Study of Sex Hormone-Binding Globulin in Type 2 Diabetes Mellitus

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Abstract: Background: Sex hormone-binding globulin (SHBG) regulates the levels of free sex hormones by sequestering circulating sex hormones and participates in some of the biological actions of sex hormones by mediating cellular uptake. Low circulating levels of sex hormone–binding globulin are a strong predictor of the risk of type 2 diabetes in women and men. However, it has been difficult to determine whether biomarkers such as SHBG can predict the risk for type 2 diabetes because of the complicated relationships between sex hormones and other risk factors for type 2 diabetes mellitus (T2DM), including hyperglycemia and insulin resistance. SHBG has emerged as one of the multiple genetic and environmental factors that potentially contribute to the pathophysiology of T2DM. **Objective**: To study the blood level of SHBG in T2DM and to determine its potential role in pathogenesis of diabetes mellitus. **Material and Methods**: In this case-control study, 40 women aged 35-65 classified to (20 postmenopausal and 20 premenopausal) with newly diagnosed type 2 diabetes mellitus (T2DM) were randomly selected and compared with 10 non-diabetic as control. Twenty men aged 37-65 with T2DM were randomly selected and compared with 10 non-diabetic men as control. Plasma levels of (SHBG), total and free testosterone were measured. The two groups were matched for their ages, body mass index (BMI) and Waist circumference. After complete observation and examination, insulin level, fasting blood glucose, 2-hpp glucose, HbA1c were measured. Also, total cholesterol, HDL-cholesterol, triglyceride, systolic and diastolic BP was measured. **Results**: Among men, higher plasma levels of SHBG than women were prospectively associated with a lower risk of type 2 diabetes. The mean serum level of SHBG was 13.9±11.2 nmol/l in diabetic patients and 9.1±4.1 nmol/l in non-diabetic subjects which was non-significantly different ($P > 0.05$). There was a significant correlation between age and SHBG. On the other hand, there was non- significant correlation between SHBG with HOMA and insulin level, and no correlation with other parameters in female premenopausal diabetic group. Also, there was non significant correlation between SHBG and insulin level and BMI and no correlation with other parameters in female postmenopausal diabetic group. SHBG have strong relationship with BMI and waist circumference, this relation is found to be a slightly negative correlation between SHBG, BMI and waist circumference in pre- and postmenopausal but there is no significant correlation between the same variable in men. **Conclusion**: Throughout this study even if increased SHBG may be associated with increased insulin resistance or associated with some etiological factors of type 2 diabetes mellitus, it can't be concluded to be a direct predictor of type 2 diabetes mellitus.

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Key words: type 2 diabetes mellitus (T2DM), sex hormone-binding globulin (SHBG), insulin resistance, homeostasis model assessment (HOMA).

1. Introduction

Type 2 diabetes mellitus (T2DM) comprises an array of dysfunctions resulting from the combination of resistance to insulin action and inadequate insulin secretion. Its disorders are characterized by hyperglycemia and associated with microvascular (i.e., retinal, renal, possibly neuropathic), macrovascular (i.e., coronary, peripheral vascular), and neuropathic (i.e., autonomic, peripheral) complications[1]. It is a common disorder with a prevalence that rises markedly with increasing degrees of obesity[2].

T2DM most likely represents a complex interaction among many genes and environmental factors. Monogenic causes of type 2 diabetes represent only a small fraction of cases and commonly inherited polymorphisms individually contribute only small degrees of risk for, or protection from, diabetes. Most of the genetic risk for type 2 diabetes results from complex polygenic risk factors[3].

The protein, called sex hormone-binding globulin (SHBG), regulates the levels of testosterone and estrogen in the blood. It also plays a role in the development of type 2 diabetes. It is believed that SHBG regulates the access and action of these hormones. Initially it was thought that when bound to SHBG these sex hormones were biologically inactive[4]. However, emerging evidence suggests that even sex hormones bound to SHBG may be biologically active. Age and obesity along with a variety of hormonal, nutritional, metabolic, and genetic factors have been found to influence the production of SHBG[5].

SHBG has emerged as one of the multiple genetic and environmental factors that potentially contribute to the pathophysiology of type 2 diabetes mellitus

(T2DM) [6]. In addition to epidemiologic studies demonstrating a consistent relationship between decreased levels of serum SHBG and incident T2DM, recent genetic studies also reveal that transmission of specific polymorphisms in the SHBG gene influence the risk of T2DM[7]. At the molecular level, the multiple interactions between SHBG and its receptors in various target tissues suggest physiologic roles for SHBG that are more complex than the simple transport of sex hormones in serum. Taken together, these data provide support for an expanded role of SHBG in the pathophysiology of insulin resistance and T2DM[8].

Over the last few years, there have been several reports demonstrating that men with T2DM have a higher prevalence of low circulating testosterone levels comparing with normal population[9]. There is further evidence suggesting that a low testosterone level is a risk factor for diabetes[10]. Low concentration of SHBG is an independent risk factor for development of type 2 diabetes mellitus in women and is strongly associated with insulin resistance[11].

Classically, the primary function of SHBG was thought to be the binding of circulating hormones in order to affect the bioavailable fraction and sequester circulating androgens and estrogens, in particular, from biologic action. However, emerging experimental evidence indicates that even sex hormones bound to SHBG may directly mediate cell-surface signaling, cellular delivery, and biologic action of sex hormones[12]. Moreover, clinical studies have associated low circulating levels of SHBG with impaired glucose control[13], implicating the globulin in the maintenance of glucose homeostasis. In addition, strong associations recently reported, between plasma levels of sex hormones and the risk of type 2 diabetes show associations of similar magnitude for free sex hormones and total sex hormones [14], further indicating the bioactivity of both free and bound fractions. However, long-term studies examining the role of SHBG in the development of type 2 diabetes remain limited, particularly among women[15].

Regardless of obesity, total testosterone and SHBG were associated inversely and estradiol was associated positively with impaired fasting glucose (IFG) and diabetes in men. Further research is warranted to better understand the underlying biological mechanisms; a large type 2 diabetes case–control study provides strong statistical support for a role of SHBG and sex hormones in the etiology of type 2 diabetes[16].

In men, however, the low level of plasma testosterone has been observed to be associated with obesity, upper body fat distribution, and increased level of glucose and insulin[17]. SHBG and total testosterone appear to be higher in male children and young adults with diabetes compared with non-diabetic male siblings, which is apparently related to the absence of endogenous insulin. This may have implications for sex hormone–dependent processes across the lifespan in male individuals diagnosed with diabetes as children[11].

Because SHBG concentrations differ between men and women, the association between this variable and incident diabetes may differ by sex. The relationship between low SHBG and the risk of incident type 2 diabetes has been reported to be stronger in women than in men[18, 19].

The purpose of this study, therefore, was to study the relationship between blood levels of SHBG in T2DM and determine its potential role in pathogenesis of diabetes mellitus (DM).

2. Subjects and Methods

This study was designed as a case-control study. The study population was women and men, aged 33-45 years old, who participated from the Inpatient and Outpatient Clinic of Endocrinology, Diabetes Unit and Clinical Pathology Department in Zagazig University Hospitals. During a period of the year 2010/2011; study participant (n = 80) were classified into two groups:

Group I:

Twenty subjects without history of hormonal disturbance manifestations and diabetes mellitus who's FBG was less than 126 mg/dl on two occasions and were matched for age BMI were assigned to control group including (10 females and 10 males).

Group II:

Sixty subjects participate with T2DM diagnosed by history of investigations and hypoglycemic drug intake further classified into :

(1) *Male group*: Twenty patients with T2DM

(2) *Female group*: Forty diabetic females divided into (20 premenopausal and 20 postmenopausal).

Methods:

After informed consent was obtained, all the participants were subjected to the following:

1. Full history taking.
   - Personal and family history
   - Present and past history of disease (surgery or other investigations), Past history of drug intake or hospital admission.
2. General examination include (measuring blood pressure, pulse rate, weight and height, body mass index (BMI) was computed by dividing weight (in kg) by the square of height (in meters). (kg/m²).
3. Clinical investigations include (pelvi-abdominal ultrasonography).
4. Laboratory investigations include:
   - Fasting (FBG) and (PPBG) levels.
   - Complete blood picture (CBC).
   - Urine analysis.

- Oral glucose tolerance test (OGTT) was performed with 75-g glucose.
- Liver function test, kidney function test and lipid profile
- HbAlc and fasting insulin levels.

• Insulin resistance was estimated by a recently validated quantitative insulin sensitivity check index based on fasting insulin and glucose concentrations ([log {insulin} + log {glucose}]$^{-1}$).[20] The insulin resistance was also calculated using the HOMA-IR method (HOMA-IR = [insulin × glucose]/22.5) [21].

5. Measurement of **Sex hormone–binding globulin** (SHBG) by Chemiluminescence immunoassay (with an Elecsys 2010 autoanalyzer, Roche Diagnostics) [22]. The procedure according to the manufacturer directions. Measuring range by the instrument; 0.350-200 nmol/L. Values below the detection limit are reported as < 0.350 nmol/L. Values above the measuring range are reported as > 200 nmol/L.

• The following criteria were considered to be exclusion criteria in our study: females on CCPs, all patients with chronic liver or renal diseases affecting levels of hormone binding proteins.

Statistical Analysis

All analyses were performed using SPSS for windows (SPSS Inc., Chicago, IL, USA, version 15.0). Data were presented as means ± SD. For the assessment of correlation between variables, Pearson correlation was used. Statistical significance was set at P < 0.05. T-student tests (*t*) and "F" test were used to compare variables. Correlation coefficients (*r*) were calculated for BMI, SHBG, HOMA, insulin and glucose to check the magnitude of the relation between these parameters.

3. Results

In this study, 60 T2DM patients were randomly selected and compared to 20 control group. **Table 1** shows the results of all individual T2DM and non-diabetic represented (control group) as a mean value ± standard deviation (X±SD). Regarding the age, the T2DM was 33.4±11.7 and in control group was 33.7±8.3 years, there were statistical non-significant differences between T2DM group and control group with (P = >0.05). Also, there were statistical highly significant differences between T2DM group and control group as regards fasting blood glucose (FBG), Fasting insulin, 2-hpp glucose, HDL-cholesterol, Triglyceride, Systolic BP and Diastolic BP ($p < 0.001$). As regard there were non-significant differences between T2DM group and control group as regards insulin level and blood level of SHBG ($P > 0.05$). Also, in total cholesterol levels, there were non-significance differences between T2DM group and control group ($p = 0.002$). Comparing other variables HOMA-IR, HbAlc, BMI and waist circumference, there were significant differences between T2DM group and control group ($P < 0.05$).

Table 2 shows 20 males T2DM with mean age of 34.2±13.9 years and 10 control group with mean age of 33.6±9.7 years compared with 40 females T2DM group with mean age of 35.5±10.6 years and 10 control group with mean age of 33.9±4.4 years. By comparing male and female patients to control in this study we found non-significant statistically differences between male T2DM group and female T2DM group ($p > 0.05$). **Table 2** showed also highly significant decrease in insulin level, 2-hpp glucose level, and HDL-cholesterol level between control group and T2DM group ($p < 0.001$).

Also, we found increase in FBG, HOMA-IR, fasting insulin level, triglyceride level, systolic BP, diastolic BP, and SHBG level in the patients group compared to control group. There were highly significant differences between patients group (diabetic male and female) and control group ($p < 0.001$). On the other hand, there was non-significant statistically increase in total cholesterol level but in waist circumference had non-significant statistically decrease in patients group compared to control group ($p > 0.05$). Also, there was statistical significant increasing in BMI between male and female subjects group comparing to control group ($p < 0.05$).

In this study we found negative correlation between SHBG and FBG, but there is no correlation between SHBG and other parameters in male diabetic group (**Table 3**).

Table (4) showed that there is significant correlation between age and SHBG; on the other hand, there was non significant correlation between SHBG with HOMA and insulin level, and no correlation with other parameters in female premenopause diabetic group.

Table (5) shows nonsignificant correlation between SHBG and insulin level and BMI and no correlation with other parameters in female postmenopause diabetic group.

• Calculating homeostasis model assessment (HOMA) was calculated by the following

Equation; HOMA = insulin level in (μ iu) × fasting glucose level in (mg\ dl)

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Table 1: **Comparison of variables studied in T2DM populations and non-diabetic control group age and other variable studies**.

Parameters	T2DM group (n=60)	Non-diabetic Control group (n = 20)	*P* value
Age (year)	33.4±11.7	33.7±8.3	>0.05**
Insulin level (μ iu/ml)	19.53±17.8	20.59±27.1	> 0.05**
FBS (mg/dl)	127.88±81.4	81.7±14.2	< 0.001***
HOMA-IR	8.7±10.4	4.07±5.09	< 0.05*
Fasting insulin (mU/L)	12.6±1.0	11.9±1.2	< 0.001***
2-h glucose (mmol/L)	6.2±0.2	6.5±0.3	< 0.001***
HbAlc (%)	8.7±1.83	6.57±0.3	0.0001
Total cholesterol (TC) (mmol/L)	5.5±0.1	5.8±0.1	0.002
HDL-cholesterol (mmol/L)	1.2±0.04	1.1±0.05	< 0.001***
Triglyceride (mmol/L)	1.8±0.1	1.6±0.1	< 0.001***
Systolic BP (mm Hg)	145.4±2	142.2±1	< 0.001***
Diastolic BP (mm Hg)	89.3±1	83.2±1	< 0.001***
SHBG (nmol/L)	13.9±11.2	9.1±4.1	> 0.05**
Waist circumference (cm)	93.6±12.6	90.6±3.9	< 0.05*
BMI (kg/m^2)	29.5±11.05	89.4±3.5	< 0.05*

FBS = fasting blood sugar, HOMA = homeostatic model assessment, IR = insulin resistance, TC = total cholesterol
HDL=high density lipoprotein, BP= blood pressure, SHBG=sex hormone-binding globulin, BMI=body mass Index
* = *p* value < 0.05 ** = *p* value > 0.05 *** = *p* value < 0.001

Table 2: Comparison of variables studied between male and female cases and control group.

Variable	T2DM Case		Control		*P*
	Male (n = 20)	Female (n = 40)	Male (n = 10)	Female (n = 10)	
Age (year)	34.2±13.9	35.5±10.6	33.6±9.7	33.9±4.4	> 0.05**
Insulin level (μ iu/ml)	20.7 ±16.2	18.9±18.7	28.58±36.7	12.6±8.08	> 0.001***
FBS (mg/dl)	188.05±70	165.3±86.3	82.7±15.4	80.7±13.8	> 0.001***
HOMA-IR	9.3±7.2	8.38±11.7	5.7±6.8	2.4±1.3	< 0.001***
Fasting insulin (mU/L)	12.6±1.0	10.5±1.2	11.9±1.2	6.5±0.2	< 0.001***
2-h glucose (mmol/L)	6.2±0.2	5.6±0.3	6.5±0.3	5.9±0.1	< 0.001***
Total cholesterol (TC) (mmol/L)	5.5±0.1	5.9±0.1	5.1±0.1	5.4±0.1	> 0.05**
HDL-cholesterol (mmol/L)	1.2±0.04	1.3±0.05	1.4±0.03	1.5±0.02	< 0.001***
Triglyceride (mmol/L)	1.8±0.1	1.6±0.2	1.5±0.06	1.3±0.04	< 0.001***
Systolic BP (mm Hg)	145.4±2	142.3±2.4	146.4±1	123.3±1.3	< 0.001***
Diastolic BP (mm Hg)	89.3±1	85.3±1	77.8±1	75.8±1	< 0.001***
SHBG (nmol/L)	13.9±11.2	12.4±14.2	9.1±4.1	8.6±7.1	< 0.001***
Waist circumference (cm)	99.6±12.8	90.6±8.7	90.6±3.9	88.3±2.7	> 0.05**
BMI (kg/m^2)	27.4±4.1	30.5±6.2	26.1±2.25	27.6±2.3	< 0.05*

FBS = fasting blood sugar, HOMA = homeostatic model assessment, IR = insulin resistance, TC = total cholesterol
HDL= high density lipoprotein,BP= blood pressure, SHBG = sex hormone-binding globulin, BMI = body mass index
* = *p* value < 0.05 ** = *p* value > 0.05 *** = *p* value < 0.001

Table 3: Correlation of SHBG with other parameters in male diabetic group

Variable	*r*	*p*
Age	0.285	> 0.05 (NS)
Insulin level	0.175	> 0.05 (NS)
FBS	-0.136	> 0.05 (NS)
BMI	0.026	> 0.05 (NS)
Waist circumference	0.126	> 0.05 (NS)

Table 4: Correlation of SHBG with other parameters in female premenopausal diabetic group

Variable	*r*	*p*
Age	-0.685	0.001
Insulin level	0.149	> 0.05 (NS)
FBG	-0.204	> 0.05 (NS)
BMI	-0.154	> 0.05 (NS)
Waist circumference	-0.170	> 0.05 (NS)

Table 5: Correlation of SHBG with other parameters in female postmenopausal diabetic group

Variable	*r*	*p*
Age	-0.124	> 0.05
Insulin level	0.106	> 0.05 (NS)
FBG	-0.141	> 0.05 (NS)
BMI	-0.181	> 0.05 (NS)
Waist circumference	0. 068	> 0.05 (NS)

4. DISCUSSION

Low circulating levels of sex hormone-binding globulin (SHBG) are a strong predictor for type 2 diabetes in both women and in men. This study tried to find out the role of SHBG in the prediction of type 2 diabetes mellitus. In the present study we found non-significant differences in age between subjects with type 2 diabetes mellitus (T2DM) comparing to non-diabetic group (control group). Circulating sex hormone–binding globulin levels are inversely associated with insulin resistance, but whether these levels can predict the risk of developing type 2 diabetes is uncertain[4]. One such possible predictor is SHBG, a protein that binds to sex hormones and controls their levels circulating throughout the body.

In this study by comparing SHBG level between diabetic and non diabetic groups a non-significant difference between both groups was found which is agreed by **McElduff *et al.,*** in across sectional study which concluded that SHBG level is not associated with glucose tolerance [23] .Also, in our study there were statistical highly significant differences between subject group comparing to control group with fasting blood sugar (FBS), Fasting insulin, 2-h glucose, HDL-cholesterol, triglyceride, systolic BP and diastolic BP ($p < 0.001$). There were non-significant differences between patients group and control group as regard insulin level and blood level of SHBG ($P > 0.05$).

Also, in total cholesterol levels, there were non-significance differences between patients group and control group (p value= 0.002). Comparing other variables homeostasis model assessment-insulin resistance (HOMA-IR), HbAlc, body mass index (BMI) and waist circumference, there were statistical significant between subject group and control group ($P < 0.05$).

This results are in agreement with **Afkhami–Ardekani *et al.,*** who found non-significant difference in SHBG in DM group and control group (p = 0.002) [11]. Also, they found statistical significant difference of HbA1c in DM group and control group ($p = 0.0001$). **Vikan *et al.,*** suggested that the patients with T2DM who developed diabetes had significantly higher mean triglycerides, HDL-cholesterol, and systolic and diastolic blood pressure ($p <0.001$)[24]. This result was not concordant with **Ding *et al.,*** who found that decreased SHBG level is associated with increased incidence of DM both in male and female [4]. **Bonnet *et al.,*** found that a decrease of SHBG level is associated with increased incidence of DM in female only [25]. But in an earlier study **Ding *et al.,*** found a protective relation between higher levels of SHBG and diabetes more in female than in male as female with high SHBG has 80% lower risk versus 52% lower risk in male [19], while **Onat *et al.,*** found that low SHBG level is associated with an increasing incidence of DM in male only in absence of obesity[26]. The same results coincident with the findings of **Lakshman *et al.,*** [27] Recent study on middle aged males and they found that SHBG is an independent predictor of incident T2DM.

This study found that SHBG has highly significant decrease between male T2DM and female T2DM and controls. Also we found that SHBG is negatively correlated with age of the diabetic premenopause cases. On the other hand, there was no correlation between SHBG and age neither in diabetic male nor in diabetic postmenopausal female. This agrees with the studies of **Onat *et al.,*** who found age-related decline in SHBG; this decline appeared to include a 'menopause' transition component identifiable as a greater decline in the 4-year period around the female menopause and a secondary decline about 6 years after the female menopause [26].

The subjects with T2DM demonstrated higher SHBG levels than control subjects. However, the more variable fasting insulin/insulin resistance in the subjects with T2DM was not reflected by similarly more variable SHBG readings compared with those of the control group. **Jayagopal *et al.,*** suggests that a low SHBG concentration is a stable integrated marker of

insulin resistance and therefore has the characteristics to be potentially used as a surrogate measure of insulin resistance, perhaps in monitoring the response of an individual to insulin sensitizers. However, although SHBG levels differed significantly between those with and without diabetes, the absolute mean difference was small; indicating that measurement of SHBG cannot be used as a simple test for insulin resistance in diabetes[29].

In our study there was non-significant correlation between fasting insulin level and SHBG. This finding differs from that of **Osuana *et al.*,**[30] who found a negative correlation between fasting insulin level and SHBG levels in men and also differs from the findings of **Onat *et al.*,** found also a negative correlation between fasting insulin level and SHBG levels in elderly men and women[26]. **Araujo and Wittert,** concluded that there is a comprehensive discussion of the epidemiology of sex hormone changes, including their age associations, prevalence of symptomatic hypogonadism, secular changes, risk factors, and the association of sex hormones with outcomes. They also found a positive correlation between fasting insulin level and SHBG levels[31].

Akin *et al.*, found that there is no correlation between SHBG and fasting insulin levels among the study group of obese female, this findings changed after weight loss and the relation between both changed to be a negative correlation relationship[32]. **Sørensen *et al.*,** found in their study of hormonal changes at puberty that there is an increase of serum level of fasting insulin associated with a decline in the level of sex hormone binding globulin i.e., negative correlation [33].

As regard, insulin resistance can be assessed using HOMA; we calculated HOMA and our findings points to a significant positive correlation between SHBG and HOMA, this coincides with the findings of **Lewis**, in (**2004**), as he found a positive correlation between SHBG and HOMA in male and found no relation between SHBG and insulin resistance in female and he concluded that SHBG is another surrogate marker for insulin resistance in obese males but not in obese females[34]. Also, **Bonnet**, found a relation between SHBG and HOMA, fasting glucose level and hence insulin resistance in female but he founds no relation between the same variables in male[25]. **Onat *et al.*,** found a negative correlation between SHBG, and HOMA, fasting glucose level thus has a negative correlation with insulin resistance[26].

SHBG level found in this study to have a strong relationship with obesity indices namely waist circumference and BMI. This relation is found to be a slightly negative correlation between SHBG, waist circumference, and BMI in both female pre- and post-menopause, but no significant correlation between the same variables in the male group. These results are similar to that of **Akin *et al.*,** who concluded that SHBG has a negative correlation with BMI and waist circumference among women[32]. **Onat *et al.*,** supports our findings as they found that SHBG has a negative correlation with BMI and waist circumference[26].

In conclusion the prospective studies of postmenopausal women and men showed that lower levels of circulating sex hormone-binding globulin (SHBG) were strongly associated with a decreased risk of type 2 diabetes. Throughout this study even if increased SHBG may be associated with increased insulin resistance or associated with some etiological factors of T2DM, it can not be concluded. Further studies are recommended to find a more relationship between SHBG and T2DM.

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