ASSOCIATION OF SERUM SEX HORMONE BINDING GLOBULIN WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: To investigate the association of circulating levels of sex hormone binding globulin with type 2 diabetes mellitus.

Study Design: Case control study.

Place and Duration of Study: The study was conducted at the Department of Chemical Pathology, Army Medical College Rawalpindi.

Material and Methods: This study consisted of two groups; A and B. Group A consisted of type 2 diabetic patients and group B consisted of healthy controls. Each group comprised of 60 participants which were randomly selected from Endocrinology Department of Military Hospital (MH), Rawalpindi. Fasting blood samples of the participants were analyzed for serum sex hormone binding globulin (SHBG), fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) and fasting insulin levels. The biochemical analysis was carried out at the Chemical Pathology Department, Army Medical College Rawalpindi. The data obtained were statistically analyzed with SPSS version 20.

Results: In this study, low levels of SHBG (39.53 ± 22.25 vs. 62.35 ± 32.52, p=<0.05) were noted in diabetic as compared to the control participants. The diabetic patients presented with significantly higher fasting plasma glucose (11.23 ± 3.65 vs. 4.35 ± 0.68, p=<0.05), HbA1c (6.84 ± 0.48 vs. 5.31 ± 0.48, p=<0.05), serum insulin (8.90 ± 6.51 vs. 6.32 ± 4.09, p=<0.05) and insulin resistance (4.84 ± 5.18 vs. 1.23 ± 0.83, p=<0.05), calculated by HOMA-IR. SHBG was negatively associated with HbA1c (r-0.101), FPG (r -0.107), serum insulin (r-0.132) and insulin resistance, IR (-0.142) in the diabetic group.

Conclusion: This study concludes that SHBG levels are markedly decreased in type 2 diabetes mellitus. Therefore, SHBG has a potential to be used as a biomarker of metabolic control in type 2 diabetes mellitus.

Keywords: Homeostatic model assessment-Insulin resistance, Insulin resistance, Sex hormone binding globulin, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a long standing metabolic disorder characterized by hyperglycemia which is caused by defective insulin secretion, ineffective insulin function or both. Diabetes mellitus involves disorders in carbohydrate, fat and protein metabolism[1]. Diabetes mellitus is broadly classified into two types, type 1 diabetes mellitus or insulin dependent diabetes mellitus (IDDM), which occurs due to deficient insulin secretion and type 2 diabetes mellitus or noninsulin dependent only diabetes mellitus (NIDDM), which involves insulin resistance and can also be accompanied by relative deficiency of insulin[2]. Chronic hyperglycemia causes structural and functional cellular changes which lead to development of complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, hypertension, hyperlipidemia, cerebrovascular diseases and atherosclerosis leading to coronary heart disease[3,4].

In the past, serum sex hormone-binding globulin (SHBG) was considered to be a way for the storage of sex hormones only. However; now it has been found to have a role in a number of biological functions[5,6]. Serum SHBG binds to sex hormones including testosterone; to regulate

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their biologically active circulating fractions[7]. Serum level of SHBG mainly determines the metabolic clearance of serum testosterone and also regulates its access to the target tissues[8,9]. This regulatory role of SHBG is explained through an intracellular signaling cascade which is mediated by a membrane-bound SHBG receptor[10]. Recently researchers have highlighted another significant aspect of SHBG that is its association with type 2 diabetes mellitus.

Research performed on different populations reports a negative association between low circulating SHBG and type 2 diabetes mellitus implying that subjects having higher serum levels of SHBG will be protected from developing type 2 diabetes[11-14]. A causal relationship has been observed between serum SHBG and type 2 diabetes mellitus by genetic studies[15].

The relationship of whole body insulin sensitivity with SHBG level is associated with fat deposition in the liver. A significant relationship of SHBG level with fasting glycemia, independent of liver fat has also been found, as fasting glycemia is highly affected by hepatic glycogenolysis and gluconeogenesis. Peter et al, showed the direct effects of SHBG on hepatic glucose production. Increased hepatic glucose output in concert with beta cell defect explains the association of circulating levels of SHBG and SHBG genetic variants in type 2 diabetes. The mechanism by which high circulating SHBG prevents development of type 2 diabetes involves regulation of fasting glycemia but not the alteration of insulin secretory function[16].

The relationship of serum SHBG level with type 2 diabetes mellitus depends on factors like age, gender and ethnicity[17] that needs to be investigated in a variety of populations belonging to different regions and racial groups[18].

Significance of Study

Pakistan has a very high prevalence of type 2 diabetes mellitus which is still increasing. This study will provide baseline information about serum SHBG levels in type 2 diabetic population in the region. This may prove helpful in the further studies based on preventive and therapeutic role of these hormones in type 2 diabetes mellitus.

MATERIAL AND METHODS

This case control study was carried out in the Department of Chemical Pathology, Army Medical College, Rawalpindi. The study population consisted of two groups. Group A contained 60 patients with type 2 diabetes. Group B contained 60 normal participants who were free of any major illness such as diabetes mellitus, coronary heart disease, kidney disease, thyroid problems. Patients were conveniently selected from the medical, endocrinology wards and OPDs of the Military Hospital (MH) Rawalpindi. Patients taking oral contraceptives were not included in the study. Normal subjects were included as control group for comparison. Consent was taken from all the participants after explanation of aims and objectives. Approval of the study was obtained from the ethical committee of Army Medical College Rawalpindi.

After an overnight fast of 8-12 hour, a total of 5 ml venous blood was obtained from the participants under aseptic conditions. Serum was separated by centrifuging blood at 4000 rpm for 5 minutes. Fresh serum was used for the analysis of fasting blood glucose and HbA1c while the remaining serum samples were frozen at -30^{o}C, for estimation of serum SHBG and insulin levels. Fasting blood glucose was measured on chemistry auto-analyzer Selectra. Serum SHBG and serum insulin were measured on a fully automated hormone analyzer, Immulite 1000, based on the principle of chemi-luminescence immunoassay technique. Insulin resistance was calculated using HOMA-IR formula (Fasting plasma glucose levels x Fasting Insulin levels/22.5). HbA1c levels were estimated by ion exchange resin method in both cases and controls.

Statistical Analysis

For qualitative variables, mean and standard deviation (SD) were calculated (SPSS-20).

Quantitative data were compared using independent t-test. Pearson's Correlation Co-efficient was used to analyze the association of SHBG with other variables. Statistical significance was considered at *p*-value <0.05.

RESULTS

Table-I shows comparison of variables among the different studied groups. Data were expressed as means ± standard deviation. Variables were compared between the two groups with student's t test and *p*<0.05 was taken as significant. Group A, diabetic, consisted of 60 participants with a mean age of 50.85 ± 11.06 while group B, control, consisted of 60 participants with a mean age of 49.23 ± 10.34. The diabetics had significantly lower serum sex hormone binding globulin (39.53 ± 22.25 vs. 62.35 ± 32.52, *p*=0.000) than the normal control. The diabetic patients presented with significantly higher serum insulin (8.90 ± 6.51 vs. 6.32 ± 4.09, *p*=<0.01) and insulin resistance (4.84 ± 5.18 vs. 1.23 ± 0.83, *p*=<0.000) calculated by HOMA-IR. Significantly higher levels of fasting plasma glucose (11.23 ± 3.65 vs. 4.35 ± 0.68, *p*=<0.000) and HbA1c (6.84 ± 0.48 vs. 5.31 ± 0.48, *p*=<0.000) were also observed in the diabetic group.

Table-II shows the correlation of SHBG with different parameters in the study groups. A clear negative association of SHBG was observed with FBG and HbA1c with correlation coefficient r -0.107 and r -0.101, respectively. Moreover, SHBG also revealed negative association with serum insulin (r -0.132) and insulin resistance (r-0.142) in the diabetic group. Negative association of SHBG was also observed with BMI in the study groups.

DISCUSSION

Levels of serum SHBG were compared between the two groups. Low level of serum SHBG were observed in the diseased group against high levels in the healthy control group, with a significant difference (*p*=0.000). It was observed that the serum SHBG level was lower in both male and female participants of cases. Same results have been reported by other studies with

Table-I: Comparison of demographic, clinical and biochemical characteristics of the studied groups.

Variables	Group A (diabetic)	Group B (control)	*p*-value
Age (years)	50.85 ± 11.06	49.23 ± 10.34	NS
BMI (kg/m2)	28.57 ± 1.97	24.46 ± 2.32	0.000
SHBG (nmol/L)	39.53 ± 22.25	62.35 ± 32.52	0.000
FBG (mmol/L)	11.23 ± 3.65	4.35 ± 0.68	0.000
HbA1C (%)	6.84 ± 0.48	5.31 ± 0.48	0.000
Insulin (µIU/mL)	8.90 ± 6.51	6.32 ± 4.09	0.01
Insulin Resistance	4.84 ± 5.18	1.23 ± 0.83	0.000

Note: **p* value <0.05 was considered as significant.

Table-II: Correlation of SHBG with different parameters in the study groups.

Variables	Group A (diabetic)	Group B (control)
	r	r
Age (years)	.056	.046
BMI (kg/m2)	-.116	.178
FPG (mmol/L)	-.107	.028
HbA1C (%)	-.101	.063
Insulin (µIU/mL)	-.132	-.138
Insulin Resistance	-.142	-.114

'r' is a coefficient of correlation.

significant low levels of serum SHBG in diabetic patients as compared to healthy control.

Ding et al[19] compared serum SHBG levels in both genders (36.9 ± 17.4 in control women vs. 22.3 ± 13.8 in diabetic women while 27.3 ± 10.7 in control men vs. 19.6 ± 7.2 in diabetic men). Goto et al[15] have also compared serum SHBG levels in diabetics versus control 76.7 ± 28.9 in control men vs. 72.6 ± 28.3 in diabetic men while 102.7 ± 32.1 in control women vs. 79.9 ± 35.9 in diabetic women).

Lakshman et al[20] compared serum SHBG levels among men (32.5 ± 0.5 in control men vs. 26.0 ± 1.6 in diabetic men). Vikan et al[21] have associated low levels of serum SHBG with type 2 diabetes mellitus (42.0 in diabetic men vs. 53.3 in control men). Stellato et al[22] compared serum SHBG levels in men (24.4 ± 1.4 in diabetic men vs. 32.3 ± 0.5 in control men).

This study observed negative association of SHBG with FBG and HbA1c having correlation coefficient r-0.107 and r-0.101, respectively. Moreover, SHBG also revealed negative association with serum insulin (r-0.132) and insulin resistance (r-0.142) in the diabetic group implying association of higher levels of serum SHBG with reduced risk of type 2 diabetes. These results are similar to results shown in studies done in different parts of the world.

Goto et al[15] in their study showed that SHBG was inversely associated with type 2 diabetes in both men and women. The association was highly significant with *p*-value of <.01. Ding et al[23] also reported negative association of SHBG with type 2 diabetes in both genders; the inverse association was stronger in women than in men. Colangelo et al[24] showed a strong inverse association of SHBG with type 2 diabetes in men. Abbiyesuku et al[25] in their study proved a significant inverse association between insulin resistance and SHBG providing an evidence that it may extend to type 2 diabetes. Fenske et al[26] in their study also showed a strong inverse association of SHBG with metabolic syndrome and type 2 diabetes.

CONCLUSION

This study confirmed the association of decreased SHBG levels with type 2 diabetes mellitus. Moreover, these decreased levels were also associated with poorly controlled glycemic status in the diabetic patients. Therefore, it is concluded that SHBG has a potential to be used as a biomarker of metabolic control in type 2 diabetes mellitus.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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