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Associations between glucose tolerance and sex hormone binding globulin among women with recent gestational diabetes mellitus

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Abstract

We examined cross-sectional associations of sex hormone binding globulin (SHBG) with glucose among women recent GDM (n=55). SHBG was associated with fasting glucose levels before and after adjustment for covariates (p=0.015), but not with 2-hour glucose. We conclude SHBG should be explored in prospective studies in GDM women.

Keywords

gestational diabetes; postpartum; sex hormone binding globulin

Introduction

The association between sex hormone binding globulin (SHBG) and glucose levels among women with histories of GDM has not been studied. However, SHBG predicts fasting plasma glucose (FPG) in healthy women [1]. Also, postpartum GDM women have lower SHBG levels than postpartum women without GDM [2]. Third, prenatal SHBG levels have been associated with prenatal glucose levels in several studies [3].

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Conflict of Interest
The authors declare that they have no conflict of interest.

Therefore, we examined the concurrent associations between postpartum SHBG and glucose measures from a 75-gram oral glucose tolerance test (OGTT) among non-pregnant women with recent GDM. We hypothesized that SHBG levels would be associated with both FPG and 2-hour post-challenge glucose and the associations would persist after consideration of potential confounders.

Materials and Methods

Study Setting and Population

Participants in this study (n=55) were women with recent GDM in the past 3 years who were participants in a randomized controlled trial of lifestyle intervention which has been previously described [4]. In addition to the GDM diagnosis, study inclusion criteria included age ≥ 18 years, enrollment at least 6 weeks postpartum, < 150 minutes of self-reported physical activity per week, and internet access. Women who were currently pregnant, currently using metformin or glucocorticoids, or had a diabetes diagnosis were excluded. For this report, women were included if they did not have previously diagnosed diabetes, but had diabetes on the study 75-gram OGTT (n=5), i.e. a FPG value of ≥ 7 mmol/l or a 2-hour plasma glucose value ≥ 11 mmol/l. The study was approved by the University of Michigan institutional review board. At the baseline assessment, women answered surveys, underwent anthropometric measurements, and 75-gram OGTT and urine pregnancy testing. These procedures were performed 13 weeks later at the conclusion of the intervention. Serum and plasma samples were stored at −70°C.

SHBG assays were conducted at the University of Michigan Central Ligand Assay Satellite Services Laboratory. Intra- and interassay coefficients of variation for SHBG were 6.1 and 9.9%. Measurements of glucose, insulin, adiponectin, and C-reactive protein (CRP) were performed at the Michigan Diabetes Research and Training Center laboratory. Intra- and interassay coefficients of variation were 2% and 2.9% for glucose, 2.7% and 3.4% for insulin,15.5% and 10.2% for adiponectin, and 5.9 % and 1.3% for CRP.

Statistical Analyses

Analyses focused on concurrent associations between SHBG and glucose, before and after adjustment for potential confounders (Table 1) of the SHBG and glucose relationship. Spearman correlation coefficients between SHBG, FPG, 2-hour glucose, insulin sensitivity, BMI, waist circumference, adiponectin, and CRP were calculated (Table 2). Multivariable regression analyses which adjusted for repeated measures within woman (baseline and follow-up) were used to examine associations between SHBG levels and concurrent FPG, before and after adjustment for age, race/ethnicity, time since delivery, randomization arm and baseline vs. follow-up visit, current oral contraceptive (OCP) use, and current breastfeeding; waist circumference; adiponectin; CRP; and insulin sensitivity (Table 3). Inclusion of smoking and parity in the models did not change regression coefficients, so these variables were not included in the final models. Similar models were constructed to examine associations between SHBG and 2-hour glucose. Stata 11.0 was used for all analyses (StataCorp., College Station, TX).

Results

Characteristics of participants at baseline are shown in Table 1. Twenty-two percent (n=12) had FPG ≥ 5.5 mmol/l, 35% (n=18) had 2-hour glucose levels ≥ 7.8 mmol/l, and 13% (n=7) had elevated FPG and 2-hour glucose levels. At baseline, lower SHBG levels were associated with greater FPG levels, but the relationship between SHBG and 2-hour glucose was not significant (Table 2). In multivariable regression which adjusted for repeated

measures within woman (Table 3), the significant association between SHBG and FPG persisted after adjustment for multiple covariates. In contrast, the association between SHBG and 2-hour glucose was not significant before or after adjustment in any statistical models.

In fully adjusted models for FPG (Model 5), other covariates significantly associated with FPG were current OCP use (β=15.6, p=0.003) and 1/fasting insulin (β=−133, p=0.045). In fully adjusted models for 2-hour glucose (Model 5), other covariates significantly associated with 2-hour glucose were adiponectin (β=−0.005, p=0.03); current OCP use was of borderline significance (β=30.0, p=0.086).

Discussion

Our findings show that lower SHBG is associated with higher concurrent FPG levels among women with recent GDM, a high-risk population for diabetes, and this association is independent of potential confounders including waist circumference, adiponectin, CRP, and fasting insulin levels. To our knowledge, this is the only examination of SHBG in non-pregnant women with recent GDM.

Our results are similar to those found among healthy middle-aged or postmenopausal women [1; 6–8], although fewer studies examine the association between SHBG and post-challenge glucose than between SHBG and FPG. The observed relationship between SHBG and FPG may have been stronger than that between SHBG and 2-hour glucose due to site-specific effects of sex steroids modulated by SHBG, for example, relatively greater effects upon liver vs. skeletal muscle resulting in lower FPG levels compared to 2-hour glucose levels.

The limitations of our findings include the lack of information on other measures of sex steroids, as study visits were not timed to the menstrual cycle and these steroids vary over the cycle. However, these limitations would have been expected to bias our results to the null. Our examination was cross-sectional, and therefore a causal relationship between SHBG and FPG cannot be deduced.

In conclusion, we found that SHBG, a marker for FPG in middle-aged and older women, was also associated with FPG in women with recent GDM, and this association persisted after adjustment for potential mediators and confounders. SHBG was not associated with 2-hour glucose. Future examinations should focus on whether SHBG predicts incident glucose intolerance among women with recent GDM, and whether associations are mediated or confounded by other risk factors for glucose intolerance.

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Table 1

Baseline participant characteristics (n=55), percents or mean (standard deviations).

Age (years)	36 (4)
Race/ethnicity (%)	
Non-Hispanic white	73
Asian	11
African-American	11
Other	5
Latina	4
Time since GDM pregnancy (months)	18 (12)
Current oral contraceptive use (%)	10
Current smoking (%)	0
Current breastfeeding (%)	31
Parity (%)	
<=2	42
3	31
>=4	27
Body mass index (kg/m^2)	31 (7)
Waist circumference (cm)	94 (15)
Fasting plasma glucose (mmol/l)	5.3 (1.2)
2-hour glucose (mmol/l)	7.2 (2.1)
1/fasting insulin (l/pmol)	0.0086 (0.0043)
Sex hormone binding globulin (SHBG) (nmol/l)	63.1 (44.8)
Adiponectin (ug/ml)	5.7 (2.5)
C-reactive protein (CRP) (mg/l)	0.35 (0.40)

Table 2

Unadjusted Spearman correlation coefficients from baseline measurements (n=55)

	BMI	Waist circumference	FPG	2-hour glucose	1/fasting insulin	Adiponectin	SHBG
Body mass index (BMI)	1.00						
Waist circumference	0.88*	1.00					
Fasting plasma glucose (FPG)	0.27	0.28	1.00				
2-hour glucose	0.07	0.12	0.46*	1.00			
1/fasting insulin	−0.55*	−0.64*	−0.29*	−0.24	1.00		
Adiponectin	−0.24	−0.28*	−0.32*	−0.40*	0.48*	1.00	
Sex hormone binding globulin (SHBG)	−0.21	−0.22	−0.30*	−0.02	0.08	0.18	1.00
C-reactive protein (CRP)	0.52*	0.53*	0.39*	0.23	−0.40*	−0.20	0.07

* significant at $p<0.05$

Table 3

Association between sex hormone binding globulin (SHBG) with fasting plasma glucose (FPG) and 2-hour glucose among women with recent gestational diabetes (GDM) in multiple linear regression analyses adjusted for repeated measures in women.

	FPG		2-hour glucose	
	Beta-coefficient	**p-value**	**Beta-coefficient**	**p-value**
Model 0-Unadjusted	−0.098	0.042	0.103	0.30
Model 1-Adjusted for age (years), white/other, time since GDM delivery (months), current oral contraceptive use, current breastfeeding, randomization arm, visit (baseline or follow-up)	−0.091	0.005	−0.014	0.90
Model 2- Model 1, and waist circumference (cm)	−0.089	0.008	0.026	0.82
Model 3-Model 2, and adiponectin	−0.084	0.012	0.050	0.65
Model 4-Model 3, and C-reactive protein (CRP)	−0.087	0.009	0.040	0.72
Model 5-Model 4, and 1/fasting insulin	−0.081	0.015	0.030	0.78