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RESEARCH PAPER

Association of Serum Cystatin C with Glycaemic Parameters and Insulin Resistance in Pregnant Women with Gestational Diabetes Mellitus

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a common metabolic complication of pregnancy characterized by glucose intolerance and insulin resistance. Early detection and management of GDM are critical to prevent adverse maternal and foetal outcomes. Cystatin C; traditionally known as a renal marker, has recently been implicated in metabolic dysfunctions such as insulin resistance and hyperglycaemia.

Objective: This study aimed to evaluate the association of high serum Cystatin C with glycaemic parameters and insulin resistance in pregnant women with GDM.

Methods: This case-control study was conducted at Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka, from March 2024 to February 2025. Total 160 pregnant women between 24–28 weeks of gestation were enrolled; including 80 diagnosed GDM (cases) and 80 age and gestational week matched healthy pregnant women (controls). Selection was done using convenient and purposive sampling. GDM was diagnosed based on the American diabetes association (ADA) 2023 criteria. Clinical, anthropometric, and biochemical parameters, including fasting plasma glucose, 2-hour post-load plasma glucose, serum insulin, HOMA-IR, and serum Cystatin C, were measured. Data were analysed using SPSS version 26, with $p < 0.05$ considered statistically significant.

Results: The mean BMI was significantly higher in the GDM group (28.97 ± 3.75 kg/m²) compared to controls (27.97 ± 4.04 kg/m², $p < 0.002$). Fasting plasma glucose (5.92 ± 2.14 mmol/L vs. 4.41 ± 0.40 mmol/L, $p < 0.001$), 2-hour post load plasma glucose (9.03 ± 2.92 mmol/L vs. 6.53 ± 1.02 mmol/L, $p = 0.041$), and HOMA-IR (5.87 ± 3.94 vs. 3.99 ± 1.78, $p < 0.001$) were significantly elevated in the GDM group. Serum insulin was higher among cases but not statistically significant ($p = 0.38$). Serum Cystatin C level was significantly elevated in the GDM group (0.932 ± 0.23 mg/L vs. 0.734 ± 0.11 mg/L, $p < 0.001$). The high level (>0.80 mg/dl) serum Cystatin C was strongly associated with GDM (OR 9.0; 95%CI, CI-5.0 to 16.3, p< 0.001). Cystatin C was positively correlated with fasting plasma glucose ($r = 0.321$, p <0.05); 2-hour post load plasma glucose ($r = 0.303$, <0.05) and HOMA-IR (0.323, P< 0.05). Correlations of Cystatin C with serum insulin ($r = 0.121$, p>0.05) and BMI ($r = 0.150$, p>0.05)) were positive but not statistically significant.

Conclusion: High serum Cystatin C levels exhibit strong, positive, and statistically significant association with the presence of GDM and a positive correlation was found with glycaemic parameters and insulin resistance. So, woman with elevated Cystatin C suggest a higher risk of developing GDM.

Keywords: Gestational Diabetes Mellitus, Cystatin C, Insulin Resistance, HOMA-IR, Glycaemic Parameters, Pregnancy, Biomarker

Introduction

Pregnancy is a complex physiological state characterized by significant metabolic and hormonal changes aimed at supporting foetal growth and development. Among these changes, alterations in glucose metabolism are particularly critical. During normal pregnancy, insulin resistance progressively increases, particularly in the second and third trimesters, as a physiological adaptation to ensure adequate glucose supply to the foetus. However, in some women, this insulin resistance becomes excessive, leading to impaired glucose tolerance and the development of Gestational Diabetes Mellitus

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(GDM)[1-5]. Gestational Diabetes Mellitus is defined as glucose intolerance of varying degrees with onset or first recognition during pregnancy. It is one of the most common medical complications of pregnancy, with global prevalence rates ranging from 7% to 25%, depending on the diagnostic criteria and population studied. GDM poses short- and long-term risks to both the mother and the foetus. Maternal risks include preeclampsia, caesarean delivery, and the future development of type 2 diabetes mellitus, while foetal risks include macrosomia, neonatal hypoglycaemia, and long-term metabolic consequences.[6-11]

Early identification and management of GDM are crucial for improving maternal and foetal outcomes. Traditionally, fasting blood glucose, oral glucose tolerance tests (OGTT), and HbA1c are used for the diagnosis and monitoring of GDM. However, these measures have limitations in sensitivity, specificity, and predictive value. Therefore, there is a growing interest in identifying novel biomarkers that can accurately reflect glycaemic status and insulin resistance in pregnant women and potentially serve as early indicators of GDM[12-17].

Cystatin C, a low molecular weight cysteine protease inhibitor produced by all nucleated cells, has emerged as a promising biomarker in recent years. Although traditionally used as a marker of renal function, recent studies have suggested a potential role of serum Cystatin C in metabolic disorders, including diabetes mellitus and insulin resistance. Cystatin C levels have been associated with obesity, impaired glucose tolerance, and features of the metabolic syndrome, indicating that it may be involved in the pathophysiology of insulin resistance and glucose metabolism.[18-23] Cystatin C sits at an interesting crossroads in gestational diabetes because it reflects more than kidney filtration. It mirrors the intertwined metabolic, inflammatory, and vascular shifts that shape hyperglycaemia during pregnancy. In women with GDM, rising insulin resistance and placental hormone activity amplify systemic inflammation and endothelial stress, which in turn upregulate Cystatin C production from nucleated cells while reducing its clearance. Studies show that Cystatin C rises early in dysglycemia, tracks with visceral adiposity, and correlates with the low-grade inflammation, altered lipid metabolism, and early renal microvascular changes common in hyperglycaemic pregnancies. Evidence from type 1 and type 2 diabetes suggests that higher Cystatin C levels predict microalbuminuria, worsened metabolic profiles, and cardiorenal risk long before traditional markers shift—patterns that extend into GDM physiology as well. Therefore, Cystatin C is not just a filtration surrogate in pregnancy; it reflects the molecular consequences of impaired insulin signalling, oxidative stress, and endothelial dysfunction that accelerate both renal stress and adverse pregnancy outcomes.[12,14,20-23]

In pregnancy, the relevance of Cystatin C as a biomarker for glycaemic status and insulin resistance is not well established. The physiological changes in renal hemodynamics during pregnancy complicate the interpretation of renal biomarkers. However, emerging evidence suggests that elevated serum Cystatin C levels may be linked to increased insulin resistance and adverse glycaemic parameters, particularly in women with GDM. These associations, if validated, could position Cystatin C as a valuable adjunct marker for early detection and risk stratification in GDM[24-27].

Given the limited and conflicting data on this topic, there is a pressing need for comprehensive studies that evaluate the relationship between serum Cystatin C levels and established glycaemic indices such as fasting plasma glucose, postprandial glucose, HbA1c, fasting insulin levels, and insulin resistance indices like HOMA-IR. Furthermore, it is essential to compare these associations between pregnant women with and without GDM to understand whether Cystatin C can differentiate between these populations.

Therefore, the present study aims to investigate the association of serum Cystatin C with glycaemic parameters and insulin resistance in pregnant women diagnosed with GDM and compare these findings with pregnant women without GDM. By elucidating these associations, the study seeks to explore the potential of Cystatin C as a biomarker that reflects glycaemic status and insulin sensitivity during pregnancy, which may have implications for early detection, monitoring, and management of GDM.

Materials and Methods

This case-control study was conducted over one year, from March 2024 to February 2025, in the Department of Obstetrics and Gynaecology & Department of Laboratory Medicine in BIRDEM General Hospital, Dhaka. A total of 160 pregnant women at 24–28 weeks of gestation were enrolled, among whom 80 were diagnosed GDM (case group) and 80 were gestationally

healthy women without GDM (control group). Participants were selected through convenient and purposive sampling. Diagnosis of GDM was established based on the American diabetes association (ADA) 2023 criteria[28], where GDM was confirmed if fasting plasma glucose was ≥5.1 mmol/L or 2-hour post load plasma glucose following a 75g oral glucose load was ≥8.5 mmol/L.

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of BIRDEM General Hospital (Ref: BIRDEM/IRB/2024/408). All participants were informed about the nature, objectives, benefits, and potential risks of the study. Written informed consent was obtained before inclusion. Participants were interviewed using a semi-structured questionnaire in English and Bengali to collect socio-demographic, clinical, and obstetric information, including age, gravidity, parity, previous obstetric history, family history of diabetes, and other relevant data. Anthropometric measurements such as body mass index (BMI), waist circumference, and hip circumference were also recorded.

Venous blood samples were collected under aseptic conditions after an overnight fast of 10 hours. A total of 5 mL of fasting venous blood was drawn from each subject; 2 mL was transferred into a sodium fluoride tube for fasting plasma glucose estimation, and 3 mL was placed in a clot activator tube to obtain serum for the analysis of Cystatin C and insulin. In case of delays in analysis, serum was separated by centrifugation at 3000 rpm for 5 minutes and stored in eppendorf tubes at -20°C until testing. Within 5 minutes of the initial blood draw, subjects were given a 75g glucose load dissolved in 300 mL of water. Two hours later, an additional 2 mL of venous blood was collected into a sodium fluoride tube to measure the post-load glucose level for oral glucose tolerance test (OGTT) interpretation.

Biochemical analyses were performed in BIRDEM general hospital. Fasting and postprandial blood glucose levels were measured using the enzymatic colorimetric method with the Beckman Coulter AU-680 auto analyzer. Serum Cystatin C and insulin levels were quantified using ELISA techniques[28].

Universal precautions were followed during specimen collection and laboratory handling. Personal protective equipment (PPE), including gloves, lab coats, and eye protection, was used. All disposable materials in contact with biological specimens were discarded into biohazard containers, while non-disposable items were properly disinfected. Hand hygiene was maintained before and after all procedures.

Data collected were systematically recorded on a predesigned data collection sheet and analysed using SPSS version 26. Strict ethical standards were maintained during the study. Confidentiality was ensured, and participants retained the right to withdraw at any stage without consequence. No sample collected was used for purposes beyond this research. All patient data were handled with utmost care to protect their privacy and well-being.

Results

A total of 160 pregnant women were enrolled, with equal numbers in the GDM group and the control group. The two groups were comparable in age and gestational age, but BMI differed significantly. Women with GDM had a higher mean BMI than controls (28.97 ± 3.75 vs 27.97 ± 4.04 kg/m², p = 0.002), while age and gestational age showed no meaningful variation between groups (table I).

The mean HOMA-IR was substantially elevated in the GDM group (5.87 ± 3.94) compared with controls (3.99 ± 1.78), and this difference was highly significant (p < 0.001). The serum Cystatin C level was

Table I: Baseline characteristics of the study participants (N=160)

Variable (Mean ± SD)	Control (n=80)	Case (n=80)	p value
Age (years)	29.05 ± 4.67	29.49 ± 4.59	0.54
BMI (kg/m^2)	27.97 ± 4.04	28.97 ± 3.75	0.002
Gestational age (week)	24.85±1.89	24.86 2.09	0.96
HOMA-IR	3.99 ± 1.78	5.87 ± 3.94	<0.001
Serum Cystatin C (mg/L)	0.734 ± 0.11	0.932 ± 0.23	<0.001

Table II: Association of gestational diabetes mellitus (GDM) with serum Cystatin C (N=160)

Serum Cystatin C(mg/L)	GDM (n=80)	Control (n=80)	Total	Odds Ratio (95% CI)	p-value
High (>0.80)	60	20	80	9.0 (5.0–16.3)	<0.001
Low (≤0.80)	20	60	80		

significantly higher in GDM patient than control (0.932 ± 0.23 mg/L vs 0.734 ± 0.11 mg/L; p < 0.001) (table-I). These findings indicate a consistent shift toward insulin resistance and impaired glycaemic regulation in the GDM group.

The participant with GDM was far more likely to have elevated serum Cystatin C levels. Three-quarters of the GDM group (60 out of 80) had values above 0.80 mg/L, compared with only one-quarter of the controls (20 out of 80). There was a strong association between raised Cystatin C (>0.8 mg/dl) and GDM (OR 9.0; 95% CI 5.0–16.3, p<0.001) (table-II).

Correlation analysis demonstrated that serum Cystatin C had a positive linear correlation with several glycaemic indices. Cystatin C correlated significantly with fasting blood glucose (r = 0.321, p < 0.05), 2-hour post-load glucose (r = 0.303, p < 0.05), and HOMA-IR (r = 0.323, p < 0.05). Correlations with serum insulin (r = 0.121) and BMI (r = 0.150) were positive but not statistically significant(Table III). These findings suggest that Cystatin C is more closely linked to glycaemic dysregulation and insulin resistance than to anthropometric or insulin level variations.

Table III: Pearson's correlation coefficients between serum Cystatin C and metabolic variables (N=160)

Metabolic Variables	Correlation Coefficient (r)	p-value
Fasting plasma glucose	0.321	<0.05
2-hour post-load plasma glucose	0.303	<0.05
HOMA-IR	0.323	<0.05
Serum insulin	0.121	>0.05
BMI	0.150	>0.05

Discussion

The present study investigated the association of serum Cystatin C with glycaemic parameters and insulin resistance among pregnant women with and without Gestational Diabetes Mellitus (GDM). The findings demonstrate a significant elevation of serum Cystatin C in women diagnosed with GDM compared to healthy pregnant controls. Additionally, Cystatin C was positively correlated with fasting blood glucose and 2-hour post-load glucose values, highlighting its potential role as a novel biomarker in assessing glycaemic status during pregnancy.

There was no significant difference in mean age or gestational age between the case and control groups, ensuring homogeneity of the study population. However, the Body Mass Index (BMI) was significantly higher in the GDM group. This finding aligns with the established understanding that increased BMI is a well-recognized risk factor for GDM, as previously reported by another study[29] and other studies indicating that maternal adiposity contributes to heightened insulin resistance and glucose intolerance during pregnancy.

In terms of glycaemic indices, both fasting plasma glucose and 2-hour post load plasma glucose values were significantly elevated in the GDM group, as expected based on diagnostic criteria. These findings are consistent with those reported by other study[30] and reaffirm the pathophysiological basis of GDM, characterized by impaired glucose regulation due to progressive insulin resistance.

Although serum insulin levels were higher among cases, the difference did not reach statistical significance. Nonetheless, a significant increase in HOMA-IR values was observed in the GDM group, suggesting a greater degree of insulin resistance. This observation is in concordance with the work of another study[31], who documented elevated insulin resistance indices among women with GDM compared to normoglycemic pregnant women.

The most notable finding of this study was the significantly elevated serum Cystatin C level in the GDM group. Traditionally recognized as a marker of renal function, recent evidence has suggested its involvement in metabolic dysregulation. The observed

increase in serum Cystatin C among GDM participants supports previous research[32-34], who reported elevated levels of Cystatin C in patients with type 2 diabetes mellitus and insulin resistance. Similarly, another study[33] found serum Cystatin C to be positively associated with multiple components of the metabolic syndrome, including hyperglycaemia and insulin resistance.

The findings of this study indicate that serum Cystatin C is significantly associated with glycaemic parameters in pregnant women and may serve as a promising biomarker for identifying metabolic alterations in GDM. These results contribute to the growing body of evidence supporting the broader metabolic implications of Cystatin C and underscore its potential utility in the early detection and monitoring of gestational diabetes. Further prospective and mechanistic studies are warranted to validate these findings and explore the clinical applicability of Cystatin C in pregnancy-related metabolic disorders.

Conclusions

High serum Cystatin C found to be associated with GDM showing significant positive correlation with glycaemic parameters and insulin resistance. Pregnant women with high serum Cystatin C were at higher risk to develop GDM, suggesting the potential role of serum Cystatin C as a biomarker for early detection of GDM. Large scale prospective study is required to establish Cystatin C as a predictor of GDM.

Conflict of Interest: There are no conflicts of interest.

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