Original Article

Lower Serum level of Adiponectin is associated with increased Insulin Resistance in Nigerian women with Gestational Diabetes Mellitus

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ABSTRACT

Background: *The exact mechanism implicated in the pathophysiology of the insulin resistance causing gestational diabetes mellitus (GDM) is still not completely understood. Adiponectin is an adipocytokine that is proposed to be a potential mediator of the insulin resistance, but its role is not clear; Findings from studies done across different ethnic groups yielded conflicting results. The aim of the study is to determine the association between serum level of adiponectin and insulin resistance in Nigerian women with GDM.*

Materials and Method: *100 pregnant women with GDM and another 100 healthy pregnant controls were enrolled in the study. Participating subjects were evaluated between 24-28 weeks gestation. Serum fasting insulin and adiponectin were measured. Insulin resistance index was calculated as homeostatic model assessment for insulin resistance (HOMA-IR).*

Results: *Pregnant women with GDM were more insulin resistant than the controls (3.14 ± 0.19 vs. 2.89 ± 0.20, $p < 0.05$). Decreased maternal serum adiponectin level was associated with higher insulin resistance in pregnant women with GDM ($r = -0.58$, $p < 0.05$). This association remained significant even after adjustment for age and body mass index.*

Conclusion: *We conclude that among the pregnant Nigerian women with GDM in this study, decreased maternal serum adiponectin level is associated with higher insulin resistance.*

Key words: Gestational diabetes mellitus (GDM); Pregnancy; Insulin resistance; Adiponectin; Homeostasis model assessment for insulin resistance (HOMA-IR); Body mass index (BMI)

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy with or without remission after the end ofpregnancy.[1]In Nigeria the prevalence ranges from 3.4 – 13.9% across the different regions of the country.[2-6]

Pregnancy normally induces marked insulin resistance, which serves to stimulate the maternal tissue cells to use alternative source of energy other than glucose, and therefore an increase in supply of glucose to the developing foetus. Pancreatic β-cells normally increased their synthesis of insulin to compensate for the increased insulin resistance during pregnancy, and therefore maintain normoglycaemia over the course of pregnancy.[7,8]

Pregnant women with gestational diabetes mellitus also have this physiological insulin resistance. However, it occurs on a background of chronic insulin resistance to which the insulin resistance of pregnancy is partially additive, and therefore tend to have even greater insulin resistance than women with normal pregnancies.

Therefore, such pregnant women with gestational diabetes mellitus are not able to up-regulate insulin synthesis relative to the degree of the insulin resistance, and therefore become

hyperglycaemic by which gestational diabetes mellitus is defined.[8]

A number of potential biochemical mediators of the chronic insulin resistance that frequently accompanies pregnant women with gestational diabetes mellitus have been investigated. Adiponectin is proposed to be one of the potential mediators of the insulin resistance, but its role is not clear. Several studies have investigated the role of adiponectin in the pathogenesis of the insulin resistance in pregnant women with gestational diabetes mellitus, but findings across different ethnic groups are inconsistent or even conflicting.[9-16.]

Studies on the relationship between circulating levels of adiponectin and insulin resistance in gestational diabetes mellitus among women of African ancestry are few, and mainly done among African Americans. To the best of our knowledge no study was done in Nigeria among women with gestational diabetes mellitus.

This study was therefore designed to investigate the relationship between circulating levels of adiponectin and insulin resistance in Nigerian women with gestational diabetes mellitus.

SUBJECTSAND METHODS

This is a cross sectional analytical study conducted among 100 women with gestational diabetes mellitus and 100 controls (women with normal gestation)at 24-28 weeks gestation. The diagnosis of gestational diabetes mellitus was based on the WHO criteria (Two-hour 75g Oral Glucose Tolerance Tests: Fasting serum glucose 7.0mmol/L or 2-hour post load serum glucose 7.8mmol/L).[17]All study subjects were recruited from women who attended antenatal clinics of Ahmadu Bello University Teaching Hospital Zaria, Sick Bay at Ahmadu Bello University Zaria, and Hajiya Gambo Sawaba General Hospital Zaria, Kaduna State from May 2014 to June 2015. The study was approved by the Health Research Ethics Committee of Ahmadu Bello University Teaching Hospital, Zaria and Kaduna State Ministry of Health, Kaduna, and all study subjects signed consent form before recruitment in to the study. Pregnant women with history of pre gestational diabetes mellitus, multiple gestations, or any pre-existing illness were excluded from the study.

History including maternal age, parity and gestational age were all obtained from the subjects at the time of enrolment. Gestational age was based on the report of ultrasound scan.
Weight was taken with only undergarments and rounded to the nearest kilogram. Height was taken to the nearest centimeter with subjects standing erect without shoes. Body mass index (BMI) was calculated as the ratio of weight in kilogram to square of height in meters and expressed as kg/m^2. The subjects were instructed to be on their normal diet 3 days prior to the oral glucose tolerance tests (OGTT), and then fasted for 10-12 hours (overnight) prior to the OGTT procedure. A fasting blood sample was taken for measurement of serum glucose, insulin and adiponectin. The subjects were then given a 75g dose of glucose (in 300ml glass of water) orally over 5-10 minutes. Blood sample was taken at 2 hours post glucose dose for measurement of 2-hour serum glucose.

BIOCHEMICAL ANALYSES

Serum glucose (fasting and 2-hours post 75g glucose dose) was measured using the glucose oxidase method (Labkit France).Serum adiponectin was measured using human adiponectin ELISA kit (Wkea Med Supplies Corp. China). Fasting serum insulin was measured using human insulin ELISA kit (Perfemed China). All the samples were analysed at the Department of Chemical Pathology, Ahmadu Bello University Teaching Hospital, Zaria. Insulin resistance was calculated as Homeostatic Model Assessment-IR (HOMA-IR).
HOMA-IR = Fasting serum insulin (FSI) × Fasting serum glucose (FSG) / 22.5[18]
FSI in milliU/mL and FSG in mmol/L

STATISTICAL ANALYSIS

SPSS version 20.0 software was used for statistical analysis. Each set of data was examined for outliers, and tested for normality of distribution using Kolmogorow-Smirnov test. Quantitative

variables were summarized using measures of central tendency and dispersion. Data presentation was done using tables and figures. Comparison of mean differences between groups was done using t-test. Correlations were examined using partial correlation analysis. A multiple linear regression analysis was performed to investigate or adjust for confounders. All p-values were 2-sided and considered significant if less than 0.05

RESULTS

Demographic parameters of the study participants are presented in Table 1. Study subjects in both the GDM and the controls groups have similar mean ages, gestational age and parity of 25.6 ± 5.4 vs. 26.9 ± 5.4 years (p> 0.05),26.5 ± 1.7 vs. 26.7 ± 1.6 weeks, (p> 0.05) and2.3 ± 1.5 vs. 2.6 ± 1.7, (p >0.05) respectively. However, when compared with women in the control group, women with gestational diabetes mellitus showed significantly greater pregnancy BMI (25.4 ± 4.0 vs. 23.4 ± 3.7 kg/m^2, p< 0.05).

Biochemical data of the study participants are shown in Table 2. No statistically significant difference in fasting serum glucose was observed between the pregnant women with gestational diabetes mellitus and the controls (4.3 ± 0.6 vs. 4.3 ± 0.7 mmol/L, p> 0.05). Pregnant women with gestational diabetes mellitus had significantly elevated 2-hour post load serum glucose values compared with women in the control group (9.0 ± 0.9 vs. 6.3 ± 0.8 mmol/L, p< 0.05). Fasting serum insulin was also observed to be higher among women with gestational diabetes mellitus than the controls (16.7 ± 2.5 vs. 15.5 ± 2.5 mU/ml, p< 0.05).

There was a negative correlation between serum adiponectin levels and HOMA-IR among the pregnant women with gestational diabetes mellitus (r = -0.58, p< 0.05) (Table 3, Figure 1). The observed relationship remained significant after adjusting for age and body mass index.

To determine the contribution of circulating level of adiponectin to HOMA-IR in the pregnant women with gestational diabetes, multiple linear regression was used. The adjusted R-Square was 0.35, indicating that 35% of the variance in insulin resistance among the pregnant women with gestational diabetes mellitus can be attributed to maternal circulating level of adiponectin. Adiponectin was found to be significant predictor of insulin resistance among the pregnant women with gestational diabetes mellitus. (Table 4)

Table 1: Demographic parameters of the study participants

	GDM(m ± SD)	Controls(m ± SD)	*p*-value
Sample size (n)	100	100	
Age (years)	25.6 ± 5.4	26.9 ± 5.4	0.074
Parity	2.3 ± 1.5	2.6 ± 1.7	0.166
Gestational age (weeks)	26.5 ± 1.7	26.7 ± 1.6	0.241
Weight (kg)	65.1 ± 15.0	61.1 ± 13.4	0.048
Height (cm)	159 ± 7.5	161 ± 7.0	0.101
Body Mass Index BMI (kg/m^2)	25.4 ± 4.0	23.4 ± 3.7	0.000
Systolic blood pressure (mmHg)	117.2 ± 7.5	118.3 ± 5.5	0.240
Diastolic blood pressure (mmHg)	78.5 ± 4.8	78.8 ± 4.1	0.635

m, Mean
SD, standard deviation
GDM, gestational diabetes mellitus

Table 2: Biochemical parameters of the study participants

	GDM(m ± SD)	Controls(m ± SD)	*p*-value
Sample size(n)	100	100	
OGTT			
Fasting serum glucose(mmol/L)	4.3 ± 0.6	4.3 ± 0.7	0.763
2 hour serum glucose(mmol/L)	9.0 ± 0.9	6.3 ± 0.8	0.000
Serum fasting Insulin(μU/mL)	16.7 ± 2.6	15.5 ± 2.5	0.000
Serum Adiponectin(μg/ml)	8.1 ± 1.6	10.2 ± 2.5	0.000
HOMA-IR	3.14 ± 0.19	2.89 ± 0.20	0.000

m, Mean
SD, standard deviation
HOMA-IR, homeostasis model assessment-insulin resistance
OGTT, oral glucose tolerance test
GDM, gestational diabetes mellitus

Table 3: Correlation of serum Adiponectin with anthropometric and biochemical factors among the study subjects

	GDM patients		Controls	
	r	*p-value*	*r*	*p-value*
Age (years)	-0.23	0.020	-0.34	0.000
BMI (kg/m^2)	-0.30	0.000	-0.59	0.000
Fastingserum insulin(μU/ml)	-0.34	0.000	-0.02	0.860
HOMA-IR	-0.58	0.000	-0.10	0.490

HOMA-IR, homeostasis model assessment-insulin resistance
BMI, body mass index
TNF-α, tumour necrosis factor-alphar, correlation coefficient

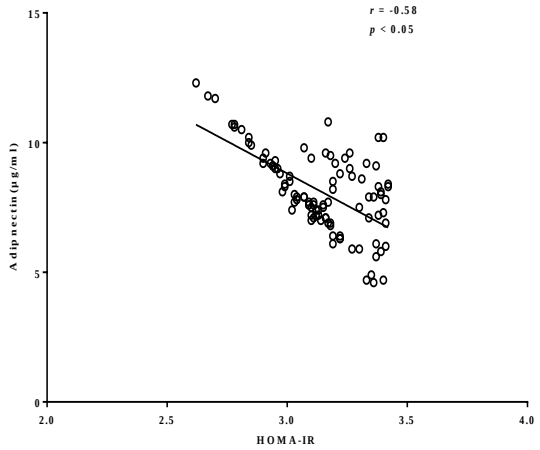

Figure 1. Correlation between serum adiponectin levels and HOMA-IR inpatients with gestational diabetes mellitus.
HOMA-IR, homeostasis model assessment-insulin resistance

DISCUSSION

It was demonstrated in this study that lower adiponectin level among the pregnant women with gestational diabetes mellitus was strongly associated with increased insulin resistance as assessed by HOMA-IR. This association remained significant even after adjustment for age and body mass index.

This is in keeping with majority of available studies showing that lower adiponectin in pregnant women are associated with increased insulin resistance and therefore higher risk of developing gestational diabetes mellitus.[9-14]

By contrast, in other reports,[15,16] no relationship was found between these parameters. Differences in sample sizes, ethnicity and body mass index of the study populations, nature of sample (serum or plasma) used and the type of assay method used in the various studies might be responsible for the discrepancies in the findings between these

Table 4: Multiple linear regression analysis with Log HOMA-IR as a dependent variable among the study subjects

Independent variables	GDM(n=100) R^2 = 0.35			Controls(n=100) R^2 = 0.00		
	β-value	SE	*p*-value	β-value	SE	*p*-value
Constant	0.67			0.48		
Log Adiponectin	-0.20	0.025	0.000	-0.02	0.028	0.438

HOMA-IR, homeostasis model assessment-insulin resistance
β, regression coefficient
SE, standard error

investigators. Although studies investigating the association between adiponectin and insulin resistance in pregnant women with gestational diabetes mellitus among black Africans were scarce; a study among non pregnant black south African women confirmed a negative relationship between adiponectin levels and insulin resistance, though the association was less pronounced when compared to that of white Afrikaner women of south Africa.[19] Another study among black American women in the United States did not find a significant relationship.[20]This discrepancy might be explained by the different environments in which the two population groups have lived.

The social and physical environments of the African American women are not usually similar to those of black African women in terms of abundance and availability of resources.

Adiponectin stimulate fatty-acid oxidation and therefore decreases tissue triglyceride content in peripheral tissues. Triglyceride in tissues interfere with insulin-stimulated phosphatidylinositol 3-kinase activation and subsequent glucose transporter 4 translocations and glucose uptake, leading to insulin resistance. Therefore, decreased tissue triglyceride may contribute to the improved insulin signal transduction. Adiponectin also lowers blood glucose levels by suppressing the expression of gluconeogenic enzymes in the liver, and thus decreases the rate of endogenous glucose production.

CONCLUSION

We conclude that among the pregnant Nigerian women with gestational diabetes mellitus in this study, decreased maternal serum adiponectin level

is associated with higher insulin resistance. We suggests that more experimental studies of the *in vitro* and *in vivo* effects of adiponectin on other cytokines, insulin signalling and glucose metabolism are needed within our population to establish the molecular link between adiponectin and insulin resistance.

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