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Original Research Article

Association of maternal serum total homocysteine level with gestational diabetes mellitus

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is diabetes first diagnosed during pregnancy, affecting a significant proportion of pregnancies worldwide. This study was conducted to determine the association between maternal serum total homocysteine levels and GDM. The aim of the study was to evaluate the association between maternal serum total homocysteine levels and the occurrence of gestational diabetes mellitus.
Methods: This case-control study was conducted in the Department of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh, from October 2023 to March 2025, including 36 pregnant women with GDM and 36 matched controls. Demographic, obstetric, and biochemical data, including serum total homocysteine (Hcy) levels measured by ELISA, were collected, and associations with blood glucose were analyzed using SPSS 27.0; GDM was diagnosed per WHO (2013) criteria and elevated Hcy defined as ≥6.38 µmol/l.
Results: Among 72 pregnant women, mean serum total homocysteine was higher in GDM cases than controls (9±3.5 vs. 6.7±3.7 µmol/l, p=0.008). Women with homocysteine ≥6.38 µmol/L had 4.55 times higher odds of GDM (95% CI: 1.69-12.25, p=0.003). Homocysteine levels correlated positively with fasting blood sugar (r=0.543, p<0.001) and 2-hour post-75g glucose (r=0.388, p=0.001).
Conclusions: This study establishes that elevated maternal serum total homocysteine levels are associated with gestational diabetes mellitus and may serve as a potential biomarker for GDM risk.

Keywords: Homocysteine, Gestational Diabetes, Pregnancy

INTRODUCTION

Gestational diabetes mellitus (GDM) is diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation.[1] Screening for GDM is a standard antenatal checkup practice, although only a minority of expectant mothers notice symptoms.[2] Based on WHO criteria, approximately 16.9% of pregnancies globally experience hyperglycemia, accounting for 21.4 million out of 127.1 million live births, with 75-90% of these cases likely due to GDM.[3] The prevalence of GDM varies across regions, affecting 3-5% of pregnant women in the United States, 3.8-21% in India depending on diagnostic methods, and 9-10% in Bangladesh (13% according to ADA criteria.[4,5] Therefore, understanding the pathogenesis of GDM, identifying risk

factors, and implementing appropriate prevention and treatment strategies is crucial.[6]

During a healthy pregnancy, physiological changes occur to meet the growing fetus's needs. In early pregnancy, insulin sensitivity increases, promoting glucose uptake into fat stores. As pregnancy progresses, placental hormones including estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone induce insulin resistance.[7] This results in a mild rise in blood glucose, facilitating fetal growth, while endogenous glucose production and fat breakdown further increase glucose and free fatty acid concentrations.[8,9] Pregnant women typically compensate through pancreatic hypertrophy, hyperplasia, and increased insulin secretion. Maternal insulin sensitivity returns to pre-pregnancy levels after delivery, highlighting the role of placental hormones. However, insufficient pancreatic compensation leads to GDM, characterized by beta-cell dysfunction, chronic insulin resistance, neurohormonal dysregulation, and involvement of leptin, adiponectin, adipose tissue inflammation, hepatic glucose overproduction, gut microbiome changes, oxidative stress, homocysteine, and placental transport.[10,11]

Homocysteine is formed during methionine metabolism and metabolized via re-methylation or trans-sulphuration. Re-methylation depends on methionine synthase (MS) with vitamin B12 as a cofactor and methyltetrahydrofolate (methylTHF) as a substrate, indirectly regulated by methylenetetrahydrofolate reductase (MTHFR). Disruptions in homocysteine metabolism, due to cofactor deficiency or genetic enzyme defects, increase plasma homocysteine levels. Elevated homocysteine promotes oxidative stress and inflammatory cytokines, impairing insulin signaling, and damages the endothelium, reducing nitric oxide (NO) availability. Since NO is involved in insulin-mediated glucose uptake, this may contribute to insulin resistance. Homocysteine also affects methylation reactions, potentially altering gene expression and insulin receptor function.

Serum homocysteine levels are normally reduced during pregnancy due to physiological adaptations, increased estrogen, hemodilution, or maternal-fetal methionine demand.[12] However, elevated homocysteine has been identified as an independent risk factor for vascular complications in diabetes and is associated with insulin resistance, although some studies report a negative relationship.[13-15]

Therefore, this study was conducted to determine the association between maternal serum total homocysteine levels and gestational diabetes mellitus.

METHODS

This case-control study was conducted in the Department of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh, over an 18-month period from October 2023 to March 2025, following approval from the Institutional Review Board (IRB). A total of 72 pregnant women were included in the study 36 diagnosed with gestational diabetes mellitus (GDM) and 36 age- and gestational age-matched pregnant women without GDM selected according to specific inclusion and exclusion criteria to evaluate the association between maternal serum total homocysteine levels and GDM.

Inclusion criteria

Cases

Diagnosed singleton pregnant women with gestational diabetes mellitus (GDM), confirmed by oral glucose tolerance test (OGTT); maternal age between 18 and 35 years; gestational age between 24 and 40 weeks; and provision of written informed consent.

Controls

Normal pregnant women without GDM, confirmed by OGTT; maternal age between 18 and 35 years; gestational age between 24 and 40 weeks; and provision of written informed consent.

Exclusion criteria

Participants were excluded from the study if they had diabetes in pregnancy (DIP); a previous history of gestational diabetes mellitus; chronic renal disease, thyroid disorder, chronic hypertension, or preeclampsia; multiple pregnancies; or were using medications known to affect glucose metabolism, such as steroids, thiazide diuretics, or beta-mimetics.

Data collection and analysis

Data on demographic, obstetric, and biochemical variables including age, education, occupation, income, gravida, gestational age, and serum total homocysteine (Hcy) level were collected using a pretested semi-structured questionnaire after obtaining written informed consent. For biochemical analysis, 3 ml of venous blood was drawn under aseptic conditions, promptly centrifuged, and analyzed for serum total homocysteine using an ELISA kit (Bio-Rad Lab, Oslo, Norway). OGTT results were recorded from recent laboratory reports.

Data were analyzed using IBM SPSS Statistics (version 27.0). Descriptive statistics were expressed as mean ± standard deviation (SD) or percentages. Inferential analyses included independent sample t-tests, chi-square tests, logistic regression, and Pearson's correlation to assess associations between serum homocysteine and blood glucose levels. A p value <0.05 was considered statistically significant.

Ethical considerations

Ethical approval was obtained from the Institutional Review Board of the Institute of Child and Mother Health (ICMH). Confidentiality, voluntary participation, and the right to withdraw at any stage were ensured.

Operational definitions

Gestational diabetes mellitus (GDM) was diagnosed according to WHO (2013) criteria: fasting plasma glucose 5.1-6.9 mmol/L and/or 2-hour plasma glucose 8.5-11.0 mmol/L following a 75 g OGTT. Gestational age was calculated from the first day of the last regular menstrual period and expressed in completed weeks. Elevated serum homocysteine was defined as a level ≥ 6.38 µmol/L.

RESULTS

In both the case and control groups, the majority of women were aged between 20 and 30 years (63.9% vs. 69.4%), with a mean age of 27.5±7.5 years in cases and 27.8±8 years in controls. Regarding educational status, most mothers had completed SSC in both groups (63.9%), followed by below SSC (19.4% vs. 16.7%) and HSC or higher (16.7% vs. 19.4%). In the case group, 66.7% of mothers were housewives, 22.2% were students, and 11.1% were working women. In the control group, 72.5% were housewives, 25% were students, and 2.8% were working women. Regarding monthly family income, half of the women in the case group (50%) and 52.8% in the control group reported an income between 10,000 and 25,000 BDT (Table 1).

The distribution of gestational age and gravida did not differ significantly between the groups, with mean gestational age of 30.4±4.2 weeks in cases and 30.8±4.3 weeks in controls, and similar proportions of primigravida and multigravida women in both groups (Table 2).

The mean serum total homocysteine level in the case group was 9±3.5 µmol/l, whereas in the control group it was 6.7±3.7 µmol/l. Serum total homocysteine levels were significantly higher in the case group compared to the control group (p=0.008) (Table 3).

Table 1: Socio-demographic characteristics of study participants (n=72).

Socio-demographic factor		Case (n=36), N (%)	Control (n=36), N (%)	P value
Age group (years)	<20	6 (16.7)	6 (16.7)	0.938
	20–30	23 (63.9)	25 (69.4)	
	>30	7 (19.4%)	5 (13.9)	
	Mean ± SD	27.5±7.5	27.8±8	0.925
Educational status	Below SSC	7 (19.4)	6 (16.7)	1.000
	SSC	23 (63.9)	23 (63.9)	
	HSC and above	6 (16.7)	7 (19.4)	
Occupation	Housewife	24 (66.7)	26 (72.5)	0.526
	Working women	4 (11.1)	1 (2.8)	
	Student	8 (22.2)	9 (25)	
Monthly family income (BDT)	<10,000	10 (26.8)	9 (25)	1.000
	10,000–25,000	18 (50)	19 (52.8)	
	>25,000	8 (22.2)	8 (22.2)	

Table 2: Obstetrical characteristics of study participants (n=72).

Obstetrical characteristic		Case (n=36), N (%)	Control (n=36, N (%)	P value
Gestational age (weeks)	<30	16 (44.4)	18 (50)	0.943
	30-34	16 (44.4)	14 (38.8)	
	35-40	4 (11.2)	4 (11.2)	
	Mean±SD	30.4±4.2	30.8±4.3	0.742
Gravida	Primi	19 (52.8)	16 (44.4)	0.638
	Multi	17 (47.2)	20 (55.6)	

Table 3: Serum total homocysteine levels of study participants (n=72).

	Case (n=36)	Control (n=36)	P value
Serum total homocysteine (µmol/L)	9±3.5	6.7±3.7	0.008

There was a significant difference in elevated serum total homocysteine levels between the case and control groups (p=0.003).

Participants with homocysteine levels ≥6.38 µmol/l had 4.545 times higher odds of developing gestational diabetes mellitus compared to participants with levels <6.38 µmol/l (OR=4.545; 95% CI=1.686-12.251) (Table 4).

Table 4: Odds Ratio and 95% CI for GDM according to maternal serum total homocysteine levels (n=72).

Serum total homocysteine (µmol/L)	Case (n=36), N (%)	Control (n=36), N (%)	Odds Ratio (OR)	95% CI	P value
≥6.38	25 (69.4)	12 (33.3)	4.545	1.686–12.251	0.003
<6.38	11 (30.6)	24 (67.7)			

Table 5: Correlation of maternal serum total homocysteine levels with blood sugar levels of pregnant women (n=72).

Variables	Correlation Coefficient (r)	P value
Serum total homocysteine vs fasting blood sugar	0.543	<0.001
Serum total homocysteine vs 2-hour post-75g glucose blood sugar	0.388	0.001

Maternal serum total homocysteine levels were positively correlated with both fasting blood sugar and 2-hour post-75g glucose blood sugar levels, and these correlations were statistically significant (Table 5).

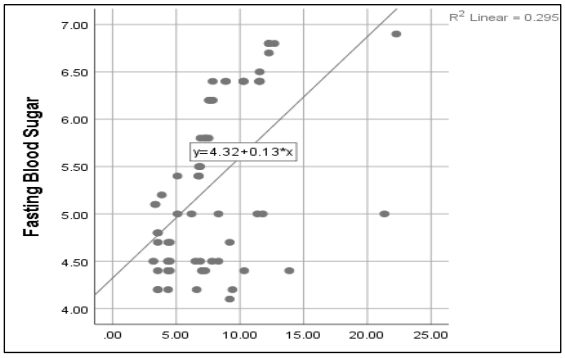

Figure 1: Scatter plot showing correlation between maternal serum total homocysteine levels and fasting blood sugar levels of pregnant women (n=72).

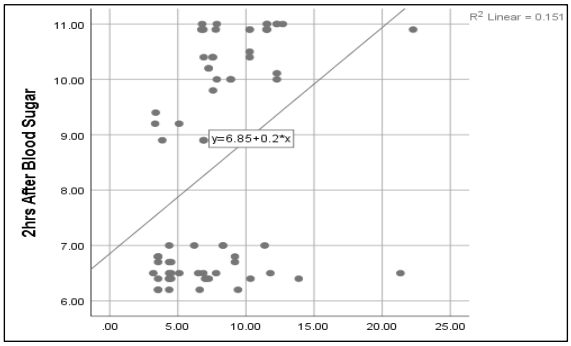

Figure 2: Scatter plot showing correlation between maternal serum total homocysteine levels and 2-hour post-75g glucose blood sugar levels of pregnant women (n=72).

Serum total homocysteine levels were positively correlated with fasting blood sugar levels (r=0.543, p<0.001) (Figure 1).

Serum total homocysteine levels were positively correlated with 2-hour post-75g glucose blood sugar levels (r=0.388, p=0.001) (Figure 2).

DISCUSSION

Gestational diabetes mellitus (GDM) is a complex condition characterized by glucose intolerance first identified during pregnancy.[16] It represents a significant public health concern due to its short- and long-term implications for both maternal and fetal health. GDM arises from a combination of hormonal, metabolic, and genetic factors that disrupt normal glucose homeostasis. The second and third trimesters are particularly critical, as increased insulin resistance driven by placental hormones, such as human placental lactogen, peaks during this time.[17] While most women compensate by increasing insulin production, a subset develops GDM due to an inability to adapt.[18] Recent studies have highlighted elevated serum homocysteine levels as a potential independent risk factor for GDM, linking it to adverse maternal and fetal outcomes. Therefore, the present study was conducted to determine the association of maternal serum total homocysteine levels with GDM. A total of 36 pregnant women with GDM (cases) and 36 without GDM (controls) were enrolled.

In the current study, the mean age of participants was 27.5±7.5 years in cases and 27.8±8 years in controls, with the majority aged 20-30 years (63.9% vs. 69.4%). These findings are consistent with Tanzin et al, who also observed most respondents aged 20-30 years (77.3%).[19] Leng et al reported a lower prevalence of GDM among younger women compared to older women.[18] In contrast, Amiri et a found a significant association between

increasing age and GDM (mean age 30.6±5.9 years in cases vs. 24.6±5.1 years in controls).[20] In the present study, no significant age difference was found between groups, likely due to the inclusion criteria for controls, suggesting that age alone may not be the sole determinant of GDM risk but may interact with factors such as BMI, lifestyle, and genetic predisposition.

Educational status, occupational status, and monthly family income were not significantly associated with GDM. Most participants in both groups had SSC-level education (63.9%), were housewives (66.7% vs. 72.5%), and had a monthly family income of 10,000-25,000 BDT (50% vs. 52.8%). These findings align with Leng et al, who emphasized the multifactorial nature of GDM, with socio-economic factors influencing risk indirectly through lifestyle, health behaviours, and access to care.[18] However, other studies have reported lower education and income as significant predictors of GDM.[17] The current study's results highlight the need for further research in diverse populations to clarify these associations.

No significant differences were observed in obstetrical characteristics, including gestational age and gravida, between cases and controls. Although some studies have suggested parity may be associated with GDM, both groups in this study were statistically similar.[20]

Significantly higher serum total homocysteine levels were observed in the case group (9±3.5 µmol/l) compared to controls (6.7±3.7 µmol/l, p=0.008), supporting an association between elevated homocysteine and GDM. This finding is consistent with a meta-analysis by Gong et al, which reported significantly higher homocysteine levels in women with GDM.[2] Similarly, Alatab et al identified hyperhomocysteinemia as a potential marker for insulin resistance and endothelial dysfunction, both of which are critical in GDM pathophysiology.[13]

In the present study, women with serum total homocysteine levels ≥6.38 µmol/l had approximately 4.545 times higher odds of developing GDM compared to those with levels <6.38 µmol/l. Tanzin et al similarly reported higher mean homocysteine levels among GDM cases (6.50±1.72) than controls (5.20±1.87, p=0.001) with a cut-off of 6.38 µmol/l.[19] Guven et al observed elevated homocysteine in GDM (9.0±3.1 µmol/l) compared to glucose-intolerant (8.1±2.5 µmol/l) and normal controls (7.4±1.6 µmol/l, p<0.01).[21] Deng et al reported a 1.79-fold increased GDM risk for homocysteine ≥7.29 µmol/l.[22] Differences in cut-off values may reflect genetic, nutritional, dietary, and environmental variations across populations.

Positive correlations were observed between serum total homocysteine and fasting blood sugar (r=0.543, p<0.001) and 2-hour post-75g glucose levels (r=0.388, p=0.001). This aligns with previous studies, including Nessa et al, who reported a significant positive correlation with fasting glucose (r = +0.600, p<0.001).[23] Other studies (Gong et al; Deng et al; Tanzin et al) have similarly reported positive correlations between maternal homocysteine and blood glucose, suggesting a role for homocysteine in GDM pathophysiology, possibly mediated through oxidative stress and endothelial dysfunction.[2,22,19]

The study had several limitations. The study was conducted at a single center, which may limit the generalizability of the findings. The sample size was relatively small, potentially affecting the statistical power of the results. The absence of randomization in sample selection could introduce selection bias. Potential confounders, such as dietary habits, physical activity, and genetic predispositions, were not accounted for. Follow-up data on maternal and neonatal outcomes were not collected, limiting insights into long-term implications.

CONCLUSION

This study establishes a significant association between elevated serum total homocysteine levels and gestational diabetes mellitus (GDM), suggesting that hyperhomocysteinemia may play a role in the pathophysiology of GDM. Higher serum total homocysteine levels were observed in women with GDM compared to those with normal pregnancies, emphasizing its potential as a biomarker for GDM risk assessment. Additionally, the positive correlation between serum total homocysteine and blood glucose levels highlights its role in glucose dysregulation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. American Diabetes Association Professional Practice Committee, American Diabetes Association Professional Practice Committee: 15. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes-2022. Diabet Care. 2022;45(Supplement_1):S232-43.
2. Gong T, Wang J, Yang M, Shao Y, Liu J, Wu Q, et al. Serum homocysteine level and gestational diabetes mellitus: A meta-analysis. J Diabet Investigat. 2016;7(4):622-8.
3. Jamieson EL, Dimeski G, Flatman R, Hickman PE, Jones GR, Marley JV, et al. Oral glucose tolerance test to diagnose gestational diabetes mellitus: impact of variations in specimen handling. Clin Biochem. 2023;115:33-48.
4. Kumari A, Singh C. A review on gestational diabetes mellitus during pregnancy. J Drug Deliver Therapeut. 2019;9(3-S):1123-5.
5. Jesmin S, Akter S, Akashi H, Al-Mamun A, Rahman MA, Islam MM, et al. Screening for gestational diabetes mellitus and its prevalence in Bangladesh. Diabet Res Clin Pract. 2014;103(1):57-62.

6. Sililas P, Huang L, Thonusin C, Luewan S, Chattipakorn N, Chattipakorn S, et al. Association between gut microbiota and development of gestational diabetes mellitus. Microorgan. 2021;9(8):1686.
7. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview'. J Endocrinol Investigat. 2017;40(9):899-909.
8. Lindsay KL, Hellmuth C, Uhl O, Buss C, Wadhwa PD, Koletzko B, et al. Longitudinal metabolomic profiling of amino acids and lipids across healthy pregnancy. PloS one. 2015;10(12):e0145794.
9. Bonet B, Viana M, Sánchez-Vera I. Intermediary metabolism in pregnancies complicated by gestational diabetes. In: Textbook of Diabetes and Pregnancy. 2nd ed. CRC Press;2008:55-60.
10. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci. 2018;19(11):3342.
11. Zielińska-Maciulewska A, Krętowski A, Szelachowska M. Insulin resistance and adaptation of pancreatic beta cells during pregnancy. Clin Diabetol. 2018;7(5):222-9.
12. Gaiday AN, Tussupkaliyev AB, Bermagambetova SK, Zhumagulova SS, Sarsembayeva LK, Dossimbetova MB, et al. Effect of homocysteine on pregnancy: a systematic review. Chem-biolog Interact. 2018;293:70-6.
13. Alatab S, Fakhrzadeh H, Sharifi F, Mirarefin M, Badamchizadeh Z, Ghaderpanahi M, et al. Correlation of serum homocysteine and previous history of gestational diabetes mellitus. J Diabet Metabol Dis. 2013;12(1):34.
14. Huang T, Ren J, Huang J, Li D. Association of homocysteine with type 2 diabetes: a meta-analysis implementing Mendelian randomization approach. BMC Genom. 2013;14(1):867.
15. Mazza A, Bossone E, Mazza F, Distante A. Reduced serum homocysteine levels in type 2 diabetes. Nutrit Metabol Cardiovas Dis. 2005;15(2):118-24.
16. Persson M, Winkvist A, Mogren I. From population control to health promotion: a qualitative study of midwives' perceptions of their work tasks and professional development in Vietnam. BMC Pregnan Childb. 2015;15.
17. MacNeill S, Dodds L, Hamilton DC, Armson BA, VandenHof M. Rates and risk factors for recurrence of gestational diabetes. Diabet Care. 2001;24(4):659-62.
18. Leng J, Shao P, Zhang C, Tian H, Zhang F, Zhang S, et al. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin, China. PloS one. 2015;10(3):e0121029.
19. Tanzin ST, Rahman MA, Begum K, Choudhury FH, Bushra RT, Akter H. Association of elevated serum homocysteine level in women with gestational diabetes mellitus. Scholars Int J Obstetr Gynecol. 2023;6(5):193-200.
20. Amiri FN, Faramarzi M, Bakhtiari A, Omidvar S. Risk factors for gestational diabetes mellitus: a case-control study. Am J Lifestyle Med. 2018;15(2):184-90.
21. Guven MA, Kilinc M, Batukan C, Ekerbicer HC, Aksu T. Elevated second trimester serum homocysteine levels in women with gestational diabetes mellitus. Arch Gynecol Obstetr. 2006;274(6):333-7.
22. Deng M, Zhou J, Tang Z, Xiang J, Yi J, Peng Y, et al. The correlation between plasma total homocysteine level and gestational diabetes mellitus in a Chinese Han population. Sci Rep. 2020;10(1):18679.
23. Nessa M, Das TR, Jahan E, Khan MM. Association of serum homocysteine with Gestational Diabetes Mellitus (GDM): a case-control study. Bangabandhu Sheikh Mujib Med Coll J. 2024;3(1):32-7.

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