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RESEARCH ARTICLE

Role of ferritin and oxidative stress index in gestational diabetes mellitus

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Abstract

Objectives To investigate the role of serum ferritin and oxidative stress in the development of GDM and to assess their relationship with the ensuing hyperglycemia.

Methods A case–control study was carried on 90 non-anemic pregnant women of 20–40 years with a gestation of 24–28 weeks. Study group (n = 65) was identified according to the Diabetes in Pregnancy Study Group India (DIPSI) criteria (2-h plasma glucose ≥ 140 mg/dl) and controls (n = 25) having 2-h plasma glucose < 120 mg/dl. DIPSI 2-h plasma glucose, HbA1c and serum ferritin were measured and oxidative stress index (OSI) was calculated. Statistical tests were performed using SPSS version 25.0.

Results Pre-pregnancy BMI showed a significant difference between control and study group. DIPSI 2 h blood glucose, HbA1c, serum ferritin and OSI were significantly higher in study group compared to control group. Both 2 h blood glucose and HbA1c were positively correlated with serum ferritin and OSI, serum ferritin and OSI were also positively correlated with each other.

Conclusion Higher pre-pregnancy BMI elevates serum ferritin, which in turn increases the OSI. Both ferritin and oxidative stress raises 2 h blood glucose and HbA1c in GDM patients possibly by causing in-vivo pancreatic β –cell injury and death (ferroptosis). Serum ferritin and OSI could become newer personalized theranostic and monitoring targets in overweight/obese pregnant females especially GDM patients.

Keywords Ferritin · Oxidative Stress Index · Gestational Diabetes Mellitus · Fenton reaction · Ferroptosis

Introduction

Gestational diabetes mellitus (GDM) is usually defined as a varying degree of glucose intolerance having either its onset or first recognition during pregnancy. GDM is estimated to affect 14% of pregnancies worldwide, accounting for about 18.4 million births annually [1]. A recent study suggests that GDM may affect between 5–8 million pregnant women in India annually [2]. Primarily, GDM develops when insulin secretion fails to overcome the pregnancy induced physiologic insulin resistance (IR). Genetic, epigenetic, and environmental factors may all contribute to the development of GDM; there is evidence of adipose expandability, low-grade chronic inflammation, gluconeogenesis, oxidative stress, and some placental factors contributing to the pathogenesis of GDM [3]. GDM may lead to both fetal and maternal complications, but still there is no uniform criterion to diagnose GDM. The frequently recommended guideline is that of the International Association of Diabetes in Pregnancy Study Group (IADPSG), but its importance is declining nowadays because it lacks standardization and needs revision. A simple test with 75-g oral glucose load to a pregnant female in either fasting or non-fasting state, having a 2-h plasma glucose value of ≥ 7.8 mmol/dl (≥ 140 mg/dl) was seen to detect GDM successfully. The Diabetes in Pregnancy

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Study Group India (DIPSI) has accepted this "single test procedure" to diagnose GDM. The National Institute of Clinical Excellence (NICE) guidelines also recommend 2-h PG ≥ 7.8 mmol/dl as one of the diagnostic criteria for GDM. This doable procedure is approved by the Ministry of Health & Family Welfare Government of India, WHO, FIGO, and IDF [4].

Iron is an essential trace element and its deficiency or excess may lead to abnormalities. Excessive iron stores have been implicated in the development of type 2 diabetes by damaging the pancreatic β-cells and causing insulin resistance [5]. Iron is stored in the body as ferritin, and measurement of ferritin in serum reflects adequately the pool of iron present in bone marrow macrophages. Ferritin is also an acute phase reactant and it is increased in many chronic diseases and inflammation. Increased cellular ferritin has been linked to pancreatic β-cell dysfunction and insulin resistance. Ferritin levels are elevated in type 2 diabetes patients, and increased serum ferritin levels in Western and Asian population were associated with an increased risk of diabetes [6]. The elevated serum ferritin might interact with other genetic and environmental factors, impairing β-cells functioning and affecting insulin secretion [7]. The raised iron leads to oxidative stress in the body further aggravating insulin resistance and hyperglycemia [8].

Oxidative stress (OS) is an imbalance between cellular pro-oxidant and antioxidant level, there is production and accumulation of reactive oxygen species (ROS) in cells. ROS are described as free radical and non-radical derivatives of oxygen, and include superoxide anion (O2 −), hydroxyl radical (•OH) and hydrogen peroxide (H_2O_2) [9]. Damage of cellular proteins, lipids and DNA by ROS leads to oxidative stress, and has been implicated in the pathogenesis of many diseases, including GDM [10]. Women with GDM are known to overproduce free radicals in addition to an impaired free-radical scavenging mechanism [11]. ROS also inhibit insulin-stimulated glucose uptake at the molecular level by interfering with insulin receptors [12], and ROS also reduces glycogen synthesis in the liver and muscle. Iron supplementation in pregnant women having adequate iron stores, is associated with the development of GDM [13]. It has been established that this effect of iron is mainly due to the increased oxidative stress as iron can catalyze the reaction from $O_{2\cdot}$ and H_2O_2 to the extremely reactive •OH (Fenton reaction) [14]. Ferritin responds to oxidative stress, however, controversy exists whether ferritin has pro- or antioxidant properties. Superoxide can mobilize stored iron from ferritin, increasing the pool of reactive iron and exacerbating oxidative stress [15]. Therefore, serum ferritin may have a direct role in the development and progression of GDM mediated via the oxidative damage mechanism. The present study attempts to seek a direct evidence of this mechanism in pregnant females.

Subjects, materials and methods

Study design

A 2 years prospective case–control study from 2018 to 2020 was carried in the Department of Pathology, Department of Biochemistry and Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh. Ethical clearance was obtained from the Institutional Ethical Committee. The participants were informed of all possible expected benefits and harms ensuing from the study and written consent was taken from the participants before enrolling them in the study.

Study participants and measures

Relevant history & detailed physical examination along with laboratory analysis was performed. 20–40 years old non-anemic pregnant women having a gestational age of 24–28 weeks, diagnosed with gestational diabetes mellitus (DIPSI ≥ 140 mg/dl) were included in the study group (n = 65). Age matched non-anemic, non-overweight/obese and euglycemic (DIPSI < 120 mg/dl) pregnant women having a gestational age of 24–28 weeks, who were apparently normal comprised the control Group (n = 25).

Inclusion and exclusion criteria

All consenting pregnant females diagnosed with GDM were included in the study. Exclusion Criteria were non-consenting females, females with a family history of diabetes mellitus, patients with (diabetes, hypertension, polycystic ovarian syndrome), patients with iron deficiency anemia, patients with acute or chronic (liver, kidney, heart, lung, thyroid) diseases, patients with acute or chronic inflammatory diseases, patients with infective diseases, patients with known malignancy and patients with seizure disorders.

Measurements

After the informed consent, detailed history and clinical examination, the blood samples were withdrawn from the subjects. Oral glucose tolerance test (OGTT) was performed according to the DIPSI criteria with 75 g oral glucose in non-fasting state and 2 ml blood was collected in sodium fluoride vial for estimation of blood glucose by glucose oxidase method, 2 ml of blood in EDTA vial was used for HbA1c estimation by HPLC. Lastly, 2 ml blood in plain vial was collected for serum Ferritin (ELISA, Calbiotech Inc.) and Total Oxidant Status (TOS, SRL, India) & Total Antioxidant Status (TAS, Sigma Aldrich) measurement

spectrophotometrically. The oxidative stress index (OSI) was calculated as the ratio of the TOS level to TAS level, as had been described earlier [16].

Statistical analysis

All the statistical tests were performed using computer program SPSS version 25.0. Descriptive analysis was done by percentages and Mean ± SD (standard deviation). To test the significance of two means, the student's 't' test was used; a p value < 0.05 was taken as significant. Pearson Chi Square test was used to analyze all the qualitative variables. All the quantitative variables were analyzed using Independent Sample t-test. Pearson Moment Correlation Analysis was also used to look for any correlation among different variables, correlation coefficient "r" between 0.4—0.7 was taken as moderate correlation, and r between 0.7—0.9 was high correlation.

Results

Body mass index (BMI) was classified as normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (˃ 30 kg/m^2). Pre-pregnancy BMI among control group was 23.86 ± 1.55 kg/m^2 while in study group it was 27.54 ± 2.50 kg/m^2, the 'p' value (< 0.001) came out to be statistically significant. Mean ± SD of 2 h glucose after 75 g load was 85.26 ± 4.49 mg/dl in control group while in study group it was 178.03 ± 13.03 mg/dl, p value (< 0.001) was statistically significant. The Mean ± SD hemoglobin concentration of study group was 11.68 ± 0.56 g % while of control group was 11.88 ± 0.67 g %, p (> 0.05) was statistically insignificant. All women in control group had HbA1c in the normal range (4–5.6%) whereas in study group 66% women had HbA1c in pre-diabetic range (5.7–6.4%) and 34% women in the diabetic range (> 6.5%). The Mean ± SD HbA1c among control group was 5.16 ± 0.25% while in study group it was 6.39 ± 0.43%, p value (< 0.001) was statistically significant. Serum ferritin among women in control group was mostly < 30 ng/ml while serum ferritin among study group was mostly > 85 ng/ml. Mean ± SD serum ferritin among controls was 32.44 ± 4.49 ng/dl while among study group it was 78.11 ± 35.38 ng/dl, p value (< 0.001) was statistically significant. Hence, higher levels of serum ferritin were seen in GDM patients. Mean ± SD of TOS among controls was 2.78 ± 1.26 µmol H_2O_2 Eq/L while among study group it was 10.18 ± 4.53 µmol H_2O_2 Eq/L, p value (< 0.001) was statistically significant. Mean ± SD TAS of controls was 3.95 ± 0.92 µmol Trolox Eq/L and in study group it was 2.10 ± 0.69 µmol Trolox Eq/L, p value (< 0.001) was statistically significant. OSI among controls was 0.81 ± 0.62 while in the study group it was 5.40 ± 3.02, p value (< 0.001) was statistically significant. Table 1 compares the above mentioned variables in the control and the study group. 2 h blood glucose was positively correlated with serum ferritin (r = + 0.526, p < 0.01) and OSI (r = + 0.581, p < 0.01), HbA1c was positively correlated with serum ferritin (r = + 0.438, p < 0.01) and OSI (r = + 0.502, p < 0.01). Serum ferritin and OSI were also positively correlated with each other (r = + 0.406, p < 0.01), Table 2.

Discussion

Overweight or obese females had an increased risk of GDM compared to lean or normal-weight females. Women having a pre-pregnancy BMI over 30 have been shown to be 3-times more at risk of developing GDM compared to women with normal pre- pregnancy BMI [17]. Obese pregnant women show major metabolic derangements, and may have up to 40% higher insulin resistance compared to normal weight women [18]. Inflammation is another possible mechanism linking obesity with GDM, adipocytes secrete pro-inflammatory cytokines which may have a role in the development of GDM [17]. Weight management through nutritional

Table 2 Correlation of S. Ferritin and OSI with 2-h glucose, HbA1c and amongst them

	S. Ferritin (Correlation coefficient, r)	OSI (Correlation coefficient, r)
GST- 2 h glucose	.526; p < .01	.581; p < .01
HbA1c	.438, p < .01	.502, p < .01
S. Ferritin	-	.406, p < .01

Table 1 Comparision of different variables between the control and study groups

	BMI (Kg/m^2)	2-h Glucose (mg/dl)	HbA1c (%)	Serum Ferritin (ng/dl)	TOS (µmol H_2O_2 Eq/L)	TAS (µmol Trolox Eq/L)	OSI
Control gp	23.86 ± 1.55	85.26 ± 4.49	5.16 ± 0.25	32.44 ± 4.49	2.78 ± 1.26	3.95 ± 0.92	0.81 ± 0.62
Study gp	27.54 ± 2.50	178.03 ± 13.03	6.39 ± 0.43	78.11 ± 35.38	10.18 ± 4.53	2.10 ± 0.69	5.40 ± 3.02
t- value	-6.865	-34.701	-13.589	-6.412	-8.032	10.364	-7.518
p-value	p < .001	p < .001	p < .001	p < .001	p < .001	p < .001	p < .001

prevention strategies could be successful in reducing the risk of GDM [19]. In the present study it was evident that raised pre-pregnancy BMI was significantly related with GDM, similar results were seen in other studies also [20].

As expected, in our study the DIPSI 2 h blood glucose showed significant difference in the study and control group, similar findings were seen in other studies also [21]. HbA1c in control group was well within the normal range; in the study group 66% women had HbA1c in the pre-diabetic range, while 34% women had HbA1c in the diabetic range. Hence, even in the study group majority of women had only mildly increased glycosylated hemoglobin. Similar results were seen in other study where majority of GDM patients had HbA1c levels in the pre-diabetic range only [21]. Similarly, Kwon et al. found a mean HbA1c level in the normal pregnant women to be significantly lower than GDM patients [22]. The first-trimester HbA1c level is a reliable predictor of complications during pregnancy, but the physiological changes occurring during pregnancy prevents the use of HbA1c for diagnosing GDM [23]. However, HbA1c could be used as a risk predictor of future type 2 DM development in patients of GDM.

Obesity causes a state of sub-clinical inflammation, compression of adipocyte by stored fat causes cellular hypoxia and releasing inflammatory cytokines and chemokines. Pro-inflammatory mediators are also released by obesity activated leukocytes, macrophages and lymphocytes [24, 25]. It has been shown that high levels of ferritin were positively correlated with the risk of metabolic syndrome, obesity and inflammatory marker CRP [26, 27]. In overweight and obese people, ferritin is more a marker of on-going inflammation rather than iron stores [28]. A recent study indicates that excessive adiposity is associated with elevated serum ferritin and hepcidin independent of dietary intake [29]. The ferritin originates from an injured cell, losing most of its iron and leaving this iron in a highly reactive un-liganded form (hydroxyl radicals production via Fenton reaction) [30]. Further, the un-liganded ferrous (Fe^{2+}) iron causes lipid peroxidation and ROS production, which can trigger ferroptosis. Pancreatic beta-cells with low expression of antioxidant enzymes are predisposed to ferroptotic cell death. Indeed, experimental evidence had suggested that pharmacologically induced ferroptosis can lead to impaired islet function and viability of human pancreatic islets [31]. In our study, we have found that serum ferritin and OSI among study group was significantly higher than controls, similar findings have also been shown very recently by Feng et al. [32]. Quercetin (flavanoid anti-oxidant) achieved normal β- cell function through amelioration of ferroptosis in T2DM [33]. Lately, evidences have started gathering that ferroptosis may play a critical role in the causation of chronic complications associated with diabetes mellitus like diabetic nephropathy [34], diabetes related cardiac events [35] and endothelial dysfunction [36]. This study also adds to the evidence that ferritin induced oxidative damage leads to poor gylcemic control in GDM which possibly results due to cell injury/ferroptosis of pancreatic β-cells.

Conclusion

Raised pre-pregnancy BMI increases serum ferritin and OSI predisposing to GDM. The un-liganded, hyper-reactive ferritin leads to generation of ROS via the Fenton reaction; ferritin and oxidative damage both are possibly responsible for pancreatic β –cell injury and death (ferroptosis) which is clinically reflected as increasing 2-h glucose and HbA1c levels in GDM. Targeting ferritin and the induced changes at multiple molecular levels along with re-enforcing the anti-oxidant mechanisms would play significant role in future management of GDM.

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