OPEN ACCESS

Scholars International Journal of Obstetrics and Gynecology

Abbreviated Key Title: Sch Int J Obstet Gynec
ISSN 2616-8235 (Print) | ISSN 2617-3492 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Investigation on the Association of Maternal Serum Visfatin Concentration with Gestational Diabetes Mellitus

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DOI: https://doi.org/10.36348/sijog.2024.v07i10.007 | **Received:** 18.09.2024 | **Accepted:** 25.10.2024 | **Published:** 30.10.2024

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Abstract

***Introduction*:** Gestational diabetes mellitus (GDM) is a common pregnancy complication that can have adverse effects on both the mother and the child. Visfatin, an adipokine, has been suggested to play a role in the pathogenesis of GDM. Still, the association between maternal serum visfatin concentration and GDM remains unclear, particularly in the Bangladeshi female population. This study investigated the association between maternal serum visfatin concentration and GDM in the Bangladeshi female population. ***Methods*:** A total of 69 patients participated in this study, including 34 patients with gestational diabetes mellitus (GDM, cases) and 35 patients without GDM (non-GDM, controls). Maternal age, gravida, pre-pregnancy BMI, family history of diabetes, fasting glucose, fasting insulin, HOMA-IR, and lipid profile were assessed. Serum visfatin concentrations were measured and compared between the two groups. ***Results*:** The GDM group had significantly lower serum visfatin concentrations compared to the non-GDM group (0.72±0.38 ng/ml vs 1.12±0.7 ng/ml, $p<0.001$). The Mean±SD of fasting glucose, fasting insulin, and HOMA-IR were 5.83±0.61, 15.77±3.95, and 4.07±1.09 respectively which were significantly higher in the GDM group. In the serum lipid profile study, the Mean±SD value of TG and HDL (3.05±0.82 and 1.63±0.32) in the GDM group were also significantly higher than that of the non-GDM group (2.45±0.88 and 1.49±0.36) ($P < 0.05$). ***Conclusions*:** This study suggests that lower maternal serum visfatin concentrations are associated with GDM and visfatin levels are inversely related to insulin resistance in women with GDM. Consequently, a potential role of visfatin in the pathogenesis and management of GDM is associated with the Bangladeshi population and thus visfatin may represent a novel diagnostic or prognostic biomarker for GDM. Therefore, further research will be valuable to elucidate the underlying mechanisms and explore the clinical implications of these associations.

Keywords: Gestational diabetes mellitus (GDM), Visfatin, Fasting Glucose, Fasting Insulin, HOMA-IR, Triglycerides, TC, HDL, LDL.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as diabetes diagnosed in the 2nd or 3rd trimester of pregnancy that is not pre-existing diabetes [1]. It is the most frequent metabolic disorder occurring during pregnancy, and its prevalence may range from 1 to 16% of all pregnancies [2]. According to estimates from the International Diabetes Federation (IDF), 21.3 million live births to women in 2017 experienced hyperglycemia during pregnancy, with GDM accounting for 86.4% of those instances [3, 4]. South East Asia had the highest prevalence of GDM at 24.2%. Some population-based studies conducted in Bangladesh at different time points have revealed an increasing trend of GDM prevalence

ranging from 6% to 14% based on using different diagnostic criteria [5].

If GDM is left untreated, it carries a risk for both the mother and child and is associated with short-term adverse maternal and neonatal outcomes. Women who experience GDM, and their offspring are also at increased risk of developing type 2 diabetes, cardiovascular disease, and obesity later in life [6].

GDM develops due to both β-cell dysfunction and insulin resistance. Insufficient insulin release from β-cells in response to glucose leads to β-cell dysfunction [7, 8]. Although early diagnosis of GDM is observed, evidence of benefits before 24-28 weeks is limited since insulin resistance peaks in the second trimester, aligning with WHO, IADPSG, and NICE recommending universal OGTT screening then [3, 9-11].

The role of adipokine visfatin in gestational diabetes mellitus (GDM) has been extensively studied. Visfatin, a novel adipokine, plays a significant role in the pathophysiology of GDM. Recent research indicates that visfatin exerts insulin-like effects by binding to the insulin receptor-1 at a distinct site from insulin, influencing blood glucose levels through mechanisms such as reducing glycogenolysis in hepatocytes and stimulating glucose utilization in adipocytes and myocytes. Studies have shown that visfatin secretion by adipocytes is influenced by hyperglycemia, highlighting its importance in glucose regulation [12-14]. https://pubmed.ncbi.nlm.nih.gov/33914332/

Several studies have shown that serum visfatin concentrations are notably higher in women with GDM compared to healthy pregnant women [15, 16]. Additionally, visfatin levels are positively correlated with parameters like ferritin, insulin, age, gravidity, and body mass index in pregnant women with GDM and impaired glucose tolerance [17]. However, some studies have reported no significant differences in visfatin levels between women with GDM and healthy pregnant women [18, 19]. Overall, while the exact relationship between visfatin and GDM may vary across studies, there is evidence supporting a notable association between visfatin levels and gestational diabetes mellitus.

A study explained visfatin can increase β-cell proliferation and prevent β-cell apoptosis by activating intracellular mitogen-activated protein kinase and PI3K-dependent signalling pathways [20]. Another study concluded that inadequate visfatin contributes to the development of GDM through reduced β-cell proliferation [21].

Taking together the current evidence regarding the insulin-like effect of visfatin besides its role in glucose homeostasis at the β-cell level, visfatin is likely to have a protective effect for GDM patients. Therefore, this study aims to find out the correlation between Visfatin and Gestational Diabetes Mellitus.

As only limited data and variability have been observed across different studies, it is necessary to find out the association of maternal serum level of visfatin with GDM in the Bangladeshi population, potentially leading to earlier diagnosis and intervention. Therefore, the findings of the study may help us to prevent hyperglycemia by improving pancreatic beta cell function through exogenous administration of visfatin in the future and thus develop effective treatment and prevention strategies for GDM patients as well as their adverse pregnancy outcomes.

MATERIALS AND METHODS

This was a case-control study conducted at the feto-maternal medicine department of Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh between July 2020 and December 2020. Gestational diabetes mellitus (GDM) and non-GDM pregnant women attending antenatal care at 24-28 weeks of gestation were recruited from both the Feto-maternal Medicine department of BSMMU and the outpatient department (OPD) of BIRDEM General Hospital. A total of 34 women with GDM and 35 age-matched, non-diabetic controls were included in the study. The study followed the principles outlined in the Declaration of Helsinki and ethical approval was obtained from the Institutional Review Board and Ethical Review Committee of the Diabetic Association of Bangladesh. All the participants provided written informed consent.

Participants and Study Population

Pregnant women between 24-28 weeks of gestation attending antenatal check-ups in both the Feto-maternal Medicine department of BSMMU and the OPD of BIRDEM General Hospital were selected. Women with singleton pregnancies were included. Those with a known history of diabetes mellitus (type 1 and type 2), overt diabetes, multiple pregnancies, hypertensive disorders of pregnancy, chronic kidney disease, thyroid disorders, liver disease, recent infections or inflammatory disease, and congenital abnormalities were excluded from the study. A total of 34 women diagnosed with GDM based on WHO 2013 criteria formed the case group. The control group comprised 35 healthy, non-diabetic pregnant women matched for age and body mass index (BMI). Women with one or more of the following glycaemic values during a 75g oral glucose tolerance test were classified as having GDM: fasting plasma glucose ≥5.1-<6.9 mmol/L and/or 2-hour plasma glucose ≥8.5-<11.0 mmol/L.

Sample Size and Eligibility

The sample size was calculated as 58 (29 cases and 29 controls) using G*Power software based on a two-sided independent t-test with an effect size of 0.8, 5% level of significance, and 80% power. To account for potential dropouts, the final sample was increased to 69

(34 cases and 35 controls). The inclusion criteria for cases were pregnant women diagnosed with GDM based on WHO 2013 criteria. Control subjects were non-diabetic pregnant women matched for age (±2 years) and pre-pregnancy BMI (±2 kg/m2). The exclusion criteria included pre-existing diabetes (type 1 and type 2), multiple pregnancies, hypertensive disorders of pregnancy, chronic kidney disease, thyroid disorders, liver disease, recent infections or inflammatory diseases, and congenital abnormalities. Women not willing to provide written informed consent were also excluded.

Data Collection and Measurements

Data on socio-demographic factors, medical, obstetric, and family history was collected using a pre-designed and pre-tested questionnaire. Anthropometric measurements including height, weight, and blood pressure were recorded. Pre-pregnancy weight was self-reported and BMI was calculated as weight in kg/height in m2. After an overnight fast of 8-10 hours, 5 mL of venous blood was collected by trained phlebotomists. The serum was separated and stored at -20°C until analysis. Fasting plasma glucose was measured using the glucose oxidase method. Fasting insulin was estimated using radioimmunoassay. Lipid profiles including total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol were analyzed using enzymatic colorimetric assays. Insulin resistance was calculated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index as follows:

HOMA-IR = Fasting plasma glucose (mmol/L) x Fasting serum insulin (μU/mL)/22.5.

Serum concentrations of visfatin were measured in duplicates using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. The detection limit of the assay was 0.1 ng/mL. According to the World Health Organization (WHO) criteria, gestational diabetes mellitus (GDM) is diagnosed by an oral glucose tolerance test (OGTT) when the fasting blood sugar level is between 5.1 and 6.9 mmol/L or the 2-hour post-load blood sugar level is between 8.5 and 11.0 mmol/L after a 75g glucose load.

Statistical analysis

Data was entered into Epidata software and analyzed using SPSS version 25. Categorical variables were expressed as frequencies and percentages. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation and compared using an independent t-test between the two groups. Non-normally distributed variables were expressed as median (IQR) and compared using the Mann-Whitney U test. Pearson's correlation coefficient was used to assess the relationship between visfatin and variables such as BMI, fasting plasma glucose, serum insulin, HOMA-IR, and lipid profiles. Multiple linear regression analysis was performed to identify independent predictors of serum visfatin levels. Statistical significance was defined as $P < 0.05$. The sample size provided 80% power to detect a minimum difference of 0.8 standard deviations for continuous variables between the two groups at a significance level of 5%. Analysis was conducted on an intention-to-treat basis.

RESULTS

Baseline characteristics of the study population

A total of 69 patients participated in this study, including 34 patients with gestational diabetes mellitus (GDM, cases) and 35 patients without GDM (non-GDM, controls). As shown in Table 1, the mean age was 29.1±4.5 years in the GDM group and 28.5±4.01 years in the non-GDM group. The difference in age between the two groups was not statistically significant (P=0.651). Similarly, the mean pre-pregnancy body mass index (BMI) was 27.63±5.34 kg/m2 in GDM patients and 25.06±3.85 kg/m2 in non-GDM patients, with no statistically significant difference (P=0.052).

Table 1: Age and BMI of the study populations (N=69)

Variables		GDM (case) N=34		non-GDM (control) N=35		P value
		N	%	N	%	
Age(yrs)	≤ 20	0	0.0	1	2.9	
	21 – 35	30	88.2	32	91.4	
	> 35	4	11.8	2	5.7	
	Mean ± SD	29.1	± 4.5	28.5	± 4.01	[a]0.651[NS]
	Range (min, max)	24.6	33.6	24.49	32.51	
Pre-pregnancy BMI (kg/m^2)	Mean ± SD	27.63	± 5.34	25.06	± 3.85	[a]0.052[NS]
	Range (min, max)	22.29	32.97	21.21	28.91	

NS= Not Significant

[a]P value reached from the Mann-Whitney U test

Obstetrical characteristics of the study population

The obstetric characteristics of the two groups are shown in Table 2. Regarding gravidity, most patients were multi-gravid in both the GDM group (67.6%) and non-GDM group (57.1%), with no statistically significant difference in proportions between groups (P=0.364).

Table 2: Distribution of characteristics of study populations

Obstetrical Characteristics	GDM N=34		non-GDM N=35		P value
Gravida	N	%	N	%	
Primi	11	32.3	15	42.8	[b]0.364 NS
Multi	23	67.6	20	57.1	
Family History of Diabetes					
Yes	23	67.6	20	57.1	[b]0.368 NS
No	11	32.3	15	42.8	
Previous History of GDM					
Yes	4	11.7	1	2.8	[b]0.198 NS
No	30	88.2	34	97.1	

NS= Not Significant

[b]P value reached from the Chi-square test

A family history of diabetes was present in 67.6% of GDM patients and 57.1% of non-GDM patients, with no statistically significant difference between groups (P=0.368). Only a small proportion of patients had a history of previous GDM, with 4 patients (11.7%) in the GDM group and 1 patient (2.8%) in the non-GDM group, and this difference was also not statistically significant (P=0.198).

Blood glucose and insulin parameters

The blood glucose and insulin parameters of the two groups are presented in Table 3. Fasting glucose levels were significantly higher in the GDM group (5.83±0.61 mmol/L) compared to the non-GDM group (4.65±0.36 mmol/L), with a highly significant difference between groups (P<0.001).

Table 3: Blood glucose parameters among the study population

Parameters	GDM N=34 Mean±SD	non-GDM N=35 Mean±SD	P value
Fasting Glucose (mmol/L)	5.83±0.61	4.65±0.36	[c]P< 0.001[S]
Fasting Insulin (µU/L)	15.77±3.95	9.98±3.93	[a]P< 0.001[S]
HOMA-IR	4.07±1.09	2.03±0.79	[c]P< 0.001[S]

S = Significant

[a]P value reached from the Mann-Whitney U test

[c]P value reached from the 't' test

Similarly, fasting insulin and HOMA-IR levels were both markedly elevated in GDM patients compared to non-GDM controls. The GDM group had mean fasting insulin of 15.77±3.95 µU/L versus 9.98±3.93 µU/L in the non-GDM group (P<0.001). HOMA-IR was also significantly higher in GDM patients (4.07±1.09) than in non-GDM patients (2.03±0.79) (P<0.001).

Lipid profile of the study population

The lipid profiles of the two study groups are presented in Table 4. Triglyceride levels were significantly higher in the GDM group (3.05±0.82 mmol/L) compared to the non-GDM group (2.45±0.88 mmol/L), with a significant difference between the two groups (P=0.005). High-density lipoprotein (HDL) cholesterol was significantly lower in GDM patients (1.63±0.32 mmol/L) than non-GDM controls (1.49±0.36 mmol/L), with a P value of 0.031.

Table 4: Serum Lipid Profile of the study population

Parameters (mmol/L)	GDM N=34 Mean±SD	non-GDM N=35 Mean±SD	P value
Total Cholesterol (TC)	5.52±0.73	5.01±1.44	[c]P = 0.07[NS]
Triglyceride (TG)	3.05±0.82	2.45±0.88	[c]P = 0.005[S]
HDL	1.63±0.32	1.49±0.36	[a]P = 0.031[S]
LDL	2.44±0.58	2.59±0.86	[a]P = 0.862[NS]

S = Significant

NS = Not Significant

[a]P value reached from the Mann-Whitney U test

[c]P value reached from the 't' testHowever, total cholesterol and low-density lipoprotein (LDL) cholesterol levels did not differ significantly between the GDM (5.52±0.73 mmol/L and 2.44±0.58 mmol/L, respectively) and non-GDM groups (5.01±1.44 mmol/L and 2.59±0.86 mmol/L respectively), with P values of 0.07 and 0.862 respectively.

Serum visfatin levels

The serum visfatin levels of the two groups are shown in Table 5. Visfatin concentration was significantly lower in GDM patients (0.72±0.38 ng/ml) than in non-GDM controls (1.12±0.7 ng/ml), with a highly significant difference between the groups (P<0.001).

Table 5: Association of serum Visfatin concentrations in GDM and non-GDM patients

Parameter	GDM N=34 Mean±SD	non-GDM N=35 Mean±SD	P value
Visfatin (ng/ml)	0.72±0.38	1.12±0.7	[a]P< 0.001[S]

S = Significant

[a]P value reached from the Mann-Whitney U test

Both mean visfatin levels lie within the normal reference range of 0.2-1.5 ng/ml for healthy individuals. However, visfatin was markedly reduced in GDM patients compared to non-GDM pregnant women without diabetes.

Correlation of visfatin with biomarkers

Table 6 shows the correlation analysis of serum visfatin levels with various biomarkers in GDM and non-GDM groups.

In GDM patients, visfatin exhibited negative correlations with fasting glucose, fasting insulin, and HOMA-IR, though the correlations were only statistically significant for fasting insulin (r = -0.349, P=0.043) and HOMA-IR (r = -0.418, P=0.014).

Table 6: Correlation analysis of Visfatin levels with BMI, Fasting Glucose, Fasting Insulin, and HOMA-IR in GDM and non-GDM groups.

Variables	GDM		Non-GDM	
	R	P	R	P
BMI	-.191	.280	-.005	.976
FG	-.212	.228	0.091	.605
FI	-.349	0.043[S]	.191	.271
HOMA-IR	-.418	0.014[S]	.225	.194

S = Correlation is significant at 0.05 level.

Visfatin also correlated negatively with BMI in the GDM group, but it was not statistically significant (r = -0.191, P=0.280). In contrast, visfatin correlated positively with all biomarkers in the non-GDM group, though none of the correlations reached statistical significance, with r values ranging from 0.091 to 0.225.

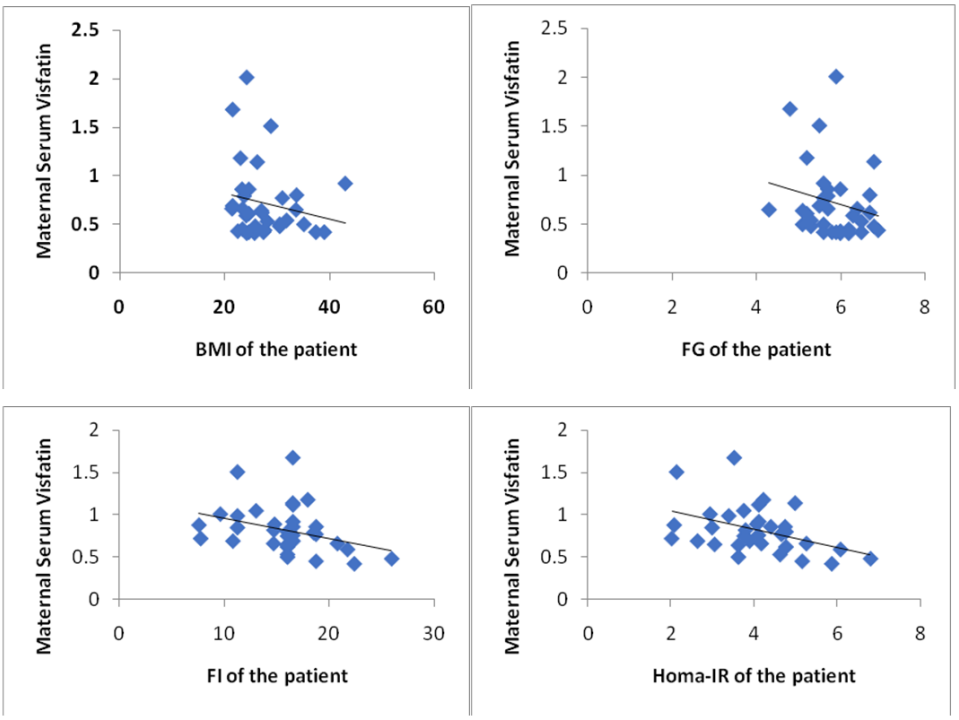

Figure 1: Represents negative correlation between Visfatin with BMI and Blood glucose parameters, e.g., FG, FI, HOMA-IR in the GDM group (r = -.191, r = -.212, r = -.349 and r = -.418 respectively)

Figure 1 graphically depicts the significant negative correlations between visfatin and biomarkers like fasting insulin and HOMA-IR in GDM patients. Figure 2 shows the positive correlations between visfatin and most of the biomarkers in non-GDM controls.

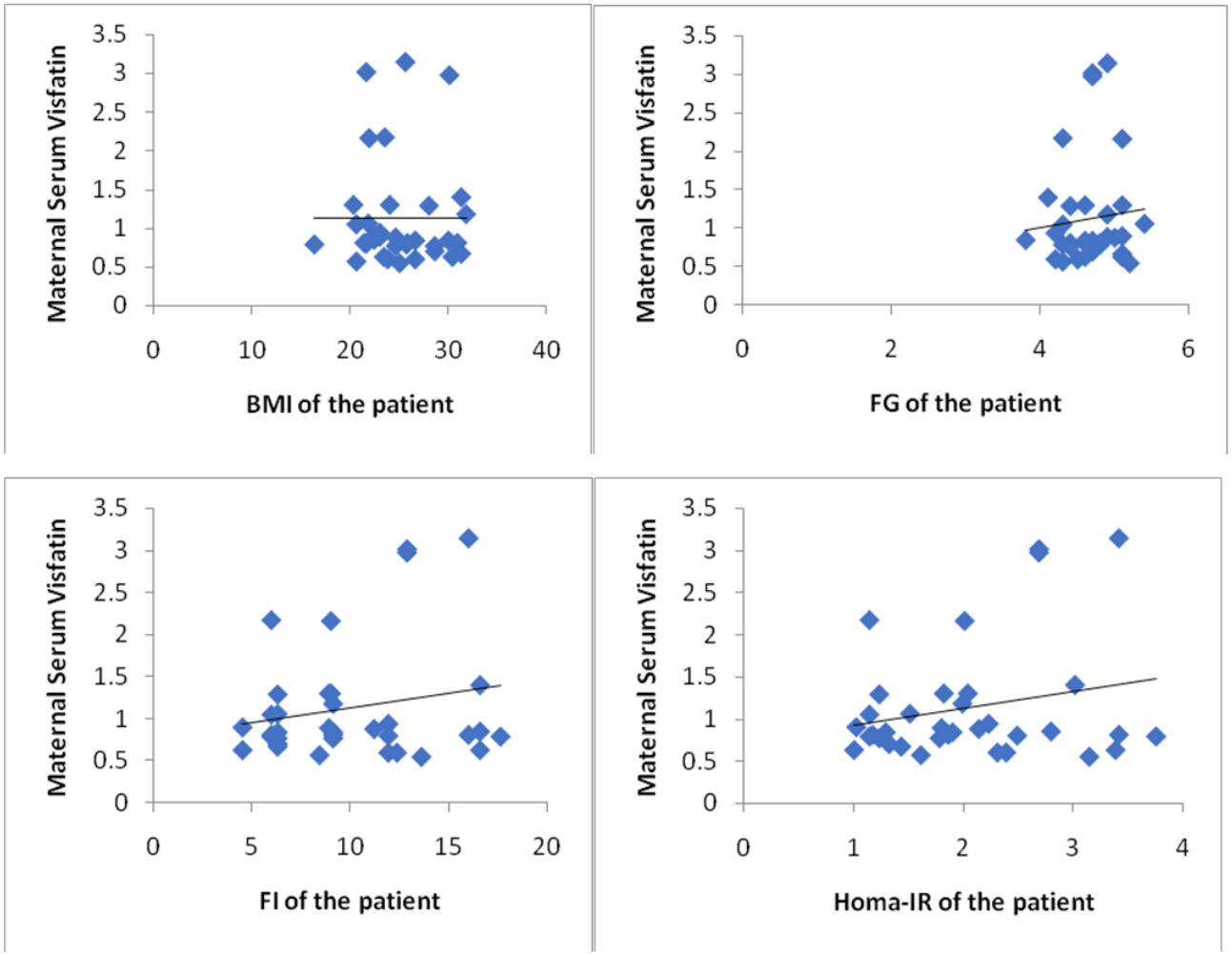

Figure 2: Shows the correlation between maternal serum visfatin with BMI, FG, FI, and HOMA-IR in the non-GDM group. A negative correlation was observed with BMI (r = -.005), and a positive correlation was observed with FG, FI, and HOMA-IR (r = 0.091, r = .191, r = .225 respectively)

Correlation of visfatin with lipid profile

Table 7 evaluates the correlation between serum visfatin levels and lipid profile parameters in both study groups. In GDM patients, visfatin showed positive correlations with total cholesterol (r = 0.106) and HDL cholesterol (r = 0.275) and negative correlations with triglycerides (r = -0.073) and LDL cholesterol (r = -0.128). However, none of these correlations were statistically significant.

Table 7: Correlation of Visfatin with Lipid profile among the participants

Variables	GDM		Non-GDM	
	R	P	R	P
TC	.106	.551	0.039	.825
TG	-0.073	.683	.145	.412
HDL	.275	.115	0.012	.945
LDL	-.128	.472	-0.023	.895

In non-GDM controls, visfatin correlated positively with total cholesterol (r = 0.039), triglycerides (r = 0.145), and HDL cholesterol (r = 0.012) and negatively with LDL cholesterol (r = -0.023). As with the GDM group, these correlations were not statistically significant.

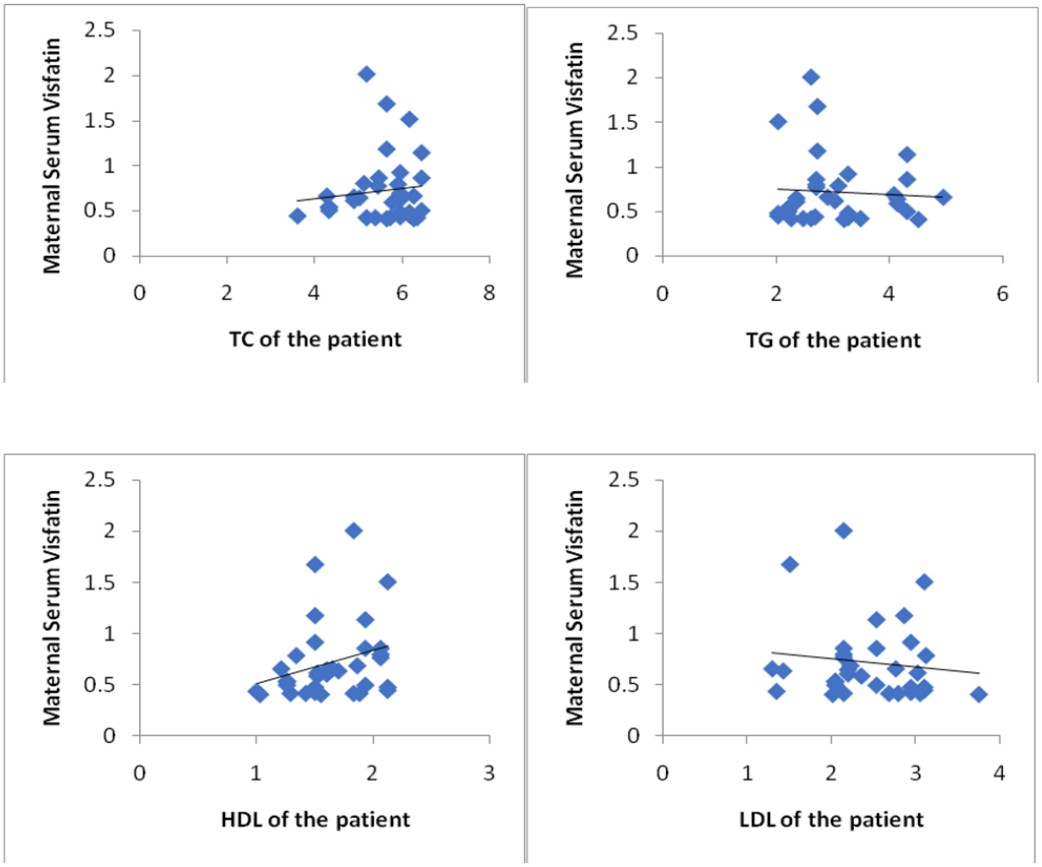

Figure 3: Represents a positive correlation of visfatin with TC and HDL (r = .106, r = .275) and a negative correlation of visfatin with TG and LDL (r = -0.073 and r = -.128) in the GDM group

Figure 3 depicts the positive and negative correlations between visfatin and components of lipid profiles in GDM patients. Figure 4 shows a similar trend of correlations in the non-GDM group.

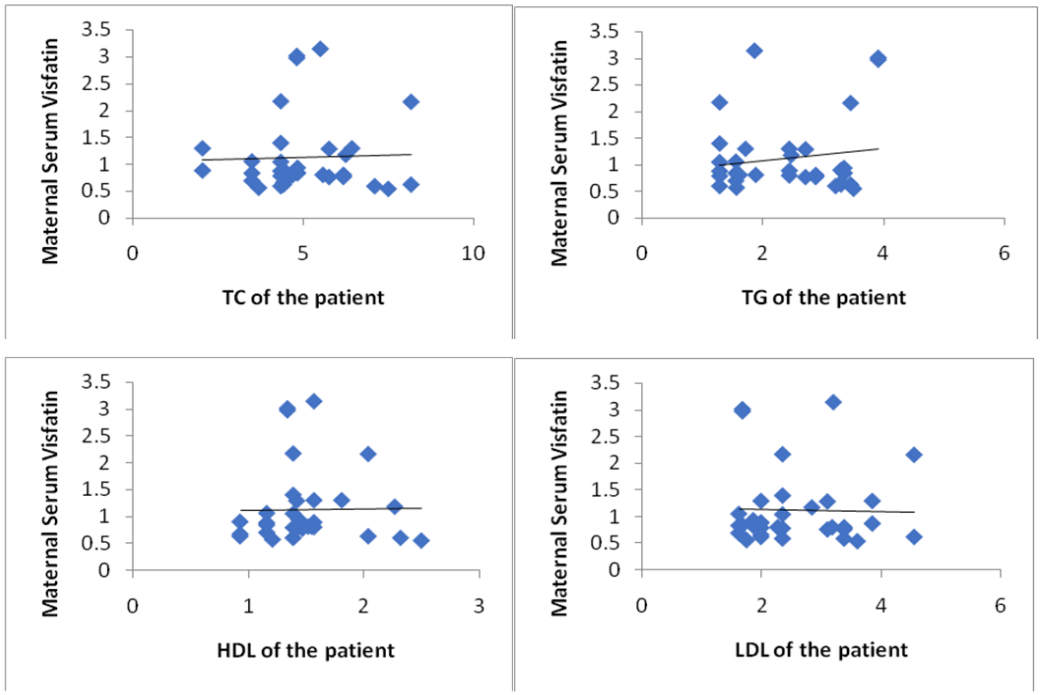

Figure 4: Shows a positive correlation of Visfatin, TC, TG, and HDL (r = 0.039, r = .145, and r = 0.012 respectively) and a negative correlation of visfatin with LDL (r = -0.023) in the non-GDM group

DISCUSSION

Traditionally, gestational diabetes mellitus (GDM) refers to a problem with glucose tolerance that immediately appears during pregnancy [22, 23]. The most common condition affecting pregnant women is gestational diabetes mellitus (GDM), which can impact up to 15%–25% of pregnancies globally. GDM is linked to several short- and long-term issues, such as type 2 diabetes, hyperglycemia, pre-eclampsia, macrosomia, etc. [24]. Therefore, understanding the pathophysiological mechanisms underlying the development of GDM is critical for developing effective prevention and treatment strategies.

Nicotinamide phosphoribosyltransferase, or visfatin, is an adipokine that is mostly released by visceral adipose tissue. This pleiotropic molecule has been implicated in the regulation of glucose and lipid metabolism, as well as insulin sensitivity [25, 26]. However, the relationship between visfatin and GDM remains incompletely characterized.

This study included 69 pregnant women attending tertiary care centers in Dhaka, Bangladesh, 34 of whom were diagnosed with GDM and 35 age- and BMI-matched healthy controls. No significant differences were observed between the groups in terms of maternal age, gravidity, history of prior GDM, or family history of diabetes.

Consistent with the diagnosis of GDM, the GDM group exhibited significantly higher fasting glucose, fasting insulin, and HOMA-IR, a surrogate marker of insulin resistance, compared to controls [27]. Notably, serum visfatin levels were significantly lower in the GDM group compared to healthy pregnant women [(0.72 ± 0.38 ng/mL) vs. (1.12 ± 0.7 ng/mL), $p<0.001$].

A study showed that a family history of diabetes in first-degree relatives was a significant factor associated with GDM in Chinese women [28]. In our study, we found no significant differences in maternal age, gravidity, previous history of GDM, and family history of diabetes between the GDM and non-GDM groups. The mean age was 29.1±4.5 years in the GDM group and 28.5±4.01 years in the non-GDM group, similar to a previous study [29]. On the other hand, no significant difference was found in pre-pregnancy BMI between the GDM (27.63±5.34 kg/m2) and non-GDM (25.06±3.85 kg/m2) groups, which is also consistent with prior findings [29].

Though not statistically significant, family history of diabetes in first-degree relatives was found higher in the GDM group (67.9%) compared to the non-GDM group (57%) [2], [28]. We also found fasting glucose, fasting insulin, and HOMA-IR were significantly higher in the GDM group compared to the non-GDM group, similar to previous reports [30, 31].

Serum visfatin concentration was observed significantly lower in the GDM group (0.72±0.38 ng/ml) compared to the non-GDM group (1.12±0.7 ng/ml) ($P<0.001$), consistent with some studies [18, 30, 32-34]. However, not all studies reported a similar trend [29, 35-37].

In the GDM group, visfatin showed a significant negative correlation with fasting insulin and HOMA-IR which is similar to the previous studies [18, 38, 39], but not in the non-GDM group.

The GDM group had significantly higher triglycerides and HDL-cholesterol compared to the non-GDM group, which is also supported by previous studies [7, 40], but no differences were observed in total cholesterol and LDL-cholesterol.

The present study provides novel insights into the potential role of adipokine visfatin in the pathogenesis of GDM. The finding of significantly lower circulating visfatin concentrations in GDM patients compared to healthy pregnant women is particularly noteworthy, as it suggests visfatin may be an important metabolic regulator involved in the dysregulation of glucose homeostasis characteristic of this condition.

Visfatin has been shown to possess insulin-mimetic properties, enhancing glucose uptake and utilization in peripheral tissues [41, 42]. The observed inverse correlation between visfatin and markers of insulin resistance, such as fasting insulin and HOMA-IR, in the GDM group further supports a potential mechanistic link between visfatin deficiency and the development of glucose intolerance during pregnancy.

From a clinical perspective, these results raise the intriguing possibility that visfatin may represent a novel diagnostic or prognostic biomarker for GDM. Moreover, therapies aimed at restoring visfatin levels or augmenting its insulin-sensitizing actions could offer promising avenues for the prevention or management of this increasingly prevalent gestational condition.

Therefore, despite the relatively small sample size, this study was strengthened by the close matching of control subjects to those diagnosed with GDM on key confounding variables, such as age and pre-pregnancy BMI.

The findings of this study warrant further investigation to elucidate the precise role of visfatin in the pathophysiology of GDM. Longitudinal studies tracking visfatin levels throughout pregnancy, from pre-conception to the postpartum period, would provide valuable insights into the temporal dynamics of this adipokine in the context of the progressive insulin resistance that characterizes gestational diabetes.

CONCLUSION

Gestational diabetes mellitus (GDM) is a serious pregnancy complication that can have lasting effects on the health of both the mother and child, particularly in the Bangladeshi population, where the burden of GDM is high. In this study, we found that lower maternal serum visfatin concentrations are associated with GDM in pregnant women, and visfatin levels are inversely related to insulin resistance in women with GDM. These findings suggest a potential role of visfatin in the pathogenesis and management of GDM in the Bangladeshi population, and therefore, more research will be necessary to explain the underlying processes and explore the clinical implications of these associations.

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