

## SEX HORMONE BINDING GLOBULIN GENE POLYMORPHISM AND RISK OF TYPE2 DIABETES MELLITUS IN EGYPTIAN MEN

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### ABSTRACT

Conditions of hypoandrogenism in men have been linked to insulin resistance, suggesting that alterations in normal sex steroid physiology could play a role in the pathogenesis of type 2 diabetes (T2DM). Sex hormone binding globulin gene polymorphisms may be the cause of sex steroid alteration. The aim of this work to study effect of sex hormone binding globulin (SHBG) gene polymorphisms on type 2 diabetes mellitus risk through its impact on testosterone and estradiol level in Egyptian men. In 185 diabetic men and 120 matched healthy controls, two polymorphisms (rs6257 and rs6259) of the gene encoding sex hormone-binding globulin were genotyped and serum levels of sex hormone-binding globulin, testosterone and estradiol were measured by ELISA; Our results showed significant decrease in sex hormone binding globulins in type 2 diabetic patients compared with the control group. Carrier of variant allele of SHBG single nucleotide polymorphism (SNP) rs6259 had a higher level of SHBG in serum (p=0.000) While carrier of SHBG rs6257 SNP had a lower level of SHBG level in serum. SHBG gene polymorphisms are associated with risk of type 2 diabetes in Egyptian men, through lowering circulating levels of sex hormone-binding globulin and consequently lowering testosterone and elevating estradiol level. SHBG rs6257 genotype may have a predictive value of developing type II diabetes mellitus

**Key words:** Diabetes mellitus, SHBG, gene polymorphism, testosterone, and estradiol.

### INTRODUCTION

Type 2 diabetes (T2DM) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency<sup>(1)</sup>. It is typically a chronic disease, associated with a ten year shorter life expectancy<sup>(2)</sup>. The number of people worldwide affected by diabetes is projected to be 366 million by the year 2030, with the vast majority of these cases being (T2DM) which makes up about 90% of cases of diabetes<sup>(3)</sup>.

Significant resources continue to be devoted to unraveling the complex pathophysiology of this disorder. It is now evident that a combination of lifestyle and genetic factors contribute collectively to the primary physiologic derangements responsible for T2DM<sup>(4)</sup>. More than 36 genes have been found contributing to type 2 diabetes risk. All of these genes comprise only about 10% of the total genetic component of the disease<sup>(5)</sup>.

Based only on serum testosterone level, most of the studies in diabetic men have defined hypogonadism<sup>(6)</sup>. Hypogonadism is a clinical condition including both symptoms and biochemical evidence of testosterone deficiency<sup>(7)</sup>. Of note, conditions of hypoandrogenism in men have been linked to insulin resistance, suggesting that alterations in normal sex steroid physiology could play a role in the pathogenesis of T2DM<sup>(8)</sup>.

In human blood, circulating sex steroid hormones such as estradiol and testosterone are

primarily bound to sex hormone-binding globulin (SHBG), a glycosylated homodimeric plasma transport protein synthesized mainly in the liver, binds the androgens testosterone and dihydrotestosterone (DHT), with higher affinity than estradiol<sup>(9)</sup>. SHBG regulates free sex hormone bioavailability to target tissues, through differential binding and transport of sex steroids<sup>(10)</sup>. Also it exerts direct effects on sex steroid cellular uptake and cell proliferation in hormone-responsive tissues via the activation of a specific, high-affinity receptor present in the plasma membrane<sup>(11)</sup>.

(SHBG) has become known as one of the multiple environmental and genetic factors that potentially has a role in the pathophysiology of type T2DM<sup>(12)</sup>. In addition to epidemiologic studies representing a steady relationship between decreased serum levels of SHBG and incident T2DM, recent genetic studies also disclose that transmission of specific polymorphisms in the SHBG gene contribute to the risk of T2DM<sup>(12)</sup>.

Human SHBG is encoded by the 4 kb SHBG gene at chromosome 17p12-p13 which comprises eight exons and seven intervening introns<sup>(13)</sup>. Several polymorphisms in the human (SHBG) gene were characterized, it have been found that genotype analysis of the exon 8 SHBG SNPs, rs6257 and rs6259 have been found to be associated with circulating levels of sex hormone-binding globulin,<sup>(14)</sup> insulin resistance,<sup>(15)</sup> and

other sex hormone– dependent conditions such as reduced bone mineral density, breast cancer, and prostate cancer<sup>(16)</sup>.

However, prospective data examining SHBG level and polymorphisms and the risk of T2DM in Egyptian male patient are lacking.

So, the aim of this study was to investigate the relations of plasma levels of sex hormone–binding globulin and SHBG polymorphisms with the risk of T2DM in a prospective study of Egyptian diabetic men.

## MATERIALS AND METHODS

### Study population:

The study included 185 male (mean age  $50.3 \pm 6.7$ ) patients with type 2 Diabetes mellitus randomly selected from the diabetes clinic of the Zagazig University Hospital. Age-matched (mean age  $49.8 \pm 6.6$ ), 120 healthy individuals (who had no DM or impaired glucose tolerance ) were selected as control group . In this study, all subjects were Egyptians. Also, the study was approved by the ethical committee of the Zagazig University and informed consent was obtained from them.

Exclusion criteria included those who had castrated for treatment on cancer testis or prostate, taking any medications known to affect sex hormone level (e.g, antiandrogenic agents for prostate cancer) and those with impaired liver and renal functions. Subjects enrolled in the study underwent routine biochemical blood analysis. (Fasting blood glucose, HbA1C, lipid profile, kidney and liver functions).

### Biochemical analysis

#### Sampling

Peripheral venous blood (6 mL) was collected and divided into 2 portions one in a tubes containing EDTA and processed immediately for DNA extraction. Another portion was collected in plain tubes for serum separation by 10 minutes double centrifugation at 1600 g to spin down any insoluble remnants in the serum then stored at  $-80^{\circ}\text{C}$  for future analysis.

### Enzyme-Linked Immunosorbent Assay

Hormonal levels were assayed using a specific commercially available ELISA Kits, Quantikine, R&D systems (GmbH - Germany), for SHBG and testotesterone and BIOVENDOR Research and Diagnostic Products (Guang Zhou, CHINA) for estradiol. We used 50  $\mu\text{L}$  of sample for SHBG and Estradiol and 100  $\mu\text{L}$  for testosterone. The instruction manual was strictly followed, and samples were assayed as duplicates.

The minimum detection limit for SHBG, testosterone and estradiol were 0.005 nmol/L, 0.030 ng/mL and 10pg/ml respectively

### DNA extraction

Genomic DNA was extracted from EDTA whole-blood sample using a spin column method according to the manufacturer's protocol (QIAamp Blood Kit; Qiagen GmbH, Hilden, Germany). The purified DNA was stored at  $-80^{\circ}\text{C}$  until further use.

### Detection of SHBG polymorphisms

All DNA samples were genotyped according to the method of Ding et al, 2009 based on the exonuclease activity of Taq DNA-polymerase using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA),. PCR amplification was carried out on 5-20ng DNA using 1 X TaqMan universal PCR master mix, 900nM forward and reverse primers, 200nM of each of the allele-specific Taqman probes labeled with VIC and FAM and in 5ml reaction volume. Amplification conditions involve the use of one cycle of  $95^{\circ}\text{C}$  for 10min, followed by 50 cycles of  $92^{\circ}\text{C}$  for 15s and  $60^{\circ}\text{C}$  for 1 min.

Quality control measures include blinded analyses, replicates of 10% of samples, and positive controls (blood-derived DNA from all known genotypes), and negative controls for contamination (no DNA) were run routinely with patient samples.

### Statistical analysis:

Statistical analysis in this study was performed using SPSS version 17.0. Most data are expressed as the mean ( $\pm\text{SD}$ ) for quantitative variables.

The results for continuous variables were expressed as means  $\pm$  SD. The means of the genotype groups were compared in a one-way analysis of variance (ANOVA). The statistical significances of differences in frequencies of variants between the groups were tested using the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as a measure of the association of the rs6257 and rs6259 genotypes of SHBG gene polymorphism. A difference was considered significant at  $P < 0.05$ .

## RESULTS

The mean age of diabetics was insignificantly higher than control ( $50.3 \pm 6.74$  and  $49.8 \pm 6.64$  years respectively). Among diabetics, the mean duration of disease was  $13.0 \pm 5.65$  years.

Positive family history of DM was significantly encountered among 35.7% of studied diabetics ( $p=0.000$ ); with Odd's ratio of 4.992,  $\text{CI}=2.559-9.735$ ). The mean  $\pm\text{SD}$  and median of biochemical parameters for diabetics and their control were summarized in table 1.

### SHBG genotypes frequencies

The genotype and allele frequencies of SHBG rs6257 and rs6259 polymorphisms among diabetic patients and control group are shown in table 2.

The rs6257 wild type (TT) had been found among 74.1% of diabetics (with Odd's ratio of 1.9, CI=1.03-3.36), and the remaining diabetics (25.9%) had either of the variant type (CT or CC) allele (Odd's ratio=0.54, CI=0.30-0.97).

The rs6259 Wild type (GG) had been detected among 85.9% of diabetics (Odd's ratio=0.43, CI=0.242-0.767) and remaining (14.1%) had either variant type AG or AA (odd's ratio=2.32, CI=1.303-4.129).

#### Association Between polymorphism and SHBG and hormonal Levels

Among both control and diabetics, there was significant difference in the level of SHBG in different rs6257 alleles ( $p=0.000$ ,  $0.003$  respectively); with significant difference among control and diabetics regarding TT and both CA & CC alleles ( $p=0.000$ ,  $0.004$ ) (Table 3).

Significant difference in testosterone level among different rs6257 alleles in diabetics was encountered ( $p=0.002$ ), with a significant differences between control and diabetics regarding TT allele only ( $p=0.000$ ) (Table 3).

Regarding estradiol level, significant difference between different alleles among diabetics was encountered ( $p=0.003$ ), with a significant differences between control and diabetics regarding different rs6257 alleles ( $p=0.000$ ,  $0.014$ , and  $0.002$  respectively) (Table 3).

Diabetics with TT allele had significantly less mean SHBG level than their control ( $28.4 \pm 9.57$ ,  $37.3 \pm 11.54$ ;  $p=0.000$ ), while those with CT allele

had insignificantly lower SHBG level than that of control ( $17.8 \pm 6.03$ ,  $21.0 \pm 4.06$ ). Also, the mean SHBG level among diabetics with CC allele was significantly lower than that of their controls ( $13.1 \pm 3.76$ ,  $17.9 \pm 1.80$ ;  $p=0.004$ ) (Table 3).

For SHBG, There was significant difference in its level among all rs6259 alleles in control and diabetics ( $p=0.000$ ,  $0.000$  respectively); with significant difference between control and diabetics regarding AA and AG alleles ( $p=0.000$ ,  $0.046$  respectively) (Table 4).

Significant differences of estradiol level were encountered between rs6259 alleles and both control and diabetics ( $p=0.000$ ,  $0.026$  respectively). Significant differences of testosterone level were encountered between rs6259 alleles and both control and diabetics ( $p=0.000$ ,  $0.003$  respectively); with significant difference between control and diabetics regarding AA allele only ( $p=0.000$ ) (Table 4).

Diabetics with TT allele had significantly less mean SHBG level than their control ( $28.4 \pm 9.57$ ,  $37.3 \pm 11.54$ ;  $p=0.000$ ), while those with CT allele had insignificantly lower SHBG level than that of control ( $17.8 \pm 6.03$ ,  $21.0 \pm 4.06$ ). Also, the mean SHBG level among diabetics with CC allele was significantly lower than that of their controls ( $13.1 \pm 3.76$ ,  $17.9 \pm 1.80$ ;  $p=0.004$ ).

Diabetics with AA and AG alleles had significantly less SHBG level than their control ( $22.5 \pm 7.27$ ,  $29.6 \pm 9.59$ ;  $p=0.000$ -  $37.0 \pm 9.49$ ,  $42.1 \pm 5.31$ ;  $p=0.046$  respectively); meanwhile there was insignificant lower SHBG level among diabetics with GG allele ( $48.3 \pm 11.85$ ,  $56.2 \pm 7.01$  respectively).

**Table 1: Biochemical profile of diabetic patients and their control**

	Control N=120	Diabetic patients N=185	p-value
<b>FBS (mg/dl)</b>			
Mean $\pm$ Sd	95.7 $\pm$ 16.16	184.6 $\pm$ 37.36	t=477.040
Median	95.5	175.0	<b>p=0.000*</b>
<b>Hb A1c (%)</b>			
Mean $\pm$ Sd	5.0 $\pm$ 0.33	8.2 $\pm$ 1.23	t=781.063
Median	5.1	8.5	<b>p=0.000*</b>
<b>SHBG</b>			
Mean $\pm$ Sd	34.6 $\pm$ 12.45	25.1 $\pm$ 10.34	t=51.592
Median	32.9	24.0	<b>p=0.000*</b>
<b>Estradiol</b>			
Mean $\pm$ Sd	22.5 $\pm$ 7.46	29.1 $\pm$ 6.53	t=64.574
Median	21.0	32.0	<b>p=0.000*</b>
<b>Testosterone</b>			
Mean $\pm$ Sd	9.0 $\pm$ 2.01	7.8 $\pm$ 2.08	t=26.411
Median	8.7	7.5	<b>p=0.000*</b>

\*p-value is significant at < 0.05 level

**Table 2: Risk assessment of different alleles among studied groups**

	Control		Diabetic patients		Odd's Ratio	Confidence Interval (CI) at 95%
	N=120	%	N=185	%		
<b>Rs 6257</b>						
TT	101	84.2	137	74.1	<b>1.9*</b>	1.03-3.36
CT-CC	19	15.8	48	25.9	<b>0.54*</b>	0.30-0.97
<b>Rs 6259</b>						
GG	87	72.5	159	85.9	<b>0.43*</b>	0.242-0.767
AG-AA	33	27.5	26	14.1	<b>2.32*</b>	1.303-4.129

**Table 3: Distribution of rs6257 and lab parameters among diabetic patients and their control**

		TT	CT	CC	p-value
		<b>SHBG</b> Mean $\pm$ SD (nmol/L)	Control	37.3 $\pm$ 11.54	21.0 $\pm$ 4.06
	Diabetic	28.4 $\pm$ 9.57	17.8 $\pm$ 6.03	13.1 $\pm$ 3.76	F=5.959 <b>p=0.003*</b>
	t-test	42.277	2.935	10.256	
	p-value	<b>0.000*</b>	0.095	<b>0.004*</b>	
<b>Testosterone</b> Mean $\pm$ SD (ng/mL)	Control	9.1 $\pm$ 2.0	8.4 $\pm$ 1.19	8.2 $\pm$ 3.32	F=1.447 p=0.239
	Diabetics	8.0 $\pm$ 2.07	7.3 $\pm$ 1.83	6.5 $\pm$ 1.92	F=6.229 <b>p=0.002*</b>
	t-test	16.642	3.286	2.752	
	p-value	<b>0.000*</b>	0.078	0.109	
<b>Estradiol</b> Mean $\pm$ SD (pg/ml)	Control	22.1 $\pm$ 7.08	24.7 $\pm$ 9.80	24.6 $\pm$ 8.61	F=0.933 P=0.396
	Diabetics	28.1 $\pm$ 6.82	31.0 $\pm$ 5.42	32.6 $\pm$ 3.75	F=5.959 <b>p=0.003*</b>
	t-test	43.396	6.625	11.916	
	p-value	<b>0.000*</b>	<b>0.014*</b>	<b>0.002*</b>	

**Table 4: Distribution of rs6259 among diabetic patients and their control**

		AA	AG	GG	p-value
		<b>SHBG</b> Mean $\pm$ SD (nmol/L)	Control	29.6 $\pm$ 9.59	42.1 $\pm$ 5.31
	Diabetic	22.5 $\pm$ 7.27	37.0 $\pm$ 9.49	48.3 $\pm$ 11.85	F=72.333 <b>p=0.000*</b>
	t-test	42.682	4.291	4.063	
	p-value	<b>0.000*</b>	<b>0.046*</b>	0.057	
<b>Estradiol</b> Mean $\pm$ SD (pg/ml)	Control	22.8 $\pm$ 7.37	22.4 $\pm$ 7.75	20.9 $\pm$ 7.96	F=0.379 p=0.685
	Diabetics	29.4 $\pm$ 6.36	26.2 $\pm$ 7.36	28.8 $\pm$ 7.61	F=1.679 P=0.189
	t-test	52.932	2.289	5.729	
	p-value	<b>0.000*</b>	0.140	<b>0.026*</b>	
<b>Testosterone</b> Mean $\pm$ SD (ng/mL)	Control	8.5 $\pm$ 1.61	9.68 $\pm$ 2.39	11.5 $\pm$ 1.62	F=18.524 <b>p=0.000*</b>
	Diabetics	7.6 $\pm$ 1.85	8.8 $\pm$ 2.65	9.3 $\pm$ 3.31	F=6.089 <b>p=0.003*</b>
	t-test	14.877	1.005	4.306	
	p-value	<b>0.000*</b>	0.323	0.050	

\*p-value is significant at &lt; 0.05 level

**Table 5: Predictors for SHBG action**

	<b>B</b>	<b>Beta</b>	<b>t-</b>	<b>Sig.</b>
<b>Estrogen</b>	-.629	-.394	-7.472	<b>0.000*</b>
<b>Testosterone</b>	2.706	.477	9.449	<b>0.000*</b>
<b>Allele 57</b>	-9.942	-.519	-10.564	<b>0.000*</b>
<b>Allele 59</b>	14.124	.689	16.526	<b>0.000*</b>

\*P value is significant at <0.05 level

## DISCUSSION

Sex hormone-binding globulin may play an important role in the pathogenesis of type 2 diabetes, by modulating the biologic effects of sex hormones (testosterone and estrogen) on peripheral tissues (i.e., liver, muscle, and fat). Studies suggest that sex hormones bound to sex hormone-binding globulin may also be biologically active, amplifying their signaling, endocytosis, or overall biologic actions<sup>(17)</sup>.

Sex hormone binding globulin has been shown to have direct cellular antagonistic properties against estrogen. Interaction of sex hormone-binding globulin with the cellular estrogen receptor can trigger a biologic antiestrogen response a form of mediation beyond simple hormone sequestration<sup>(18 & 14)</sup>.

In the present study it was found that there was a significant decrease in sex hormone binding globulins in type 2 diabetic patients compared with the control group. These findings were in accordance with the results reported by **Ding ,et al.**,<sup>(16)</sup>.

This finding can be explained by that the risk of type 2 diabetes associated with a low level of sex hormone binding globulin is due in part to an inverse correlation between insulin resistance and plasma levels of sex hormone-binding globulin<sup>(16)</sup>. Insulin decreases hepatic production of sex hormone-binding globulin in vitro and inhibition of insulin release increases plasma levels of sex hormone-binding globulin in humans. Hyperinsulinemia induced by insulin resistance probably causes low levels of sex hormone-binding globulin in insulin-resistant conditions such as obesity, type 2 diabetes, and the polycystic ovary syndrome<sup>(19)</sup>.

In our study it was also found that there was a significant decrease in testosterone level and significant increase in estradiol level in diabetic group compared to normal control. These findings were in accordance with the results reported by **Ding, et al.**,<sup>(16)</sup>. The reduction in SHBG levels results in low total testosterone levels in type II diabetic patients. SHBG levels are inversely related to obesity and to insulin levels. Studies proved that total testosterone levels could be

merely a manifestation of reduced SHBG levels<sup>(20 & 21)</sup>.

Another study suggested that lower testosterone levels may promote insulin resistance through impairment of mitochondrial function. Thus, as to whether male hypogonadism plays a causal role in the development of insulin resistance and diabetes or is a consequence of it. As sex hormone binding globulins decrease in type 2 diabetes this leads to increase level of free estradiol in blood. Studies proved that SHBG has a higher affinity to estradiol than testosterone. E2 may have direct effects on glucose transport or metabolism as proved by different studies<sup>(22)</sup>.

Our study revealed that carriage of variant rs6257 was associated with lower levels of sex hormone-binding globulin and higher risk of T2DM, whereas carriage of rs6259 was associated with higher levels of sex hormone-binding globulin and lower risk of T2DM. These results were in accordance with results obtained by **Ding et al.**,<sup>(16)</sup>. Elevated levels of circulating sex hormone-binding globulin among carriers of an rs6259 variant allele warrant further functional studies; the elevation may be due to an amino acid substitution of asparagine for aspartic acid (D356N) at rs6259. This locus is an N-glycosylation consensus site that alters the binding of sex hormone binding globulin to membrane receptors and other proteins and reduces its clearance from the circulation, resulting in higher plasma levels of the globulin<sup>(23)</sup>.

The associations found for rs6257, a SNP that flanks, and is located 17 bp upstream of, exon 2 also suggests the presence of potential key splicing or regulatory elements in that region<sup>(16)</sup>.

Linking plasma levels of sex hormone binding globulin to the risk of T2DM obtained from our genotyping analysis may represent the average lifetime risk attributable to sex hormone-binding globulin alone, independent of traditional risk factors.

In the present study we found also a great association between type 2 DM and different genotypes of rs6257 and different genotypes of rs6259 and normal control. These different distributions were associated with changes in hormonal levels regarding SHBG, testosterone

and estradiol shown in the results in details. These results were in accordance with **Ding et al.**,<sup>(16)</sup>.

### CONCLUSION

Sex hormone-binding globulin may play an important role in the development of type 2 diabetes at both the genomic and phenotypic levels and that sex hormone-binding globulin could be an important target in stratification for the risk of type 2 diabetes and early intervention.

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### Conflict of interest

No conflict of interest

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## دراسة علاقة التعدد الشكلي الجيني للجلوبيولين الملازم للهرمون الجنسي بخطر حدوث البول السكري من النوع الثاني في الرجال المصريين

مقدمة:

ترتبط حالات الضعف الجنسي عند الرجال بمقاومة الأنسولين، مما يجعل هناك احتمالاً أن التغيرات الوظيفية للهرمون الجنسي يمكن أن تلعب دوراً في إحداث مرض البول السكري من النوع الثاني. التعدد الشكلي الجيني للجلوبيولين الملازم للهرمون الجنسي يمكن أن يكون السبب في هذه التغيرات في الهرمون الجنسي.

الهدف من البحث:

تهدف الدراسة إلي معرفة تأثير التعدد الشكلي الجيني للجلوبيولين الملازم للهرمون الجنسي علي خطورة إحداث السكري من النوع الثاني عن طريق تأثيره علي قيم ومعدلات التستوستيرون والاسترادايول في الرجال المصريين.

طريقة البحث:

تم إجراء الدراسة علي ١٨٥ من الرجال المصابين بالسكري من النوع الثاني وتم مقارنتهم بعدد ١٢٠ من الأشخاص الأصحاء كمجموعة ضابطة. تم دراسة النمط الجيني لاثنتين من التعددات الشكلية للجين الحامل لشفرة الجلوبيولين الملازم للهرمون الجنسي (rs6259&rs6257) كما تم قياس قيم الجلوبيولين الملازم للهرمون الجنسي والتستوستيرون والاسترادايول في المصل.

نتائج البحث:

وقد أسفرت نتائج البحث عن وجود نقص ذو دلالة إحصائية في الجلوبيولين الملازم للهرمون الجنسي في مرضي السكري من النوع الثاني عن نظرائهم بالمجموعة الضابطة. كما وجد أن الحاملين للنمط الجيني rs6259 لديهم نسب أعلى من هذا الجلوبيولين في المصل عن الحاملين للنمط الجيني rs6257 والذين وجد لديهم نسب أقل من هذا الجلوبيولين.

الخلاصة:

وقد خلصت هذه الدراسة إلي أن التعدد الشكلي الجيني للجلوبيولين الملازم للهرمون الجنسي له تأثير علي إحداث السكري من النوع الثاني في الرجال المصريين من خلال التقليل من معدلات الجلوبيولينات الملازمة للهرمون الجنسي بالدم وبالتبعية الإقلال من معدلات التستوستيرون وزيادة معدلات السترادايول بالدم. وبالتالي فالنمط الجيني rs6257 له قيمة تنبؤية لحدوث السكري من النوع الثاني.