Association between Insulin Resistance and Insulin like Growth Factor-1 in Gestational Diabetic Women

Noor Thair Tahir
Ph.D.

Abstract:

Background: Insulin resistance has been identified as a pathogenic of diabetes mellitus, serum insulin-like growth factor-1, and may have a role in the maintenance of glucose homeostasis.

Objective: The aim of the present work is to study the relation between insulin resistance and insulin-like growth factor-1 in diabetic women with gestational age of (24-28) weeks and after 3 months of delivery.

Patients and Methods: A total of 88 women with gestational age of (24-28) weeks and after 3 months of delivery were enrolled in the study. Fourty four (44) women with diabetes mellitus and a case control study consists of 44 women without diabetes mellitus were recruited from AL-Yarmuk Teaching Hospital and the National Diabetic Center/ Al- Mustansiriya University during the period from May 2014 to July 2015; their age range was (20-40) years. Fasting blood samples were collected from all the subjects to measure serum glucose, glycated hemoglobin, serum insulin, lipid profile, and insulin like growth factor-1.

Results: The results showed that the means value of fasting serum insulin, homeostasis model assessment-2 for insulin resistance, and insulin like growth factor-1 were significantly increased in diabetic women with gestational age of (24-28) weeks when compared to the control group and in diabetic women after 3 months of delivery when compared to their levels in the control group, ($P<0.05$). There was a significant positive correlation between serum insulin like growth factor-1 levels verse homeostasis model of assessment-2 for insulin resistance in diabetic women with gestational age of (24-28) weeks and after 3 months of delivery. A significant positive correlation was found between insulin like growth factor-1 levels verse homeostasis model assessment-2 for sensitivity and beta cell dysfunction in diabetic women with gestational age of (24-28) weeks.

Conclusions: Higher maternal insulin like growth factor-1 levels at mid gestation may indicate greater placental and fetal growth, and insulin resistance.

Key Words: Gestational diabetes mellitus, insulin resistance, homeostasis model assessment-2 , insulin like growth factor-1.

Introduction:

Gestational diabetes mellitus (GDM) is a condition of glucose intolerance with onset or earliest recognition in pregnancy that is not obviously overt diabetes [1, 2]. Normal pregnancy is characterized by pancreatic β-cell hyperplasia resulting in higher fasting and postprandial insulin levels. Increased secretion of placental hormones leads to increasing insulin resistance (IR), particularly throughout the third trimester. Gestational diabetes mellitus occurs when β-cell function is insufficient to overcome this IR [3].

Insulin resistance is typically distinct as decreased sensitivity or responsiveness to the metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production. There are a variety of tools used for quantifying insulin sensitivity and resistance straightforwardly (hyperinsulinemic euglycemic glucose clamping and insulin suppression tests) and indirectly [frequently sampled intravenous glucose tolerance test, oral glucose tolerance test, meal tolerance test, and homeostasis model of assessment-IR (HOMA-IR)] [4].

Generalized IR occurs chiefly as a result of obesity, a consequence of caloric excess, physical inactivity, genetics, and age. Insulin resistance is related with many serious medical conditions such as type 2 diabetes mellitus, hypertension, atherosclerosis, and metabolic syndrome [5].

Insulin like growth factor-1 (IGF-1) is a 7.7 kDa single-chain polypeptide encoded by chromosome 12. The 70 amino acid IGF-1 protein consists of four domains [6] , and is produced primarily in the liver under the direct stimulation of growth hormone (GH) [7].

Syncytiotrophoblast cells secrete placental GH predominantly into the maternal circulation that regularly replaces pituitary GH during pregnancy, whereas placental GH stimulates maternal secretion of IGF-1, which may promote placental nutrient transfer to enhance fetal growth [8]. This placental GH-driven IGF-1 production may clarify the substantial increase in maternal IGF-1 concentration from the second to the third trimester of pregnancy [9].

The aim of the present work is to study the relation between insulin resistance and IGF-1 in diabetic women with gestational age of (24-28) week and after 3 months of delivery.

Patients and Methods:

A total of 88 women with gestational age of (24-28) weeks and after 3 months of delivery were enrolled in the study. Fourty four (44) women with diabetes mellitus and a case control study consists of 44 women without diabetes mellitus were recruited from AL-Yarmouk Teaching Hospital

and the National Diabetic Center/ Al- Mustansiriya University during the period from May 2014 to June 2015; their age range was (20-40) years. All women underwent clinical and biochemical examinations. Fasting venous blood samples were collected from all the subjects. Laboratory evaluations consisted of glycemic control including (fasting serum glucose (FSG), glycated hemoglobin HbA1c, fasting serum insulin) and lipid profile [total cholesterol (TC), triacylglycerol (TAG), and high density lipoprotein cholesterol (HDL-C)], were measured. Glucose levels were determined using kits supplied by Randox, UK. Glycated hemoglobin were estimated by high performance liquid chromatography (HPLC) supplied by Variant Company, USA. Insulin resistance (IR) parameters calculated from Homeostasis Model Assessment-2 for Insulin Resistance (HOMA2-IR), Homeostasis Model Assessment-2 for Sensitivity (HOMA2-S%) and Homeostasis Model Assessment-2 for beta cell dysfunction (HOMA2-β%) which were calculated using HOMA2-Calculator software downloaded freely. Furthermore, Insulin like Growth Factor-1 (IGF-1) concentrations were determined by IRMA-IMMUNOTECH, France. Serum TC, TAG, and HDL-C were determined using kits from biomaghreb, France. Low density lipoprotein levels (LDL-C) were calculated mathematically using the Friedwalds formula. Additionally, all these biochemical examinations was determined after 3 months of delivery.

Statistical Analysis:

Study analysis of data was performed using statistically package for social science (SPSS) version 17.0. Results are expressed as mean ± SD. Student-t test was used to compare the significance of the difference in the mean values of any two groups (P - value of less than 0.05 was considered significant).

Results:

Table (1) showed the comparison of biochemical parameters between GDM (24-28) week and control. The results showed that the means of FSG, HbA1c, insulin, HOMA2-IR, and IGF-1 were significantly increased in GDM group when compared to the control group, ($P<0.05$), while HOMA2-S% and HOMA2-β% were significantly decreased in GDM group when compared to their levels in the control group ($P=0.001$). Moreover, serum TC, TAG, and LDL-C showed a significant increased in GDM group when compared to the control group, ($P=0.01$).

Table (1): Comparison of biochemical parameters between GDM (24-28) week and control group.

Parameters	GDM group	Control group	P-Value
Number	44	44	-
Gestational age at study (week)	24-28	24-28	-
FSG (mg/dl)	126.21±12.42	92.53±9.08	0.05
HbA1c%	8.76±1.81	5.49±0.94	0.05
Insulin (µU/ml)	19.46±6.94	9.60±2.33	0.01
HOMA2-IR	13.57±1.23	9.40±1.52	0.05
HOMA2-S%	51.72±40.73	77.23±14.9	0.001
HOMA2-β%	56.76±22.17	88.40±22.32	0.001
IGF-1 (ng/ml)	477.12±51.30	219.62 ±38.32	0.0001
TC (mg/dl)	217.17±45.92	175.20±36.42	0.01
TAG (mg/dl)	175.21±40.7	136.11±21.4	0.01
HDL-C (mg/dl)	43.31±8.12	46.01±5.32	0.53
LDL-C (mg/dl)	142.28±33.01	99.70±21.33	0.01

Table (2) showed the comparison of biochemical parameters between GDM group (after 3 months of delivery) and controls. The results showed that the means of FSG, insulin, HOMA2-IR, and IGF-1 were significantly increased in GDM group when compared to the control group, ($P<0.05$), while HOMA2-S% and HOMA2-β% were significantly decreased in GDM group when compared to the control group ($P=0.001$). Moreover, serum TAG showed significantly increased in GDM when compared to their levels in the control group, ($P=0.01$). Serum TC and LDL-C levels were elevated, but they were not significant.

As shown in table (3), there was a significant positive correlation between serum IGF-1 levels verse HOMA2-IR in GDM (24-28) week and after 3 months of delivery. Also, a significant positive correlation was found between IGF-1 levels verse HOMA2-S% and HOMA2-β% in GDM (24-28) week, while there was no significant correlation between IGF-1 levels verses HOMA2-S% and

HOMA2-β% in gestational diabetes mellitus after 3 months delivery.

Table (2): Comparison of biochemical parameters between GDM (after 3 months of delivery) and control group.

Parameters	*GDM group*	*Control group*	*P-Value*
Number	44	44	**-**
Gestational age at study(months)	*3 months after delivery*	*3 months after delivery*	-
FSG (mg/dl)	107.33±22.18	81.16±7.11	0.04
HbA1c %	6.81±1.89	5.21±0.95	0.16
Insulin (µU/ml)	12.23±5.12	7.57±4.28	0.05
HOMA2-IR	11.02±3.71	7.04±2.45	0.05
HOMA2-S%	66.61±51.61	110.11 ±28.91	0.001
HOMA2-β%	62.03±58.78	94.17±33.40	0.001
IGF-1 (ng/ml)	221.20±92.14	190.52±83.16	0.001
TC (mg/dl)	195.18±36.5	183.41±25.21	0.06
TAG (mg/dl)	157.77±37.34	122.87±20.17	0.05
HDL-C (mg/dl)	53.10±4.32	60.42±6.14	0.07
LDL-C (mg/dl)	109.82±18.21	97.14±12.45	0.06

Table (3): Correlation coefficients between GDM (24-28) weeks and after 3 months of delivery.

Parameters	*GDM group (24-28) week*	*GDM group (3 months after delivery)*
	r	***R***
IGF-1 vs. HOMA2-IR	0.569**	0.481**
IGF-1 vs. HOMA2- S%	0.299*	0.143
IGF-1 vs. HOMA2- β%	0.322*	0.186

Discussion:

This study evaluated the biochemical change in pregnant diabetes women at the time during pregnancy when most women have an oral glucose tolerance test for diagnosis of GDM, 24–28 weeks.

There were a significant difference in FSG, insulin, HOMA2-IR, HOMA2-S%, HOMA2-B%, and IGF-1 in women with GDM before and after delivery as compared to the control group.

Insulin resistance has been recognized as a common causal factor for poor pregnancy outcomes [(10)]. The ability to diagnose abnormal IR in pregnancy is complicated by the natural reduce in insulin responsiveness that occurs in all pregnant women [(11)]. The IGFs are vital regulators of placental and fetal development, as well as postnatal growth and metabolism, IGFs abundance is also altered by pregnancy [(12)]. Variable changes in circulating IGF-1 during the first two trimesters of human pregnancy have been reported with modest increases of 25-40% compared to non-pregnant women [(13)] , or a gradual generally rise with growing gestation and highly variable concentrations between women [(14)]. Longitudinal studies have shown stable concentrations from early pregnancy (8-10) weeks and after 30 weeks' gestation [(15)], while decreased concentrations in the 1st 61 trimester until 24 weeks' gestation compared to preconception [(16)]. All these studies concur that maternal circulating IGF-1 is 45-200% higher in the 3rd trimester when compared to non-pregnant women and early pregnancy.

The increases in circulating IGF-1 were reported in later pregnancy it was possibly a response to increasing maternal circulating GH concentrations which stimulated by rapid increases in placental GH production during the second trimester [(17)]. Plasma IGF-1 normalize across gestation in women who were deficient in pituitary GH [(18)], implying that placental GH is a major regulator of IGF abundance during pregnancy. Furthermore, the human placenta itself expresses *IGF1* and *IGF2*, and *IGF1* gene and protein expression occurs on both maternal and fetal sides of the human placenta, and placental tissues might be a source of circulating IGFs during pregnancy [(19)].

Additionally, the present data suggests that IGF-1 is determinant of maternal insulin sensitivity and altered IGF-1 levels may contribute to the progress of GDM which is reported in other studies [(20, 21)].

Maternal IGF-1 levels were positively correlated with pre-pregnancy and the HOMA-IR in individuals with GDM but not in control

pregnancies suggesting that elevated IGF-1 may contribute to IR in women with GDM [22].

In this study, there was a positive correlation between IGF-1, HOMA2-IR, HOMA2-S%, and HOMA2-B% when data from all participants were combined suggesting that IGF-1 may be involved in adaptable maternal insulin sensitivity in mid-pregnancy.

Metabolically, women with GDM differed from those who were without diabetes by having a higher level of IR (higher fasting glucose, HbA1c, and HOMA-IR scores), as well as a dyslipidemia with higher TAG, LDL-C, and lower HDL-C. The IGF-1 levels have been previously implicated as an important factor for metabolic health in pregnancy and dyslipidemia associated with GDM [23].

Conclusion:

High serum IGF-1 levels in diabetic women with gestational age of (24-28) weeks may indicate greater placental and fetal growth. There was a highly significant positive correlation between IGF-1 and HOMA-IR in GDM group, this suggest that IGF-1 may be involved in regulating maternal insulin sensitivity in mid-pregnancy and these changes are mechanistically linked to the development of GDM in pregnant women with GDM.

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