivariate Spearman's correlation analysis between SHBG and clinical markers

	SHBG, nmol/L	
	ϱ	P
Age, years	-0.110	0.182
BMI, kg/m2	-0.645	<0.001
WC, cm	-0.628	<0.001
SBP, mmHg	-0.443	<0.001
DBP, mmHg	-0.418	<0.001
Menopause duration, years	-0.126	0.123
TC, mmol/L	-0.037	0.652
HDL-c, mmol/L	0.347	<0.001
LDL-c, mmol/L	-0.161	0.049
TG, mmol/L	-0.275	0.001
Glucose, mmol/L	-0.227	0.005
AST, U/L	0.093	0.258
ALT, U/L	-0.297	<0.001
GGT, U/L	-0.301	<0.001
Total bilirubin, μmol/L	-0.011	0.892
Creatinine, μmol/L	-0.162	0.048
Uric acid, μmol/L	-0.498	<0.001
HsCRP, mg/L	-0.474	<0.001
Fibrinogen, g/L	-0.297	<0.001
RBP4, g/L	-0.201	0.014
Cystatin C, mg/L	-0.320	<0.001
Estradiol, pmol/L	-0.022	0.788
Testosterone, nmol/L	-0.121	0.142
Insulin, μIU/L	-0.699	<0.001
HOMA-IR	-0.696	<0.001

Data are presented as correlation coefficient Rho (ϱ)

justed odds for uric acid given in the Model (OR=0.990, 95% CI 0.983-0.988, p=0.018), demonstrated that rise in uric acid level by 1 μmol/L decreased the probability of higher SHBG concentration by 1%. Nagelkerke R^2 for the Model was 0.464 which indicated that 46.4% of variation in SHBG concentration could be explained by this Model (Table 4).

Table 4. Estimated odds ratios after ordinal regression analysis for SHBG tertile groups as dependent variable

Unadjusted			
	OR (95% CI)	p	Nagelkerke R^2
Uric acid, μmol/L	0.983 (0.978-0.989)	<0.001	0.267
HDL-c, mmol/L	4.315 (2.004-9.291)	<0.001	0.109
hsCRP, mg/L	0.656 (0.530-0.811)	<0.001	0.129
RBP4, g/L	0.962 (0.931-0.995)	0.023	0.040
Cystatin C, mg/L	0.004 (0.000-0.079)	<0.001	0.098
Adjusted			
Model	OR (95% CI)	p	Nagelkerke R^2
Uric acid, μmol/L	0.990 (0.983-0.998)	**0.018**	0.464
HDL-c, mmol/L	1.359 (0.456-4.051)	0.582	
hsCRP, mg/L	0.882 (0.702-1.100)	0.284	
RBP4, g/L	0.997 (0.954-0.959)	0.909	
Cystatin C, mg/L	1.820 (0.027-122.364)	0.780	

Data are given as OR (95% CI)
Model included continuous variables: WC, glucose, ages, HDL-c, LDL-c, TG, creatinine, RBP4, cystatin C, hsCRP, fibrinogen and uric acid

Discussion

The finding of the current study reveals an independent relationship between high uric acid and low SHBG levels in the cohort of postmenopausal women. Even though we reported the negative correlation between SHBG and anthropometric indices, as well as with most markers of inflammation and HOMA-IR, respectively, only high uric acid remained the independent predictor of lower SHBG levels. In addition, not only that uric acid independently correlated with SHBG, but it explains even 46.4% of variation in SHBG concentration.

Our results are in line with previous study which showed that women with hiperuricemia (i.e., defined as uric acid ≥ 420μmol /L) displayed lower levels of SHBG compared with women without hyperuricemia (16). Similarly, in male population with diabetes mellitus type 2 uric acid was inversely correlated with SHBG (17).

It is known that SHBG is regarded to be a reliable parameter of nutritional status showing that obesity status greatly influences SHBG levels, both in women (5, 18) and men (19). Women during menopausal transition tend to increase in abdominal fat mass, thus resulting in increased insulin resistance and inflammation level compared to females in reproductive age (1, 2). Enlaged visceral adipose tissue secretes variety of adipokines and cytokines (such as RBP4, interleukin-1, tumor necrosis factor-α, cystatin C, hsCRP) (1, 2, 20, 21). Indeed, we have shown the highest proportion of overweight/obese

females in the lowest SHBG tertile group, as well as, the negative association of SHBG with adipokine, such as RBP4, but also with inflammation markers (i.e., hsCRP and cystatin C) in unadjusted model. Additionally, we have also shown positive correlation of SHBG with HDL-c in unadjusted model, although controversy exists whether these associations are mediated by obesity (18, 22, 23).

Saéz-López et al. (24) have demonstrated reduced SHBG levels in circulation of obese mice when compared with their lean counterparts, suggesting that liver fat accumulation is the main culprit for the decrease of plasma SHBG levels during obesity occurrence and progression. Hepatic lipogenesis, which is known to be enhanced during obesity development, leads to increase in palmitate level in hepatocytes, thus resulting in decrease in hepatocyte nuclear factor 4 (HNF-4α) protein levels, which is the key transcription factor for SHBG expression. Moreover, hepatic lipogenesis during obesity progression results in an increase in peroxisome proliferator-activated receptor (PPARγ) protein levels (25), which is the key factor that regulates the enlargement of adipocytes (26).

On the other hand, adipose tissue also secrets uric acid (27) since the former is accompanied with enhanced synthesis of free fatty acids, which is closely associated with *de novo* synthesis of purine through the pentose phosphate pathway activation (28). This might explain higher levels of uric acid in obese individuals (27). Moreover, study conducted on animal models showed that adipose tissue is characterized with increased expression and activity of xanthine oxidase (XO), the key enzyme responsible for uric acid production (28). Also, its decrease was accompanied with reduction in fat mass (29). This is in line with our previous study where we have reported an independent association between XO activity and BMI in overweight/obese population (30). It is assumed that XO plays an important role in adipocytes differentiation through regulation of the PPARγ activity (29). Moreover, XO inhibition was shown to decrease oxidative stress and inflammation associated with insulin resistance through amelioration of dyslipidemia (31).

Sex hormones may also impact hepatic XO activity, showing that oophorectomy leads to increased XO activity in female rat model, along with decreased urinary uric acid excretion (32). Additionally, diminished renal clearance of uric acid after menopause may be associated with lower levels of estrogen, as well as SHBG, but the underlying mechanisms of that relationship are not yet clearly elucidated (11).

Relatively small sample size of examined postmenopausal women and cross-sectional design are the main limitations of the current study. Also, we were not able to measure adipose tissue depots with precise imaging techniques (33), but with simple anthropometric measurements that are most frequently used in human research that comprise large population sample. Therefore, longitudinal studies with larger number of participants are needed to confirm our results.

Conclusion

Although higher levels of adipokine (i.e., RBP4), inflammation markers (i.e, hsCRP and cystatin C) and lower levels of HDL-c were associated with lower levels of SHBG, only uric acid was found to be independently negatively correlated with SHBG in postmenopausal women. New studies are needed to confirm our findings.

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