ORIGINAL ARTICLE

ASSOCIATION BETWEEN IRON STATUS AND GESTATIONAL DIABETES MELLITUS

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Background: Early identification of risk factors for gestational diabetes may result in its prevention and better management. In this study, we aimed to compare serum iron, total iron binding capacity and transferring saturation in pregnant women with and without gestational diabetes. **Methods:** A comparative cross sectional analytical study was conducted at Army Medical College and Centre for Research in Experimental and Analytical Medicine (CREAM) in association with Pak Emirates Military Hospital. Thirty healthy pregnant women and thirty patients of gestational diabetes mellitus matched for age, gestational age and body mass index (BMI) were recruited for the study. The diagnosis of gestational diabetes was made on the basis of abnormal glucose tolerance test at twenty four weeks of gestation. Serum iron and total iron binding capacity of all subjects were measured using colorimetric assay and transferrin saturation was calculated. Analysis of data was carried out using SPSS-22. Mean values were calculated for all variables and compared by two sample *t*-test. Pearson correlation was determined to find association between different quantitative variables in two groups and $p \leq 0.05$ was considered significant. **Results:** Serum iron was significantly higher ($p=0.007$), TIBC significantly lower ($p=0.004$) and transferrin saturation significantly higher ($p<0.001$) in gestational diabetes group as compared to control group. **Conclusion:** Markers of iron status including serum iron and transferrin saturation were higher in patients of gestational diabetes and may pose a risk of developing gestational diabetes mellitus.

Keywords: Iron, Total iron binding capacity, Transferrin saturation, Gestational diabetes mellitus

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INTRODUCTION

Gestational diabetes mellitus (GDM) is the most prevalent disease of pregnancy that leads to many complications in both mother and offspring. It is the diabetes that is first diagnosed during second or third trimester of pregnancy and is not clearly overt diabetes.[1] Though it is the most common metabolic disorder of pregnancy, its prevalence varies considerably worldwide depending upon the population as well as the diagnostic criteria used. It has a high prevalence of approximately 14% in Southeast Asia.[2] Though exact data regarding prevalence of GDM in Pakistan is not available, some recent data suggests a prevalence varying from 8 to 26% across various cities of Pakistan.[3] GDM not only poses risk of type 2 diabetes in mother but can also cause life threatening complications in offspring including foetal macrosomia, respiratory distress as well as increased risk of developing diabetes in future.[4] Early diagnosis and management of the condition may result in better outcome for both mother and foetus.

Although exact aetiology of the disease is not known, many factors are considered to promote development of gestational diabetes. Many hormones during pregnancy like oestrogen, progesterone as well as human placental lactogen cause a switch in the metabolism resulting in increased fat utilization and generation of free fatty acids.[5] The imbalance may result in insulin resistance leading to hyperglycaemia and eventually gestational diabetes. The compensation for this developing insulin resistance is made by increased β cell secretion. However, insufficient release of insulin in the background of insulin resistance results in gestational diabetes.[6] Inflammation as well as oxidative stress are considered to be an important factor in pathogenesis of gestational diabetes.[7]

Iron is regarded as a transition metal that has powerful pro oxidant properties. Raised levels of iron may result in oxidative stress that is the basis of many pathologies including diabetes.[8] The oxidative stress not only causes damage to β cells resulting in decreased insulin secretion but is also associated with decreased insulin sensitivity. Moreover, the reactive oxygen species also cause an increase in hepatic glucose output in addition to decreasing uptake of glucose in peripheral tissues.[9] Studies have shown that iron can affect insulin metabolism in the absence of significant iron overload and excess body iron plays a role in impaired glucose tolerance in type-2 diabetes as well as gestational diabetes. However, data is inconsistent regarding relationship between iron status and development of gestational diabetes.[10]

Though additional iron is required for foetus and iron demands are usually increased during

pregnancy, iron loss is also reduced during pregnancy due to absence of menstruation. At the same time, iron supplementation is prescribed too many pregnant females. Usually 30–60 mg supplemental iron is recommended during pregnancy.[11] However, this supplemental iron along with the usual dietary iron intake provides with approximately 16 mg of absorbed iron per day which is much higher than the required amount.[12] In many countries, including Pakistan, there are no proper guidelines regarding iron supplementation and iron supplementation without proper monitoring is a common practice. It is seen that raised levels of iron biomarkers even within the normal range may be associated with development of gestational diabetes especially in those who have iron supplementation in the early pregnancy without its deficiency.[7]

Data regarding iron biomarkers in gestational diabetes patients in Pakistani population is lacking. We aimed to determine serum iron, TIBC and transferrin saturation in patients of gestational diabetes as well as healthy pregnant females and compared the same between two groups to find any association between these and gestational diabetes.

METHODOLOGY

This cross-sectional study was carried out at Physiology Department, Army Medical College and Centre for Research in Experimental and Analytical Medicine (CREAM) in collaboration with Pak Emirates Military Hospital. The study was conducted after the formal approval from Ethical Review Committee of the institute. Using non-probability purposive sampling technique, 30 patients of gestational diabetes mellitus and 30 healthy pregnant women at 24 weeks onwards gestation were recruited. WHO sample size calculator[13] was used to estimate sample size. Considering 3.5% estimated prevalence of GDM in Pakistan and with 95% confidence level along with 5% margin of error, a sample size of 54 was calculated. The subjects in two groups were matched for age, gestational age and BMI. Oral glucose tolerance test was carried out and diagnosis of gestational diabetes was made according to the criteria established by International Association for Diabetes and Pregnancy Study Group (IADPSG).[14] The demographic data and history were recorded on the proforma. Relevant clinical examination was carried out. Participants fulfilling inclusion criteria were selected for study and those with anaemia, haemoglobinopathies, hormonal disorders including type 1 and 2 diabetes and past history of gestational diabetes were excluded.

For biochemical tests, 5 ml of blood was collected through peripheral venipuncture. Glucose Tolerance Test with 75 gram glucose was performed after an overnight fast of at least 8 hours. For estimation of plasma glucose, blood was collected in collection tubes containing sodium fluoride and potassium oxalate. Analysis of plasma glucose was performed using Roche Cobas C 501 analyser. For iron biomarkers, blood was collected in serum separator tubes and allowed to clot, after which it was centrifuged and serum was collected within an hour of sample collection. Serum iron and TIBC were determined by colorimetric method using Roche Cobas C 501 system. Transferrin saturation was calculated by dividing serum iron with TIBC and was expressed as percentage by multiplying the result with 100. Data were analysed through SPSS-22. Two sample *t*-test was used for comparing mean values of all biochemical parameters between two groups. To find association between plasma glucose and serum iron as well as transferrin saturation, Pearson's coefficient was determined, and $p \leq 0.05$ was regarded as significant.

RESULTS

Serum iron levels were significantly higher in gestational diabetes patients compared with control group (p=0.007). Total iron binding capacity was lower in GDM patients compared to controls (p=0.004). Transferrin saturation was higher in gestational diabetes group compared to control group (p<0.001).

Table-1: Comparison of mean values of fasting blood glucose, serum iron, TIBC and transferrin saturation between two groups

Test parameters	Control group	GDM group	*p*
Fasting plasma glucose (mmol/L)	4.52±0.47	5.98±1.04	<0.001*
Serum iron (µg/dL)	52.21±8.28	65±25.17	0.007*
TIBC (µg/dL)	439.3±168.32	325.39±146.24	0.004*
Transferrin saturation (%)	13.43±4.85	22.86±10.9	<0.001*

*Significant $p \leq 0.05$

A positive correlation of serum iron and transferrin saturation was found with fasting plasma sugar, 1-hour and 2-hour postprandial plasma glucose (Table-2). All these correlations were statistically significant except that between serum iron and 2 hour plasma glucose.

Table-2: Correlation of serum iron and transferrin saturation with plasma glucose

Parameters correlated	*r*	*p*
Serum iron		
Fasting plasma glucose	0.306	0.01*
1-hour plasma glucose	0.281	0.02*
2-hour plasma glucose	0.158	0.19
Transferrin saturation		
Fasting plasma glucose	0.385	0.001*
1-hour plasma glucose	0.401	0.001*
2-hour plasma glucose	0.372	0.002*

*Significant $p \leq 0.05$

DISCUSSION

We compared iron status of normal pregnant women with patients of gestational diabetes mellitus as reflected by serum iron, TIBC and transferrin

saturation. We found a significant high serum iron, a low TIBC and high transferrin saturation in gestational diabetes group as compared to control group. Also, these parameters correlated positively with fasting as well as 2-hour plasma glucose levels.

Iron being transition element is involved in generation of oxidative stress which may play a role in development of gestational diabetes.[15] Considering the increased demand of iron by foetus during pregnancy, iron supplementation is a common practice and is exercised in many developing countries without prior confirmation of its deficiency. Though WHO recommends 30–60 mg elemental iron as supplementation in pregnancy[16], there are no proper guidelines regarding ion supplementation in many developing countries[17]. In a few cases, iron supplementation is self-prescribed both before and after pregnancy. Iron supplementation in already iron replete women may result in more harm than benefit as is shown in few earlier studies.[18–20]

We included thirty healthy pregnant women at 24 weeks onwards gestation and thirty women with gestational diabetes mellitus. A few other similar studies also included comparative number of subjects in their study.[21] We diagnosed gestational diabetes by conducting oral glucose tolerance test at 24 weeks of gestation and applied IADPSG criteria for diagnosis as recommended by WHO.[14]

Significant higher serum iron levels was observed in GDM group than controls. A study conducted in China by Lao *et al* revealed significant high levels of iron in GDM patients as compared to healthy pregnant women. They measured these levels between 28 to 30 weeks of gestation.[22] The mean serum iron in their study is comparable to that found in our study, though they studied a larger group of subjects and included 97 GDM patients and 194 healthy subjects. Another recent study conducted on 150 subjects showed similar results with higher serum iron in GDM patients in all age groups.[23]

Afkhami-Ardekani conducted a study recruiting subjects during 24 to 28 weeks of gestation and found similar results.[21] The study was conducted in Iran where similar socioeconomic and regional factors exist. Serum iron in their study was significantly higher in GDM group. Another study conducted in Iran by Behboudi-Gandevani showed similar results with relatively higher serum iron levels in all subjects.[24] The relatively higher values of serum iron may be because they measured them at earlier gestation of 14–20 weeks and then performed OGTT at 24–28 weeks of gestation.

Derbent *et al* measured serum iron in 30 GDM patients and 72 healthy controls around same time of gestation and discovered statistically significant difference between the two groups.[25]

A few earlier studies compared TIBC in GDM patients and healthy controls and obtained diverse results. Lao *et al* found statistically significant lower TIBC in GDM patients in addition to higher serum iron.[22] Similar results were found in some other studies.[21,25]

We also calculated transferrin saturation and found it to be significantly higher in GDM patients than in healthy controls. Our finding is consistent with earlier work.[21]

CONCLUSION

Serum iron and transferrin saturation were significantly higher in gestational diabetes patients as compared to normal pregnant women. Iron excess may pose a risk for development of gestational diabetes.

LIMITATIONS OF THE STUDY

The limitations of the study were its cross-sectional design in addition to a relatively smaller sample size considering the vast variation in diet, life style and genetics of population. Further prospective studies should be conducted to elaborate the role played by iron in occurrence of gestational diabetes mellitus. There is a need to review the practice of routine iron supplementation during pregnancy without iron deficiency.

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TN: Study design, initial writing, data analysis
UA: Drafting, critical review
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UA: Data acquisition, final review
JS: Data interpretation, final review
ES: Final drafting, critical review

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