Research Article

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Association of central obesity with sex hormone-binding globulin: a cross-sectional study of 1166 Chinese men

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Abstract: Background Both sex hormone-binding globulin and central obesity have been found to be associated with metabolic and cardiovascular diseases. However, the direct relation between sex hormone-binding globulin and central obesity has not been demonstrated.

Methodology We performed a cross-sectional study of 1166 male participants from Zunyi, Guizhou, western China, in 2013. Each participant completed a questionnaire and had a brief clinical exam with a fasting blood sample taken. All blood samples underwent standard laboratory testing for sex hormone-binding globulin. Level of serum sex hormone-binding globulin was compared by demographic characteristics, and multiple linear regression was used to evaluate the independent association of variables and sex hormone-binding globulin level.

Results The mean serum level of sex hormone-binding globulin was increased in old-aged men (older than 40 years; mean 44.68±20.58 nmol/L), low diastolic blood pressure (<90mmHg; 43.76±20.50 nmol/L), waist-to-height ratio <0.5 (48.73±20.59 nmol/L), no education (52.36±22.91 nmol/L), farm occupation (43.58±20.60nmol/L), non-alcohol or former user (44.78±20.94 nmol/L) and long-term medication history (44.79±21.50 nmol/L). Factors independently associated with sex hormone binding globulin level on multiple regression were waist-to-height ratio (β=-11.84 [95% confidence interval -13.96,-9.72]), age(β=12.40 [9.63,15.17]) and diastolic blood pressure (β=-5.07 [-7.44,-2.71]).

Conclusions Central obesity has an independent inverse relation with serum level of sex hormone binding globulin among western Chinese men

Keywords: Cardiovascular risk; Metabolism; Cross-sectional study

1 Introduction

Sex hormone-binding globulin (SHBG) is a kind of glycoprotein that binds to androgen or estrogen hormones in blood circulation and is mainly produced by human hepatocytes. Low serum level of SHBG has been found a risk factor of metabolic syndrome (MS) in both cross-sectional and longitudinal studies [1-3]. Also, a reverse relation was found between SHBG and cardiovascular disease (CVD) [4].

Central obesity, also known as abdominal obesity, is one of the National Cholesterol Education Program Adult Treatment Panel (ATP-III) criteria [5], the most widely used criteria in diagnosing MSat present. Moreover, CVD risk is associated more strongly with central obesity than general obesity [6-8].

Some diseases seem to be part of both SHBG and central obesity. However, studies that focused on their direct relation are few. Furthermore, central obesity is

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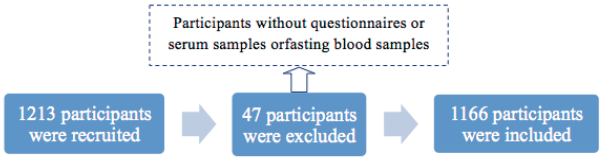
often defined by waist circumference (WC) only, even in the ATP-III criteria. Waist-to-height ratio (WHtR) is more appropriate in defining central obesity than WC and waist-to-hip (WHR) ratio because WC and WHR do not include height, which can influence the distribution of abdominal fat and differs by age and race. Also, WHtR shows better predictive ability than WC and BMI for diabetes, hypertension, and CVD [6, 9, 10]. The most commonly use index, body mass index (BMI), is used for substance adipose tissue not visceral adipose tissue, and it cannotdistinguish muscle type obesity or adipose type obesity.

The data for this cross-sectional study were from the Chinese Middle-aged and Elderly Men of Reproduction Health Project. In this study, we used WHtR rather than WC or WHR to define central obesity to investigate the direct association of SHBG level with central obesity after adjustment for confounding factors (demographic characteristics and lifestyle), to support existing evidence of both biochemical and epidemiological research.

2 Methods

2.1 Subjects

We performed this cross-sectional study from August 20 to September 20, 2013, in Zunyi, Guizhou, located in the southwest of China, with a population of 1.2 million. We used a stratified cluster design. Among 80 communities in this city, 50 km away from the downtown, 7 communities were targeted (2 urban communities, 2 suburban communities and 3 rural communities). Males older than 20 years from the 7 communities were qualified to participate in a questionnaire and a brief clinical exam voluntarily. We included 1213 participants initially, and 1166 participants were finally included. See in the flow chart below.



2.2 Study design

Every participant was asked to sign consent before the test and each was anonymized for research and confidentiality purposes.

The questionnaire mainly collected the basic information of participants, including age, marital status, education status, smoking, drinking, occupation and previous history, including vasectomy and long-term medication status.

Trained study staff measured body weight, height, waist circumference, systolic blood pressure, diastolic blood pressure, and WHtR [waist circumference (cm)/ height (cm)] for participants. Fasting venous blood samples were collected by trained nurses and were centrifuged for 15 min at 4°C to obtain serum and stored at -80°C until analysis.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration.

2.3 Laboratory assessments

We used chemiluminescent immunoassays to measure SHBG on a Beckman Access Immunoassay System (Beckman Coulter, Brea, CA, USA).

2.4 Statistical analysis

Data were analyzed by using analyzed by SPSS 18.0 (SPSS Inc., Chicago, IL, USA). We re-coded the independent variables in the multiple models as binary variables. The cutoff of WHtR was set as 0.5 as per the literature and as a suitable predictor of diabetes, CVD and MS(11-15). The other independent variables were defined by common clinical standards. Quantitative data are presented as mean±SD and categorical data as frequency (%). SHBG level in groups was compared by one-way ANOVA. $P<0.05$ was considered statistically significant. We used multiple linear regression to evaluate the association of independent variables with SHBG level and the results are shown as beta values and 95% confidence intervals (95%CIs).

3 Results

3.1 Demographic characteristics

For 631 participants, WHtR was ≥ 0.5 and for 535 it was < 0.5. The mean age, systolic blood pressure (SBP), diastolic blood pressure (DBP) and fasting blood glucose (FBG) was 51.56±12.82 years old, 128.81±19.04 mmHg, 83.79±12.03

Table 1: Demographic characteristics by WHtR

Characteristics	WHtR ≥0.5 n=631	<0.5 n=535	Total
Education, N(%)			
Uneducated	63(5.4)	47(4.0)	110(9.4)
Educated	538(48.7)	488(41.9)	1056(90.6)
Occupation, N(%)			
Farmer	503(43.1)	453(38.9)	956(82.0)
Other	128(11.0)	82(7.0)	210(18.0)
Marital status, N(%)			
Married (including co-habitating)	596(51.1)	494(42.4)	1090(93.5)
Single, divorced or widowed	35(3.0)	41(3.5)	76(6.5)
Vasectomy, N(%)			
Yes	52(4.5)	45(3.9)	97(8.3)
No	579(49.7)	490(42.0)	1069(91.7)
Smoking, N(%)			
Current	491(42.1)	428(36.7)	919(78.8)
Never or former	140(12.0)	107(9.2)	247(21.2)
Alcohol use, N(%)			
Current	373(32.0)	295(25.3)	668(57.3)
Never or former	258(22.1)	240(20.6)	498(42.7)
Long-term medication, N(%)			
Yes	128(11.0)	88(7.5)	216(18.5)
No	503(43.1)	447(38.3)	950(81.5)

Uneducated=Never went to school for formal education; Educated=At least received a primary education; WHtR=waist-to-height ratio; SBP=systolic blood pressure; DBP=diastolic blood pressure; FBG=fasting blood glucose.

mmHg and 5.56±1.56nmol/L respectively. Other details are shown in Table 1.

3.2 Serum level of SHBG by demographic characteristics.

Table 2 shows only significant results of the association of characteristics with SHBG level. Mean serum level of SHBG significantly differed by age, DBP, WHtR, education, occupation, alcohol use and long-term medication.

3.3 Factors associated with SHBG level on multiple regression

Table 3 shows factors associated with SHBG level on adjusted multiple linear regression. Except for SBP because of its colinearity with DBP, factors significantly associated with SHBG level were WHtR(β=-11.84), age(β=-12.04), DBP(β=-5.07), education(β=-8.70) and occupation(β=-4.03).

Table 2: Mean SHBG level by demographic characteristics

Characteristics	SHBG, nmol/L	P value
Age		
≥40 years	44.68±20.57	0.000
<40 years	31.67±14.59	
DBP(mmHg)		
≥90	38.11±18.91	0.000
<90	43.76±20.50	
WHtR		
≥0.5	36.56±18.11	0.000
<0.5	48.73±20.59	
Education		
Uneducated	52.36±22.91	0.000
Educated	41.08±19.62	
Occupation		
Farmer	43.58±20.60	0.000
Other occupation	35.63±16.93	
Alcohol use		
Current	40.18±19.44	0.000
Never or former	44.78±20.94	
Long-term medication		
Yes	44.79±21.50	0.033
No	41.55±19.87	

Data are mean±SD. SHBG=Sex hormone-binding globulin; DBP=diastolic blood pressure; WHtR=waist-to-height ratio; Uneducated=Never went to school for formal education; Educated=At least got a primary education.

Table 3: Multiple linear regression of factors associated with SHBG level.

Variables	β	95%CI
WHtR	-11.84**	(-13.96,-9.72)
Age	12.40**	(9.63,15.17)
DBP	-5.07**	(-7.44,-2.71)
FBG	-0.86	(-2.96,1.25)
Education	-8.70**	(-12.34,-5.06)
Occupation	-4.03*	(-6.79,-1.26)
Marital status	-2.16	(-6.42,2.09)
Vasectomy	-0.17	(-3.96,3.62)
Smoking	0.97	(-1.62,3.56)
Alcohol	-2.04	(-4.19,0.12)
Long-term medication	1.67	(-1.10,4.43)

WHtR=Waist-to-height ratio; DBP=diastolic blood pressure; FBG=-fasting blood glucose.
**p<0.001, *p<0.05

3.4 Relation between WHtR and SHBG level

The following scatter grams show the relation between WHtR and SHBG level by factors presented in Table 2. The range of the X-axis was 0.35-0.72(16). Despite central obesity, SHBG level was higher for male solder than younger than 40 years and was higher with DBP <90 than > 90 mmHg (Figure 1). SHBG level was higher for uneducated than educated males. It was higher for farmers than other occupations in the non-central-obesity group, but with increasing WHtR in the central-obesity group, the SHBG level between groups approached concordance (Figure 2). SHBG level was lower for men who were alcohol users than never or former users. It was higher for men with than without long-term medication history in the non-central-obesity group, but in the central-obesity group, SHBG level between groups approached concordance with increasing WHtR (Figure 3).

4 Discussion

This was a cross-sectional study of1166 male participants from the Chinese Middle-aged and Elderly Men of Reproduction Health Project. Each participant took a questionnaire, a brief clinical exam and a blood sample; the one-way ANOVA was used to compare the differences

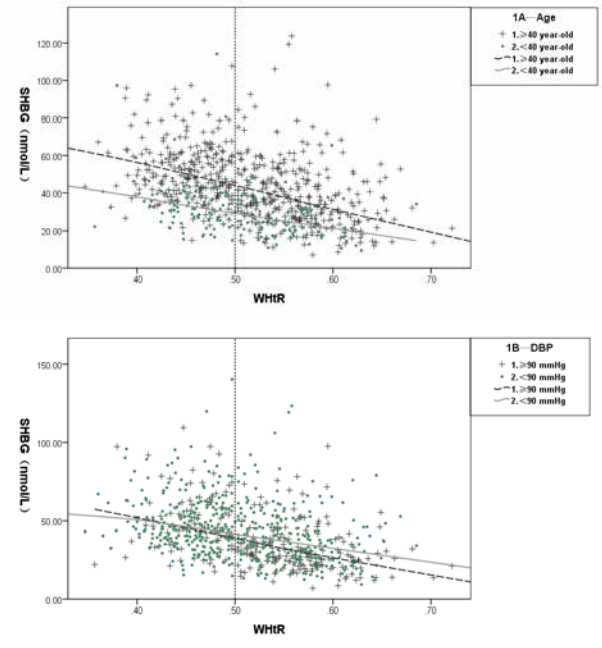


Figure 1: Relation between WHtR and SHBG level by physiologic characteristics (A) age and (B) DBP. The 0.50 cutoff of WHtR is shown by the upright dotted line.

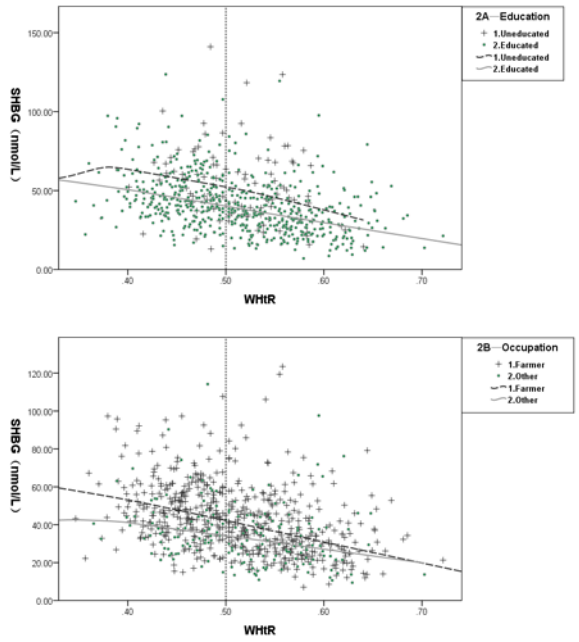


Figure 2: Relation between WHtR and SHBG level by sociological characteristics (A) education and (B) occupation.

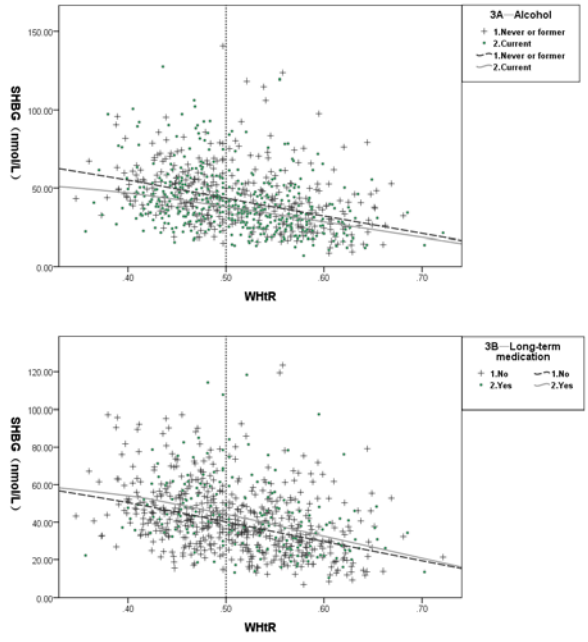


Figure 3: Relation between WHtR and SHBG level by life style characteristics (A) alcohol use and (B) long-term medication.

between groups, and significant results were also showed in figures (Figure1-3). The main results were revealed in the multiple linear regression (Table 3). Serum level of SHBG was inversely related with central obesity (WHtR). In addition, age, DBP, education and occupation were independently related to serum SHBG level.

In our findings, central obesity defined by WHtR was inversely related to SHBG level. The result is similar to research from the Endocrinology Unit at the University Hospital of Los Andes Merida and Venezuela, finding in 70 men aged 20 to 62 years old, that SHBG level was inversely correlated with WC (r=-0.322, P<0.01) (17). A cross-sectional study from Korea also found SHBG level inversely related to WC and BMI [18]. However, those two indices cannot define central obesity better than WHtR. Our result might show a more precise relation between central obesity and SHBG level. A transgenic animal experiment from Selva et al [19] showed the mechanism of SHBG decreasing with increased lipid levels in hepatocytes: increasing monosaccharide-induced lipogenesis caused a down-regulation of hepatocyte nuclear factor 4and reduced expression of SHBG gene in hepatocytes, thus decreased SHBG level. This research provides a biological explanation for our study results showing decreased SHBG level with obesity.

Our results show that SHBG level was in dependently and positively associated with age. A large cross-sectional study offered more precise results to support this relation(20): the study of 58,162 men among 110,712 participant saged from 10 to 90 years old tested blood testosterone, SHBG and calculated free testosterone levels together with sex and age and created smoothed age-specific centiles (2.5%, 5%, 25%, 50%, 75%, 95%, 97.5%) for males and females. After early childhood, serum SHBG level declined to a nadir in males at age 20 years and remained stable until the sixth decade of age, with a gradual, progressive increase thereafter. Our study did not reveal a decline in SHBG level in young males because we examined male solder than 20 years, so the results of SHBG level only show the increasing trend with age. Longitudinal study from two Australian [21], geographically widely separated regions, of 610 men at baseline and adding 370 and 200 men on the second and third occasion from 1989 to 2004, revealed that SHBG level increased annually and the increase was steeper in middle-aged and older men versus young men(P<0.001). The result of SHBG level increasing with age in our study is consistent with both cross-sectional and longitudinal studies. However, we lack the molecular biology evidence of this phenomenon.

We observed SHBG level inversely related to DBP, but with no significant difference in SBP (Tables 2-3). In MS, lower serum SHBG concentration is found related to DBP and SBP [1, 22]. We have no direct evidence to prove this phenomenon in our study. Across-sectional study [23] used echocardiography, pulse-wave Doppler and tissue Doppler imaging to measure the structure and function of the left ventriclein participantsgrouped according to number of MS criteria (ATP-III) met; the results suggested

a progressive impairment in left-ventricle relaxation with increasing number of MS criteria, which indicates impaired diastolic function with increasing burden of MS. Another more than4-year longitudinal study used similar techniques to measure ventricular-arterial function under general and central adiposity. Weight gain was associated with significant increases in LV diastolic stiffness in both men and women, whereas central obesity and insulin resistance were associated with large increases in end-systolic elastance in women but not men, which indicates sex difference in the biology of age-related ventricular systolic stiffening [24]. Our finding of central obesity inversely associated with SHBG level can explain why SHBG level is negatively related with only DBP.

SHBG level is inversely related with insulin resistance (IR) among men [17], so SHBG should have the same relation with blood glucose because IR would lead to high blood glucose status. However, in our study, SHBG showed no relation with FBG. The reasons may be that 1) we did not collect the biochemical criteria for IR in high FBG participants, so we can not declare whether is the IR or the pancreas beta cell dysfunction leading to high fasting blood glucose condition; 2)even if some participants had IR, the resistant status might be weak so that FBG did not increase enough to be defined by a medical test; 3) a cohort of participants who were normoglycemic at baseline but hyperglycemic at 3years(glycemia≥6.1mmol/L or Type2 diabetes) and matched for sex, age, and BMI with control participants who remained normoglycemicin 3 years found serum SHBG level significantly associated with risk of developing hyperglycemia among women but not men [25]. This suggests that the interaction between SHBG level and blood glucose may be bridged by estrogens in part.

Males who were educated or with a non-agriculture occupation showed lower SHBG level than uneducated males or farmers. Early research found the prevalence of obesity inversely associated with education of individuals, which suggests an inverse association between socioeconomic position and obesity [26]. To our best knowledge, education and occupation are highly associated with socioeconomic status. High socioeconomic levels maybe more likely to be associated with obesity, and obesity leads to lower levels of SHBG, so that educated men or men with a non-agriculture occupation showed lower a SHBG level.

This is a large study of1166 men from western China, which may imply less sampling bias. We used WHtR not WC or WHR, which could be more suitable for defining central obesity because height differs between races and the western China region is multiracial.

We cannot declare whether the relation of SHBG level with central obesity was causal because this was a cross-sectional study. The data in this study came from the Chinese Middle-aged and Elderly Men Reproduction Health Project, and it did not survey all risk factors for metabolic and CVD. Also, we did not exclude the subjects with some special diseases that may affect SHBG level, such as hepatic or thyroid disease [27]. Further studies could focus on the mechanism of how SHBG influences diastolic function and blood glucose.

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Conflicts of interest: The authors have no conflicts of interest to declare.

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