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Sex Hormone Binding Globulin (SHBG) Levels Correlate With Insulin Resistance In Post-Menopausal Women With Type 2 Diabetes Mellitus.

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ABSTRACT

To determine the association of Sex hormone binding globulin (SHBG) levels with insulin resistance in postmenopausal women with type 2 diabetes mellitus**.** Serum SHBG and insulin levels were measured by enzyme linked immunosorbent assay in 105 postmenopausal women with type 2 diabetes mellitus and 85 control subjects. Insulin resistance was assessed using homeostasis model of assessment for insulin resistance and was calculated as HOMA=(fasting plasma glucose (nmol/l)*insulin(IU/ml)/22.5. Serum lipid profile, plasma glucose levels, body mass index and waist circumference were also measured. Spearman's correlation was calculated to compare SHBG with Insulin resistance. Reduced level of SHBG was found in diabetic postmenopausal women when compared with the non diabetic control women. An inverse negative association was observed between SHBG and insulin resistance among diabetic women. Reduced levels of SHBG is found to be associated with hyperinsulinemia, insulin resistance, abdominal adiposity in postmenopausal women with diabetes.

Keywords: Sex hormone binding globulin, insulin, insulin resistance, postmenopausal women,

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INTRODUCTION

Menopause is a permanent cessation of menses that marks the end of women's fertility. An abrupt changes occur in the hormonal patterns during menopause resulting in the declination of estradiol and relative increase in androgen production. Previous studies suggest that menopause is accompanied by weight gain in the abdominal region [1, 2] resulting in the the production of cytokines, free fatty acids, reactive oxygen species that leads in the development of insulin resistance [3] .

Sex hormone binding globulin (SHBG) is an important glycoprotein involved in transporting the sex steroids mainly androgen and estrogen . Estrogen promotes the synthesis of SHBG in the hepatocytes whereas testosterone acts as an inhibitory factor [4, 5] . Large amount of data also suggest that SHBG synthesis is inhibited by insulin [5] and reduced circulating SHBG in women shown to be associated with abdominal fat along with hyperinsulinemia, glucose intolerance, insulin resistance and the risk of cardiovascular disease and type 2 diabetes mellitus(T2DM) [6-11]. The strong relationship between altered blood lipid profile with low level of SHBG including reduced HDL-C are very well established.[12, 13].

Considering the hormonal changes during menopause, the objective of the present study is to determine the levels of SHBG and its association with insulin resistance in postmenopausal women with type 2 diabetes mellitus .

MATERIALS AND METHODS

Study Population

It is a case control study. One hundred and five postmenopausal women with type 2 diabetes mellitus and eighty-five control subjects were enrolled for the study under the age group of 45-65 years. The patients were recruited from the outpatient department of K.S Hegde charitable hospital, Deralakatte, Mangalore between the year August 2018- July 2019. The study was approved by the central ethical committee of K.S Hegde Medical academy. Oral and written consent about the nature and purpose of the study was given to each patient. Signed inform consent was obtained from the patient before the data collection. Postmenopausal status was defined as no menstruation for >12 months. Those who had undergone hysterectomy or oophorectomy within 12 months of menopause, subjects with hormone replacement therapy and with any other chronic medical condition were excluded from the study. Women only with type 2 diabetes mellitus were included in the study. Diabetes was diagnosed according to American diabetes association criteria.

Antropometric Measurements

Height and weight of each patient were measured. BMI was computed as weight in kilograms (kg)/height in meter squared (m^2). Body circumference were measured in the standing position at the waist and hips[1] (smallest circumference between lateral coastal margin iliac crest , widest circumference over the greater trochanters respectively).

Experimental Procedure

Fasting venous blood samples were collected from all the recruited women in fluoride tubes for the estimation of blood glucose and plain tubes for the estimation of SHBG, insulin and lipid profiles. 2- hr postprandial blood glucoe were also collected from the subjects. After collection, blood samples were centrifuged at 3000rpm within 60 minutes. Plasma glucose levels and lipid profile were estimated . The remaining sera was then stored at -80° separately for the analysis of SHBG and insulin .

SHBG and insulin were measured by enzyme linked immunosorbent essay (diamitra). Plasma glucose was measured by glucose oxidase method using semi-automated biochemistry analysers. Total cholestrol, HDL-C, and TG were measured using commercially available kit method (Agappe,India,pvt,Ltd) by using semi-automated machine(star 2plus). LDL-C was calculated using Friedwalds equation. To estimate the degree of insulin resistance Homeostasis model assessment (HOMA) was applied. The equation for HOMA is as follows: HOMA= (fasting plasma glucose (nmol/l)*insulin (IU/ml)/22.5.

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Statistical Analysis

Inferential statistics of 105 cases and 85 controls are presented. Parametric test was expressed as mean ± standard deviation. Non-parametric data was expressed as median and interquartile range. Spearmans correlation were calculated to compare the SHBG levels between other parameter.

RESULTS

Baseline data for 105 postmenopausal diabetic and non-diabetic controls are summarized in Table 1. Women with diabetes were older, had higher BMI and significantly obese than normoglycemic women. Fasting blood sugar, 2-hr postprandial sugar, insulin levels and HOMA-IR were significantly higher in diabetic post-menopausal women (p<0.001).

Table 1: Baseline data of postmenopausal women with and without diabetes

	Post-menopausal Women with T2DM	Normo glycemic postmenopausal women	P value
n	105	85	
Age (years)	59 (54,63)	54(51,57)	NS
BMI(wt. in kg/ ht. in m^2)	26.32 ± 5.21	24.1 ± 3.93	NS
Waist circumference (cm)	96 (86,102)	86 (81,94)	0.000
Hip circumference (cm)	104 (94,109)	91 (86,100)	0.000
FBS (mg/dl)	142(122,175)	99 (89,106)	0.001
PPBS(mg/dl)	205 (145,256)	128 (122,134)	0.001
Insulin(IU/ml)	21.4(3.02,30.9)	3.74(1.77,7.70)	0.001
HOMA-IR	7.6(0.79, 13.9)	1.0 (0.4, 1.8)	0.000

Data are expressed as mean ± SD, median(interquartile range).
Abbreviations: FBS: fasting blood glucose ;PPBS: post prandial blood glucose; BMI: body-mass index

Table 2: Lipid profile and Insulin levels between the groups

	Case	control	p-value
Cholestrol (mg/dl)	159 (138, 189)	148 (123, 174)	0.008
Triglyceride (mg/dl)	125 (95, 162)	118 (94,150)	0.57
HDL-C (mg/dl)	43 (36,51)	51 (42,58)	0.000
LDL-C (mg/dl)	93(72,145)	74 (54, 97)	0.000
VLDL (mg/dl)	26 (20,32)	23 (18,31)	0.05

Values are presented as median (interquartile range).HDL-C-high density lipoprotein; LDL-C- low density lipoprotein; VLDL-very low density lipoprotein; HOMA-IR- homeostasis model of insulin resistance. P value <0.05* is considered as significant . p value <0.001** is considered to be highly significant.

Lipid profile between the case and control are listed in table 2. Compared with a control subjects it was observed that the diabetic women had significantly higher cholestrol(p<0.05), LDL-C(p<0.001) and lower levels of HDL-C(p<0.001). Concentrations of Triglycerides were higher in case group but it was not statistically significant.

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Figure 1 shows the difference in SHBG levels between the groups. Diabetic postmenopausal women had lower levels of SHBG compared to control subject with p value <0.03.

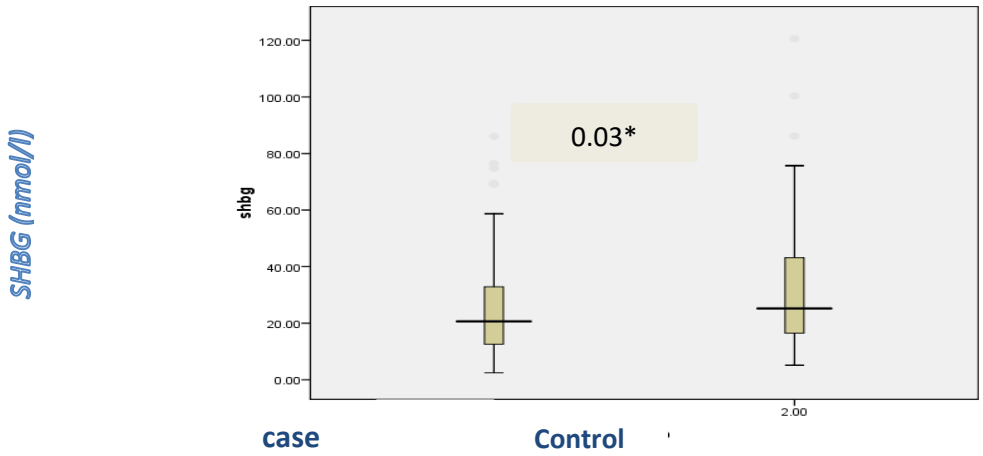

Figure 1: Graphical representation depicting the level of SHBG among case and control subjects(p<0.05)

SHBG levels was found to be significantly negatively correlated with fasting blood sugar (p<0.05), HOMA-IR (p<0.04), BMI(p<0.05) (Table: 3). Though negative correlation is observed between SHBG and Cholestrol ,TG,LDL-C, it was not statistically significant

Table 3: Spearman's correlation coefficient of SHBG with fasting plasma glucose, homa-ir, and lipid profiles.

	SHBG			
	Case		Control	
	Spearmans Correlation	P- value	Spearmans Correlation	P value
FBS	-0.297	0.003	-0.025	0.821
Insulin	-0.101	0.007	-0.180	0.099
BMI	-0.26	0.006	-0.245	0.501
Homa-ir	-0.223	0.04	-0.162	0.137
Cholestrol	-0.154	0.11	0.003	0.97
Triglycerides	- 0.166	0.09	-0.239	0.27
HDL-C	0.040	0.68	0.166	0.13
LDL-C	-0.173	0.79	-0.012	0.92

p<0.01**. p<0.05*

DISCUSSION

Significant reduced levels of SHBG were found in diabetic postmenopausal population when compared with control women. These results are concordant with a previous cross sectional[14] and prospective studies [8] which found low levels of SHBG in diabetic women when compared with non-diabetics . But in a study by Haffener et.al [15] no significant association between SHBG and incident type 2 diabetes mellitus in postmenopausal women was shown. The failure of this study however may be due to the less sample size of 19 postmenopausal women.

Elevated HOMA –IR and hyperinsulinemia were observed among diabetic postmenopausal women. In addition, an inverse association of SHBG with insulin resistance is also observed. These finding are in consistence with a study by Yesui.et, al [16], where a stronger relation was demonstrated with SHBG and HOMA-IR in postmenopausal women than in men without its relation with sex steroids.

Low levels of SHBG in T2DM may be probably due to hyperinsulinemia induced by insulin resistance. In vitro experiments suggest that insulin acts as an inhibitory factor in the production of SHBG by human hepatoma (HepG2) cell line [17].

Significantly elevated levels of cholestrol and TG with reduced HDL-C were observed among the diabetic postmenopausal women. HDL-C also showed a positive association with SHBG. This is concordant with previous findings that reduced SHBG levels have been associated with adverse lipid profile in women. .SHBG exerts a prime role in the metabolism of HDL-C through regulatory effect of hepatic lipase activity [18],[19].

The waist and hip circumference of diabetic women was significantly higher among postmenopausal women with T2DM. Menopausal transition has been associated with abdominal adiposity with increased free testosterone and lower SHBG [20],[21] . The abrupt change in the hormonal milieu during menopause is responsible for the changes in the body fat distribution[22].

CONCLUSION

This study indicates that reduced levels of SHBG are found to be associated with hyperinsulinemia, insulin resistance, abdominal adiposity in postmenopausal women with diabetes. These results imply that low levels of SHBG are associated with T2DM in postmenopausal women. Further long term studies are required to conclude the exact relationship and the mechanism behind the association of SHBG and T2DM in postmenopausal women.

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