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Serum sex hormone–binding globulin, a determinant of cardiometabolic disorders independent of abdominal obesity and insulin resistance in elderly men and women

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Abstract

Serum sex hormone–binding globulin (SHBG) is related to cardiometabolic disorders; but whether or not this relationship is purely secondary to hyperinsulinemia and/or obesity, which down-regulates SHBG, is unknown. The aim of the study was to investigate the association of SHBG and total testosterone with atherogenic dyslipidemias, metabolic syndrome (MS), and diabetes among predominantly elderly Turkish adults. After appropriate exclusions, 777 randomly selected male and female subjects with available measurements of both variables were eligible and were analyzed cross-sectionally, with diabetic subjects analyzed separately. Free testosterone was calculated. Metabolic syndrome was identified by the modified criteria of the Adult Treatment Panel III. Metabolic syndrome was identified in half the sample, which had a median age of 58 years. The odds of low SHBG concentrations (<45 nmol/L in men, <55 nmol/L in women) for the likelihood of 2 types of dyslipidemias, MS, and diabetes were examined by regression analyses in standard models including age, smoking status, presence of abdominal obesity, and insulin resistance (homeostasis model assessment of insulin resistance). In both sexes, low SHBG was associated independently with high triglyceride/low high-density lipoprotein dyslipidemia and with MS, at significant 2.2- to 4.5-fold odds ratios, independent of waist circumference or homeostasis model assessment of insulin resistance index. Low SHBG among women was additionally associated with the likelihood of hypertriglyceridemia with elevated apolipoprotein B and—at borderline significance—with that of diabetes, again when adjusted for the same confounders. In an elderly population with prevalent MS, low SHBG levels significantly associate with high triglyceride/low high-density lipoprotein dyslipidemia, MS, and, in women alone, diabetes and a dyslipidemia marking small dense low-density lipoprotein particles, all independent of abdominal obesity and insulin resistance. Low SHBG may be an important independent factor for cardiometabolic risk, particularly in women.

1. Introduction

The decline in endocrine function in elderly men includes a decrease in total testosterone (TT) concomitant with an increase in sex hormone–binding globulin (SHBG), lowering further the bioavailable testosterone levels. Hypoandrogenemia in men and hyperandrogenemia in women are associated with visceral obesity, insulin resistance (IR), low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and plasminogen activator inhibitor-1 (PAI-1) [1]. Visceral adipose tissue, insulin levels, and SHBG concentrations seemed to be independent correlates of lipoprotein concentrations in men [2]. In postmenopausal women, SHBG also correlated positively with HDL-C and inversely with insulin after adjustment for adiposity [3]. The sex steroid changes are modified by increasing body mass index (BMI) and waist circumference (WC) as markers of

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overall and abdominal obesity in older people, associated with a tendency to IR. Low levels of bioavailable or free testosterone were shown to predict IR in normogonadal men, but not independent of subcutaneous fat tissue or of regional or overall body fat [4].

Low levels of SHBG and of TT predicted the development of metabolic syndrome (MS) [5,6] and of diabetes mellitus (DM) in men [5,7,8]. Hyperandrogenemia and low levels of SHBG were frequently found in premenopausal women with MS [9]. More recently, a meta-analysis of prospective studies showed that higher TT levels predicted lower risk of type 2 diabetes mellitus in men and increased risk in women [10]. It was also found in the same meta-analysis that SHBG was more protective of DM in women than in men.

Little is known about the distribution of TT and SHBG levels among elderly Turkish adults and especially their relation to various cardiometabolic disorders. In the Turkish Adult Risk Factor Study, an adverse risk profile had been confined to obese postmenopausal women with hypertriglyceridemia and elevated apolipoprotein (apo) B [11], which is reported to reflect increased numbers of small dense low-density lipoprotein (LDL) particles [12]. Although SHBG is affected inversely by both insulin levels and obesity, knowledge on the independent relation of SHBG to cardiometabolic disorders and dyslipidemia is sparse.

The purpose of the present study is to examine cross-sectionally the associations between the cardiometabolic risk profile—specifically atherogenic dyslipidemia, MS, and diabetes—and levels of SHBG in a predominantly elderly, nondiabetic Turkish male and female sample and to assess the dependence of such an association of abdominal obesity and IR, 2 of its main regulators, and the modulation by sex.

2. Population and methods

The study sample is derived from the cohort of the Turkish Adult Risk Factor Study, a prospective survey on the prevalence of cardiac disease and risk factors in a representative sample of adults in Turkey carried out periodically since 1990 throughout all geographical regions of the country; details of sampling were described previously [13]. The last follow-up of the cohort was made in 2005/2006; in two fifths of these participants, serum concentrations of both TT and SHBG were assayed. The following exclusions were made: age less than 40 years or greater than 89 years, hormone replacement therapy, individuals with values of creatinine >1.5 mg/dL in men and 1.3 mg/dL in women, thyroid-stimulating hormone >6.0 or <0.25 μU/mL, and γ-glutamyltransferase >100 μU/mL. Persons with diabetes numbering 116 were analyzed separately. This left 646 nondiabetic subjects (377 men and 269 women) for analysis who form the study sample. The study was approved by the Istanbul University Medical Faculty Ethics Committee. Individuals of the cohort signed consent for participation after having read an explanatory note.

2.1. Definitions

Individuals with diabetes were diagnosed by the criteria of the American Diabetes Association [14], namely, when plasma fasting glucose was ≥126 mg/dL (or 2-hour postprandial glucose >200 mg/dL) and/or the current use of diabetes medication. Subjects with concentrations of triglycerides >150 mg/dL combined with low (<40 mg/dL in men, <50 mg/dL in women) HDL-C were designated as having atherogenic dyslipidemia. Those with hypertriglyceridemia and elevated levels (>120 mg/dL) of apo B were identified. Individuals with MS were identified when 3 of the 5 criteria of the National Cholesterol Education Program (Adult Treatment Panel III) [15] were met, modified only for prediabetes (fasting glucose 100-125 mg/dL) [16] and for male abdominal obesity (cut point of ≥95 cm), as recently assessed in the Turkish Adult Risk Factor study [17]. A cut point of ≥88 cm for female abdominal obesity and being under antihypertensive treatment or having a blood pressure ≥130 mm Hg systolic and/or ≥85 mm Hg diastolic constituted the remaining criteria. *Hypertension* was defined as a blood pressure ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic, and/or use of antihypertensive medication.

Serum free testosterone (in picomoles per liter) was calculated (cfT) from the following equation: (2.28 −{1.38 × log[SHBG (nmol/L/10)]}) × TT (nmol/L) × 10 [18].

Among individuals with normal glucose regulation, IR was assessed from fasting insulin and glucose concentrations with the homeostasis model assessment (HOMA) equation: HOMA = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5 [19].

Insulin resistance (HOMA-IR) was defined as a HOMA index greater than 2.4, a cutoff that represented the 74th percentile in the nondiabetic cohort of the Turkish Adult Risk Factor Study.

2.2. Measurement of risk factors

Blood pressure was measured in the sitting position on the right arm, and the mean of 2 recordings at least 3 minutes apart was recorded. Never smokers, former smokers, and current smokers formed the categories in cigarette smoking. Weight was measured without shoes in light indoor clothes using a scale. The BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest.

Blood samples were collected in an 11-hour or longer fasting state in 95% of individuals in this study. Samples were shipped within a few hours on cooled gel packs to Istanbul to be stored in deep freeze at −75°C until analyzed at the Yildiz Technical University. Serum concentrations of TT, SHBG, and insulin were carried out by electrochemiluminescence immunoassay on Roche Elecsys 2010. Elecsys SHBG uses 2 monoclonal antibodies specifically directed against human SHBG, and testosterone assay is based on a

Table 1
Age-adjusted estimated marginal means and prevalences of selected characteristics of the nondiabetic sample

	Men			Women			*P*
	n	Mean	95% CI	n	Mean	95% CI	
Crude age (y)	377	59.2	52-68	269	57.4	51-65	.024
SHBG[a] (nmol/L)	377	44.3	42.2-46.5	269	55.1	52-58.2	.001
TT[a] (nmol/L)	377	15.5	14.5-16.7	268	0.72	0.66-0.78	.001
Free testosterone[a] (pmol/L)	377	210.9	195.9-226.9	268	8.77	8.02-9.57	.001
WC (cm)	377	95.6	94.4-96.8	268	92.7	91.3-94.1	.002
Fasting triglycerides (mg/dL)	350	165.8	154.5-177.2	264	152.9	139.8-165.9	.14
HDL-C (mg/dL)	377	40.1	39-41.2	269	47.1	45.8-48.4	.001
Apo B (mg/dL)	332	107.8	103.7-112	253	108.1	103.3-112.8	.93
Apo A-I (mg/dL)	324	135.4	132.5-138.3	246	149.3	146-152.6	.001
Fasting glucose (mg/dL)	350	90	88.2; 91.8	264	89.7	87.6-91.7	.81
Fasting insulin[a] (mIU/L)	315	7.96	7.38-8.59	243	8.51	7.82-9.29	.26
LDL-C (mg/dL)	347	115	111.3-118.8	258	126.4	122-130.8	.001
Total cholesterol (mg/dL)	377	191	186.5-195.6	269	206	200.6-211.3	.001
CRP[a] (mg/L)	355	1.90	1.70-2.13	260	2.65	2.33-3.02	.001
Hypertension[b] (%)	377	46.2		269	53.1		.054
MS (%)	377	43.7		269	46.8		.09
Current/former smokers (%)	377	33.7/39.9		269	8.4/8.8		.001

LDL-C indicates low-density lipoprotein cholesterol.
[a] Log-transformed values.
[b] At least 140/90 mm Hg.

competitive test principle using monoclonal antibody specifically directed to testosterone. For normal and pathological controls (PreciControlUniversal Elecsys, Roche Diagnostics, Mannheim, Germany), respectively, intraassay coefficients of variation were 1.2% and 1.7% for TT and 3.8% and 3.7% for SHBG; and interassay coefficients of variation were 4.1% and 6.5% for TT and 5.9% and 6% for SHBG.

Serum concentrations of total cholesterol, fasting triglycerides, glucose, HDL-C (directly without precipitation), and creatinine were determined by using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer (Tokyo, Japan). Concentrations of C-reactive protein (CRP) and apo B were measured by Behring kits and nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA).

2.3. Data analysis

Because of the skewed distribution of concentrations of TT, SHBG, insulin, HOMA index, and CRP, these were log-transformed for calculations and presentation. Descriptive parameters were shown as age-adjusted estimated marginal means ± SE. Pair-wise comparisons with Bonferroni adjustment were made to detect significance between sexes; 2-sided *t* tests and Pearson χ^2 tests were used to analyze the differences in means and proportions between other groups. Because diabetes was associated in women with low SHBG (odds ratio [OR], 1.83, $P = .053$) after age adjustment, likelihoods for cardiometabolic risk other than diabetes were analyzed with diabetic subjects excluded from the main analyses to eliminate possible confounding.

A possible interaction between WC and SHBG was examined by forming 4 groups of the 2 mentioned parameters via dichotomizing across the near-median values of 95 cm and 45 nmol/L in men and 92 cm and 55 nmol/L in women. Multiple linear regression analyses were performed with continuous parameters. Likelihood estimates and 95% confidence intervals (CIs) were obtained by the use of logistic regression analyses in models controlled for confounders. The increment corresponding to a 2-fold rise in SHBG by logistic regression analysis was calculated by multiplying the log of the OR value with a factor of 0.2 and then taking its antilog. A value of $P < .05$ on the 2-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS, Chicago, IL, no. 9026510).

3. Results

Median (interquartile range) age was 58 (52-68) years in men and 57 (51-63) years in women. Diabetes, present in

Table 2
Linear regression analysis for SHBG[a]

	Men (n = 305)		Women (n = 239)	
	β coefficient	*P*	β coefficient	*P*
Age (y)	1.016	.001	1.008	.025
Waist girth (cm)	0.9943	.006	0.9887	.001
Triglycerides (mg/dL)	0.9993	.008	0.9983	.035
HDL-C (mg/dL)	1.004	.15	1.0114	.001
Testosterone[a] (nmol/L)	1.726	.001	0.973	NS
Apo B (mg/dL)	0.9998	NS	0.9988	.21
Smoking status	1.042	.20	0.958	NS

Models were significant in men ($F = 17.1$, $P < .001$) and in women ($F = 8.8$, $P < .001$), explaining 28% and 20% of variance of SHBG, respectively. NS indicates not significant.
[a] Log-transformed values.

Table 3
Association between low SHBG levels and abdominal obesity for dyslipidemias, adjusted for age, smoking, testosterone, and HOMA-IR

	Hypertriglyceridemia with elevated apo B [a]				Triglyceride/HDL dyslipidemia [b]			
	Men (n = 275)		Women (n = 221)		Men (n = 307)		Women (n = 235)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age (y)	0.99	NS	1.04	0.99-1.09	1.00	NS	1.00	NS
HOMA >2.4	1.30	NS	1.53	NS	2.58	1.50-4.49	2.23	1.19-4.17
WC >95/>92 cm	1.14	NS	1.12	NS	1.09	NS	1.38	NS
SHBG <45/<55 nmol/L	1.23	NS	2.81	1.17-6.71	2.97	1.63-5.4	2.19	1.16-4.14
TT [c]	0.69	NS	0.53	NS	0.963	NS	0.76	NS
Current smokers	0.85	NS	1.53	NS	1.42	NS	0.43	NS

Former smoking included in models not significant.

[a] Included were 50 men and 31 women with triglyceride >150 mg/dL + apo B >120 mg/dL. One hundred forty-three men and 116 women with abdominal obesity encoded.

[b] Ninety-five men and 61 women with dyslipidemia (triglyceride >150 mg/dL + HDL <40/50 mg/dL) were included. One hundred forty men and 119 women with low SHBG encoded. One hundred fourteen men and 86 women with HOMA-IR encoded.

[c] Log-transformed values.

16.9% of men and women, was separately analyzed multivariately for a possible association with SHBG. The full study sample comprised MS among 49% of men and 54% of women. A WC greater than 95 cm in men and greater than 92 cm in women was encountered in 52% of the nondiabetic sample.

3.1. Values stratified by sex and correlates

Table 1 gives age-adjusted estimated marginal means of certain characteristics of the nondiabetic study sample. A tendency to abdominal obesity, high triglyceride, and low serum levels of total cholesterol, HDL-C, and LDL cholesterol when compared with Western populations may be noted. Median (interquartile range) values in men were 16.1 (12.4-19.9) nmol/L TT, 44.3 (32.7-62) nmol/L SHBG, and 222.2 (179-260) pmol/L cfT. Corresponding figures in women were 0.70 (0.45-1.05) nmol/L TT, 54.6 (38-75.1) nmol/L SHBG, and 8.3 (5.5-13.1) pmol/L cfT.

Inverse correlations of SHBG were significant in men with fasting insulin ($r = -0.17$) and in women with apo B ($r = -0.24$) and CRP ($r = -0.21$).

Linear regression analysis for SHBG (Table 2) revealed that significant independent associations existed positively with age and inversely with WC and serum triglycerides in both sexes, positively with HDL-C in women, and positively with TT in men. Increments of 12 cm of waist girth or 80 mg/dL of triglycerides each corresponded to a 13% decline in the SHBG value in women.

3.2. Relation to atherogenic dyslipidemia

Analyses contained in Tables 2–4 are confined to subjects who had no missing values with respect to triglyceride and/or insulin in the fasting state. In logistic regression analysis for hypertriglyceridemia with elevated apo B in a model with 496 men and women including age, smoking status, HOMA-IR, TT, presence of abdominal obesity, and dichotomized SHBG concentrations, associations were not independently significant except for low SHBG (<55 nmol/L) in women (OR, 2.81; 95% CI, 1.17-6.71) (Table 3).

In a similar analysis for high triglyceride/low HDL-C dyslipidemia, which comprised 542 men and women (because inclusion of apo B was not required), low SHBG levels were significantly associated with dyslipidemia at approximately 2.9-fold ORs in both sexes, in addition to HOMA-IR.

3.3. Associations with MS and DM

Table 4 shows logistic regression models for MS in which age, smoking status, and HOMA-IR were adjusted for and in which a possible interaction between WC and SHBG was examined in 4 groups. Apart from a significant association of HOMA-IR with MS in both sexes, SHBG contributed significantly and independently to the association of WC, an association also graphically represented in Fig. 1. The contribution of low SHBG to abdominally obese men's association with MS was modest (1.3-fold). By contrast,

Table 4
The SHBG and WC for the association with MS adjusted for age, smoking, and HOMA-IR

	Men (n = 307)		Women (n = 236)	
	OR	95% CI	OR	95% CI
Age (y)	1.033	1.002-1.064	1.008	0.98-1.04
HOMA >2.4	2.86	1.61-5.08	2.45	1.32-4.55
WC <95/<92 cm, SHBG <45/<55 nmol/L	4.48	1.69-11.9	3.30	1.29-8.48
WC >95/>92 cm, SHBG >45/>55 nmol/L	17.4	6.55-46	6.41	2.59-15.8
WC >95/>92 cm, SHBG <45/<55 nmol/L	22.2	8.8-55.9	14.6	5.86-36.4
Former smokers	1.07	NS	1.98	NS
Current smokers	1.10	NS	0.68	NS

One hundred thirty-one nondiabetic men and 107 women with MS were included in the model. Referents for ORs are the group with low WC and high SHBG, HOMA index ≤2.4, and never smokers, respectively.

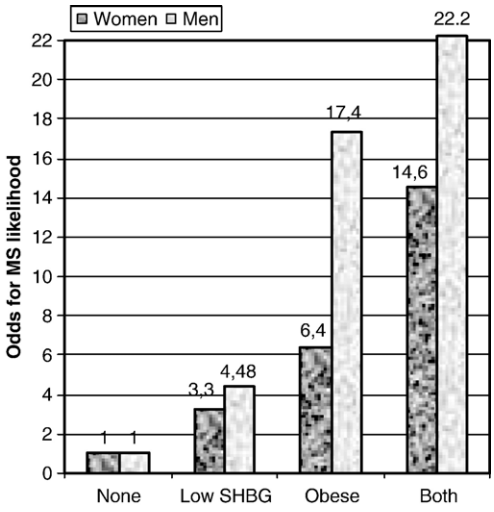

Fig. 1. Graphic illustration of the sex-specific independent associations of abdominal obesity and low SHBG with MS. *Low SHBG* denotes nonobese + low SHBG, *obese* denotes abdominally obese + high SHBG, *both* denotes abdominally obese + low SHBG. In men, abdominal obesity overwhelmingly dominated the likelihood for MS, low SHBG contributing significantly in nonobese men. Among women, low SHBG rather than abdominal obesity seemed to be the more important factor related to MS because it seemed operative both in nonobese women (3.3-fold OR) and in obese women (2.3-fold OR), contrasted to isolated abdominal obesity (6.4-fold OR).

women with low—compared with high—SHBG levels displayed a 2.5- to 3-fold likelihood for MS, regardless of the presence of abdominal obesity, which was weakly associated with MS independent of HOMA-IR and low SHBG. In other words, low SHBG seemed to be an equally or more important determinant for the MS likelihood than abdominal obesity, being relevant not only in obese but also nonobese women.

When 116 individuals with diabetes were included and diabetes was taken as dependent variable in a regression model that also comprised age, smoking status, HOMA-IR, presence of abdominal obesity, and low SHBG levels, none other than age and HOMA-IR attained statistical significance in either sex. Among women, low SHBG levels were borderline significantly associated (OR, 1.83; 95% CI, 0.924-3.6).

4. Discussion

This study on predominantly elderly Turkish men and women suggested low SHBG to be a salient element of cardiometabolic risk by apparently contributing significantly among both sexes to the association with triglyceride/low HDL dyslipidemia and to that with MS independent of HOMA-IR and abdominal obesity. In women, low SHBG exhibited additionally significant associations with hypertriglyceridemia with elevated apo B, a dyslipidemia recognized to reflect increased small dense LDL particles, and—at a borderline significance—with diabetes, again independent of HOMA-IR and abdominal obesity. It is thus suggested that the recognized association of SHBG with certain metabolic disorders due to down-regulation by insulin and obesity [20] may be extended to include a component directly affecting these disorders.

Although comparison with published reference levels should be made with caution, age-matched values for cfT tended to be on the low side in women compared with reference levels [21], whereas SHBG levels seemed to be (1.6-fold) somewhat high in men and cfT correspondingly low [21]. This is reflected also in high SHBG concentrations in men compared with those in women (equivalent to 80% of the values in women, rather than being 1/2 to 2/3). Nonetheless, the independent associations between SHBG and WC, serum triglycerides, and, in men, TT, as well as the inverse correlation with insulin, attest to the validity of hormone measurements.

4.1. Relation of SHBG levels with obesity and dyslipidemias

Sexes were similar in the independent inverse associations of SHBG with markers of abdominal obesity, the women showing twice as strong an association. Low SHBG levels were strongly associated with high triglyceride/low HDL dyslipidemia in both sexes, remarkably independent of HOMA-IR and abdominal obesity. This has not been documented previously in a general population sample and is in agreement with cross-sectional findings in postmenopausal women in the Atherosclerosis Risk in Communities study [22] and in 352 men aged 50 to 59 years of the PRIME study [23] in which associations of SHBG separately with serum triglycerides and HDL-C persisted despite adjustment for adiposity and markers of IR.

Sex modulated the independent association of SHBG inasmuch as this protein was associated only in women with a dyslipidemia involving elevated apo B and tended to being associated with diabetes. Hypertriglyceridemia with elevated apo B, recognized to reflect the presence of increased small dense LDL particles [12], exhibited an association with low SHBG levels in women independent of abdominal obesity and HOMA-IR. A hyperandrogenic risk profile has already been previously reported by us in postmenopausal Turkish women to be linked with an array of proatherogenic risk factors [11]. Because the mentioned dyslipidemia is thought to represent increased very low-density lipoprotein secretion due to excessive release of fatty acids from adipocytes [12], our novel observation in women implicates the involvement of SHBG in this process. Haffner et al [24] had reported that LDL size (as determined by gradient gel electrophoresis) in 87 normoglycemic men was positively associated with SHBG and TT, a relationship that tended to be stronger in nonobese subjects. Our findings in women support their suggestion that SHBG may have an independent modifying effect on LDL composition.

4.2. Sex-specific associations of SHBG with cardiometabolic disorders

Even after adjustment for HOMA-IR and abdominal obesity, diabetes tended to be associated with low SHBG in women. This is in line with a recent meta-analysis on endogenous sex hormones and type 2 diabetes mellitus [10] in which SHBG levels were more protective in women (>60 vs ≤60 nmol/L; relative risk, 0.20) than in men (>28.3 vs <28.3 nmol/L; relative risk, 0.48). The independent association of SHBG with the presumed atherogenic dyslipidemia exclusively in women that was shown in this study may be a relevant factor in its association with diabetes.

Low levels of SHBG and TT predicted MS in middle-aged men [5], were associated with increased prevalence of MS, and marked increased cardiovascular and coronary disease mortality in elderly Finnish men [25]. An inverse association between MS and SHBG after adjustment for insulin levels or markers of obesity was found in 400 predominantly elderly Dutch men in whom a positive relationship with insulin sensitivity was also observed [26]. In view of the described associations of SHBG with the 2 dyslipidemias involving low HDL-C or a surrogate of small dense LDL particles (and diabetes), it is not surprising that low SHBG level was linked strongly to MS. In this regard, low SHBG, adjusted for HOMA-IR, was strongly related to MS likelihood in men having no abdominal obesity, but contributed weakly among abdominally obese men. This is in line with the recent observation in which lower levels of SHBG were predictive of MS among men with BMI less than 25 kg/m^2 but not significantly so in men with BMI greater than 25 kg/m^2 [27].

The reasons for the link between low SHBG and MS only in nonobese men are unclear; but in women of the present study, as a further novel finding, low SHBG seemed to be an equally or more important determinant for the MS likelihood than abdominal obesity, a central component of MS, irrespective of the presence of the latter, because it was relevant not only in the obese but also in the nonobese women. It may be hypothesized that low SHBG levels enhance the development of cardiometabolic disorders by affecting serum triglycerides and/or LDL composition independently of IR or obesity. The action of SHBG on triglycerides seems operative in both sexes, whereas that in Turkish women involves additionally apo B, the LDL composition, and possibly the regulation of dysglycemia. The effect of SHBG on lipids might be mediated by regulation of hepatic lipoprotein lipase activity [28], thereby inhibiting release of fatty acids from adipocytes.

Low SHBG levels may be the explanation to our previously reported analysis in Turkish adults with normal glucose regulation concerning a significant prediction of the development of diabetes in women with MS [29], who are prone to harbor low SHBG levels, regardless of the presence of abdominal obesity. Yet in men with MS, diabetes was not independently predicted by MS [29] because an accompanying low SHBG would contribute substantially only in men without abdominal obesity. Furthermore, low SHBG levels may underlie the high susceptibility to high triglyceride/low HDL-C dyslipidemia and the prediction of MS in Turkish men [17] and women [30] already at WC quartile II, namely, in the absence of true abdominal obesity. The question as to the relevance of the association of low SHBG with MS in the high prevalence of MS among Turkish adults, particularly in women, needs further investigation in the future.

The cross-sectional design limits the study to make causal inferences. The lack of data on serum estrogens precludes the elimination of a confounder, but estrogen is known not to exhibit as high an affinity to SHBG as testosterone. Conclusions derived from this middle-aged and elderly study sample with a high prevalence of MS may not be entirely applicable to young adults or to populations among whom MS prevails infrequently. The study's being based on a random population sample, the separate analysis of diabetic subjects, the inclusion of women permitting the emergence of differentially modulating [24] sex-specific differences, its evaluation using concomitant adjustment for confounders such as HOMA-IR and WC, and its capability to assess in a combined fashion associations with various cardiometabolic disorders constitute the strengths of the study.

We conclude that SHBG seems to be an important independent element of cardiometabolic risk in populations with a high prevalence of MS, low levels associating significantly with both high triglyceride/low HDL dyslipidemia and MS and, in women alone, with a dyslipidemia marking small dense LDL particles and diabetes, invariably independent of abdominal obesity and IR. Recognition of this may carry important implications in risk assessment and prevention of cardiometabolic disorders. Prospective studies on the independent relation of SHBG with cardiometabolic disorders, especially with dyslipidemias, are warranted.

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