ORIGINAL ARTICLE
ASSOCIATION OF ADIPONECTIN WITH INSULIN RESISTANCE IN GESTATIONAL DIABETES MELLITUS

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Background: Adiponectin is a major adipokine, with a leading role in insulin resistance and type 2 Diabetes Mellitus. Low levels of adiponectin during pregnancy are linked to gestational diabetes mellitus. The objective of our study was to determine the association of serum adiponectin with insulin resistance in gestational diabetes mellitus. **Methods:** This study was carried out at Department of Physiology and Centre for Research in Experimental and Applied Medicine of Army Medical College in alliance with Military Hospital, Rawalpindi, from July 2017 to February 2018. It was a descriptive study. A total of thirty age and BMI matched diagnosed cases of gestational diabetes mellitus were included in this study through non-probability purposive sampling. Females having history of recent miscarriage, pre-existing diabetes mellitus and females with gestational diabetes mellitus on insulin therapy were excluded. Data collection was done after taking informed written consent. Serum adiponectin and insulin levels were evaluated by ELISA. HOMA-IR was used to determine insulin resistance and value >1.5 was considered significant. Pearson correlation test was applied to assess the correlation between serum adiponectin and insulin resistance, $p<0.05$ was considered statistically significant. **Result:** There was a strong negative correlation between fasting insulin levels and HOMA-IR values with serum adiponectin levels, assessed by Pearson correlation test ($p<0.001$). **Conclusion:** There is a negative correlation between serum adiponectin levels and insulin resistance indicating that adiponectin plays a significant role in the development of insulin resistance in gestational diabetes mellitus.

Keywords: Insulin resistance, Adiponectin, gestational diabetes, Type-2 diabetes mellitus

INTRODUCTION

Diabetes mellitus represents a group of multiple disorders with heterogeneous aetiology, defined by chronic hyperglycaemia and other metabolic abnormalities caused from insulin deficiency or its defected action.[1] Diabetes mellitus is one of the most common chronic diseases in nearly all countries, and continues to increase in number and significance, as changing lifestyles lead to reduced physical activity, and increased obesity.[2] Gestational diabetes mellitus (GDM) a category of DM is defined as impaired glucose tolerance which has its onset or first recognition during pregnancy. This condition is associated with adverse pregnancy outcomes, including foetal macrosomia, stillbirth, neonatal metabolic disturbances, and other related problems. Women with GDM are more likely to develop diabetes in the years following pregnancy. GDM can affect between 1.4–14% of pregnancies varying with the population under study. Among Pakistani women, around 3.3% are diagnosed with GDM.[3]

During pregnancy, maternal insulin demands increase due to the insulin resistance which is related to weight gain, placental hormone production, increased fetal burden and increased food intake. Maternal islets adapt to this increased demand mainly through enhanced insulin secretion per β-cell and increased β-cell proliferation. Women unable to adapt to these pregnancy-induced physiological changes develop GDM. The resulting insulin resistance starts in the middle of the second trimester and continues progressively in the third trimester.[4]

Obesity is one of the most well-known risk factors of GDM even though GDM can still ensue without any known risk factors. Increasing adiposity is correlated with the secretion of pro-inflammatory cytokine from adipose tissue, resulting in a state of chronic low-grade inflammation.[5] Regulation of the lipid stores is strictly done by adipocyte-specific proteins, referred to as adipocytokines or adipokines that interfere with insulin action. Among these, the current view is that TNF-α, interleukin-6 and resistin negatively regulate insulin action, in contrast to the insulin-sensitising action of leptin and adiponectin. Adiponectin is the most abundant adipocyte-derived product identified to date. It is a signalling protein that is synthesized and secreted by adipose tissue and is one of the most abundant plasma proteins in humans.[6,7]

Adiponectin level are reduced in individuals with obesity, insulin resistance, and type 2 diabetes and GDM. The adiponectin level is also inversely associated with other traditional cardiovascular risk factors, such as blood pressure, total and low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels, and is

positively related to high-density lipoprotein (HDL) cholesterol levels.[8,9]

The decreased adiponectin levels in GDM are independent of pre pregnancy body mass index (BMI) and insulin sensitivity. Moreover GDM is characterized by an amplification of low-grade inflammation already existing in normal pregnancy and increased circulating concentrations of inflammatory cytokines including TNFα and IL-6. TNFα and IL-6 are presumed as negative regulatory factors of the adiponectin gene. Thus, TNFα and other pro inflammatory mediators suppress the transcription of adiponectin in adipocytes, and this might explain the lower levels of the adipokine in individuals with GDM.[10]

As adiponectin has insulin-sensitizing effects, low levels of this adipokine might further aggravate insulin resistance. Moreover, insulin is able to suppress plasma adiponectin concentrations and hyper-insulinaemia seen in GDM, might cause a significant decrease in plasma adiponectin levels.[11]

This study was intended to assess the association of serum adiponectin levels with insulin resistance in GDM.

METHODOLOGY

This study was carried out at Military Hospital, Rawalpindi and Physiology department Army Medical College, Rawalpindi. A formal approval was taken from ethical review committee of Military hospital and Army Medical College. An informed written consent was taken from all the subjects before sample collection. Thirty diagnosed cases of GDM were included in the study. Females having history of recent miscarriage, pre-existing diabetes mellitus and females with gestational diabetes mellitus on insulin therapy were excluded. Complete history was taken followed by a thorough general physical examination of all the subjects. To determine BMI, height and weight of all the subjects was measured.

$$BMI = Weight~(Kg)/[Height~(m)]^2$$

Strict aseptic measures were taken while collecting blood samples and 5 ml of blood was withdrawn by venipuncture. After transferring the sample to the gel separator tube, centrifugation was done. Pipetted serum was transferred to the polypropylene tubes and stored at -20 °C in Centre for Research in Experimental and Applied Medicine Lab Army Medical College.

The measurement of plasma insulin levels was done with a commercial assay kit (Chemux Bioscience, Inc, USA). Following equation was used to calculate insulin resistance from fasting glucose and insulin levels:

$$HOMA\text{-}IR = insulin~(uU/ml) \times glucose~(mmol/l)/22.5^{12}$$

A value >1.5 for HOMA-IR was considered significant.

Serum adiponectin levels were assessed by performing ELISA with the help of a commercially available human ADP ELISA kit (Elab Science, Inc, USA).

Computer software SPSS-22 was used to analyze the statistical data. Mean values and standard deviation (SD) were evaluated for all the quantitative variables. Pearson correlation coefficient was used to assess association between serum adiponectin levels and insulin resistance and $p<0.05$ was considered statistically significant.

RESULTS

In this study, we recruited thirty pregnant females diagnosed with GDM, all during 12th to 24th week of gestation.

The mean values of serum insulin, HOMA-IR and serum adiponectin levels of all the subjects are summarized in Table-1 along with the standard deviation values. Table-2 depicts the association of serum insulin and HOMA-IR values with adiponectin in GDM.

Table-1: Descriptive statistics of study parameters in GDM patients

Variable	Mean±SD	Min	Max
Serum insulin (uU/ml)	21.80±2.57	17.16	26.01
HOMA-IR	7.78±1.16	5.73	10.37
Serum Adiponectin	6.35±1.25	3.75	8.93

Table-2: Correlation of study variables with serum Adiponectin in GDM patients

	Parameter	r	p
Pearson's correlation	Serum insulin	-0.73	<0.001*
	HOMA-IR	-0.83	<0.001*

*Significant

DISCUSSION

Gestational diabetes mellitus is associated with decreased responsiveness of maternal body tissues to insulin.[13] Thus raised values for serum insulin and high HOMA-IR values are expected in GDM patients.[14] The same has been depicted in our study as HOMA-IR values are found to be much higher than the normal cut-off value of 1.5 in GDM patients.

In this study we demonstrated a negative correlation between serum adiponectin levels and insulin resistance in GDM patients. As mentioned in previous studies, adiponectin is a signalling protein involved in glucose homeostasis and regulation of insulin resistance.[15,16] In GDM, a pro-inflammatory state prevails, thus raised levels of TNF-α suppress adiponectin levels. Hypoadiponectinaemia leads to increased resistance to insulin in the maternal body.[17]

The results of our study are comparable to a research carried out in Canada in 2013 by Lacroix *et al*[18] who measured serum adiponectin levels during

first and second trimester in normal pregnant females and those with GDM. They correlated serum adiponectin values with HOMA-IR values. Their results revealed a negative correlation between serum adiponectin levels and insulin resistance, independent of adiposity.[18]

Similar results were reproduced in a study carried out by Halil G. Pala *et al*[19] in 2015 in Turkey. They enrolled 31 healthy pregnant controls and 34 GDM patients during their second trimester of gestation. They concluded that serum levels of adiponectin were lower in GDM group and were inversely related to HOMA-IR values of the same group indicating the negative correlation of adiponectin with insulin resistance. Decrease in adiponectin levels became more prominent as glucose intolerance develops in the second trimester. The results of the current study also support this.

As adiponectin plays a major role in regulating glucose metabolism and insulin resistance in GDM, it can be proposed as a diagnostic tool for GDM.[20] However we cannot draw a definitive conclusion from this data due to small sample size, limited time period and financial constraints. Also, we were unable to determine the exact mechanism of adiponectin leading to insulin resistance. More advanced studies are required in this regard.

CONCLUSION

Our study demonstrates a negative correlation between serum adiponectin levels and insulin resistance that in turn may lead to GDM.

FUNDING DISCLOSURE

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