ORIGINAL ARTICLE

SERUM C REACTIVE PROTEIN AS AN INFLAMMATORY MARKER IN GESTATIONAL DIABETES MELLITUS

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Background: Gestational diabetes mellitus is the most prevalent metabolic disorder of pregnancy. A number of factors are implicated in its causation. Inflammation may play a role in development of diabetes. This study aimed to look for an association between serum C reactive protein and gestational diabetes mellitus. **Methods:** This cross-sectional analytical study was carried out at Physiology Department, Army Medical College in collaboration with Pak Emirates Military Hospital from July 2019 to March 2020. Thirty healthy pregnant females and 30 gestational diabetes mellitus patients with 24–32 weeks of gestation were selected. The diagnosis of gestational diabetes was made on the basis of abnormal glucose tolerance test according to International Association for Diabetes and Pregnancy Study Group (IADPSG) criteria. Blood samples were evaluated for serum CRP. Data were analyzed on SPSS-22. Data were expressed as mean and standard deviation. Comparison of data was performed using independent samples *t*-test. Pearson correlation coefficient was determined to find association between numerical variables. Results were considered significant at $p \leq 0.05$. **Results:** Mean Serum C reactive protein level was significantly higher in gestational diabetes group compared with healthy control group and had significant positive correlation with plasma glucose levels as well as glycosylated haemoglobin. **Conclusion:** High CRP levels in GDM had positive correlation with blood sugar levels. Early diagnosis of inflammation with raised CRP level may be helpful in identifying the subjects at risk.

Keywords: Gestational diabetes, inflammation, C-reactive protein

Pak J Physiol 2023;19(3):3–6

INTRODUCTION

Normal pregnancy is associated with significant anatomical, physiological and biochemical changes. Sometimes, these changes may lead to pathological conditions and diseases. One of such diseases is gestational diabetes mellitus (GDM). GDM is the most prevalent metabolic disorder in pregnancy that affects more than 14% pregnancies in Southeast Asia.[1] Prevalence of diabetes is highly variable in different populations and is partially affected by the criteria used for its diagnosis.[2] A comprehensive data regarding its prevalence in Pakistan is not available. However, different local studies have shown a prevalence of 8% to 26% in different areas of Pakistan.[3] Increased prevalence of GDM in recent years is in direct proportion to high prevalence of obesity and type 2 diabetes mellitus.[4] Further, GDM can lead to type 2 diabetes both in mother and offspring in addition to causing complications like foetal macrosomia, shoulder dystocia and respiratory distress.[5]

GDM is an independent type of diabetes in which glucose intolerance is first recognized after 24th week of pregnancy.[6] Both genetic and environmental factors are implicated in aetiology of GDM. Pregnancy is associated with changes in carbohydrate, protein and lipid metabolism owing to placental hormones like estrogens, progesterone, human placental lactogen and cortisol etc. This alteration in metabolism serves the purpose of foetal development.[7] Even during the normal pregnancy, insulin sensitivity can be decreased up to 70%. This insulin insensitivity is compensated by increased insulin secretion by beta cells of pancreas.[8] However, an insufficient insulin secretion in the presence of insulin resistance state during pregnancy results in gestational diabetes.

Inflammation is involved in causation of many diseases including cardiovascular diseases and type 2 diabetes.[9] Pregnancy is a pro-inflammatory condition and maternal immune response is disrupted during pregnancy. As a matter of fact, inflammation plays a significant role in early pregnancy during the process of implantation and decidualization.[10,11] However, uncontrolled inflammation may be a cause of gestational as well as neonatal complications.[12] Increased cytokine production in inflammation interacts with post synaptic insulin receptors and interferes with the normal physiological tyrosine phosphorylation of insulin receptor substrate thereby affecting the normal glucose metabolism. The subclinical inflammation results in development of insulin resistance.[6]

Many studies are conducted to device methods and tests for early diagnosis of gestational diabetes. Considering the role of inflammation in pathogenesis of

insulin resistance, studies are carried out to find association between inflammatory markers and diabetes type 2.[13] The increased level of CRP and other inflammatory mediators like interleukin-6 and plasminogen is found to be associated with development of insulin resistance and diabetes.[14] Increased level of inflammation is found to be an additional factor for GDM development.[15] Identifying the association between inflammation and GDM can help in early diagnosis and timely management of GDM and thus can prevent many gestational and neonatal complications. We measured serum CRP levels in GDM patients and compared them with those in normal pregnant women during same gestational period to find any association between inflammation and gestational diabetes.

PATIENTS AND METHODS

The comparative cross-sectional study was conducted at Physiology Department in association with Pak Emirates Military Hospital after formal approval from Ethical Review Board of the Institution. Sample size was calculated using WHO calculator[16] for which confidence level was taken at 95% and margin of error as 5%. With an estimated GDM prevalence of 3.5% in Pakistan, sample size of 54 individuals was calculated. After written informed consent, a total of 60 pregnant women were included in study, 30 were diagnosed having gestational diabetes while 30 were healthy pregnant women. All pregnant women were within 24 to 32 weeks of gestation.[6] The diagnosis of gestational diabetes was made on basis of International Association for Diabetes and Pregnancy Study Group (IADPSG) criteria approved by American Diabetes Association (ADA).[17] Detailed history was taken from all subjects and relevant clinical examination was carried out. Women with acute or chronic infection or inflammation as discovered during history and clinical examination were excluded from study.

Blood samples for glucose estimation were collected under aseptic technique in collection tubes containing sodium fluoride and potassium oxalate. Analyses for glucose were performed within two hours of sample collection using Roche Cobas C Analyzer. For CRP estimation, blood samples were collected in serum collection tubes. The test was performed using immunoturbidimetric assay on Roche Cobas C Analyzer. For glycosylated haemoglobin (HbA1c), blood samples were collected in tubes containing anti-coagulant. The concentration of both haemoglobin and HBA1c was determined and HbA1c/haemoglobin ratio was expressed as percentage HbA1c (%HbA1c). Data were analyzed on SPSS-22. The numerical variables were compared for their Mean±SD value by employing independent samples *t*-test whereas correlation between different numerical variables was interpreted using Pearson's correlation coefficient. The results were regarded significant at $p \leq 0.05$.

RESULTS

Thirty patients of GDM and 30 healthy pregnant women were included in the study. The subjects were matched for age and gestational age. There were no significant differences in GDM and control group regarding BMI and parity. A significant difference was found in mean serum CRP value between the two groups (p=0.005) (Table-1). Further analysis revealed a significant positive correlation of CRP with fasting, 1 hour postprandial, 2 hour postprandial glucose, as well as with HbA1c. (Table-2)

Table-1: Comparison of OGTT, CRP and HbA1c between two groups. (Independent Samples *t*-test)

Variable	Control group	GDM group	*p*
BMI (Kg/m^2)	27.34±1.56	27.46±1.94	0.79
Fasting plasma glucose (mmol/L)	4.52±0.47	5.98±1.04	<0.000*
1 hour plasma glucose (mmol/L)	6.87±1.22	10.07±1.95	<0.000*
2 hour plasma glucose (mmol/L)	5.58±0.81	8.29±1.41	<0.000*
CRP (mg/dL)	4.75±2.6	7.93±5.7	0.005*
HbA1c (%)	5.3±0.59	5.8±1.05	0.012*

*Significant

Table-2: Correlation of CRP with different parameters

Parameter correlated	*r*	*p*
Fasting plasma glucose	0.393	0.001*
1 hour plasma glucose	0.389	0.001*
2 hour plasma glucose	0.238	0.050*
HbA1c	0.258	0.033*

*Significant

DISCUSSION

We compared serum CRP levels in healthy pregnant women and patients of GDM. Serum CRP levels were significantly raised in GDM patients compared to healthy pregnant women. CRP levels also correlated positively with fasting plasma glucose, postprandial glucose and HbA1c levels.

Our findings are consistent with other studies.[18] Mostafa *et al* conducted a study recruiting 60 pregnant women divided into two groups of healthy women and GDM patients with 30 subjects in each group. They found a significant difference in CRP level in both groups with high CRP levels in GDM group (p=0.04).[19] That study was carried out in Egypt. Sample size of both studies is comparable and similar diagnostic criteria were implicated for diagnosis of GDM. In addition, a significant positive correlation of CRP was shown with BMI. In our study, positive correlation between CRP and BMI was not significant. This difference may be due to the fact that in our study, both groups did not have significant differences in mean

BMI. Inflammation as depicted by raised CRP levels appears to be a significant risk factor for GDM.

Farghaly *et al* conducted a prospective cohort study including 496 women. They measured serum CRP of all the women in 1st trimester and followed them for development of GDM by performing OGTT at 24–28 week of gestation, and found that CRP was higher in GDM group (p=0.000). Moreover, CRP levels correlated positively with glucose load test (GLT) as well as 1 hour and 2 hour GLT. They also found that sensitivity, specificity and accuracy of CRP in diagnosing GDM were acceptable.[15]

Another study carried out by Xiang *et al* at China included 96 healthy and 95 GDM patients. They measured levels of CRP along with other inflammatory markers at 24–28 weeks gestation. Their findings are also comparable to ours and showed a significant positive association between CRP and GDM in addition to a significant positive correlation of CRP with plasma glucose levels and HbA1c.[20] Their findings also emphasized the role of inflammation in GDM as a number of inflammatory markers were assessed and found to be raised in GDM group.

Siddiqui *et al*[21] conducted a study in India with similar study design. They recruited 50 healthy pregnant and 53 GDM patients. They compared CRP levels in both groups and found a significant difference in IL-6 levels but the differences in CRP levels in both groups were not significant. However, CRP levels correlated positively with FBS and postprandial blood sugar levels. In their study, GDM was positively correlated with BMI, age and positive family history of diabetes.

In contrast, a study carried out by Hezareh *et al*[22] in Iran did not reveal a significant difference in CRP levels in GDM and normal pregnant women. They also measured CRP levels in early pregnancy and followed them with OGTT at 24–28 weeks of gestation.

CRP has appeared as sensitive indicator of inflammation in cardiovascular diseases.[23] Moreover, sufficient evidence is available that suggests the role of inflammation in type 2 diabetes and insulin resistance.[24] A number of cross-sectional studies have depicted the role of CRP and other inflammatory markers in GDM. Results of a multitude of prospective cohort studies also implicate the role of inflammation in developing GDM.[15]

The results of the current study further support the hypothesis that inflammation plays a role in the pathogenesis of glucose intolerance and gestational diabetes. Thus measurement of CRP levels may be helpful in identifying women at risk of developing GDM and early diagnosis of GDM.

The small sample size and a cross-sectional study design are the limitations of our study. Future prospective studies involving a large number of subjects may prove helpful.

CONCLUSION

CRP levels are significantly higher in GDM and were positively correlated with blood sugar level. Early diagnosis of inflammation with raised CRP level may be helpful in identifying patients at risk of developing GDM.

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Received: 6 Mar 2023 **Reviewed:** 4 Sep 2023 **Accepted:** 13 Sep 2023

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TN: Study design, initial writing and data analysis
BR: Data interpretation and critical review
AM: Literature review and data analysis
ES: Data interpretation and final drafting
MSN: Drafting and critical review
LG: Data acquisition, proofreading and literature search

Conflict of interest: None
Funding: The study was partially funded by a research grant from National University of Medical Sciences, Rawalpindi.