Association between sex hormone-binding globulin and kidney function in men: results from the SPECT-China study

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Abstract

Background: The association between sex hormone-binding globulin (SHBG) and renal function has rarely been reported in men. We aimed to investigate the above association in a community-based Chinese population.

Methods: A total of 5027 men were included from the survey on prevalence for metabolic diseases and risk factors, which is a population-based study conducted from 2014 to 2016 in Eastern China. The estimated glomerular filtration rate (eGFR) was calculated according to the chronic kidney disease Epidemiology Collaboration equation. Low eGFR was defined as eGFR <60 mL·min^{-1}·1.73 m^{-2}.

Results: After adjusting for age, smoking, metabolic factors, and testosterone, through increasing quartiles of SHBG, a significantly positive association between SHBG quartiles and eGFR was detected in men (Q1 *vs.* Q4, β -2.53, 95% confidence interval -3.89, -1.17, $P_{trend} < 0.001$). Compared with the highest quartile of SHBG, SHBG in the lowest quartile was associated with 96% higher odds of low eGFR (odds ratio 1.96, 95% confidence interval 1.10, 3.48) in the model after full adjustment. According to the stratified analyses, the associations between a 1-standard deviation increase in serum SHBG and the prevalence of low eGFR were significant in men aged ≥60 years old, waist circumference <90 cm, diabetes (no), hypertension (yes), dyslipidemia (no), and nonalcoholic fatty liver disease (no).

Conclusions: Lower serum SHBG levels were significantly associated with lower eGFR and a higher prevalence of low eGFR in Chinese men independent of demographics, lifestyle, metabolic-related risk factors, and testosterone. Large prospective cohort and basic mechanistic studies are warranted in the future.

Keywords: Estimated glomerular filtration rate; Sex hormone-binding globulin; Testosterone

Introduction

The estimated glomerular filtration rate (eGFR) is a common test to measure kidney function and determine the kidney disease stage. eGFR <60 mL·min^{-1}·1.73 m^{-2} is regarded as low eGFR, which is closely related to chronic kidney disease (CKD). CKD is a common and costly condition that is associated with substantial morbidity and mortality.[1] For most noncommunicable chronic diseases, the prevalence of CKD is increasing most rapidly in low- and middle-income countries, such as China, and has brought a serious burden to society.[2]

Previous animal studies have shown that sex hormones may contribute to kidney disease.[3] Human studies have also demonstrated that sex hormones, such as follicle stimulat-ing hormone and testosterone, play an important role in the prevalence of low eGFR[4,5]; however, few studies have explored the association of renal function and sex hormone-binding globulin (SHBG). SHBG can bind androgens and estrogens with high affinity in blood and regulate their bioavailability. In recent years, low serum SHBG concentrations have been used as a biomarker for metabolic syndrome[6] and a predictor of type 2 diabetes (T2D)[7] and cardiovascular disease.[8] A recent study showed that lower SHBG levels were associated with the development of low eGFR in men[9]; however, this study focused on a population with obesity and glucose intolerance. Limited studies have investigated the association between SHBG and eGFR in the general population.

The Survey on Prevalence in East China for metabolic diseases and risk factors (SPECT-China) is a large

investigation that was performed in 2014–2016 in the general population in Eastern China. Using data from this study, the objective of the present study was to investigate whether SHBG levels were associated with a low eGFR in Chinese men.

Methods

Ethical approval

The study protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine (No. 2013 [86]). All participants provided written informed consent before data collection.

Study design and subjects

We used a data source from populations of Asian descent. SPECT-China is a community population-based cross-sectional survey that aims to study the prevalence of metabolic diseases and risk factors in East China, which is made up of Shanghai and seven provinces, including approximately 29.2% of the Chinese population (ChiCTR-ECS-14005052, www.chictr.org.cn). We used a stratified cluster sampling method to select a sample from the general population at 23 sites across Shanghai and four provinces including Zhejiang, Jiangsu, Anhui, and Jiangxi. The sampling process was stratified by urban/rural areas and economic status. Generally, in urban areas, one city with low economic status and one with high economic status were randomly selected. Three districts were randomly selected from each city, and one community was then randomly sampled from each of the districts. In rural areas, six villages with low economic status and six with high economic status were randomly selected. All eligible participants in each region were identified through local residential records and were invited during house visits by community healthcare workers, following extensive advertising campaigns. A total of 12,666 Chinese adults aged ≥18 years were recruited for the study from 2014 to 2016 (response rate >90%). Detailed sampling information was reported in previous studies.[10,11] Briefly, this study recruited participants aged 18 years or older who lived in their current residence for six months or longer. Those who had an acute illness, severe communication problems, or refused to participate in were excluded from the study. A total of 12,666 people participated in this investigation. Among them, there were 5121 men. Residents with missing SHBG data ($n = 82$) or who had a history of kidney disease (including chronic nephritis, kidney cancer, nephrectomy; $n = 12$) were excluded. Finally, 5027 men were enrolled in this study (Supplementary Figure 1, http://links.lww.com/CM9/A972).

Clinical, anthropometric, and laboratory measurements

At every study site, all data were collected by the same trained staff group. The trained staff used a questionnaire to collect information about demographic characteristics, disease history, and lifestyle risk factors. Height, body weight, waist circumference, and blood pressure were measured with standard methods.[12] Body mass index

(BMI) was calculated as weight in kilograms divided by height in meters squared. The homeostatic model assessment of insulin resistance was calculated as fasting glucose (mmol/L) × fasting insulin (mU/mL)/22.5.

Venous blood samples of each participant were collected after at least 8 hours of fasting. After immediate centrifugation, the blood, serum, and plasma were frozen in a central laboratory certified by the College of American Pathologists. Hemoglobin A1c was measured by high-performance liquid chromatography (MQ-2000PT, Med-conn, China). Fasting plasma glucose, plasma glucose, and lipid profiles, including triglycerides, high-density lipoprotein, and low-density lipoprotein (LDL), were assessed by a Beckman Coulter AU 680 analyzer (USA). SHBG was obtained by electrochemiluminescence immunoassay (ROCHE E601, Roche Diagnostics, Rotkreutz, Switzerland). Total testosterone (TT) was assessed by the chemiluminescence method (SIEMENS Immulite 2000, Germany). The interassay and intra-assay coefficients of variation were 6.6% and 5.7% for TT and 4.5% and 7% for SHBG, respectively.

Definition of variables

The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR = $175 \times$ standardized $Scr^{-1.154} \times age^{-0.203}$), in which the value of eGFR is reported in units of mL·min^{-1}·1.73 m^{-2} of body surface area and Scr is serum creatinine expressed in mg/dL.[13] The participants were divided into two groups by low eGFR, which was defined as eGFR < 60 mL·min^{-1}·1.73 m^{-2} in sex specificity.[14] Diabetes was diagnosed if the patient had a prior history of diabetes or if the following criteria were met: fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or hemoglobin A1c $\geq 6.5\%$.[15] Dyslipidemia included participants who had been diagnosed with dyslipidemia by professional physicians or had a combination of increased total cholesterol (≥ 240 mg/dL [6.20 mmol/L]), LDL-C (>160 mg/dL [4.13 mmol/L]), triglyceride levels (>200 mg/dL [2.25 mmol/L]) or decreased high-density lipoprotein-C (<40 mg/dL [1.03 mmol/L]).[16] Current smoking was defined as currently smoking cigarettes and having smoked at least 100 cigarettes in one's lifetime.[12] Liver fat accumulation (steatosis) was detected by ultrasound (Mindray M7, MINDRAY, Shenzhen, China).[17] According to the criteria proposed by Saadeh et al,[18] the presentation of steatosis included increased liver echogenicity, stronger echoes in the hepatic parenchyma compared to the renal parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins. We excluded participants with viral hepatitis (B or C), excessive alcohol consumption, aspartate aminotransferase, or alanine aminotransferase >500 U/L to define nonalcoholic fatty liver disease (NAFLD).[19]

Statistical analysis

IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA) was used. All analyses were two-sided. A P value <0.05 indicated a significant difference. Continuous variables were expressed as the mean ± standard deviation (SD), and categorical variables were

described as a percentage (%). To compare the characteristics between low eGFR and normal eGFR, Student's *t* test was used for continuous variables with a normal distribution, the Mann–Whitney *U* test was used for continuous variables with a skewed distribution, and the chi-squared test was used for categorical variables.

SHBG was divided into quartiles, with the first quartile representing the lowest quartile and the fourth quartile representing the highest quartile. The β and 95% confidence intervals (CIs) were calculated using linear regression to investigate the association between the level of eGFR and the quartiles of SHBG or 1-SD increment of log-serum SHBG. The odds ratios (ORs) and 95% CIs were calculated using binary logistic regression to reveal the odds of low eGFR for each quartile of SHBG and for a 1-SD increment of log-serum SHBG, with the highest quartile as the reference. Because adiposity and TT are two potential confounding factors very strongly associated with SHBG, three statistical models were used. Model 1 adjusted for age, smoking, dyslipidemia, diabetes, hypertension, and NAFLD. Model 2 additionally adjusted for waist circumference. Model 3 adjusted for terms in Model 2 and naturally log-transformed TT.

In subgroup analyses, to explore the potential interaction association, we further investigated the relationship between serum SHBG (1-SD increment of naturally log-transformed SHBG) and low eGFR in men stratified by age (≥60 years or <60 years), waist circumference (≥90 or <90 in men), diabetes (yes or no), hypertension (yes or no), dyslipidemia (yes or no), and NAFLD (yes or no).

In the sensitivity analyses, we adjusted BMI instead of waist circumference, systolic blood pressure (SBP) instead of hypertension, and total cholesterol, LDL-C, and triglycerides instead of dyslipidemia to test whether the results were robust.

Results

Participant characteristics

This study included 5027 men. Table 1 summarizes the comparisons of the variables between low eGFR and normal eGFR. In Chinese men, compared with normal eGFR participants, the low-eGFR group was older and had significantly higher smoking prevalence, SBP, homeostatic model assessment of insulin resistance, waist circumference, and BMI, a higher prevalence of diabetes, hypertension, and dyslipidemia, and lower TT (all *P* < 0.05).

Association of SHBG with low eGFR and the level of eGFR

We found a positive association between SHBG quartiles and eGFR after adjustment for age, smoking status, dyslipidemia, diabetes, hypertension, and NAFLD in men (Q4 Ref.; Q1 β – 1.65, 95% CI – 2.85, – 0.45, *P* value for trend = 0.002; Table 2, Model 1). The positive association persisted after further adjustment for waist circumference (Model 2). After further adjustment for TT, a significant positive relationship remained between SHBG quartiles and eGFR (Model 3). We further found that as each SD of log-serum SHBG increased, eGFR increased by 1.44 after full adjustment in men (β 1.44, 95% CI 0.95, 1.94, *P* < 0.001; Table 2).

As shown in Table 3, compared with those having the highest quartile of SHBG, men in the lowest quartile had

Table 1: General characteristics of subjects by low eGFR or normal eGFR.			
Items	eGFR <60 mL·min^{-1}·1.73 m^{-2}	eGFR ≥60 mL·min^{-1}·1.73 m^{-2}	*P* value
n	198	4829	
Age (years)	68.3 ± 10.2	54.9 ± 12.9	<0.001
SHBG (nmol/L)	47.2 (32.7, 67.8)	51.7 (29.1, 59.4)	0.011
eGFR (mL·min^{-1}·1.73 m^{-2})	51.7 ± 9.0	88.0 ± 13.0	<0.001
SBP (mmHg)	140.3 ± 22.4	133.9 ± 20.3	<0.001
LDL (mg/dL)	3.16 ± 0.89	3.13 ± 0.76	0.516
HDL (mg/dL)	1.25 ± 0.31	1.33 ± 0.32	<0.001
Triglycerides (mg/dL)	1.50 (1.14, 2.12)	1.42 (1.00, 2.13)	0.707
Total cholesterol (mg/dL)	5.17 ± 1.52	5.11 ± 1.01	0.659
HOMA-IR	1.37 (1.00, 2.08)	1.13 (0.74, 1.72)	<0.001
Waist circumference (cm)	87.7 ± 8.5	84.7 ± 9.4	<0.001
BMI (kg/m^2)	25.6 ± 4.1	24.9 ± 3.4	0.003
TT (nmol/L)	15.6 (11.0, 19.7)	15.7 (12.6, 19.8)	0.048
Diabetes (%)	26.8	16.2	<0.001
NAFLD (%)	57.8	56.5	0.712
Current smoker (%)	58.1	50.1	0.007
Hypertension (%)	73.2	50.7	<0.001
Dyslipidemia (%)	49.0	40.4	0.015

Data are summarized as the mean ± SD or median (interquartile range) for continuous variables. The Kruskal–Wallis test and analysis of variance were used for continuous variables with a skewed or normal distribution, and the Pearson χ^2 test was used for categorical variables. BMI: Body mass index; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; HOMA-IR: The homeostatic model assessment of insulin resistance; LDL: Low-density lipoprotein; NAFLD: Nonalcoholic fatty liver disease; OR: Odds ratio; SBP: Systolic blood pressure; SD: Standard deviation; SHBG: Sex hormone-binding globulin; TT: Total testosterone.

Table 2: Among men, associations between quartiles of SHBG and eGFR (beta and 95% CIs).

Items	Model 1	Model 2	Model 3
Quartiles of SHBG			
Q1 (4.70–29.2 nmol/L)	−1.65 (−2.85, −0.45)	−1.41 (−2.63, −0.19)	−2.53 (−3.89, −1.17)
Q2 (29.3–41.8 nmol/L)	−2.20 (−3.27, −1.13)	−2.02 (−3.11, −0.94)	−2.83 (−3.99, −1.67)
Q3 (41.9–59.6 nmol/L)	−1.14 (−2.15, −0.12)	−1.05 (−2.06, 0.03)	−1.52 (−2.57, −0.47)
Q4 (59.7–187.6 nmol/L)	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)
P value for trend	0.002	0.009	<0.001
1-SD increment of log-serum SHBG	0.99 (0.56, 1.41)	0.90 (0.47, 1.34)	1.44 (0.95, 1.94)
P value	<0.001	<0.001	<0.001

95% CI are shown in parentheses. Linear regression has been used. Model 1 adjusted for age, smoking, dyslipidemia, diabetes, hypertension, and NAFLD. Model 2 additionally adjusted for waist circumference. Model 3 adjusted for terms in Model 2 and naturally log-transformed TT. CIs: Confidence intervals; eGFR: Estimated glomerular filtration rate; NAFLD: Nonalcoholic fatty liver disease; SD: Standard deviation; SHBG: Sex hormone-binding globulin; TT: Total testosterone.

Table 3: Among men, associations between quartiles of SHBG and risk of low eGFR (ORs and 95% CIs).

Items	Model 1	Model 2	Model 3
Quartiles of SHBG			
Q1 (4.70–29.2 nmol/L)	2.24 (1.32, 3.82)	2.15 (1.25, 3.68)	1.96 (1.10, 3.48)
Q2 (29.3–41.8 nmol/L)	1.62 (1.03, 2.54)	1.57 (0.99, 2.47)	1.46 (0.90, 2.36)
Q3 (41.9–59.6 nmol/L)	1.18 (0.77, 1.80)	1.16 (0.75, 1.77)	1.11 (0.72, 1.72)
Q4 (59.7–187.6 nmol/L)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
P value for trend	0.002	0.004	0.019
1-SD increment of log-serum SHBG	0.69 (0.57, 0.83)	0.70 (0.58, 0.85)	0.71 (0.58, 0.88)
P value	<0.001	<0.001	0.001

95% CI are shown in parentheses. Logical regression has been used. Model 1 adjusted for age, smoking, dyslipidemia, diabetes, hypertension, and NAFLD. Model 2 additionally adjusted for waist circumference. Model 3 adjusted for terms in Model 2 and naturally log-transformed TT. CIs: Confidence intervals; eGFR: Estimated glomerular filtration rate; NAFLD: Nonalcoholic fatty liver disease; OR: Odds ratio; SD: Standard deviation; SHBG: Sex hormone-binding globulin; TT: Total testosterone.

1.24 times higher odds of low eGFR after adjustment for age, smoking status, and metabolic-related risk factors (OR 2.24, 95% CI 1.32, 3.82, *P* value for trend = 0.002; Table 3, Model 1). After further adjustment for waist circumference, the association was slightly attenuated (*P* value for trend 0.004; Table 3, Model 2). After further adjustment for ln-TT, compared with men in the fourth quartile of SHBG, those in the first quartile still had a significantly higher OR of low eGFR (OR 1.96, 95% CI 1.10, 3.48) [Table 3, Model 3]. With a 1-SD log-serum SHBG increment, the odds of low eGFR decreased by 29% in the fully adjusted model (OR 0.71, 95% CI 0.58, 0.88, *P* = 0.01; Table 3). After further adjusting BMI instead of waist circumference, SBP instead of hypertension, and total cholesterol, LDL-C, and triglycerides instead of dyslipidemia in Supplementary Tables 1 and 2, http://links.lww.com/CM9/A972, the results remained stable, and lower serum SHBG levels were still significantly associated with lower eGFR and a higher prevalence of low eGFR in Chinese men independent of demographics, lifestyle, metabolic-related risk factors, and testosterone.

Subgroup analysis

We performed stratified analyses to determine the ORs of low eGFR with a 1-SD increment in natural log-serum SHBG concentration in subgroups of strata variables in Chinese men [Figure 1]. According to the stratified analyses, although the associations between SHBG and the prevalence of low eGFR were significant in age strata (≥60 years), waist circumference strata (<90 cm), diabetes status (no), hypertension status (yes), dyslipidemia status (no), and NAFLD (no) (all *P* < 0.05), the interaction was significant only in diabetes and hypertension status (*P* value for interaction 0.024 and 0.048, respectively).

Discussion

In the current study, we found that lower SHBG levels and lower quartiles of SHBG were associated with decreasing renal function estimated by the eGFR level and increasing prevalence of low eGFR in men, even after adjustment for TT in the fully adjusted model. To the best of our knowledge, this study is the first to investigate the association between SHBG and renal function in men in the general population in China.

The relationship between eGFR and CKD has been studied previously, but the results were not entirely consistent. A previous cross-sectional study performed in 735 male patients with T2D mellitus showed that a nonstatistically significant relationship was found between SHBG and kidney disease.[20] However, another 15-year cohort study composed of 1277 eligible males showed that a higher hazard ratio of CKD progression was found in male adults with low levels of testosterone than in those with normal levels,[21] which was consistent with our results.
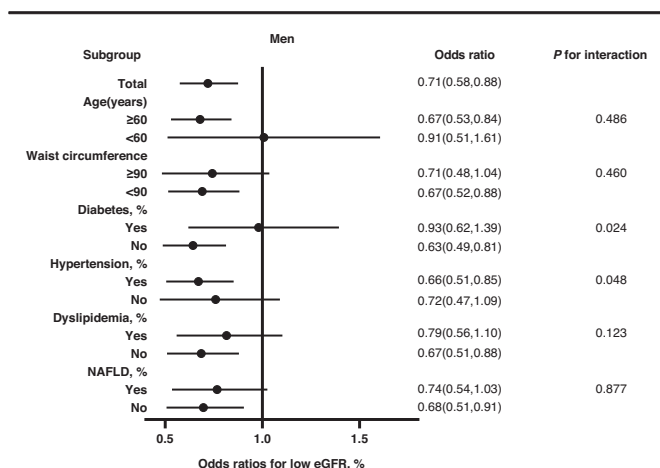
Figure 1: Adjusted ORs for a 1-SD increase in log-serum SHBG concentration associated with low eGFR in the total population and in subgroups. Logical regression has been used. The ORs with corresponding 95% CIs were adjusted for age, smoking, dyslipidemia, diabetes, hypertension, NAFLD, waist circumference, and naturally log-transformed TT. CI: Confidence interval; eGFR: Estimated glomerular filtration rate; NAFLD: Nonalcoholic fatty liver disease; ORs: Odd ratio; SD: Standard deviation; SHBG: Sex hormone-binding globulin; TT: Total testosterone.

Although SHBG is also regarded as an important transport protein for testosterone and other steroids, few population-based studies have measured the associations of SHBG with eGFR and the prevalence of low eGFR. One recent study primarily found that in men with overweight and glucose intolerance, relative to the lowest quartile, SHBG concentrations in the highest quartile were inversely associated with a risk of low eGFR,[9] which is consistent with our results; however, a cross-sectional study of the National Health and Nutrition Examination Surveys showed no significant correlation between SHBG levels and eGFR in men.[22] Compared with these studies, our study has a much larger sample population. Most of the participants were Han Chinese, and we did not perform an ethnic breakdown analysis similar to the National Health and Nutrition Examination Surveys study. Differences in ethnicity, adjusted variables, and sample size may result in different results.

In our study, after adjustment for age, smoking, and metabolic-related risk factors due to diabetes, hypertension, or NAFLD may influence the associations to some extent,[23,24] a significant association remained between SHBG and the prevalence of low eGFR. After further adjustment for waist circumference, the association between SHBG and markers of renal disease was significant but lessened. For our study, we further adjusted ln-testosterone, which is closely related to SHBG, and the association between SHBG and the prevalence of low eGFR was significant in men, which implies that the effect of testosterone on the relationship between SHBG and low eGFR is relatively limited. The potential mechanisms of SHBG influencing proximal convoluted tubules have been investigated in previous animal studies.[25] Furthermore, SHBG can accentuate androgen-dependent Kap protein expression in proximal convoluted tubule cells,[26] which can slow the decrease in kidney function. Therefore, SHBG may ameliorate the status of low eGFR by androgen-mediated tissue-specific effects, which warrants further exploration.

Several diseases, such as obesity,[27] thyroid hormone disorders,[28] and anorexia nervosa,[29] can cause SHBG plasma levels to fluctuate, which may be helpful for the early diagnosis of these diseases. Furthermore, as previously mentioned, some epidemiological studies have reported that low plasma SHBG levels are associated with a higher risk of T2D,[30] metabolic syndrome,[31] and cardiovascular disease.[8] If further randomized controlled trials can demonstrate the causal relationship between increasing levels of SHBG and decreased risks of low eGFR, changes in SHBG concentrations may predict the occurrence of several diseases. Low SHBG levels reduce the effect of androgen on the kidney in the early stages of low eGFR, as mentioned above, which might be an early biomarker for the prevention of low eGFR in the general population.

This study has some strengths. First, we focus on men in China to investigate the association between circulating SHBG and low eGFR in a large sample, and we further investigated and adjusted ln-testosterone in the regression models. Second, our data are from a general community-based population, so the findings may be more representative. This study had some limitations as well. First, we could not draw a conclusion on the causal relationship between serum SHBG and the prevalence of low eGFR because of the cross-sectional design. Second, according to the latest literature, CKD is defined as eGFR <60 mL·min^{-1}·1.73 m^{-2} and/or the presence of significant albuminuria[32]; however, we did not have urinary albumin and creatinine data, and only eGFR was used to define low eGFR. Third, the sample of participants with CKD was relatively small. Dividing CKD into different stages to perform analysis was not feasible. Fourth, we adjusted for TT, which had a strong positive relationship with SHBG rather than uncollected free testosterone, which may confound the results, and although we adjusted for most of the risk factors for CKD, residual confounding factors could not be excluded. Fifth, due to the lack of cystatin C data, eGFR was calculated by serum creatinine rather than serum cystatin C, which is a reliable marker of GFR and has higher diagnostic accuracy.

In conclusion, a negative association of high SHBG levels with low eGFR was found in Chinese men. The causal relationship and the underlying mechanisms should be investigated in additional prospective cohorts and basic studies.

Conflicts of interest

None.

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