Role of Maternal Iron Status in the Pathogenesis Of Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus (GDM) is one of the commonest complications of pregnancy, but its pathophysiology is still not fully understood. Recently attention has been focused on the relation between iron metabolism and glucose intolerance in the genesis of GDM. The present study was conducted to investigate the association of body iron store with various covariates of metabolic syndrome. A total 100 subjects were included in this study: 43 were healthy nondiabetic and nonanemic pregnant women (Control group) and 57 were pregnant women having Diabetes Mellitus (GDM group). Glucose level was measured by using glucose-oxidase method, fasting serum C-peptide by chemiluminescent enzyme immunoassay, Glycosylated hemoglobin (HbA1c) by using a modified high performance liquid chromatography (HPLC) method and insulin sensitivity (HOMA%S) and insulin secretory capacity (HOMA%B) were calculated by Homeostasis Model Assessment. Serum transferrin receptor (sTfR) was measured by Enzyme-Linked Immunosorbent Assay and serum ferritin level was assessed by Microparticle Enzyme Immunoassay. Serum iron concentration was measured by IRN method.

Key words: GDM, Iron overload, Ferritin, Soluble Transferrin Receptor, Anemia in pregnancy, Anemia in pregnancy

Introduction

Pregnancy is a diabetogenic condition1 and abnormalities of carbohydrate metabolism occur frequently during pregnancy. Gestational diabetes mellitus (GDM) is defined as glucose intolerance that has its onset or first recognition during pregnancy. Women with a history of GDM are at significantly increased risk of developing Type 2 diabetes in the future. In majority of GDM patients, glucose regulation will return to normal after delivery. Clinical and historical risk factors are associated with an increased risk for gestational diabetes and those include older maternal age, obesity, a history of diabetes in a first degree relative, a previous pregnancy with gestational diabetes, delivery of an infant with macrosomia and unexplained near term fetal death. Recently attention also has been focused in the relation between iron metabolism and glucose intolerance in the genesis of GDM. There may be some association between iron metabolism and onset of GDM. It has been suggested recently that an elevated ferritin concentration is a part of picture of insulin resistance and that leads to GDM. Another marker of total body iron status is the transferrin receptor (sTfR). Transferrin receptor is a cellular transmembranous protein found especially on cells requir

The age of the study groups were found to be matched (p=0.522). Gestational weeks and parity of the study groups were significantly higher in GDM than Controls (p=0.004 and p=0.015 respectively). HbA1c level (%), M±SD was significantly higher in GDM group (6.09±1.1) as compared to Control among the marker of body iron status hemoglobin level showed no difference between GDM (11±1.25) and Control groups (10.6±0.8), but serum iron concentration [median (range)] was significantly lower in GDM group [6(2-19)] as compared to Control [12(2-36)]. Serum iron was strongly correlated with HOMA%B in univariate Spearman correlation analysis (r =0.347, P=0.008). On multivariate linear regression analysis also found Serum iron associated (p=0.011) with HOMA%B in GDM group.

GDM in Bangladeshi subjects does not seem to be associated with iron deficiency or elevated body iron store. GDM subjects may show lower serum iron, but this is probably related to chronic inflammatory state of diabetes rather than iron deficiency.

The concentration of sTfR is increased in the presence of iron deficiency anemia. The main clinical use of sTfR measurement has been demonstrated in the assessment of erythropoietic activity and functional iron deficiency and in distinguishing the iron deficiency of chronic diseases. It is still controversial whether sTfR can be used as an iron marker in an iron overload condition, because in some pathophysiological states which are related to iron overload its decrease parallel the ferritin concentration. Circulating concentration of sTfR is proportional to cellular expression of the membrane associated TfR. Circulating sTfR are derived by proteolytic cleavage from sTfR expressed on the cell surface. Intracellular iron influences the post-transcriptional regulation of expression of ferritin, the sTfR, and several other genes are important in mammalian iron metabolism. Serum sTfR concentration is closely related to cellular iron demands and, as a consequence, the higher the ferritin levels the lower the sTfR concentration. Iron supplementation during pregnancy increases maternal iron status during pregnancy including hemoglobin, serum iron, MCV, transferrin saturation, and serum ferritin. Iron overload and the associated oxidative stress contribute to the pathogenesis and increase risk of type 2 diabetes and other disorders. Iron overload, the accumulation interferes with the extraction, synthesis and secretion of insulin. However, moderately elevated iron stores also increase the risk of type 2 diabetes.

Rationale

Poor health care infrastructure and widespread public ignorance of nutrition causes a large number of uncontrolled DM with anemia in Bangladesh. Iron is frequently prescribed without knowing its status in the pregnant, hence a probability of getting pregnancy with iron overload in
Bangladesh. In spite of the possibility of a link between iron status and diabetes only few studies (and mostly with insufficient number of subjects) have been conducted on this issue. Its manifestation also depends on racial variation and thus it should be studied in different populations. In western countries, due to better and early management of GDM, it is difficult to design a study to explore the interrelationship of glycemic status and maternal iron stores. Unfortunately, due to poor health care infrastructure and ignorance in our country a large number of uncontrolled diabetes mellitus with anemia is available. On the other hand, there is a chance of getting patients with iron excess because during pregnancy iron is prescribed without knowing iron status. This provides an opportunity to study the correlation between the degree of hyperglycemia and body iron status in pregnant women. Availability of up to date markers of body iron store can add substantial value in such studies. Materials and methods: Study design It was a cross-sectional study.

Subjects A total 100 subjects were included in this study: Among them, 43 were healthy nondiabetic with nonanemic pregnant women (Control group) and 57 were pregnant diabetic (GDM group).

Selection criteria
Inclusion criteria
• Control group: Healthy nondiabetic with nonanemic pregnant women.
• GDM Group: Positive on the basis of a 2 - sample OGTT (fasting and 2 hour after 75 g Oral glucose) following the WHO criteria (1997) as adapted in BIRDEM. GDM Subject also with anemia and non-anemia.

Exclusion criteria
• Diabetic pregnant women with acute or chronic diabetic complications.
• Pregnant subjects with renal disease.
• Pregnancy with acute or chronic medical diseases, connective tissue diseases and chronic hypertension without proteinuria.
• Pregnancy with acute infections.
• Pregnancy with advanced grading of heart disease.

Place and duration of the Study
The study was carried out for a period of 1 year 6 month from June 2006 to December 2007. The subjects were collected from the Department of Gynecology and Obstetrics Out-patient Department of BIRDEM on the basis of availability.

Data Collection instruments
Fasting and 2 hour after (75 gm glucose) blood sample were collected, who satisfied the selection criteria of the study subjects. Detailed sociodemographic data, family history and medical history were recorded on a data sheet appropriately. All interviews were conducted in the hospital. Physical examination was done and anthropometric measurements (height, weight) of each subject were taken and recorded in a pre-designed checklist form. Obstetric examination was performed and recorded for every patient. The data and specimen (blood) were collected on every morning at BMRG, BIRDEM. The subjects were biochemically investigated for glycemtic status (fasting & 2hr ABF glucose and HbA1c), insulinemic status (fasting C-peptide) and body iron status (serum iron, ferritin & transferrin). Glucose level was measured by using glucose-oxidase method (Randox laboratories, UK), fasting serum C-peptide by chemiluminescent enzyme immunoassay (Immulaite, EURO/DPC,UK), HbA1c by using a modified HPLC method (Bio-Rad,USA) and insulin sensitivity (HOMA%S) and insulin secretory capacity (HOMA%B) were calculated by Homeostasis Model Assessment. Serum transferrin receptor (STfR) was measured by Enzyme-Linked Immunosorbent Assay (ELISA), and serum ferritin level was assessed by Microparticle Enzyme Immunoassay (MEIA) technology (Immulaite, EURO/DPC,UK). Serum iron concentration was measured by IRN method (Dade Behring,UK).

Data Processing and analysis
Data were expressed as M±SD for parametric values and median (range) for non-parametric values. Comparison between groups were done using Independent t-test to compare means and Mann-Whitney U test for skewed data. The relationship between serum Iron, hemoglobin, ferritin and serum transferrin receptor with other variables was examined using Pearson’s parametric coefficient correlation (r) analysis. Multiple regression analysis was done to better assess the relationships within the variables and the influencing other variables. A p value of <0.05 was considered as significant. All the statistical analysis were performed with the SPSS data (SPSS Inc, Chicago, IL, USA).

Ethical Aspect
Before participation, informed and written consent was obtained from all subjects. The study was approved by the ethical committee of BIRDEM ACADEMI and was in accordance with the principles of the Declaration of BMRG, BIRDEM.

Results
The age of the study groups were found to be matched (p=0.522). Gestational weeks and parity of the study groups were significantly higher in GDM than Controls (p=0.004 and p=0.015 respectively). HbA1c level (% M±SD) was significantly higher in GDM group (6.09±1.1) as compared to Control (5.8±0.7, P=0.001). Serum insulin level [ng/ml, Median (range)] as assessed by C-peptide, was significantly higher in GDM group [2.5(1-6.6)] compared to Control [1.5(1-3.3), P<0.001], but the insulin secretory capacity (HOMA% B) was not different between the two groups [median (range) 144(102-270) in GDM vs 165(100-281) in Control]. HOMA%S [Median (range)] was significantly lower in GDM group
data are presented as mean±SD; mean were compared using independent sample ‘t’ test and median (range) are presented skewed date and compared using man Whitney U test as a appropriate test, p<0.005 are considered as statistically significant; n= Number of subjects; STfR, Serum Transferrin Receptor.

GDM affects a considerable number of pregnancies and in spite of its well known clinical features the etiopathogenesis of the condition is still poorly understood. Recently the relation between iron metabolism and glucose tolerance has attracted attention and it has been implicated in the genesis of GDM. It has been observed that secondary cause of iron overload such as excessive blood transferrin is associated with glucose intolerance in diabetes. It has also been suggested that elevated ferritin concentration is a part of picture of insulin resistance which leads to GDM. Moreover, the relation between iron metabolism and glucose tolerance has been implicated in the genesis of GDM. It has been observed that secondary cause of iron overload such as excessive blood transferrin is associated with glucose intolerance in diabetes. It has also been suggested that elevated ferritin concentration is a part of picture of insulin resistance which leads to GDM.
GDM in a possible iron deprived situation has also not been properly investigated.

Hemoglobin is a crude but commonly used marker for body iron status and it showed no significant difference in GDM subjects as compared Controls (p=0.085). The normal Hb in GDM was accompanied by a paradoxically low value of serum iron which was highly significant (p<0.001) when compared to control. The reference range for serum iron in Bangladeshi population has not yet been worked out, but in general, the reference values are 6 – 27 µmol/dl. Thus the GDM patients, with a median serum iron of 6 µmol/dl (range 2-19 µmol/dl), shows iron deficiency as measured by this parameter. Serum Iron in diabetic patients has been shown to be marginally lower, but so far it has not been investigated in GDM cases. It is interesting to see that the lower value of this rapidly available pool was not paralleled by any change in serum ferritin or STfR which are better and long-term markers of body iron stores. Ferritin (ng/ml) has found to be 24 (15-59) in Controls and 27 (10-77) in GDM cases. Serum ferritin has been claimed to be a reliable and sensitive parameter for the assessment of iron stores in healthy subjects. Quantitative phlebotomy has shown a close relationship between serum ferritin concentration and mobilizable iron stores, and it has been demonstrated that 1 ug/L of serum ferritin corresponds to 8-10 mg of storage iron. In pregnant women, serum ferritin levels fall dramatically to below 20 ug/l during the second and third trimester, even in women taking supplements. In a study it was found that women with mild GDM had raised serum iron and transferrin saturation, prior to diagnosis and treatment, and the post-partum Hb level was significantly higher. Furthermore, there were significantly positive correlations between the OGTT 2-h glucose value with not only ferritin concentration but also transferrin saturation. In a study Lao et al suggested a relationship between increased maternal iron store and glucose intolerance in pregnancy. Although this finding appears at variance with the reported features of iron deficiency in diabetic mothers and their offsprings, it was compatible with the previous observation in the same population that the incidence of GDM was significantly lower in pregnancies complicated by iron deficiency anemia compared with pregnancies complicated by anemia as a result of thalassaemia traits. In a study there was an extensive body of data suggesting that higher iron stores are associated with risk of type 2 diabetes in nonpregnant subjects. In pregnant women, Lao et al. found that higher Hb (>13 g/dl) was an independent risk for GDM and that women with iron deficiency anemia had a reduced risk of GDM. Lower STfR signifies higher body iron store. The normal range for STfR is 3-9 mg/l. In a study by Flow- ers et al found to be 5.6 mg/l and for iron deficiency anemia was 18 mg/l. Levels of three to four times normal have been reported for iron deficiency anemia. No significant difference between GDM and Controls was found regarding STfR. This may indicate that GDM may not be associated with change in total body iron store. In the present study a number of parameters which may potentially affect body iron stores were investigated in GDM cases. The GDM patient had significantly higher body weight, duration of gestation and also higher values of systolic blood pressure, diastolic blood pressure and mean blood pressure as compared to Control. GDM cases, however, didn’t show any difference in lipid levels compared to Control. Thus, some clinical features of metabolic syndrome were present in GDM subjects which are known to affect iron metabolism. Serum Iron was strongly correlated with HOMA%B in univariate Spearman correlation analysis. On multivariate linear regression analysis, also found Serum Iron associated with HOMA%B in GDM group. GDM in Bangladeshi subject may be associated with iron deficiency or elevated body iron store. Lower serum iron in GDM is probably due to chronic inflammatory state rather than iron deficiency itself. The data also suggest that interpretation of body iron status in this condition, using the available markers (like serum iron, serum ferritin and STfR), needs to be made with caution due to the presence of concurrent factors like pregnancy and chronic inflammatory state.

References

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