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Original Article

Elevated Homocysteine Levels might be the predictor of Gestational Diabetes Mellitus

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ABSTRACT

Objective: *The main goal of this study is to assess the homocysteine levels and its relation with gestational diabetes mellitus in pregnant women.* ***Methods:*** *This case control study was conducted on the pregnant women between 24 weeks to 40 weeks of gestational period attending the inpatients and outpatient department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2011 to June 2013. Pregnant women between 24 weeks to 40 weeks of gestation attending the inpatient and outpatient department of Obstetrics and Gynecology, BSMMU hospital were included in the study.Microsoft Excel and SPSS version 22 used for statistical analysis.* ***Result:*** *The mean levels of homocysteine (Hcy) in Gestational Diabetes Mellitus (GDM) group were significantly higher but folic acid and vit B12 were significantly lower. Hcy levels were decreased in both groups after six weeks folic acid but decrease in Hcy for group 5mg was significantly more than 1mg group.* ***Conclusion:*** *High-dose folic acid can lower Hcy levels more effectively than low-dose folic acid, and it could be a safe, easy, and economical remedy to avoid serious pregnancy problems.*

Keyword: *homocysteine, gestational diabetes mellitus.*

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INTRODUCTION

Homocysteine is a naturally occurring amino acid that has sparked a lot of study interest recently. Hyperhomocysteinemia, or high levels of homocysteine in the blood, has been linked to a variety of venous and arterial vascular diseases. Homocysteine levels

in the blood are an independent risk factor for peripheral vascular disease and coronary artery disease [1].The prevalence of the MTHFR C677-T polymorphism in pregnant women with type 1 diabetes mellitus, as well as the associated morbidity with vascular dysfunction during pregnancy, such as preeclampsia, hypertension, varying degrees of albumin excretion rate and retinopathy, and preterm delivery, were discovered [2]. Folate deficiency has been linked to an increase in homocysteine levels in studies [3].

Diabetes mellitus (DM) is a clinical illness defined by hyperglycemia due to insulin insufficiency, either absolute or relative. Type 2 diabetes is more complicated than type 1 diabetes because it involves a combination of insulin resistance in the liver and muscle, as well as reduced pancreatic b cell activity, resulting in relative insulin insufficiency. Both type 1 and type 2 diabetes are becoming more common. In the year 2000, 171 million individuals were predicted to have diabetes, with this number expected to double by 2030. Diabetes is prevalent in metropolitan areas across the Indian subcontinent, with a frequency of more than 12%. Patients with diabetes who have had it for a long time are at risk for both microvascular and macrovascular problems. Nephropathy, neuropathy, and retinopathy are microvascular problems, while myocardial infarction, stroke, and peripheral arterial disease are macrovascular complications [4].

Homocysteine is a thiol-containing amino acid that is formed as an intermediary in the methionine metabolism [5].Methionine synthase, a vitamin B12-dependent enzyme, uses 5 methyltetrahydrofolate as a carbon donor for folate-dependent homocysteineremethylation (MTRR). The carbon donor for betaine-homocysteine methyltransferase (BHMT) is betaine. As a result of the mutation or insufficient intake of necessary nutrients, high homocysteine levels can lead to thrombophilias and, in certain cases, placental abruption [6].Furthermore, recent studies have suggested that high homocysteine plasma levels may predict the onset of preeclampsia in the early second trimester [7]. Neural tube abnormalities, multiple miscarriages, abruptio placentae, fetal mortality, pre-eclampsia, and IUGR have all been linked to hyperhomocysteinemia during pregnancy. Hyperhomocysteinemia has been linked to microvascular disease of the placenta [8].

Gestational diabetes mellitus develops in susceptible women during pregnancy and usually goes away after the baby is born. In the long run, this disease is linked to type 2 diabetes and hypertension [9]. Women with GDM are seven times more likely than controls to acquire type 2 diabetes 22 to 28 years later, as well as hypertension and hyperlipidemia. GDM also raises the risk of arteriosclerosis and coronary heart disease in patients. Hyperhomocysteinemia has been found in people with type 1 and type 2 diabetes, and it has been linked to atherosclerosis [10].

OBJECTIVE

The main goal of this study is to asses the homocysteine levels and its relation with gestational diabetes mellitus in pregnant women.

METHODS

Types of study: This study was a case control study conducted on pregnant women

Place of study: The study was conducted on the pregnant women between 24 weeks to 40 weeks of gestational period attending the inpatients and outpatient department of

Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Duration of study: This study was conducted from July 2011 to June 2013.

Study population: Pregnant women between 24 weeks to 40 weeks of gestation attending the inpatient and outpatient department of Obstetrics and Gynecology, BSMMU hospital were included in the study.

Inclusion criteria:

- Pregnant women with gestational age between 24 weeks to 40 weeks with GDM.
- Pregnant women with gestational age between 24 weeks to 40 weeks who were glucose tolerant.

Exclusion criteria:

- Pregnant women who had a history of GDM in previous pregnancy.
- Pregnant women with major medical and surgical disorder.
- Patients receiving chemotherapy for malignancy.
- Patients reviving drugs like methotrexate, carbamazepine, phenytoin, nitrous oxide.

Sample size: This study was conducted on 80 patients.

Data collection: A structured questionnaire was used to obtain data from the study population. The data was collected directly by questioning the patients and by physical examination, daily follow up of patients till their discharge and also from clinical research of the patients. The variables studied include the socio-demographic profile, educational status, occupational status, marital history, detailed obstetric history. Informed written consent was taken from all study participants prior to study initiation.

Data analysis: Clean coded data was input into Microsoft Excel and exported to SPSS version 22 for further analysis. The descriptive statistical analysis was described using sentences, graphs, tables, frequencies, percentages, and mean and standard deviation. The frequencies of the variables were used in a descriptive analysis, and the 95 % confidence intervals (CIs) were produced. The statistical analysis was omitted from questionnaires that were incomplete. In multivariable logistic regression, statistically significant was considered at $p < 0.05$.

RESULT

A total of 80 patients were included in this study. Among those 80 patients, 40 women were assigned to non-diabetic group and 40 women were assigned to diabetic group. The mean age of diabetic and non-diabetic group was 30.5±4.2 and 29.05±4.2 years respectively. The women in diabetic group were older than those in non-diabetic group. The BMI of two groups were similar. The mean level of homocysteine, LDL, TG, Cholesterol in diabetic group was higher than non-diabetic group. Details were shown in table 1.

Table 1: Demographic and clinical variables of diabetic and normal groups:

Variables	Diabetic	Non diabetic	p-value
	Means ± SD	Means ± SD	
Age (years)	30.5±4.2	29.05±4.2	0.13
BMI	28.9±3.4	28.53±2.9	0.60
Homocysteine (µmol/L)	8.1±1.3	6.5±1.7	0.00
Serum folate (ng/ml)	6.6±1.1	8.2±3.1	0.00
Vit B12(pg/ml)	239±53.1	330±193.7	0.00

Parity	1.2±1.0	0.7±0.9	0.50
LDL (mg/dl)	106±22	97±26	0.20
HDL (mg/dl)	48.3±15.5	61.2±14	0.00
TG (mg/dl)	259±43	220±93	0.01
Cholesterol (mg/dl)	216.6±29	205±36	0.10
Uric acid	4.6±1.3	3.8±0.74	0.00

In phase I, the level of vitamin B12, serum folate and HDL in diabetic group was lower than non-diabetic group. In diabetic group vitamin B12 was 246±56 pg/ml; serum folate 6.8±0.9 ng/ml and HDL 52.03±12.5 mg/dl. In non-diabetic group vitamin B12 was 250±43 pg/ml; serum folate 8.1±1.4 ng/ml and HDL 55.6±3 mg/dl.

Table 2: Diabetic patients with 1mg folic acid:

Variables	Before treatment	After treatment	p-value
	Means ± SD	Means ± SD	
Homocysteine (µmol/L)	7.6±1.6	6.5±1.4	0.00
Serum folate (ng/ml)	6.8±0.9	8.1±1.4	0.20
Vit B12(pg/ml)	246±56	250±43	0.50
Triglyceride (mg/dl)	249±44.3	240±32.7	0.03
LDL (mg/dl)	108±19	107.5±17	0.80
HDL (mg/dl)	52.03±12.5	55.6±3	0.01
Cholesterol (mg/dl)	201.6±25.3	197.3±18	0.06
Uric acid	5.04±1.24	5.01±1.20	0.70

In both groups, homocysteine levels were lower than they were at the start. But the decrease in homocysteine levels was more in 5mg group than 1mg group. Serum folate was increase in group 5mg. these was no significant changes found for vitamin B12, triglyceride, LDL and uric acid.There was an increase in HDL in group 5mg, before treatment HDL was 50.03±16.5 and after treatment HDL was 59.6±15.1.

Table 3: Diabetic patients with 5mg folic acid:

Variables	Before treatment	After treatment	p-value
	Means ± SD	Means ± SD	
Homocysteine (µmol/L)	7.89±1.8	6.2±1.2	0.00
Serum folate (ng/ml)	6.6±1.4	8.9±1.7	0.01
Vit B12(pg/ml)	236±42.6	240±37	0.75
Triglyceride (mg/dl)	245±47.3	243±51.7	0.81
LDL (mg/dl)	106±20	103.5±18.4	0.50
HDL (mg/dl)	50.03±16.5	59.6±15.1	0.01
Cholesterol (mg/dl)	216.6±29.5	199.3±20.7	0.04
Uric acid	4.04±1.26	4.6±1.14	0.10

DISCUSSION

The mean levels of Hcy and TG, as well as BMI, were greater in the diabetic group than in the control group, whereas the mean levels of vit B12, folic acid, and HDL were significantly lower. In a phase II trial, it was discovered that folic acid administration reduced Hcy levels in both groups, but that the reduction was greater in the 5 mg group, which was also true for an increase in HDL cholesterol. If high Hcy is a risk factor for many pregnancy complications such as recurrent pregnancy loss, abruption, preterm labor, preeclampsia, vascular

thrombotic events, gestational diabetes, diabetes mellitus, and increased diabetes complications and neonatal anomaly, it appears that anything that lowers Hcy levels will help to prevent these complications. However, in our study Hcy levels were reduced with 5mg folic acid more than 1mg.Low HDL levels are a risk factor for cardiovascular disease (CAD), and diabetic people are at a higher risk for CAD. Treatment with 5mg folic acid dramatically raises HDL levels, suggesting that it may help prevent CAD. GDM patients had greater plasma homocysteine levels than normal pregnant women in our study. The suppression of the urea cycle function in normal pregnancy appears to be reflected in reduced ucAA concentrations [11]. When comparing pregnant women to non-pregnant controls, the authors discovered a substantial drop in ucAA levels [12].Another study found that diabetic pregnant women had significantly higher ucAA levels than glucose-intolerant pregnant women and controls [13]. Nonetheless, in the third trimester, when insulin resistance became more apparent, the variations in ucAA values seen in gestational diabetes in the second trimester vanished [9].Other researchers recently attempted to establish whether folate metabolism in pregnant diabetes women differed considerably from that in non-diabetic women, potentially predisposing them to bearing offspring with serious congenital defects, but no changes were found [14].

Data demonstrated that folic acid can lower Hcy levels, and that this action is likely dose dependent, meaning that when a large dose of folic acid was administered, the drop in Hcy was greater [8, 11]. Our findings do, however, support Murphy et al's finding that folic acid intake lowers homocysteine levels[15]. There is evidence that folic acid supplementation can reduce plasma homocysteine levels and vascular events outside of pregnancy [16].

CONCLUSION

However, more large-scale research are needed to see if this little change in homocysteine levels caused by folic acid treatment during pregnancy is useful in preventing unfavorable pregnancy outcomes. To summarize, we were unable to find a study in which a dose of 5 mg folic acid was prescribed to gestational diabetic women at 24-40 weeks for 6 weeks and a comparison of its effect with 1 mg folic acid. As a result, we were unable to compare the results of our study with those of others regarding pregnancy outcome and Hcy levels in two regimens. The small sample size of our study constituted a drawback. A substantial clinical trial with varied doses of folic acid and even different doses of vitamin B should be conducted to assess their effects on Hcy, HDL, LDL, and pregnancy outcomes.

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