Sex Hormone-Binding Globulin and Insulin Resistance 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. Sex hormone binding globulin (SHBG) is the principal transport protein for testosterone and estradiol. Low circulating levels of SHBG are a strong predictor of the risk of type 2 diabetes (T2DM) in women and men. The association between SHBG and incidence of type 2 DM is explained by insulin resistance. **Objective:** To study the serum level of SHBG and insulin resistance and to determine their risk in T2DM. **Subjects and Methods**: 80 participants were included in this study were classified into two groups: Control group; Twenty subjects (10 females and 10 males) aged 37.25±9.05 years without history of diabetes mellitus who's fasting blood glucose (FBG) was less than 126 mg/dl on two occasions and were matched for age, sex and body mass index (BMI). Patients group; Sixty patients aged 37.85±12.5 years with T2DM further classified into: Male group; twenty patients aged 38.2 ±13.9 years with T2DM, female group; Forty diabetic females (20 premenopausal and 20 postmenopausal) aged 37.5±10.6 years. Plasma level of SHBG, insulin levels, fasting blood glucose (FBG), 2-h pp glucose (PPBG), HbA1C were measured. Also total cholesterol, HDL-cholesterol, triglyceride, systolic, diastolic BP, BMI were measured and HOMA-IR was calculated. **Results**: Among women, lower levels of SHBG (8.6±5.1 nmol/l in T2DM and 11.4±4.8 nmol/l in non diabetics) than men (10.1±4.1 nmol/l in T2DM and 13.9±7.2 nmol/l in non diabetics**)** were associated with increased insulin resistance and hence a higher risk of T2DM. The mean serum level of SHBG was 9.35±5.6 nmol/l in diabetic patients and 12.5±6.9 nmol/l in non-diabetic subjects which was non-significantly different. A significant negative correlation between SHBG and HOMA-IR in males and females T2DM were reported. **Conclusion**: Lower concentration of SHBG was associated with increased insulin resistance (HOMA-IR) and hence a higher risk of development of T2DM.

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Key words: Type 2 diabetes mellitus (T2DM), sex hormone-binding globulin (SHBG), Homeostasis model assessment- insulin resistance (HOMA-IR)

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), macro vascular (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[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 life span 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 2diabetes has been reported to be stronger in women than in men[18, 19].

The aim of this works; was to study the serum level of SHBG and insulin resistance and to determine their risk in T2DM.

2. Subjects and Methods:

This study was carried out in the Inpatient and Outpatient Clinics of Endocrinology, Diabetes Unit and Clinical Pathology Department in Zagazig University Hospitals.

80 participants included in this study were classified into two groups:

Control group: Twenty subjects (10 females and 10 males) aged 37.25±9.05 yeras without history of diabetes mellitus who's FBG was less than126 mg/dl on two occasions and were matched for age, sex and BMI.

Patients group: Sixty patients aged 37.85±2.25 years with newly diagnosed T2DM further classified into; (1) **Male group**: Twenty patients aged 38.2 ±13.9 years with T2DM.

(2)**Female group**: Forty diabetic females (20 premenopausal and 20 postmenopausal) aged 37.5±10.6 years.

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 included (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/m^2).

3.Clinical investigations included (pelvi-abdominal ultrasonography).

4. Laboratory investigations included:

- FBG and PPBG levels.
- Complete blood picture (CBC).
- Urine analysis.
- Liver function test, kidney function test and lipid profile.
- HbAlC and 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 Homeostasis model assessment (HOMA-IR = [insulin (μU/ml)) × glucose(mmol/l)]/22.5)[21].

5. Measurement of **Sex hormone-binding globulin** (SHBG) by **Chemiluminescence** immunoassay (Elecsys 2010 autoanalyzer, Roche Diagnostics)[22].

Principle; Sandwich technique; 1st incubation; 10 µL of sample, a biotinylated monoclonal SHBG-specific antibody and a monoclonal SHBG-specific antibody labeled with a ruthenium complex forming a sandwich complex. 2nd incubation; After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode, Unbound substances are then removed with ProCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument- specifically generated by 2-point calibration and a master curve provided via the reagent barcode. Measuring range by the instrument; 0.350-200 nmol/L. Values below the detection limit are reported as < 0.350 nmol/L, where values above the measuring range are reported as > 200 nmol/L.

The exclusion criteria in our study; females on contraceptive pills (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-IR, insulin and to check the magnitude of the relation between these parameters.

3. Results

In this study, 60 T2DM patients were randomly selected with mean age 37±12.25 compared to 20 control group with mean age 37.25±9.05 years. Non-significant difference in age, SHBG, PP insulin and total cholesterol levels between T2DM and non-diabetic control group were reported. In the other hand, fasting and 2-hour blood glucoses (FBG-PPBG), homeostasis model assessment- insulin resistance (HOMA- IR) HA1C, triglyceride, systolic BP, diastolic BP were significantly increased in the patient than control group. HDL cholesterol, fasting insulin level, waist circumference and BMI were significantly lower in the patient than control group (table -1).

By comparing variables studied between males and females in diabetics and non diabeticts control groups, we found non-significant differences as regards age, total cholesterol and waist circumference. A significant increased of HDL-cholesterol and SHBG in males than in females. In the other hand, FBG, 2-hour glucose, insulin level, HOMA-IR,triglyceride, systolic BP, diastolic BP and BMI were significantly increased in females than males. (Table -2).

As regards, insulin resistance can be assessed by using HOMA; we calculated HOMA-IR. A significant negative correlation between SHBG and HOMA-IR in male and females was observed. Low SHBG is linked with an elevated HOMA-IR (consistent with increased insulin resistance). In female premenopausal diabetic group, there was a significant correlation between age and SHBG, also there was a significant negative correlation between SHBG with obesity indices (BMI and waist circumference) in female (pre- and post-menopause) but not in men diabetics patients. On the other hand, no significant correlation between SHBG and fasting insulin in both male and female (pre-and post-menopausal) diabetic patients. (Tables; 3-4-5).

HOMA = insulin level (µU/ml) × fasting glucose level (mg/dl)
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405

Table (1): Comparison of variables studied in T2DM and non-diabetic control group

Parameters	T2DM group (n=60)	Non-diabetic Control group (n = 20)	*P* value
Age (year)	37.85±12.25	37.25±9.05	>0.05
P.P insulin level (µU/ml)	19.8±6.95	22.09±8.89	> 0.05
FBS (mg/dl)	158.5±41.1	81.7±14.6	< 0.001
HOMA-IR	4.52±0.54	2.44±0.18	< 0.05
Fasting insulin (µU/ml)	11.55±4.3	12.2±5.2	< 0.001
2-h glucose (mg/dl)	192.5±59.6	89±17.1	< 0.001
HbAlc (%)	7.7±1.83	4.8±0.6	0.001
Total cholesterol (TC) (mg/dl)	218.9±34.35	175.5±20.64	> 0.05
HDL-cholesterol (mg/dl)	39.6±12.1	47.8±15.3	< 0.001
Triglyceride (mg/dl)	129±30.25	84.9±12.8	< 0.001
Systolic BP (mm Hg)	118.5±16.5	106.5 ±9	< 0.001
Diastolic BP (mm Hg)	83±10	73±7.5	< 0.001

SHBG (nmol/L)	**9.35±5.6**	**12.5±6.9**	**> 0.05**
Waist circumference (cm)	89.6 ±5.3	94.6±9.6	< 0.05
BMI (kg/m^2)	26.4±2.5	28.5±3.5	< 0.05

FBG = fasting blood glucose, 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.

Table (2): Comparison of variables studied between male and female in patient and control groups.

Variable	T2DM Case		Control		*P*
	Male (n = 20)	Female (n = 40)	Male (n = 10)	Female (n = 10)	
Age (year)	38.2±13.9	37.5±10.6	37.5±10.6	36.9±8.4	> 0.05
P.P insulin level (µ U/ml)	18.9 ±6.7	20.7±7.2	21.6±8.08	22.58±9.7	< 0.001
FBS (mg/dl)	151.05±36	166.3±46.3	80.6±15.8	84.6±15.4	< 0.001
HOMA-IR	3.91±0.42	5.1±0.66	2.17±0.22	2.6±0.16	< 0.001
Fasting insulin (mU/ml)	10.5±3.7	12.6±4.9	11.0±4.3	12.5±6.1	< 0.001
2-h glucose (mg/dl)	188.1±58.2	197.3±61.4	88.1±17.8	90.3±16.4	< 0.001
Total cholesterol (TC) (mg/dl)	214.5±37.2	223.4±32.3	171.7±21.9	180.1±19.4	> 0.05
HDL-cholesterol (mg/dl)	40.9±10.3	38.6±13.9	49.3±16.5	46.4±14.1	< 0.001
Triglyceride (mg/dl)	124.±27.3	133.5±33.2	78.8±11.5	91±13.4	< 0.001
Systolic BP (mm Hg)	117±18	120±15	108±8	105±10	< 0.001
Diastolic BP (mm Hg)	80±10	85±10	70±5	75±10	< 0.001
SHBG (nmol/L)	**10.1±4.1**	**8.6± ±5.1**	**13.9±7.2**	**11.4±4.8**	**< 0.001**
Waist circumference (cm)	88.6±4.9	90.3±5.7	90.9.±9.8	98.6±8.5	> 0.05
BMI (kg/m^2)	26.1±2.25	28.1±2.3	27.4±4.1	30.5±6.2	< 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

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

Variable	**r**	**p**
Age	0.285	> 0.05 (NS)
HOMA-IR	-0.585	< 0.001
FBS	0.136	> 0.05 (NS)
BMI	-0.126	> 0.05 (NS)
Waist circumference	0.106	> 0.05 (NS)
Fasting Insulin level	-0.211	< 0.05(NS)

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

Variable	r	**P**
Age	-0.685	0.001
HOMA-IR	-0.361	< 0.05
FBG	0.194	> 0.05 (NS)
BMI	-0.354	< 0.05
Waist circumference	-0.402	< 0.05
Fasting Insulin level	0.139	> 0.05(NS)

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

Variable	***r***	***p***
Age	-0.124	> 0.05 (NS
HOMA-IR	-0.323	< 0.05
FBG	0.141	> 0.05 (NS)
BMI	-0.381	< 0.05
Waist circumference	-0. 301	< 0.05
Fasting Insulin level	-0.206	> 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 men. Circulating sex hormone-binding globulin levels are inversely associated with insulin resistance, but these levels can predict the risk of developing type 2 diabetes is uncertain.[4]

The aim of this work was to study the serum level of SHBG and insulin resistance and to determine their risk in T2DM. Our results showed that, HA1C, triglyceride, systolic BP, diastolic BP, were significantly increased in the patient than control group, but, HDL cholesterol was significantly lower in the patient than control group.

These results were in agreement with **Afkhami-Ardekani** et al., who found non-significant difference in SHBG in DM and control groups. Also, they found statistical significant difference of HbA1C in DM and control groups.[11]

Vikan et al., suggested that the patients with T2DM had significantly higher mean triglycerides, systolic, diastolic blood pressure and lower HDL-cholesterol.[23]

Our results was showed that a lower SHBG level was consistent with increased insulin resistance and hence increased risk of T2DM, this in concordant with **Ding et al.**, who found that decreased SHBG level is associated with increased incidence of DM 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.[24] But in an earlier study **Ding et al.,** found aprotective 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**., reported that low SHBG level is associated with an increasing incidence of DM in male only in absence of obesity.[25] The same previous results obtained by **Lakshman et al**., who studied on middle aged males, and found that SHBG may contribute to the risk of T2DM through non androgenic mechanisms (independent of action of total and free testosterone).[26]

A significant increased of SHBG in male than in female (diabetics and control). Also SHBG is negatively correlated with age of the diabetic premenopausal patients. On the other hand, there was no correlation between SHBG and age neither in diabetic male nor in diabetic postmenopausal female.

This agreed with the studies of **Onat** et al., who found age-related decline in SHBG; this decline appeared to include '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[25].

Our T2DM patients demonstrated non-significant difference in SHBG levels with control subjects. In the other hand, a significant increased of insulin resistance in T2DM than control group was observed. **Jayagopal et a**l., suggest 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.[27]

In our study there was non-significant correlation between fasting insulin level and SHBG. This finding differs from that of **Osuana et al**.,[28] who found a negative correlation between fasting insulin level and SHBG levels in men and also differs from the findings of **Onat et al**., who found also a negative correlation between fasting insulin level and SHBG levels in elderly men and women[25]. **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 level[29].

Akin et al., found that there is no correlation between SHBG and fasting insulin levels among the study group of obese female[30]. **Sørensen et al**., found in their study of hormonal changes at puberty that there is a negative correlation between SHBG and fasting insulin level [31].

As regards, insulin resistance can be assessed using HOMA; we calculated HOMA-IR and our findings point to a significant negative correlation between SHBG and HOMA in both men and women, this in harrmony with **Onat et al.,** who found a negative correlation between SHBG, and HOMA, fasting glucose level thus has a negative correlation with insulin resistance[25]. Also, **Bonnet et a**l., found a negative relation between SHBG and HOMA, fasting glucose level and hence insulin resistance in female but not in male[24]. Our results not coincided with the findings of **Lewis**, who found a positive correlation between SHBG and HOMA in male and not in female and he concluded that SHBG is another surrogate marker for insulin resistance in obese males but not in obese females[32].

SHBG level found in this study to had a negative correlation with obesity indices (waist circumference and BMI) in female pre- and post-menopause, but not in male group. These results are similar to that of **Akin et al**., who concluded that SHBG had a negative correlation with BMI and waist circumference among women[30]. **Onat et al**., supported our findings as they found that SHBG has

a negative correlation with BMI and waist circumference.[25]

In conclusion; the prospective study of diabetics men and women showed that decreased SHBG level was associated with increased insulin resistance and hence increased risk of T2DM. Further studies are recommended to find a more relationship between SHBG and T2DM.

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