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Study of serum adiponectin, IL-1 beta and HbA1c levels in women with Gestational diabetes mellitus

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Abstract

Introduction:

Pregnancy is a unique state where there is a physiological and temporary surge in the insulin resistance. Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy. Though, the exact mechanism for insulin resistance in GDM is not well established, various studies have shown significant relation of the parameters like Adiponectin, IL-1-beta and HbA1C with GDM. We aim to study these parameters and their relationship in women with GDM with a cohort of normoglycemic pregnant women.

Materials & methods:

A total thirty pregnant women between 24th to 28th weeks of pregnancy with Gestational Diabetes and no other comorbidities and thirty age matched healthy control pregnant women without Gestational Diabetes presenting in the outpatient department of the hospital were included in our study over a period of 1 year. Levels of serum adiponectin, IL-1-beta and HbA1C were analyzed and correlated.

Results:

The data shows that the GDM group have a higher pre-pregnancy BMI, lipid profile and HbA1c levels as compared to those with normal pregnant women and a lower serum adiponectin level. The findings of Pearson method showed a significant positive correlation between HbA1c level with GCT, BMI and serum cholesterol ($p=<0.05$, $r=0.53$). however, serum adiponectin level showed an inverse correlation with HbA1c, GCT, BMI and lipid profile.

Conclusion:

Our study demonstrated a decreased adiponectin levels and a normal but higher level of HbA1C in women with GDM when compared to normal pregnant women. However, in our study, serum IL-1beta played no significant role in the development of Gestational diabetes and does not correlate with any of the parameters measured.

Keywords: Antenatal screening, adiponectin, insulin resistance, GDM.

INTRODUCTION

Gestational diabetes (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy".[1] This definition acknowledges the possibility that patients may have previously undiagnosed diabetes mellitus or may have developed diabetes coincidentally with pregnancy. Whether

symptoms subside after pregnancy is also irrelevant to the diagnosis.[2] Gestational diabetes mellitus (GDM) manifests in all trimesters of pregnancy.[3] It has been suggested that GDM is a partially acquired and partially inherited insulin resistance preceding pregnancy.[4]

In India, according to a random national survey conducted in 2004, the prevalence of GDM was 16.55%.[5] In 2008, a hospital-based survey showed a combined prevalence of Gestational Diabetes (GDM) and Impaired Glucose Tolerance (IGT) to be 21.6%.[6]

During pregnancy, metabolism undergoes important changes due to the increasing metabolic needs of the mother as well as the growing foetus and placenta. Pregnancy is associated with alterations in the regulation of glucose metabolism caused by actions of various hormones such as placental lactogen, placental growth hormone production[7] and other substances that antagonize the action of insulin, leading to a state of relative insulin resistance as pregnancy progresses. Recent studies have also shown that human placenta and adipose tissue produce various pro- and anti-inflammatory cytokines such as Interleukin–1 beta (IL-β) and Adiponectin[8,9] respectively.

Adiponectin is an adipose tissue derived protein with profound insulin sensitizing, anti-inflammatory and anti – atherogenic effects. Low serum adiponectin levels are an independent risk factor for future development of Diabetes Mellitus. Conversely, higher adiponectin levels are consistently associated with a lower risk of type 2 diabetes in prospective studies of diverse populations. Currently, Adiponectin is among the strongest and most consistent biochemical predictors of type 2 diabetes.[10]

Interleukin -1 beta, a pro inflammatory cytokine is known to mediate auto inflammatory process resulting in beta cell destruction and thereby participate in glucotoxicity and impaired insulin secretion.[11]

Glycated haemoglobin (HbA1c) is formed by a non-enzymatic glycation pathway by haemoglobin's exposure to plasma glucose.[12] As the average amount of plasma glucose increases, the fraction of glycated haemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous 4 weeks to 3 months prior to the measurement[13] and can help in identification of women who were already diabetic before pregnancy but undiagnosed and thereby distinguishing them from women who have true gestational diabetes, HbA1c is not recommended because of its low sensitivity.

Since, GDM is associated with increased body mass index (BMI) and decreased insulin sensitivity, the evaluation of plasma Adiponectin and IL-1beta levels in these patients can have a potential role in the future management and further follow up of women who have a higher risk of developing type 2 Diabetes Mellitus later in life.

AIMS AND OBJECTIVES:

The aims of this study are:

1. To evaluate serum Adiponectin, Interleukin –1 beta and HbA1c levels in women with Gestational Diabetes
2. To correlate their levels with blood glucose level.

MATERIALS AND METHODS

Thirty pregnant women between 24th to 28th weeks of pregnancy with Gestational Diabetes and no other comorbidities and thirty age matched healthy control pregnant women without Gestational Diabetes presenting in the outpatient department of the hospital over a period of 1 year and fulfilling the inclusion criteria were included in the study. An informed consent was taken from all the patients participating in the study and a detailed clinical history along with meticulous general physical examination was conducted.

Anthropometric measurement: Height was measured in meters and weight was measured in kilograms. Also, pre-pregnancy weight was taken as well as first trimester body weight from their antenatal clinic card. Pre–pregnancy body mass index (BMI) was calculated for all the patients using the formula BMI =weight (kg)/height (meter)^2.

Screening and diagnosis of case of Gestational Diabetes:

A screening test was performed on pregnant females attending the antenatal clinic in the hospital at 24th to 28th weeks of pregnancy. A 50 gms, glucose challenge test (GCT) was done and 1 hour blood glucose level measured. All patients with 1 hour blood glucose level >/=140mg/dl were further taken up for confirmation of diagnosis. Gestational Diabetes was diagnosed after a

Volume 4, Issue 5; September-October 2021; Page No 413-418

100-gram Oral glucose tolerance test (OGTT) as per the American Diabetes Association criteria.

Biochemical Assay: The Quantitative determination of serum adiponectin (DRG) and IL-1beta (Gen-Probe Diaclone) was done by ELISA and determination of HbA1c was done using an RX Daytona automated analyser.

Statistical analysis:

The statistical analysis was done by using the Statistical Package for Social Sciences (SPSS) version 20.0. The data were expressed as mean+/-standard deviation. Besides descriptive statistics, the comparison of the parameters (serum adiponectin, IL-1beta and HbA1c) between the cases and controls was done using "Mann Whitney U test" for non-parametric data and "independent sample t test" for parametric data. Correlation of the parameters was done using Pearsons correlation test among the parameters themselves and also with GCT, OGTT, BMI, lipid profile and parity in both the study groups. The "p value" of <0.05 was considered to be significant. Also, a receiver–operator characteristic curve was plotted for determination of their sensitivity and specificity in the detection of cases of gestational diabetes.

Results:

Anthropometric and metabolic characteristics of the study participants in the normal and Gestational Diabetes group are shown in table 1.

The data shows that the GDM group have a higher pre-pregnancy BMI, lipid profile and HbA1c levels as compared to those with normal pregnant women and a lower serum adiponectin level.

The findings of Pearson method showed a significant positive correlation between HbA1c level with GCT, BMI and serum cholesterol (p=<0.05, r =0.53). however, serum adiponectin level showed an inverse correlation with HbA1c, GCT, BMI and lipid profile.

By plotting an ROC curve, a critical value of HbA1c>5.15% has a sensitivity of 80% and a specificity of 96.7%. Meanwhile, at a critical value of 8.75microgm/ml, serum adiponectin has a sensitivity and specificity of 100% for detection of GDM cases. However, serum IL-1beta has an area of 0.633 (p=0.076) and is therefore rendered insignificant.

Eight out of 22 cases (26.7%) showed serum IL-1beta higher than the lowest detectable level provided by the ELISA kit used. Therefore, their values are not representative of the cases.

Table 1. Mean and standard deviation of baseline level of anthropometric and metabolic characteristics of studied subjects.

Variables	GDM group	Control group
Age (years)	27.06+/-4.8	26.64 +/- 3.1
Pre-pregnancy BMI (kg/m^2)	23.49 +/- 2.1	20.95 +/- 1.1
GCT (mg/dl)	152.6 +/- 13.5	98.9 +/- 33.9
S. cholesterol (mg/dl)	196.36 +/- 41.7	161.83 +/- 24.9
S. triglyceride (mg/dl)	173.74 +/-68.1	123.06 +/- 26.5
HbA1c (%)	5.89 +/- 0.79	4.63 +/- 0.38
S. adiponectin (microgm/dl)	5.76 +/-2	14.12 +/- 4.9
S. IL-1beta (pg/ml)	21.45 +/- 14.3 (n = 8) *	< 6.5

*Of the 30 cases, only 8 have a serum IL-1beta level of >6.5 pg/ml which is the lowest detectable level by the kit provided. The remaining 22 cases as well as all the control groups showed levels which were undetectable, i.e., <6.5 pg/ml.

Volume 4, Issue 5; September-October 2021; Page No 413-418

DISCUSSION:

Our study findings showed that HbA1c level was significantly higher in women with Gestational diabetes (GDM) as compared to that of controls. Similar findings were seen by Saleh et al (2008)[14] and Rajesh et al (2012)[15]. Also, there was a significant positive correlation between pre-pregnancy BMI, blood glucose level at GCT and serum cholesterol which were significantly higher in women with GDM.

Pre–pregnancy BMI is known to be the primary factor in determining BMI during pregnancy, with high pre–pregnancy BMI being a risk factor for GDM as well as post-partum glucose intolerance. Torloni M R et al (2009) [16] in their systematic review with meta-analysis found that for every 1 kg/m^2 increase in BMI, the prevalence of GDM increased by 0.92% (95% CI 0.73 to 1.10). Similar findings were seen by Culha C et al (2011)[17] and Weerakiet S et al (2006) [18] who also found that the mean BMI was significantly higher in women with GDM than in women with normal pregnant women prior to pregnancy as well as during pregnancy.

Serum adiponectin is known for its insulin sensitizing and anti- atherosclerotic actions. In the present study, its level was significantly lower in cases of GDM as compared with normal pregnant women. Similar findings were observed by Altinova AE et al (2007) [19], Vitoratos N et al (2008) [20] and Culha C et al (2011)[21]. Williams MA et al (2004) [21] also reported lower adiponectin levels in women with GDM compared with normal pregnancy controls and that women with adiponectin concentrations below 6.4 ug/ml has an increased risk for developing GDM by 4.6-fold compared with the risk at higher concentrations. On the contrary, McLachlan KA et al (2006)[22] found no difference in the adiponectin level between pregnant women with and without GDM.

There was also an inverse correlation between adiponectin level pre – pregnancy BMI, glucose level at GCT, lipid profile including serum cholesterol and triglyceride levels as well as with HbA1c. Sedigheh S et al (2009)[23], Culha C et al (2011)[17] and Sahriian V et al (2012)[24] also found that the amount of serum adiponectin has an inverse relationship with the body mass index in normal pregnant women and that reduction in adiponectin in- turn increased the synthesis of lipids and fatty acids and accumulation of the surplus in the tissue. These results are inconsistent with the finding of Worda C et al (2006)[25] who found no correlation between BMI and serum adiponectin level. Also changes in adiponectin level is known to be related to decreased insulin sensitivity and glucose disposal and are reported to be negatively correlated with triglyceride levels and positively correlated with HDL levels and that these relationships are independent of systemic insulin resistance and are affected by central obesity.[25-29] Kinalski M et al (2005) [26] and Altinova AE et al (2007) [19] also found a significant correlation between serum adiponectin and triglyceride levels in normal glucose tolerant pregnant females.

Similar to our findings an inverse correlation between serum adiponectin level and blood glucose level at GCT and OGTT was also found by Sedigheh et al (2009)[23] and Nicholson W et al (2013)[27]. By using logistic regression analysis, they demonstrated adiponectin as an independent predictive factor for GDM and that at baseline, higher adiponectin concentrations were inversely and statistically significantly associated with maternal response to GCT and adjustment for lifestyle factors like BMI did not alter the association of adiponectin with GCT. Altinova AE, et al (2007)[19] also found that adiponectin levels correlated negatively with insulin resistance and 0 hour and 1 hour glucose both at glucose challenge test and oral glucose tolerance test in GDM cases.

In the present study, 22 out of 30 (73.3%) cases and all the thirty controls showed serum Il-1beta value of less than 6.5 pg/ml which was below the detectable level. Only 8 out of 30 (26.7%) cases showed levels more than 6.5pg/ml with a range of 12.18 pg/ml to 34.62 pg/ml (mean =23.82 pg/ml +/-14.3), p =0.006. However, this cannot be a representative of mean serum IL-1-beta in the cases as it represents only 26.7% of the cases. Our findings were contrary to Vitoratos N et al (2008) [20] who found a significantly higher serum IL -1beta levels in women with GDM as compared to normal pregnant women [median 1.39 (0.73 – 1.58) vs 0.55 (0.42 – 0.91) ng/ml, respectively, p<0.001]. Their findings were in accordance with recent studies reporting that pregnancies with GDM are associated with an increased levels of TNF alpha, IL – 6 and high sensitivity (hs) CRP, all indicators of a proinflammatory status and shows that IL-1beta

Volume 4, Issue 5; September-October 2021; Page No 413-418

levels follow a pattern like the other pro inflammatory cytokines in pregnancies with GDM.

CONCLUSION:

Gestational diabetes is associated with hypoadiponectinemia and a normal but higher value of HbA1c as compared to normal pregnant women. However, serum IL-1beta played no significant role in the development of Gestational diabetes and does not correlate with any of the parameters measured. The discrepancy between these studies and our results may be related to the difference in race of patients and other risk factors in pathogenesis of GDM.

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LIMITATIONS:

The study was of a small sample size.

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Volume 4, Issue 5; September-October 2021; Page No 413-418

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Volume 4, Issue 5; September-October 2021; Page No 413-418