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ORIGINAL ARTICLE

Relationship between sex hormone-binding globulin level and blood glucose in middle-aged and elder males of Uygur ethnic group

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Abstract

OBJECTIVE: To investigate the relationship between sex hormone-binding globulin (SHBG) and blood glucose in elder men of Uygur ethnic group.
METHODS: A total of 467 males of ugyur ethnic group resident in Urumqi, Tuokesun County, and Turpan were included by cluster sampling, classified by ages and SHBG level, and compared the metabolic index to define the risk factors by regression.
RESULTS: BMI, waist circumference (WC), glycosylated hemoglobin (GH), fasting insulin level (FIL), SHBG, testosterone, free testosteroneindex (FAI), and HOMA-IR were statistically different in different age groups ($P<0.05$); the differences in the age, BMI, WC, fasting blood glucose (FBG), OGTT 2-hr blood glucose, HOMA-IR, FIL, GH, testosterone, and F among the study subjects grouped according to SHBG level were statistically significant ($P<0.05$); the logistic regression analysis revealed that FIL and testosterone were the independent factors that will affect SHBG in the models using FIL, HOMA-IR, and other indexes with statistical significance as the continuous variables and the interquartile grouping of SHBG as the independent variables.
CONCLUSIONS: Among middle-aged and elder males, there are differences in the sex hormone and SHBG levels. The independent influencing factors of SHBG are HOMA-IR, testosterone, and FIL.

INTRODUCTION

Previous epidemiological studies have revealed that testosterone is associated with the metabolic abnormalities of hypertension, insulin resistance, or central obesity (Kelly and Jones 2015). Many T2D patients show low testosterone levels while hypogonadal men seem to be prone to become

diabetic (Fink *et al.* 2018). Testosterone plays a major role in the regulation of muscle mass, adipose tissue, inflammation and insulin sensitivity and is therefore indirectly regulating several metabolic pathways; on the other hand, T2D is commonly triggered by insulin resistance, increased adipose tissue, and inflammation, which shows a negative correlation between the testosterone level and T2D (Magnussen 2017). Since testosterone improves insulin sensitivity via β cell protection and lipolysis, high testosterone may be the protective factor for T2D (Pietras 2018).

A recent study has revealed that the level of SHBG instead of that of total or free testosterone, after adjusting the age and weight conditions, is associated with T2D and metabolic syndrome (Bhasin *et al.* 2011; Lakshman *et al.* 2010). In children and adolescents, SHBG may also be used as a biomarker of metabolic syndrome risk. Recent studies have shown that the plasma level of SHBG is related to some components of metabolic syndrome (Alinezhad and Jafar 2019). Compared with females, males with low SHBG are at greater risk of metabolic syndrome (Al-Daghri *et al.* 2016; de Oya *et al.* 2010), which further proves that SHBG has gender differences in metabolism (Shen *et al.* 2016). Although it is possible that the association in males with T2DM, among the combination of SHBG and total testosterone and age-related mortality is driven by free hormone levels, which is unproven until now (Ramachandran 2019). This study intended to explore the relationship between the influencing factors of SHBG and blood glucose in middle-aged and elder males who haven't reached the diagnostic criteria for impaired glucose tolerance or overt T2D.

MATERIALS AND METHODS

Subjects

This study used the cluster sampling method and selected 6 communities in Tianshan District, Urumqi City, Xinjiang Uygur Autonomous Region, and residents of 3 towns and 4 villages in Toksun County, Turpan, Xinjiang Uygur Autonomous Region, for cross-sectional survey. The basic information, physical examination results, and related laboratory examination results of a total of 2989 local residents were collected from September to December 2015. All the research subjects were informed the research contents on site (with bilingual translation) and signed the informed consent. This research plan had been approved by the ethics committee of the First Affiliated Hospital of Xinjiang Medical University. Inclusion criteria: (1) Male over 40 years old; (2) with pure ethnic descent, namely the subject's parents and the subject are of Uygur ethnic group; (3) having lived in the community (village) of the survey for more than 5 years; (4) Being able to cooperate with recording the past health status and current medication treatment in details; (5) with outany history of diabetes and the results of the OGTT test showed that the serum glucose level was normal. Exclusion criteria: (1) with severe heart, lung, kidney, liver, brain, or other important organ dysfunctions; (2) with severe thyroid dysfunction; (3) with severe psychological or mental illnesses; (4) with a history of gonadal-related tumors or was using exogenous hormones at the time of screening (including glucocorticoids, sex hormones, thyroid hormones, or growth hormones). (5) with a history of pituitary diseases (including pituitary tumors,

Tab. 1. Comparison of different clinical indicators among different age groups

	40-49 years old(N=153) mean/ median SD/ P25,P75		50-59 years old(N=167) mean/ median SD/ P25,P75		60-69 years old(N=88) mean/ median SD/ P25,P75		≥70 years old(N=59) mean/ median SD/ P25,P75		F/2	*P*
BMI (Kg/m^2)	26.22	4.17	26.31	4.48	25.33	3.75	24.35	3.41	4.18	0.01
WC (cm)	92.46	11.48	94.77	12.47	93.49	12.10	88.15	11.39	4.60	0.00
FBG (mmol/L)	4.89	0.57	4.83	0.58	4.85	0.58	4.84	0.40	0.39	0.76
OGTT2h blood glucose (mmol/L)	4.91	1.30	5.12	1.32	5.39	1.35	5.19	1.33	2.50	0.06
GH (%)	5.22	0.82	5.51	0.93	5.46	0.99	5.37	0.43	3.16	0.02
FIL (uIU/mL)	9.20	5.85,29.80	10.10	6.1,38.10	15.20	6.05,58.30	47.90	6.90,79.20	24.37	0.00
SHBG (nmol/L)	27.27	10.30,34.05	24.90	7.7,38.00	17.10	5.4,45.53	7.60	4.70,44.80	8.46	0.04
Testosterone (nmol/L)	17.73	9.86,22.66	18.51	12.23,25.39	21.87	13.39,27.93	24.10	17.70,33.38	31.32	0.00
FAI	65.54	43.39,157.89	61.58	46.46,250.67	68.76	40.15,438.21	276.17	48.64,625.00	15.59	0.00
HOMA-IR	2.11	1.31,5.85	2.39	1.30,7.80	3.19	1.34,12.45	9.39	1.60,16.77	24.29	0.00

Tab. 2. Difference analysis of clinical indicators among different SHBG levels

	Q1(N=118)		Q1(N=118)		Q1(N=118)		Q1(N=118)		F/2	P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age (year)	59.93	10.76	53.91	9.32	51.91	7.65	57.76	9.87	45.72	0.00
BMI (Kg/m^2)	24.33	3.56	26.46	4.31	27.30	4.20	25.32	3.98	12.22	0.00
WC (cm)	89.37	10.78	94.41	13.61	96.31	11.68	91.68	11.07	7.76	0.00
FBG (mmol/L)	4.58	0.60	4.82	0.52	5.10	0.48	4.92	0.48	19.77	0.00
2-hr BG (mmol/L)	5.15	1.27	5.26	1.30	5.06	1.40	4.97	1.33	1.04	0.38
GH (%)	5.31	0.64	5.27	0.79	5.48	1.00	5.49	0.97	10.25	0.02
FIL (uIU/ml)	62.61	32.73	28.62	23.46	10.87	12.61	7.88	8.05	260.02	0.00
testosterone (nmol/L)	25.72	7.90	16.07	8.15	14.41	6.85	19.14	12.00	105.30	0.00
FAI	627.13	335.41	153.05	109.37	50.01	23.41	34.54	21.43	328.31	0.00
HOMA-IR	12.93	7.36	6.01	4.95	2.48	3.00	1.72	1.76	255.24	0.00

Tab. 3. Influencing factors of SHBG by orderly logistic regression analysis

	SD	Wald	P	OR	(95% CI)
FIL	0.25	141.33	0	0.05	(0.03:0.08)
testosterone	0.13	10.53	0	1.50	(1.17:1.92)

increased secretion of pituitary-related hormones, or hypopituitary function); (6) was using drugs that may affect the serum glucose level.

Research methods and contents

Questionnaire surveys were used to collect the demographic information and routine biochemical index tests were performed, including the blood glucose, GH, testosterone, and FIL. The luminescence method (Abbott, USA) was used to determine fasting SHBG. Free testosterone index (FAI) = total testosterone × 100/SHBG.

Statistical analysis

SPSS21.0 statistical software was used; all the measurement data were expressed as mean ± standard deviation. The analysis of intergroup measurement data usedthet test and the rank sum test, and the count data were compared using the 2 test; the variance analysis among multiple groups used ANOVA; the non-parametric Spearman rank correlation analysis was used for the correlation among variables, and the analysis of the influencingfactors of SHBG was performed using the orderly logistic regression analysis. The detection level was α=0.05, and P<0.05 was set as the standard of statistical significance.

RESULTS

General situation and differences in clinical indexes

The study subjects were grouped by the age for comparing the differences in clinical indexes, and the results showed that BMI, WC, GH, FIL, SHBG, testosterone, FAI, and HOMA-IR were different among different age groups, and the differences were statistically significant (P<0.05) (Table 1).

Analysis of differences in clinical indexes among different levels of SHBG

Using the interquartile range method, the subjects were divided into four groups according to their different SHBG levels: Q1: <6.9 nmol/L, Q2: 6.9-21.1 nmol/L, Q3: 21.1-36.8 nmol/L, and Q4: ≥36.8 nmol/L, for comparing the intergroup differences, and the parameter test was used for the data that did not meet the conditions of ANOVA. The age, BMI, WC, FBG, OGTT 2-hr blood glucose, HOMA-IR, FIL, GH, testosterone, and FAI were significantly different among different age groups (P<0.05) (Table 2).

Orderly logistic regression analysis of influencing factors

The orderly logistic regression analysis revealed that FIL and testosterone were the independent factors that will affect SHBG in the models using FIL, HOMA-IR, and other indexes with statistical significance as the continuous variables and the interquartile grouping of SHBG (assignment: 1=Q1, 2=Q2, 3=Q3, 4=Q4) as the independent variable (Table 3).

The Spearman correlation analysis revealed that the correlation of SHBG with testosterone and GH was not statistically significant, but FAI was negatively correlated with GH (Table 4).

Tab. 4. Correlation analysis of clinical indicators and HbA1C level

	r	P
SHBG	0.076	0.98
Testosterone	0.009	0.842
FAI (log)	-0.102	0.02

DISCUSSION

Testosterone is the main male hormone, and the level of testosterone in adult males is about 7-8 times that in adult females. The ability to secrete testosterone from the male testes after birth gradually increases with age. In this study, the subjects were grouped into different age groups, and the results show that there are statistical differences in testosterone levels among different age groups. In addition, testosterone also plays an important role in metabolism, including increasing the muscle mass and strength, stimulating linear growth and bone maturation, and increasing bone density and strength. An important theory in endocrinology, as well as the so-called "free hormone hypothesis", believes that the biological activity of hormones is determined by their free parts. SHBG is a homologous glycoprotein secreted by the liver, as a protein with high binding affinity to androgens and estrogen, its binding force to testosterone is much higher than that of estrogen (Torjesen and Sandnes 2004). Previous studies (Wu and Hammond 2014) have shown that SHBG increases the concentration of androgens by increasing the level of total testosterone, inhibiting thalamic-pituitary feedback regulation, and extending the half-life of ligands. This study finds that under different levels of SHBG, the differences in testosterone levels are statistically significant. Considering the factors of insulin sensitivity and insulin concentration, the testosterone level is an independent factor that may affect SHBG, and the model is stable.

Research on relationship between SHBG and blood glucose

A large number of studies have found the relationship between the testosterone level and the blood glucose level (Laurent *et al.* 2016; Wang *et al.* 2018). Compared with non-diabetic controls, the serum total testosterone level inT2D patients are significantly lower. After adjusting the confounding factors, the difference in testosterone among groups is still statistically significant. In addition, studies conducted by Ding, Schipf, Corona, etc. also find that the serum testosterone level in T2D patients are significantly reduced, suggesting a significant association between the prevalence of T2D and the testosterone level in males. In addition, many studies have found a close relationship between serum free testosterone level and T2D. However, the concentration of free testosterone in the body is small, so the measurement results are unstable, and the test cost is expensive. SHBG measurement has been widely carried out in clinical practice. Research by Lakshmanhas shown no independent correlation between free testosterone and T2D, but SHBG is an independent index that can predict the onset of T2D.

The results of this study reveal that there is no linear correlation between testosterone and GH. After logarithmic conversion of FAI, it is found that FAI has a negative correlation with GH, suggesting that FAI has a better correlation with the levels of testosterone and GH.

Some studies believe that because free testosterone is not affected by albumin and SHBG, free testosterone may be a better indicator of biological activity than testosterone alone (Pham *et al.* 2018). However, other studies believe that the effects of total testosterone and SHBG on metabolic syndrome seem to be more important than biologically active testosterone and free testosterone (Diver and Clinical Scince Reviews Committee of the Association for Clinical Biochemistry 2006). In this study, total testosterone and SHBG are independent and closely related to metabolic syndrome. These findings are consistent with other recent reports (Chubb *et al.* 2008; Li *et al.* 2010). In another study (Laaksonen *et al.* 2004), although SHBG and gonadotropins increase in non-diabetic males (N=201), the calculated free testosterone concentration decreases significantly with age. The research clues to the relationship between SHBG and T2D come from many studies, showing that the serum testosterone level is related to insulin resistance (Chen and Ng 2010; Tsai *et al.* 2004). Therefore, it is speculated that unbound or "free" testosterone and unbound ("bioavailabile") testosterone may better, than the total testosterone, reflect the biological activity of circulating testosterone (Pitteloud *et al.* 2005).

In this study, among people with normal blood glucose metabolism, the levels of SHBG in different age groups are different. Although there are differences in the levels of SHBG among different GH levels, there is no correlation between SHBG and GH in people with normal glucose metabolism, and the reason can be considered as: GH usually increases with the increase of blood sugar, and the change of blood sugar appears after obvious insulin resistance, so SHBG may not have a linear correlation with GH in people whose blood sugar has not risen yet.

CONCLUSIONS

Among middle-aged and elder males, there are differences in the levels of sex hormone and SHBG at different ages. Although the age difference among different levels of SHBG is statistically significant, age does not become an independent factor influencing SHBG. The independent influencing factors of SHBG are HOMA-IR, testosterone, and FIL.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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