

Original article:

Association of ferritin and endothelin-1 as risk factors in patients of gestational diabetes mellitus (GDM)

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ABSTRACT

Background- Gestational diabetes mellitus (GDM) is the most common metabolic disorder during pregnancy. GDM causes substantial morbidity, mortality and long-term complications. GDM-related risk factors have not been completely identified yet. Some studies have found relationship between increased serum ferritin and endothelin-1 with impaired oral glucose tolerance test (IGT). But the relationship between serum ferritin, endothelin-1 and risk of GDM has been controversial.

Aims and objective- The aim of the study was to determine serum ferritin levels and endothelin-1 in women with GDM and comparison with normal pregnant women.

Materials and Method- 50 pregnant women of gestational age between 24-28 weeks with impaired glucose tolerance test were taken as cases (group-I) and 50 pregnant women of same gestational age with normal IGT served as control (group-II). Ferritin and Endothelin-1 were measured by ELISA at 24-28 week of gestation.

Results- ferritin and endothelin-1 were significantly raised in GDM patients as compared to control group (p value <0.005 (for ferritin) and <0.05 (for endothelin-1)). A positive correlation was found between ferritin and endothelin-1 (r value-0.488).

Conclusions - From this study it can be concluded that both ferritin and endothelin-1 are increased in GDM patients. There was a positive correlation between ferritin and endothelin-1. Thus these parameters may be considered as risk factors for the development of GDM.

Key words - GDM (gestational diabetes mellitus), ferritin, endothelin-1

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common medical disorders of pregnancy. GDM as defined by American Diabetes Association (ADA) is "any degree of glucose intolerance with the onset or first recognition during pregnancy", irrespective of treatment with diet or insulin¹. Prevalence varies from 2 to 10 percent and sometimes higher depending upon population being tested and the diagnostic criteria being used².

Risk factors for GDM include a history of macrosomia, presence of polycystic ovarian syndrome, obesity, age older than 25, and persistent glucosuria.³ Gestational diabetes mellitus (GDM) increases the risk of macrosomia and perinatal morbidity and mortality for the foetus, while presaging a long-term risk of development of type 2 diabetes for the mother^{4,5}.

The pregnancy is a state of insulin resistance and is the mechanism for this decreased sensitivity is not

completely understood. In the post the major focus was on feto-placental unit and hormones secreted in pregnant state like estrogen, progesterone, cortisol, and placental lactogen. These hormones are increased in pregnancy and increase as pregnancy advances and are thought to mediate insulin resistance.³ however these does not explain fully the increasing prevalence of increasing GDM and sometimes their levels does not correlate with the insulin resistance that is seen in these patients.

Recently the role of serum ferritin is being increasingly recognised. Iron overload and the associated oxidative stress contribute to the pathogenesis and increase risk of type 2 diabetes and other disorders. In iron overload, the accumulation interferes with the extraction, synthesis and secretion of insulin⁶. moderately elevated iron stores have been found to increase the risk of type 2 diabetes. Women from the Nurses Study with high levels of ferritin (>107 ng/mL) were nearly 3 times more likely to develop type 2 diabetes over a 10-y interval, independent of other risk factors such as body mass index (BMI), age, and ethnicity⁷. High levels of ferritin were a risk factor for the development of gestational diabetes mellitus (GDM) in pregnant women.⁸

Endothelial cells play a crucial role in the regulation of vascular tone through the release of vasoactive substances, including nitric oxide (NO)⁹. Endothelin-1 (ET-1) is a vasoconstrictor, proinflammatory and proliferative endothelial cell-derived peptide that is of significant importance in the regulation of vascular function. It is involved in the development of endothelial dysfunction including important interactions with nitric oxide. Endothelial dysfunction is an early finding in insulin resistance and diabetes. Increased vasoconstrictor responsiveness due to diminished NO signalling in skeletal muscle arterioles precede the development of diabetes and hypertension in a rat model of type 2

diabetes¹⁰. Increased production of ET-1 and its receptors mediate many pathophysiological events contributing to the development of atherosclerosis and vascular complications in diabetes mellitus¹¹. Endothelin-1 is implicated in many complications of diabetic like microangiopathy, neuropathy, and nephropathy¹².

Levels of Ferritin and ET-1 are not studied in GDM in Indian population and hence is the aim of the study.

MATERIAL AND METHODS

The present study was conducted in the Deptt. Of Biochemistry, Lady Hardinge Medical College (LHMC), New Delhi. The study protocol was approved by the Ethics committee LHMC. Pregnant women with gestational age of 24-28 weeks were eligible for the study. All women with acute or chronic inflammatory, infective diseases, history of malignancy, DM, seizure disorders, acute or chronic liver disease, acute or chronic renal disease, drug or alcohol abuse, and iron deficiency anemia were excluded. All women were screened for GDM with glucose tolerance test as per ADA criteria¹³. A 2 step approach was used. Participants were initially screened with 50 gram of glucose. If the plasma glucose level measured 1 hour after the load was ≥ 140 mg/dl then 100-g OGTT (oral glucose tolerance test) was performed in fasting state. The diagnosis of GDM is made when the plasma glucose level measured 3 hour after the test was ≥ 140 mg/dl.

50 women with confirmed GDM were taken as cases and 50 women with normal OGTT served as controls.

Fasting blood samples of the participants were collected at 24-28 weeks of pregnancy. Samples were taken in EDTA tube and both ferritin¹⁴ and Endothelin-1¹⁵ were measured by ELISA method using DRG kit.

RESULTS

Participant's parameters like age, gestational age, weight, body mass index (BMI), serum ferritin, ET-1 levels are presented in Table 1. The age, gestational age, Haemoglobin were similar in both groups. In women with GDM weight (68.4 ± 3.5 vs 64.5 ± 4.1 , $p < 0.001$) and BMI (25.2 ± 2.4 vs 23.1 ± 3.3 , $P = < 0.05$) were higher compared to women with normal OGTT. In women with GDM serum ferritin (216.7 ± 45.7 vs 154.8 ± 26.8 ng/ml, $P = < 0.005$) and ET-1 (2.3 ± 0.43 vs 1.5 ± 0.31 pg/ml, $P = < 0.05$) were higher in women with women with normal OGTT. Correlation between serum ferritin and ET-1 in patients with GDM was done and is shown in

Table 2 and FIGURE -1.

Baseline characteristic parameters like age, Hb, BMI, wt and endothelin-1 and ferritin were compared between group I and II (table-1).

Correlation of endothelin-1 and ferritin in cases (table-2, fig-1).

Out of 40 GDM patients, 14 had the strong family history of diabetes mellitus. We divided the group-I patients into 2 subgroups as Group-Ia- GDM patients having strong family history of diabetes mellitus and Group-Ib- GDM patients without family history of diabetes mellitus. Comparison of values of ferritin and endothelin-1 in group-Ia and group-Ib (table-3)

DISCUSSION

We found a significant association between serum ferritin levels and GDM. Ferritin has been identified as a marker of inflammation, and pregnancy is considered an inflammatory and insulin resistant state but it is not clear how ferritin is related to insulin deficiency or to insulin resistance. Whether or not elevated serum ferritin in GDM is a consequence of inflammation is not very well reported in literature.¹⁶.

Jiang et al found that high serum ferritin and C-reactive protein levels are independent risk factors for type 2 diabetes. These data are inconsistent with

the role of inflammation in raising ferritin levels in GDM and other insulin-resistant states¹⁷.

Ferritin can reflect body iron stores. Higher iron stores can be associated with insulin resistance in nonpregnant subjects¹⁸. Lao et al found that higher hemoglobin (> 13 g/dL) was an independent risk for GDM¹⁹ and that iron deficiency anemia is associated with a lower risk of GDM²⁰.

Only a few studies in the literature have evaluated ET-1 in pregnancies complicated by diabetes mellitus, and the results of these studies have been inconsistent. In this study the levels of endothelin -1 were significantly raised in GDM patients as compared to control group. An accumulating evidence indicates that, in poorly controlled diabetes, abnormal production of oxidative stress and accumulation of advanced glycation end products induce vascular endothelial cell damage and dysfunction²¹. Diabetes is associated with vascular dysfunction, which may be due in part to altered vascular response to endogenous peptides such as ET-1²². The concentration of ET-1 in maternal blood is increased, by an unresolved mechanism, during normal pregnancy and reaches a peak value at term and this increase is accelerated in GDM¹³.

Common pathogenic pathways may underlie in the association between both GDM and pre-eclampsia leading to an increased risk of diabetes. Firstly, each of these conditions is associated with insulin resistance²³. Secondly, endothelial dysfunction and markers of chronic vascular inflammation have been found in women with pre-eclampsia as well as women with GDM, both during and after pregnancy. Both these entities have been shown to precede the development of overt hyperglycemia in patients and making them at risk for type 2 diabetes²⁴.

There is a positive correlation between ferritin and endothelin -1 in this study, suggesting both inflammation and endothelial dysfunction play an important role in the pathogenesis of GDM.

No significant difference was found between the levels of ferritin and endothelin -1 in the subgroups of GDM patents based upon the family history of DM. so with these parameters we can't conclude that patients with strong family history of DM are at a greater risk of developing GDM.

CONCLUSIONS

From this study it is concluded that markers of both inflammation and endothelial injury are increased in GDM patients. The positive correlation between ferritin and endothelin-1 suggest their role in the pathogenesis of GDM. So the monitoring of these

parameters may help in the management of GDM and to assess the risk of other complications due to endothelial injury in these patients.. Further prospective studies with large sample size are required to prove this fact.

CONFLICTS OF INTEREST DISCLOSURE

We the author's of the manuscript titled" Ferritin and endothelin-1 in patients of gestational diabetes mellitus" declare that there is no conflict of interest with either pharmaceutical companies or other non-government organization.

TABLES AND FIGURES

Table 1

COMPARISION OF BASELINE PARAMETERS, ENDOTHELIN-1, AND FERRITIN BETWEEN WOMEN WITH AND WITHOUT GDM.

	Women with GDM	Women with normal glucose tolerance	P value
Age (years)	25.22±3.5	23.56±4.2	>0.05
Gestational Age (weeks)	26.22± 2.2	26.64±2.7	>0.05
Weight (Kg)	68.4±3.5	64.5±4.1	<0.001
BMI (Kg/m ²)	25.2±2.4	23.1±3.3	<0.05
Hemoglobin (gm/dl)	10.9±1.4	10.4±1.8	>0.05
Ferritin (ng/ml)	216.7±45.7	154.8± 26.8	<0.005
Endothelin-1 (pg/ml)	2.3±0.43	1.5±0.31	<0.05

Table 2

CORRELATIN OF ENDOTHELIN-1 AND FERRITIN IN CASES

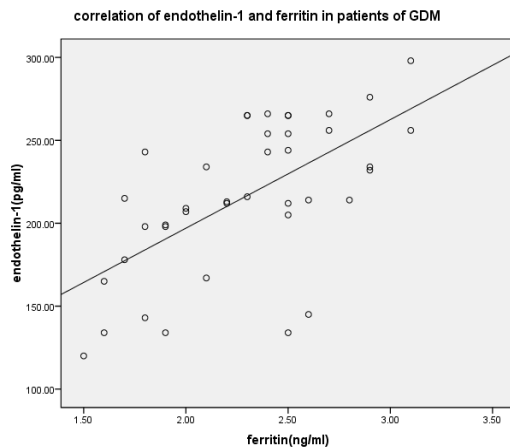
	Ferritin	ET-1	r value
Gp I	216.7±45.7ng/ml	2.3±0.43pg/ml	0.488

Table 3

COMPARISION OF VALUES OF FERRITIN AND ENDOTHELIN IN gp-1a and gp 1b

	Gp-1a	Gp-1b	P value
Ferritin	219.6±46.7ng/ml	215.18±44.6ng/ml	>0.05
Endothelin-1	2.4±0.32pg/ml	2.2±0.29pg/ml	>0.05

FIGURE -1



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