Original Article

Sex hormone binding globulin in Bangladeshi women with gestational diabetes mellitus

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Abstract

Background: Sex hormone-binding globulin (SHBG) is suppressed by hyperinsulinemia and insulin resistance.

Aim: The aim of this study was to compare maternal SHBG levels between gestational diabetes mellitus (GDM) and normal glucose tolerant (NGT) women in our population.

Methods: This study enrolled 42 women with GDM and 45 women with NGT screened by 75-gm 3-samples oral glucose tolerance test (OGTT) following WHO 2013 criterion for GDM. Plasma glucose was analyzed by the glucose oxidase method. Serum insulin levels were measured by the chemiluminescent immunoassay method. Quantitative determination of serum SHBG levels was done by immunochemiluminescent assay. Equations of homeostatic model assessment (HOMA) were used to calculate indices of insulin resistance (HOMA-IR), β-cell function (HOMA-B), and insulin sensitivity (HOMA-%S).

Results: SHBG did not show any significant difference between the two groups (GDM vs. NGT: 795.74±122.01 vs. 718.73±50.67 nmol/L, p=0.55). There is no significant difference in trimester-wise SHBG concentration between NGT and GDM (p=0.370). Insulin resistance as measured by HOMA-IR (2.18±0.17 vs. 1.50±0.17, p <0.001) was significantly higher while insulin sensitivity HOMA-%S (61.99±6.05 vs. 134.53± 30.73, p <0.001) was significantly lower in GDM than those of NGT.

Conclusion: There was no association between SHBG and glucose tolerance in this cross-sectional study of pregnant women. *[J Assoc Clin Endocrinol Diabetol Bangladesh, July 2022; 1 (2): 39-43]*

Keywords: Sex hormone binding globulin (SHBG), Gestational Diabetes Mellitus (GDM)

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Introduction

Sex hormone-binding globulin (SHBG) is a glycoprotein produced by the liver that binds sex steroids in circulation. Insulin suppresses its secretion and low levels of SHBG are associated with insulin resistance. It has been studied as a potential predictor of the development of type 2 diabetes mellitus (T2DM).[1,2] Insulin resistance is the hallmark of gestational diabetes mellitus (GDM) and it is pathogenically related to T2DM. SHBG levels have been found to be lower in women with GDM, particularly in those requiring insulin.[3-6] Some studies suggested low SHBG level as a predictor of GDM if found lower in the first trimester of pregnancy.[7,8]

GDM is a global health concern as it is associated with increased maternal and neonatal morbidity. The prevalence of GDM is increasing in our population remarkably. SHBG is a simple, inexpensive blood test that can be performed in the non-fasting state,[9] with no diurnal variation.[10] This makes SHBG a valuable marker for GDM diagnosis. The aim of this study was to compare maternal serum SHBG levels between GDM and normal glucose-tolerant women in our population.

Methods

Study population and design

This observational study, carried out from April 2018 to February 2019, enrolled 42 women with GDM (age: 26.95±0.69 years, body mass index, BMI: 26.0±0.6 kg/m^2; mean±SEM) and 45 women with normal glucose tolerance (NGT) (age: 26.16±0.61 years, BMI: 24.5±0.5 kg/m^2; mean±SEM) screened by 75-gm 3-samples oral glucose tolerance test (OGTT)

following WHO 2013 criterion for GDM.[11] Women irrespective of their duration of gestation with singleton pregnancy attending the 'GDM clinic' of the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU) were screened and enrolled consecutively. Women with prior history of DM were excluded from the study.

Study procedure

Before the commencement of this study, the research protocol was approved by the Institutional Review Board (IRB). After recording relevant clinical data, OGTT was performed following an overnight fast. Study subjects were enrolled as GDM or NGT based on WHO 2013 diagnostic criteria. Fasting venous blood (6 ml) was collected for SHBG and insulin. Serum was separated to be preserved at -80°C until assay.

Analytic method

Plasma glucose was analyzed by glucose oxidase method using Dimension EXL 200 Integrated Chemistry System (Siemens, Germany) on the same day of collection. Serum insulin levels were measured by chemiluminescent immunoassay method using Access Immunoassay System (REF- 33410), Beckman Coulter, Inc., USA. Quantitative determination of serum SHBG level was done by immunochemiluminescent assay. The coefficient of variation (CV) for glucose was 2.02% for low-level values and 2.07 % for high-level whereas intra-assay CV for insulin was 2.54%. Intra-assay CV for SHBG was 2.34%.

Assessment of insulin secretion and sensitivity index

Insulin resistance and secretion were evaluated using the equations of the original homeostatic model assessment (HOMA) model described by Matthews et al.[12]

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp, Armonk, NY, USA). Qualitative data were expressed as frequencies or percentages. Assessment of the normality of quantitative data was done by the Shapiro-Wilk test. All the quantitative data were found normally distributed and expressed as mean±SEM (standard error of mean). Between subgroups made on the basis of clinical and metabolic (hormonal & derived insulin indices) findings, comparisons were done by

chi-square test and independent sample t-test. Correlation among BMI, SHBG, insulin indices, and derived variables was analyzed by Pearson's correlation test. P-value <0.05 was considered statistically significant.

Results

Table-I compares the demographic variables between the two groups. Only multiparity was significantly higher in the GDM group than those of NGT (64% vs. 39%, p=0.007) while other variables like BMI, age, bad obstetric history, gestational age, and family history of diabetes didn't show any remarkable difference between the two groups (p=ns for all).

The level of SHBG was not significantly different between the two groups (GDM vs. NGT: 795.74±122.01 vs. 718.73±50.67 nmol/L, p=0.55; table-II). All the glucose values obtained during OGTT were significantly higher in GDM than those of NGT (p<0.001). HOMA-IR (2.18±0.17 vs. 1.50±0.17, p<0.001) were significantly higher while HOMA-%S (61.99±6.05 vs. 134.53±30.73, p<0.001) were significantly lower in GDM than those of NGT.

Table-I: Demographic characteristics of the study participants

Variables	Groups		p
	GDM (n=42)	NGT (n=45)	
Age (years)[a]	26.95±0.69	26.16±0.61	0.389*
BMI (kg/m²)[a]	26.0±0.6	24.5±0.5	0.083*
Duration of gestational age (weeks)[a]	20.5±1.58	20.0±1.3	0.834*
SBP (mm of Hg)[a]	101.79±1.66	100.00±1.65	0.450*
DBP (mm of Hg)[a]	65.23±1.03	65.66±1.00	0.770*
Multiparity[b]	41 (64.06%)	22 (39.29%)	0.007**
Bad obstetric history[b]	8(19.0%)	6(13.3%)	0.450**
Family History of DM[b]	10(23.8%)	17(37.7%)	0.159**

GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; BMI: body mass index; SBP: systolic blood pressure and DBP: diastolic blood pressure; Bad obstetric history included abortion and/or macrosomia; Family history of DM: In 1st-degree relatives.
[a]expressed as mean±SEM; [b]expressed as frequency and percentage over column total;
*p-values calculated by independent samples t-test and ** p-value calculated by Chi-square test

Table II: Fasting glucose, insulin, and SHBG in GDM and NGT

Variables	Groups		p
	GDM (n=42)	NGT (n=45)	
SHBG (nmol/L)	795.74±122.01	718.73±50.67	0.550
FBG (mmol/ml)	5.20±0.10	4.40±0.05	<0.001
1h BG (mmol/ml)	9.88±0.30	7.60±0.17	<0.001
2h BG (mmol/ml)	8.36±0.29	6.41±0.17	<0.001
Fasting Insulin (μIU/ml)	9.38±0.69	7.66±0.89	0.130
HOMA-IR	2.18±0.17	1.50±0.17	<0.001
HOMA-B	129.39±13.44	183.86±27.22	0.080
HOMA-%S	61.99±6.05	134.53±30.73	<0.001

expressed as mean±SEM; p-values calculated by independent samples t-test

SHBG: sex hormone binding globulin; GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; FBG: fasting blood glucose; 1h BG: 1-hour blood glucose; 2h BG: 2-hour blood glucose; HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-B: homeostasis model assessment of β-cell function; HOMA-%S: homeostasis model assessment of insulin sensitivity.

Table III: Trimester wise SHBG concentration

Trimester	Population		p
	GDM	NGT	
1st trimester[a]	808.50±377.18 (12)	623.50±111.11 (10)	0.669
2nd trimester[a]	653.80±103.11 (15)	729.65±276.59 (20)	0.511
3rd trimester[a]	927.46±139.05 (15)	767.67±106.67 (15)	0.370

SHBG: sex hormone binding globulin; GDM: gestational diabetes mellitus; NGT: normal glucose tolerance
[a]expressed as mean±SEM; within parenthesis are number of participants in the particular group.
p-values calculated by independent samples t-test

Fasting insulin (9.38±0.69 vs. 7.66±0.89, p=0.13) and HOMA-B (129.39±13.44 vs. 183.86±27.22, p=0.08) did not show any significant difference between the two groups.

In pregnant women with normal glucose tolerance, SHBG concentration increases with gestational age; third trimester > second trimester > first trimester (table-III). However, in the case of GDM, SHBG concentration is highest in the third trimester and lowest in the second trimester. There is no statistically significant difference in trimester-wise SHBG concentration between NGT and GDM (p=ns for all). Table IV illustrates the correlations of SHBG with various maternal parameters. There was no significant correlation between SHBG and age, BMI, or FBG in GDM or NGT (p=ns for all).

Discussion

The present study was designed to compare maternal serum SHBG levels between GDM and normal glucose-tolerant women. It demonstrated that SHBG level does not differ significantly between women with GDM and NGT despite higher corresponding blood glucose, being more insulin resistant in the GDM group. GDM is usually considered a consequence of insulin resistance as in T2DM. Therefore, it is expected that SHBG should be lower in GDM but it was not the result we found in our study. So, there is a likely possibility of other factors for the expression of GDM, especially in lean mothers. This finding is contrary to the observations by some other investigators where SHBG levels were significantly lower in the GDM population.[12-14]

Pregnant mothers were included in the study irrespective of the gestational week, and hence throughout all trimesters of pregnancy, SHBG was measured to see whether it varied between GDM and NGT. Pregnancy significantly increases SHBG concentration because estrogen boosts its production. In our investigation, the GDM population had considerably higher levels of insulin resistance than

Table IV: Correlation of SHBG with different maternal parameters

Maternal Parameters	GDM (n=42)		NGT (n=45)		All cases (N=87)	
	r	p	r	p	r	p
Age	-0.084	0.598	0.025	0.872	-0.025	0.816
BMI	0.070	0.660	-0.089	0.561	-0.048	0.657
FBS	-0.003	0.986	-0.236	0.119	-0.126	0.246

SHBG: sex hormone binding globulin; GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; BMI: body mass index; FBS: fasting blood sugar
p - values calculated by Pearsons correlation test

the NGT population, as measured by HOMA. As a result, it was anticipated that SHBG, which has been observed in several previous research, may be lower in the GDM group.[3,5,7,8] Even though the GDM women had higher FBS, and 2-hour post-glucose load values and were more insulin resistant, there was no discernible difference in SHBG concentration between the two groups. As a result, GDM cannot be accurately predicted using SHBG. Our findings are consistent with a researcher who looked into the SHBG concentration in Australian pregnant mothers but which did not correspond with the majority of the study.[15]

Why do these findings differ from those of previous studies? Although Thaldani, who suggested that SHBG would be a powerful marker, had a study population with a similar size, our sample size is small. The majority of studies looked at SHBG during the first trimester of pregnancy as a potential indicator of GDM. We recruited pregnant ladies irrespective of their gestational age. Another finding is that there were no significant differences in age, weight, BMI, or gestational age between our GDM and NGT groups. Two key observations have been established by our GDM study group. Instead of only being insulin resistant, Tania-Tofail et al. observed that lean GDM mothers exhibit a significant impairment in insulin secretion.[16] Additionally, Mashfiqul-Hasan et al. found that lean GDM mothers had higher single nucleotide polymorphisms.[17] Here comes the role of the thrifty phenotype hypothesis which can explain the inadequate insulin secretion by lean mothers leading to GDM rather than being insulin resistant as the primary mechanism. Whereas SHBG concentration correlates inversely with insulin resistance and is subsequently found to be lower in many studies conducted in the western population. A poor functional capacity for insulin secretion would not be detrimental to individuals who continued to be poorly nourished and remained thin and, therefore, insulin-sensitive. Glucose intolerance would be triggered by a positive calorie balance as a result of increased food intake and decreased energy expenditure leading to obesity as occurs during pregnancy. The combination of malnutrition during fetal life and infancy followed by overnutrition in childhood and adult life characterizes populations undergoing the transition from chronic malnutrition to adequate nutrition and the development of the metabolic syndrome.[18] Therefore, the genetic basis of the development of GDM and the deficiency

in insulin secretion are important determining factors in our population to have GDM. Consequently, GDM cannot be accurately predicted by insulin resistance and SHBG.

Conclusion

In summary, we found no association between SHBG and glucose tolerance in a cross-sectional study among pregnant women.

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