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Original Research Article

Relationship of maternal serum zinc level with gestational diabetes mellitus

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a prevalent pregnancy disease in Bangladesh that poses risks to the health of both mother and fetus. Glycosuria-related nutritional deficiencies are often associated with GDM. Zinc, an essential micronutrient, plays a central role in insulin-mediated glucose metabolism and storage. Because of its importance in insulin-related processes, zinc deficiency is potentially relevant to pregnancy-related carbohydrate intolerance. The aim of this study was to evaluate the relationship of maternal zinc deficiency with gestational diabetes mellitus.
Methods: This case-control study, conducted from October 2020 to September 2022, involved 160 pregnant women aged 18-35 from the Department of Obstetrics and Gynecology, BSMMU, Dhaka. Of these, 80 women diagnosed with GDM (24-40 weeks gestation) and 80 matched healthy controls were included in our study.
Results: The mean (SD) zinc level was much lower in the cases than in the controls (59.60±19.37 µg/dl and 91.84±38.19 µg/dl, respectively; p-value = <0.001). There was a significant negative correlation of serum zinc levels with both FBG (r=-0.406, p<0.001) and 2HABG (r=-0.381, p<0.001). The likelihood of developing gestational diabetes was approximately 4.2 times higher in mothers with low serum zinc (<68 g/dL) than in mothers with zinc levels of 68 g/dL (p<0.001; OR=4.214; 95%- CI=2.158-8.231).
Conclusions: Low maternal serum zinc levels have been found to be associated with gestational diabetes mellitus. Therefore, the serum zinc level can be used as a predictor to determine the risk of developing gestational diabetes mellitus.

Keywords: Gestational diabetes mellitus, Pregnancy, Zinc

INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disorder characterized by glucose intolerance during pregnancy and variable degrees of hyperglycemia in the absence of overt diabetes.[1] The current prevalence ranges from 1.7% to 15.5%, depending on factors such as race, maternal age, and diagnostic criteria.[2] The prevalence has increased substantially over the past two decades. It is crucial to comprehend the pathogenesis, risk factors, and effective prevention and treatment strategies of GDM.[3]

The World Health Organization (WHO) Global Diabetes Report highlights that 75-90% of cases of hyperglycemia during pregnancy are due to GDM.[4] According to conventional diagnostic criteria, the prevalence of GDM in the United States ranges from 5.8% to 9.2%.[5] Asia has an 11.5% pooled prevalence of GDM[6], whereas India has 4.6-14% urban and 1.7-13.2% rural rates.[7] Bangladesh has a 15% GDM prevalence, with 60% of affected women developing permanent diabetes within a decade.[8] In Bangladesh, where access to healthcare and nutritional disparities are associated with women's low social

standing, the problem of undiagnosed GDM cases is of particular concern.[9]

While GDM can affect any pregnant woman, certain maternal factors increase the risk. Factors that cannot be modified include advanced maternal age (≥30 years), family history of type 2 diabetes, and previous history of GDM. Modifiable risk factors include pre-pregnancy obesity (BMI ≥30 kg/m^2), a high-glycemic diet, a sedentary lifestyle, reduced physical activity, increased maternal stress, and disorders associated with insulin resistance (e.g., polycystic ovary syndrome). Obstetric factors such as recurrent abortions, stillbirths, perinatal/neonatal deaths, and previous macrosomic infants (>3.5 kg) also contribute to GDM manifestation.[10]

Screening and diagnosing GDM typically occurs in the late second or early third trimester to maximize detection as pregnancy advances. Two diagnostic approaches are employed: a one-step approach using a 75-g oral glucose tolerance test (OGTT) following an 8-hour overnight fast, or a two-step approach involving a non-fasting 50-g screen and a subsequent 100-g OGTT for positive cases.[11]

The pathophysiology of GDM involves placental hormones, including human placental lactogen, which act as anti-insulin agents and increase insulin resistance and carbohydrate intolerance during pregnancy. β-cell dysfunction and insulin resistance are hallmarks that lead to hyperglycemia. The correlation of GDM with reduced maternal insulin sensitivity and potential nutrient depletion from glycosuria is also noted.[12-14]

Zinc, an essential trace element found in enzymes, performs various biological functions. Zinc requirements increase during pregnancy and lactation.[15] It supports insulin action by regulating tyrosine kinase receptors, insulin storage and secretion. Zinc's antioxidant properties and insulin-related functions can be impaired by deficiency, impairing the insulin response and contributing to oxidative stress, apoptosis and inflammation.[16,17]

Zinc's role in insulin release is important because it forms a complex with insulin in the cells of the pancreas, which is crucial for hormone secretion. It also affects glycogen synthesis by stimulating glycogen synthase kinase 3 (GSK-3) and fork-head box protein O1 (FoxO1). Zinc deficiency can affect thyroid hormones, androgens and growth hormones and impair cell function.[18,19] In particular, previous studies have reported differential serum zinc levels in GDM cases, necessitating the need for further investigation of the association between maternal serum zinc and GDM.[20-23]

The global health importance of GDM lies in the potential complications during pregnancy and childbirth, affecting both maternal and fetal well-being. Untreated GDM can lead to neonatal and obstetric problems such as preterm delivery, prolonged labor, cesarean section, fetal macrosomia, and neonatal complications. In addition, it increases the risk of obesity and diabetes in both the mother and offspring later in life.[24-25]

Given the existing discrepancies in serum zinc levels in GDM cases, this study aims to investigate the association between maternal serum zinc levels and gestational diabetes mellitus. This research has the potential to support preventive measures and alleviate GDM-related maternal and fetal complications.

METHODS

This case-control study was conducted on pregnant women attending the outpatient clinic and enrolled for prenatal care in the Department of Obstetrics and Gynecology and Feto-Maternal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from October 2020 to September 2022. Ethical approval was obtained from the Institution Review Board (IRB) of the BSMMU. A total of 160 patients who agreed to participate in the study were enrolled after meeting the eligibility criteria.

Pregnant women with multifetal gestation, a history of GDM and a diagnosis of chronic kidney disease, liver disease, PCOS, autoimmune disease and thyroid disease were excluded from the study.

Cases (n=80) were pregnant women aged 18 to 35 years of gestational age between 24 and 40 weeks with GDM, and controls (n=80) were healthy pregnant women who 1:1 match on age and duration of conception. GDM cases were confirmed by their oral glucose tolerance (OGTT) reports according to WHO criteria. A thorough clinical examination was performed on all subjects. A separate data collection sheet was used for each study participant. Data on variables of interest were collected from the patients using the semi-structured questionnaire developed for interviews, observations, hematological examinations and from the patient's medical history sheet. Subsequently, 5 ml of venous blood was collected in a red-colored Vacutainer blood collection tube from the antecubital vein of each subject using a standardized phlebotomy procedure. The samples were then sent to the laboratory of the Department of Biochemistry and Molecular Biology of the BSMMU for analysis. Serum zinc concentration was measured with a fully automated Thermo Scientific™ Indiko™ Plus Clinical Chemistry Analyzer (Thermo Scientific, USA) using a colorimetric method. Maternal serum zinc level of 68.0 mcg/dL was considered the cut-off value in determining the risk of developing GDM.

Statistical analysis

Statistical analyses were performed using the Windows-based Statistical Package for Social Sciences (SPSS-27.0). The descriptive statistics include frequency, percentage, and mean (SD). A p-value less than 0.05 was considered statistically significant.

RESULTS

In Table 1, it was shown that the mean maternal age was 29.09±3.91 years in the cases and 27,99±4.04 years in the control group. Two-fifths (40.0%) of the respondents in the control group were urban residents and 71.3% of the cases were rural residents. The frequency distribution of the respondents' occupations showed that among the GDM cases, housewives were more (72.5%) than healthy pregnant women (61.2%). The majority of women in both groups belonged to middle-class social status (case: 65.0% and control: 73.8%). All results on sociodemographic variables were statistically not significant (p => 0.05).

Table 1: Categorization of the study subjects according to socio-demographic characteristics by group (n = 160).

Socio-demographic characteristics	Groups		*P*-value
	Case (n = 80) n (%)	Control (n = 80) n (%)	
Age (in years)			
≤20 years	1 (1.3)	4 (5.0)	[a]0.211[NS]
21-30 years	49 (61.2)	54 (67.5)	
31-35 years	30 (37.5)	22 (27.5)	
Mean±SD	29.09±3.91	27.99±4.04	[b]0.082[NS]
Residence			
Urban	23 (28.8)	32 (40.0)	[c]0.134[NS]
Rural	57 (71.3)	48 (60.0)	
Occupation			
Housewife	58 (72.5)	49 (61.2)	[a]0.364[NS]
Student	7 (8.8)	13 (16.3)	
Government service	11 (13.7)	15 (18.8)	
Garments worker	4 (5.0)	3 (3.7)	
Social status (according to monthly income in Tk.)[#]			
Lower class	20 (25.0)	9 (11.2)	[c]0.067[NS]
Middle class	52 (65.0)	59 (73.8)	
Upper class	8 (10.0)	12 (15.0)	

[a]Fisher's exact [b] Unpaired student's t-test [c] Chi-square test
[NS] = not significant
Parentheses ( ) represent the percentage of the column's total
[#]Low income ≤ 8,585 BDT/month, lower middle income = >8,585-1,04,391 BDT/month, and high income ≥1,04,391 BDT/month (World Bank and UNDP, 2022)

Table 2 shows that three-fifths (60.0%) of the cases were multigravida compared to 51.3% in the control group. The mean gestational age of the case group was 32.59±3.81 weeks compared to 33.16±4.02 weeks of the control group respondents. The majority of participants belonged to the overweight group (case: 70.0% vs. control: 63.8%) with an average BMI of 26.17±1.91 kg/m^2 in the cases compared to 25.80±1.92 kg/m^2 in the control group of the participants.

Table 2: Categorization of the study subjects by group according to obstetric and anthropometric parameters (n=70).

Socio-demographic characteristics	Groups		P-value
	Case (n = 80) n (%)	Control (n = 80) n (%)	
Gravida			
Primigravida	32 (40.0)	39 (48.8)	[c]0.265[NS]
Multigravida	48 (60.0)	41 (51.3)	
Gestational age (in weeks)			
Mean (±SD)	32.59±3.81	33.16±4.02	[b]0.355[NS]
BMI (kg/m^2)			
Normal (18.5-24.9)	23 (28.8)	29 (36.3)	[a]0.389[NS]
Overweight (25.0-29.9)	56 (70.0)	51 (63.8)	
Obese (≥30.0)	1 (1.3)	0 (0.0)	
Mean±SD	26.17±1.91	25.80±1.92	[b]0.229[NS]

[a] Fisher's exact [b]Unpaired student's t-test [c]Chi-square test
[NS] = not significant
Parentheses ( ) represent the percentage of the column's total

The mean (±SD) serum zinc level was substantially lower among the cases (59.60±19.37 µg/dL) compared to controls (91.84±38.19 µg/dL), which was found statistically highly significant (p<0.001) (Table 3).

Table 3: Categorization of the study subjects according to mean maternal plasma zinc level by group (n=160).

Maternal plasma zinc level (µg/dL)	Groups		P-value
	Case (n = 80) (Mean±SD)	Control (n = 80) (Mean±SD)	
Maternal plasma zinc	59.60±19.37	91.84±38.19	b<0.001*

[b]Unpaired t-test.
[*] = significant
Parentheses ( ) represent the percentage of the column's total

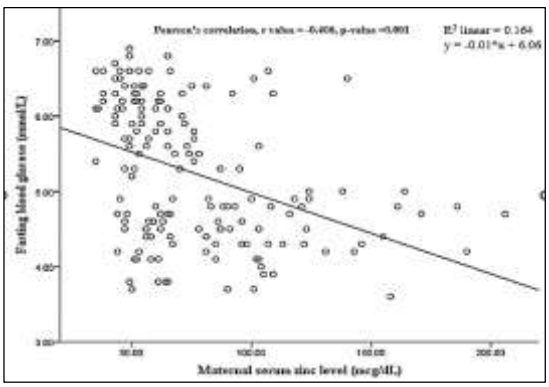

Figure 1: Scatterplot diagram showing the correlation between maternal blood sugar level (FBS) with serum zinc levels in patients with GDM.

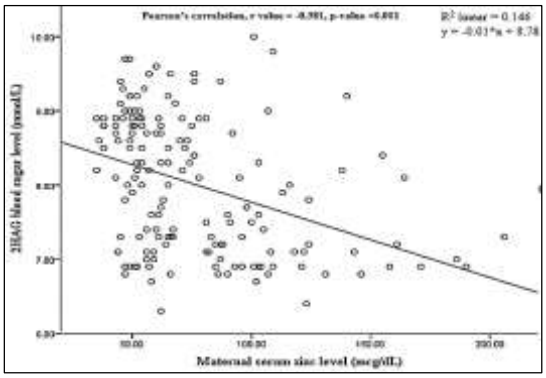

Figure 2: Scatterplot diagram showing the correlation between maternal blood sugar level (2HABG) with serum zinc levels in patients with GDM.

Figure 1 and 2 depicts the significant inverse correlation between maternal serum zinc and fasting blood glucose levels (Pearson's correlation coefficient, r = -0.406, p <0.001) and between maternal serum zinc and glucose levels 2 hours after 75 g glucose (r-value. = -0.381, p-value <0.001).

Respondents with a serum zinc level <68 µg/dL had a 4.2 times greater risk of developing gestational diabetes mellitus than those with a zinc level of 68 µg/dL (OR = 4.214, 95% CI = 2.158-8.231; p-value). = <0.001).

Table 4: Odds ratios (OR) and 95% confidence intervals (CI) for the study subjects according to plasma zinc level in pregnancy (n=160).

Maternal plasma zinc level (µg/dl)	Group		P-value	OR (95% CI)
	Case (n = 80) n (%)	Control (n = 80) n (%)		
<68	59 (73.8)	32 (40.0)	[c]<0.001*	4.214 (2.158-8.231)
≥68	21 (26.3)	48 (60.0)		

[a]Chi-square test was done to measure the level of significance;
* = significant
The figure within parenthesis indicates in percentage.
CI = Confidence Interval

DISCUSSION

Maternal micronutrient deficiencies are a global problem that is particularly pronounced in low- and middle-income countries (LMICs) due to limited access to health care and adequate nutrition. Zinc, an essential trace element, plays a crucial role in glucose uptake, cellular glucose utilization, and reducing insulin resistance. It is essential for embryogenesis, fetal development, and lactation. The aim of this study was to investigate the possible association between maternal serum zinc levels and gestational diabetes mellitus (GDM).

The sociodemographic characteristics of the study participants were examined, with the majority of participants residing in rural areas (case: 71.3% vs. control: 60.0%). Almost three-quarters (72.5%) of the cases and over three-fifths (61.2%) of the participants in the control group were housewives, followed by employees (case: 13.7% and control: 18.8%). Most of the study participants belonged to the lower-middle class social status (case: 65.0% vs. control: 73.8%). No statistically significant differences were observed between age, place of residence, occupation and social status (p>0.05).

These results were consistent with other studies reporting different correlations between sociodemographic factors and GDM due to demographic differences and the diversity of definitions of social status.[26-28]

Gestational age, gravida and body mass index (BMI) were also determined. The majority of the participants were multigravida (case: 60.0% vs. control: 51.3%). The current study observed that the mean (±SD) BMI was slightly higher, 26.17±1.91 kg/m^2 in the case group and 25.80±1.92 kg/m^2 in control patients. Though majorities were found distributed in the overweight group (70.0% cases and 63.8% controls), none of these differences in the distribution of the respondents between the two groups was statistically significant (p>0.05). Akter et al also conducted a cross-sectional study suggesting that multiparity or pregnancy may be a risk factor for metabolic syndromes.[29] Torlonin et al and Yen et al also pointed out a significant association between BMI and GDM, however weight gain during pregnancy was not considered in this study, therefore no significant connection could be established.[30,31]

The results of the present study suggest that serum zinc levels are significantly lower in GDM cases compared to healthy pregnant participants (59.6±19.37 vs. 91.8±38.19 µg/dL). This finding confirms previous research emphasizing the role of zinc in insulin sensitivity, where its deficiency can lead to oxidative stress, apoptosis and inflammation and potentially contribute to GDM development.[14,16,32]

Odds ratio analysis revealed that pregnant women with serum zinc levels below 68 µg/dl had a 4.2-fold greater risk of developing GDM (OR = 4.214; 95% CI = 2.158 8.231). An inverse correlation between maternal and fasting serum zinc levels (r=-0.406, p<0.001) and 2HA75g blood glucose levels (r=-0.381, p<0.001) further supported this observation. These results suggest that decreased serum zinc levels can lead to elevated blood glucose levels (both fasting and 2HA-75 g blood glucose). In addition, the study showed that maternal serum zinc levels can predict a significant fraction of the variance in both fasting and postprandial blood glucose levels. These results support the hypothesis that low serum zinc levels are associated with GDM risk.

The results of this study are consistent with a growing body of evidence. Bo et al have shown that serum zinc and

selenium levels are inversely associated with gestational hyperglycemia and impaired glucose tolerance.[33] Wang et al have shown a decrease in serum Zn levels in pregnant women with GDM compared to normal pregnant women.[34] Similarly, several other studies have also reported lower zinc levels in pregnant diabetics.[35,36]

Several studies have also examined the effects of zinc supplementation on GDM outcomes. A randomized study found that zinc supplementation improved metabolic profiles and reduced fasting plasma glucose and serum insulin levels in GDM patients.[37] In addition, a cohort study in China showed that maternal blood zinc levels are inversely related to birth weight, potentially affecting GDM-related complications.[38]

Therefore, in the current study, all the findings showed the association of low zinc levels among GDM women.

Our study was a single-centre study. Conducting the study at a single institution could limit its external validity to different settings. We took a small sample size due to our short study period. A small sample size limits the study's statistical power and generalizability to larger populations. After evaluating those patients, we did not follow up with them for a long period and do not know other possible interference that may happen in the long term with these patients.

CONCLUSION

The results of this study suggest that low maternal serum zinc level is significantly associated with an increased risk of developing GDM. Therefore, this study concludes that low serum zinc levels can be considered an important risk factor for the development of GDM.

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