COMPARISON OF SERUM FERRITIN LEVELS IN PREGNANT WOMEN WITH AND WITHOUT GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Objective: To compare serum ferritin levels in pregnant women with and without gestational diabetes mellitus.
Study Design: Comparative cross sectional study.
Place and Duration of Study: Physiology Department, Army Medical College in collaboration with Pak Emirates Military Hospital, Rawalpindi, from Mar to Nov 2019.
Methodology: Pregnant females after twenty four weeks of gestation were subjected to oral glucose tolerance test. Thirty healthy pregnant females with normal glucose tolerance test and thirty patients of gestational diabetes mellitus were selected. The diagnosis of gestational diabetes mellitus was based on International Association for Diabetes and Pregnancy Study Group (IADPSG) criteria. Serum ferritin levels of all the subjects were evaluated using electrochemiluminescence immunoassay. Data were analyzed using statistical package for social sciences (SPSS) version 22. Quantitative variables were expressed as mean ± SD. The two groups were compared using independent samples t test. Pearson correlation coefficient was used to assess the association between different quantitative variables. A *p*-value of ≤0.05 was considered significant. Result: Mean serum ferritin levels were significantly higher in women with gestational diabetes mellitus (49.61 ± 42.43 ng/mL) compared with healthy controls (18.30 ± 15.7 ng/mL). Moreover, serum ferritin levels correlated positively with fasting plasma glucose, 1 hour and 2 hour post prandial plasma glucose as well as hemoglobin (*p*-value <0.05).
Conclusion: Serum ferritin levels were markedly higher in gestational diabetes mellitus patients than healthy controls. Higher serum ferritin may be regarded a possible risk factor for the development of gestational diabetes mellitus.

Keywords: Ferritin, Gestational Diabetes Mellitus, Hemoglobin.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia and deranged lipid, protein and carbohydrate metabolism caused by either decreased insulin secretion or defective insulin action[1]. It is a global pandemic and ninth leading cause of mortality today[2]. It is a multifactorial disorder that affects almost all the organs of the body. American Diabetes Association (ADA) has defined gestational diabetes mellitus (GDM) as diabetes first diagnosed during pregnancy that is not clearly overt diabetes[3]. It is the most common metabolic disorder of pregnancy and its prevalence varies from 1% to 14% depending upon the population as well as the criteria used for its diagnosis[4]. During past two decades, its prevalence has increased >30%. In Pakistan, around 1.7% to 3.7% pregnancies are complicated by GDM[1]. GDM can harm two lives and results in both short term as well as late complications in both mother and off-spring. It also increases the risk of type 2 diabetes in both mother and child[5].

During pregnancy, there is a gradual decline in insulin sensitivity. Placental hormones including estrogen, progesterone and human placental lactogen shift the maternal metabolism to increased utilization of lipids resulting in increased production of free fatty acids which may contribute to insulin resistance occurring during pregnancy. This insulin resistance is compensated by increased beta cell secretion of insulin. Inability to

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produce increased amounts of insulin in the presence of insulin resistance results in GDM[6].

Many risk factors are associated with development of GDM including older age, family history of type 2 diabetes and obesity. Recent studies have suggested a possible association between serum ferritin and GDM. Ferritin is the storage form of iron and serum ferritin level reflects body iron stores. Iron is a transition metal and a strong pro oxidant. It can catalyze oxidation reactions through Fenton reaction and causes formation of reactive oxygen species. The iron related oxidative stress can cause damage to pancreatic beta cells and thus decreased insulin secretion. In addition to beta cell dysfunction, serum ferritin is also associated with decreased insulin sensitivity[7]. An increased prevalence of diabetes of up to 60% has been reported in patients of hemochromatosis[8]. Iron related oxidative stress can contribute to β cell dysfunction and insulin resistance even in the absence of significant iron overload[9].

Moreover, serum ferritin is an acute phase reactant and its level may increase in case of inflammation so raised serum ferritin in GDM may imitate inflammation[10]. Early identification of risk factors for gestational diabetes is helpful in improving the prognosis. In this study, we determined serum ferritin levels in pregnant women with GDM and compared them with the same in healthy pregnant females.

METHODOLOGY

The study was carried out at Department of Physiology, Army Medical College in collaboration with Pak Emirates Military Hospital, Rawalpindi. A formal approval from Ethics Review Committee (ERC) of the college was obtained. It was a cross sectional study carried over a period of one year. The sample size was calculated by WHO calculator. With an estimated prevalence of 3.5%, confidence level of 95% and 5% margin of error, the sample size were calculated to be 54[1]. Thirty patients of GDM (cases) and thirty healthy pregnant females without diabetes (controls) after 24 weeks of gestation were recruited from Obstetrics and Gynaecology department of the hospital. The control group was matched for age and body mass index (BMI) with the cases. Non probability consecutive sampling technique was used for sample selection. The diagnosis of GDM was made on the basis of International Association for Diabetes and Pregnancy Study Group (IADPSG) criteria recommended by American Diabetes Association (ADA). Subjects with anemia, hemoglobinopathies, other endocrine abnormalities and history of infection/inflammation were excluded from the study. An informed written consent was taken from all subjects. The basic demographic data of the subjects was recorded along with the relevant history and clinical examination.

Blood sampling was done under strict aseptic technique. For determination of hemoglobin, blood samples were collected in ethylenediamine tetraacetic acid (EDTA) containing tubes. Hemoglobin levels were measured using automated hematology analyzer XP. For determination of serum ferritin, blood samples were collected in serum separator tubes. The samples were allowed to clot, centrifuged and serum was separated. Analysis was performed using automated Roche/Hitachi cobas c analyzer that worked on the principle of electrochemiluminescence immunoassay (ECLIA). Data were analyzed using computer software SPSS-22. Quantitative variables were expressed as mean ± SD. The statistical comparison between two groups was done using independent samples t-test. Pearson's correlation coefficient described the association between different numerical variables. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Thirty cases of GDM were recruited in the study. The healthy controls were matched to cases regarding age and BMI. Serum ferritin of all subjects was measured. There was no significant difference regarding gestational age or parity between the two groups. Mean serum ferritin was 18.30 ± 15.7 ng/mL in healthy controls and 49.61 ± 42.43 ng/mL in GDM subjects. The difference in two groups was statistically significant

(*p*-value of <0.001) (table-I). Moreover, serum ferritin levels correlated positively with fasting plasma glucose, 1 hour and 2 hour post prandial plasma glucose and hemoglobin. However, no significant correlation was found between serum ferritin and BMI (table-II).

Table-I: Comparison of different variables between two groups.

Variable	Control Group (n=30)	Gestational Diabetes Cases (n=30)	*p*-value
Age (years)	28.12 ± 3.12	29.28 ± 3.99	0.183
Body Mass Index (kg/m^2)	27.34 ± 1.56	27.46 ± 1.94	0.79
Gestational age (week)	28.97 ± 2.36	29.08 ± 2.68	0.22
Fasting Plasma Glucose (mmol/L)	4.52 ± 0.47	5.98 ± 1.04	<0.001*
1 hour Plasma Glucose (mmol/L)	6.87 ± 1.21	10.07 ± 1.95	<0.001*
2 hour Plasma Glucose (mmol/L)	5.582 ± 0.81	8.29 ± 1.41	<0.001*
Serum ferritin (ng/ml)	18.30 ± 15.7	49.61 ± 42.43	<0.001*

Table-II: Correlation of serum ferritin with different study parameters

Parameters Correlated	r value	*p*-value
Body Mass Index	0.123	0.316
Fasting Plasma Glucose	0.359	0.002*
1 hour plasma glucose	0.343	0.004*
2 hour plasma glucose	0.349	0.003*
Hemoglobin	0.306	0.010*

DISCUSSION

GDM is becoming an increasingly common metabolic disorder which compromises the health of both mother and offspring. Though exact cause of the disease is not established, a number of factors are considered to contribute in its development. Several earlier studies have shown an association between elevated iron stores and development of type 2 diabetes[11,12]. However, data on association between serum ferritin and gestational diabetes is limited. In addition, whether or not serum ferritin is a risk factor for development of gestational diabetes independent of other known risk factors is controversial[13].

As pregnancy results in increased demand of iron, iron supplementation given to pregnant women is a routine practice in many developing countries, without confirming iron deficiency before therapy. Moreover, self-prescribed iron supplementation before and during pregnancy is also commonly observed. This may result in excess body iron especially in iron replete women that may have a role in the pathogenesis of GDM.

As ferritin is an iron storage protein, high serum ferritin reflects excess iron stores. Iron related oxidative stress may mediate damage to beta cells and thus insulin deficiency. In addition, higher serum ferritin is associated with hepatic dysfunction by impairing glucose metabolism and causing insulin resistance by reduced hepatic insulin extraction and impaired insulin signaling[14]. Ferritin is also an acute phase reactant and increases in inflammatory conditions. Bowers *et al* conducted a study in Denmark on 700 subjects and found raised serum ferritin levels in pregnant women which positively correlated with C reactive protein suggesting the role of higher serum ferritin in GDM as a marker of inflammation[15]. Recent studies have suggested a possible role of iron stores in development of gestational diabetes[16,17].

In our study, serum ferritin levels were markedly higher in patients of gestational diabetes compared with healthy pregnant females. Earlier studies have also shown similar results. Afkhami-Ardekani and Rashidi conducted a study in Iran involving 68 study subjects and found a significantly high serum ferritin level in GDM cases (*p*-value <0.001). The mean serum ferritin levels

in this study were little higher compared to our study. Though serum ferritin was measured during the same period of gestation and similar inclusion/exclusion criteria were followed in both studies, the difference may result from different methods for measurement of serum ferritin in two studies (immunoradiometric assay versus electrochemiluminescence immunoassay) as well as a different criteria followed for diagnosis of GDM[18].

Another similar study conducted on 200 subjects in Iran showed comparable serum ferritin levels across two groups with higher mean serum ferritin in GDM group[19]. The study by Bowers *et al* revealed significantly higher serum ferritin in GDM cases with relatively higher mean value of serum ferritin compared to our study. However, the levels were measured at 9 weeks of gestation and the subjects were followed during the period of pregnancy for development of GDM[15]. Many other studies have shown similar results[8,13,20,21]. Guo *et al* conducted a prospective study and found a positive association between high serum ferritin and development of GDM[22]. Soheilykhah also conducted a prospective study and found a 1.4 fold risk of developing GDM with higher serum ferritin levels[23].

In our study, serum ferritin correlated positively with fasting plasma glucose as well as 1 hour and 2 hour post prandial plasma glucose suggesting possible role of ferritin in development of GDM. A similar positive correlation with fasting blood sugar was observed by Lao *et al*[24]. Sharifi *et al* and Sarkar *et al* also found positive association with both fasting blood sugar and 2 hour post prandial plasma glucose[10,25]. In our study, a significant positive association was not found between ferritin and BMI. Amiri *et al* also did not find any correlation between ferritin and BMI[19]. However, Lao *et al* found a significant positive correlation between ferritin and BMI which further suggests the possible role of serum ferritin in causation of metabolic syndrome and insulin resistance syndrome[24]. To summarize, serum ferritin levels were significantly higher in GDM patients compared to healthy pregnant females. The major limitation of the study is its cross sectional design with a single measurement of serum ferritin at the time of diagnosis of gestational diabetes mellitus.

CONCLUSION

Serum ferritin levels were markedly higher in gestational diabetes mellitus patients than healthy controls. Higher serum ferritin may be regarded a possible risk factor for the development of gestational diabetes mellitus.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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