Original Article

Association of Ferritin and Serum Iron with Insulin Resistance Indices in Gestational Diabetes

Fazloddin Fahimi Moghaddam [1], Jamshid Mehrzad [2*], Jafar Saeidi [3], Ahmad Ghasemi [4]

[1] PHD Candidate of Biochemistry, Department of Biochemistry, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran. [2] PHD of Biochemistry, Department of Biochemistry, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran. [3] PHD of Physiology, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran. [4] PHD of Clinical Biochemistry, Department of Basic Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran.

Abstract

Objectives: Investigation of the association of serum iron and ferritin with insulin resistance (IR) indices in pregnant women with gestational diabetes mellitus (GDM). Methods: Serum ferritin and iron and IR indices were measured in the 50 pregnant women with GDM and 350 non-GDM, and association of IR indices with serum iron and ferritin was evaluated. Results: Ferritin in the GDM group was significantly correlated with all IR indices except HOMA-B. No significant relationship found between iron levels and IR indices, except HOMA-IR. Conclusion: Increased serum iron and ferritin levels may increase insulin resistance and the risk of developing GDM.

Keywords: Gestational diabetes; Ferritin; Serum iron; Insulin resistance

INTRODUCTION

Between 3 and 10 percent of pregnancies lead to gestational diabetes mellitus (GDM), which is different in various populations under study [1, 2].

Any degree of glucose resistance that is detectable at the beginning or during pregnancy is defined as GDM [3].

Insulin resistance (IR) naturally develops during pregnancy, especially from the second trimester onwards, and GDM occurs in the women whose pancreas is unable to increase insulin secretion in proportion to this increased IR [4].

The first evidence about the role of iron overload in diabetes was found when scientists found that patients with hemochromatosis were at greater risk for type 2 diabetes. It was then observed that repeated blood donation and a decrease in body iron stores, decrease IR. One possible hypothesis of the mechanism of iron-induced diabetes is the association between iron overload in the liver with hepatic function and IR [5].

The observed association between plasma ferritin and the risk of developing GDM is biologically acceptable. Iron overload has been consistently associated with the risk of type 2 diabetes [6] and GDM [7].

A study showed that increased iron levels in the second trimester, based on higher ferritin levels, were associated with a much greater risk of developing GDM than iron in the first trimester. This research suggests that high sources of iron in the body may be involved in triggering GDM from the beginning of the first trimester [8], however, its exact molecular mechanism is still unclear [9].

In some epidemiological studies, serum ferritin has been the second strongest determinant of blood glucose (after BMI) in regression models and the third strongest determinant of serum insulin (after BMI and age) [10].

Insulin resistance defined as a decrease in the body cells' responsiveness to the metabolic effects of insulin and is closely linked to the development of the metabolic syndrome and the pathogenesis of type 2 diabetes [11].

The determination of IR is done by different methods, with their complexity. Tests such as the "Euglycemic Clamp" are

Address for correspondence: Jamshid Mehrzad, PHD of Biochemistry, Department of Biochemistry, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran.
E-mail: mehrzadjam @ yahoo.com

How to cite this article: Fahimi Moghaddam, F., Mehrzad, J., Saeedi, J., Ghasemi, A. Association of Ferritin and Serum Iron with insulin resistance indices in gestational diabetes. Arch Pharma Pract 2019;10(2):110-5.

direct measurement techniques for IR and however, are time-consuming, expensive and perilous methods. On the other hand, methods such as the HOMA, QUICKI, 1/Insulin, HOMA-B and Glucose/Insulin (G/I) indices are indirect and computational techniques for IR assessment using fasting glucose and insulin. Evaluation of these indices is very simpler and affordable than direct methods in IR measurement. Numerous studies have shown that screening for insulin resistance can predict the likelihood of diabetes in a person between 10 and 20 years before diabetes occurs [12].

In the present study, we investigated the IR indices in pregnant women with GDM and normal glucose tolerance pregnant (NGT) women, as well as the levels of serum iron and ferritin in these two groups. Then we looked at the relationship between the amount of serum iron and ferritin with insulin resistance in the two above groups. So, we did not find any study similar to what was done in this study on the association of IR indices with serum ferritin and iron levels in pregnant women with gestational diabetes.

METHODS

Participants

In this case-control study, all pregnant women at 24 to 28 weeks of gestation referred for a screening of GDM to the Kashmar Central Laboratory (Iran; Razavi Khorasan province) for 6 months (between September 2018 and March 2019) were considered as samples. So, the sampling method and its models were nonprobability and convenience, respectively. All 50 women with GDM (Case) and 350 of 584 non-diabetic pregnant women (randomly selected) (Control) participated in the current study and a research questionnaire was completed for each participant, finally, the consent form was signed by each of them.

Laboratory measurements and assessments

Oral glucose tolerance test (OGTT), ferritin, iron, and fasting insulin were evaluated in all participants sera. IADPSG (International Association of the Diabetes and Pregnancy Study Group) criteria was used for the GTT test that has determined the diagnosis of GDM using 75 grams of oral glucose. This criterion indicates that if the blood sugar in fasting status (FBS), one hour and two hours after glucose intake were greater than or equal to 92, 180 and 154 mg/dl, respectively, GDM will be proven, and even one of those three is enough for this.

Blood glucose and serum iron were measured by glucose oxidase and FerroZine methods, respectively (Selectra XL auto analyzer, Vital Instrument Co. Netherlands; Bionik kit, Iran). An enzyme immunoassay (ELISA) method was used for insulin and ferritin measurement (Autobio Elisa Reader, China; DiaMetra kit, Italy and Autobio Elisa Reader, China; PishtazTeb kit, Iran, respectively).

Insulin resistance and sensitivity indices

Insulin resistance indices (HOMA-IR, QUICKI, and HOMA-B, 1/Insulin, G /I) were calculated by the following mathematical formulas [13-16].

HOMA-IR= (Fasting Glucose, mmol/l× Fasting Insulin, μIU/ml)/22.5

QUICKI = 1/ [log (Fasting insulin, μU/ml) +log (Fasting glucose, mg/dl)]

HOMA-B= (360×insulin, micro-unit/lit)/Glucose, mg/dl - 63)

Two other indices, 1/Insulin (1/fasting insulin) and G/I (fasting glucose/fasting insulin) were measured too. The association between insulin resistance (IR) and increased levels of serum ferritin and iron in GDM and non-GDM patients were assessed with statistical analysis.

Statistical analysis

Data were expressed as medians and interquartile ranges. To search the distribution of data, the Kolmogorov-Smirnov test was used. According to data distribution, the Mann-Whitney U used to investigate the difference of ferritin, iron, and IR indices (with abnormal distribution) between the two groups and independent sample t-test was used for evaluation of differences age, BMI and weight gain (with normal distribution) between the two groups mentioned. Finally, for investigating the relationship between IR indices and two other analytes (serum iron and ferritin), a linear regression test was used and p-value < 0.05 was considered to indicate statistical significance. Data were analyzed using SPSS version 16.0 for Windows software.

RESULTS

Table 1 shows some results of the experiments and some anthropometric indices in this study. The fasting insulin levels in the GDM group were significantly higher than the non-GDM group ($P < 0.001$). For IR indices, the median of the 1/insulin index showed a statistically significant decrease in the GDM group compared to the NGT group. FBS/fasting insulin (G/I) was significantly higher in diabetic pregnant women than the NGT group ($p < 0.001$). The difference in HOMA-IR between case and control groups was statistically significant ($p < 0.001$). QUICKI had a statistically significant difference in the two groups ($p < 0.001$). However, the difference in HOMA-B between these two groups was not significant.

The difference between ferritin and serum iron in the diabetic and healthy group was statistically significant (($p < 0.001$) and ($p = 0.002$), respectively).

High levels of plasma ferritin in pregnant women with GDM was significantly correlated with all IR indices (1/insulin, FBS/insulin, HOMA- IR, QUICKI) except HOMA-B (Table 2).

This study also showed that there was no significant relationship between serum iron levels and IR indices (1/insulin, FBS/insulin, QUICKI, HOMA-B) except HOMA-IR (Table 3), taking into account two age and group factors (healthy women and diabetic women groups).

Discussion

As far as we know, this is the first study about the relationship between resistance and insulin sensitivity index with ferritin and serum iron in pregnant women with gestational diabetes.

The importance of insulin resistance in the development of diabetes is clear. Gestational diabetes also occurs in women due to this insulin resistance. Discovering the factors that can increase insulin resistance in these women can be crucial in preventing and detecting gestational diabetes in pregnant women. Previously, some articles have mentioned the effect of high levels of iron and ferritin in the development of type 2 diabetes, but the effects of these two substances on insulin resistance in pregnant women have been less addressed, and we studied this article in this article.

It is believed that since iron is a redox-active transition metal and is a potent oxidant, iron-dependent Fenton reactions can produce reactive oxygen species (including hydroxyl radicals) that would be able to disrupt insulin signaling in liver and skeletal muscle tissue and at the same time, they also damage pancreatic β cells, however, the precise mechanism by which excessive iron leads to diabetes has not been fully elucidated [17]. Due to minimal endogenous antioxidant defense, pancreatic β cells are particularly susceptible to oxidative damage. Also, because iron elimination is low in the body (especially in pregnant women who have menstrual cessation) and because of a diet containing iron and taking iron supplements, it is more likely to cause iron excess in the body [18].

However, studies who examined the relationship of ferritin to GDM risk have been limited and inconsistent in their findings [19, 20].

For example, a study based in Lebanon [19] found that high ferritin in early pregnancy is significantly associated with impaired glucose tolerance but not GDM, although the latter can be attributed to the low sample size in GDM cases (n = 16).

On the other hand, a recent case-control study [20] reported that there was a significant positive relationship between ferritin and risk of GDM, even after adjustment for plasma CRP (C-Reactive Protein) levels and several risk factors of GDM (including pre-pregnancy BMI).

In our present study ferritin was significantly higher in the GDM group (P<0.001). To rule out inflammation or infection in the participants and to confirm that ferritin is not increased due to those conditions (ferritin is an acute-phase protein), CRP evaluation was performed for each serum sample and all sera were negative for CRP.

The outcome of a prospective case-control study in pregnant women showed that high plasma ferritin concentrations in early pregnancy were associated with the risk of GDM (even after adjusting for BMI and other pre-pregnancy GDM risk factors). This association remained significant, even after adjusting for systemic inflammation markers and oxidative stress [20].

In a prospective cohort study in 1033 pregnant women regarding their nutrition and serum iron levels in early GDM and GDM incidence, there was a positive correlation between iron serum levels and GDM incidence [21].

Therefore iron overload may play a role in increasing insulin resistance (IR), and since there is a physiological prediction of IR in pregnancy due to hormonal and homeostatic changes, the potential effect of iron overload on the increased risk of GDM seems to be a rationale [22]. This raises potential concerns about the recommendation for supplemental iron intake in pregnant women [8].

Our current study also supports the results of many studies about serum iron levels in diabetic compared to healthy pregnant women. Iron was significantly higher in the diabetic mothers' group (*P-value = 0.002*). This result is also consistent with what was obtained with ferritin in this study.

In a regular meta-analysis study published in 2016, there was a significant relationship between serum ferritin and serum iron levels and the risk of GDM, but no association was found between serum transferrin and GDM [22].

Several previous studies have reported that moderate iron intake in non-anemic pregnant women can impair blood glucose and also cause hyperinsulinemia and oxidative damage in their offspring [23] and that fetal hyperinsulinemia is associated with macrosomia [24].

In the Atari-Hajipirloo S. et al. Study, iron has been shown to affect glucose metabolism, and they found that the concentration of free iron in patients with T2DM is higher than in healthy participants, which can lead to tissue damage and to potentially leading to T2DM-related complications [25].

In a study at a Finnish primary health care center, an increase in total iron intake (including medicinal iron) during pregnancy was associated with a higher risk of developing GDM, but it was significant only among women who started pregnancy without anemia [26].

High levels of iron and ferritin in the serum of people with GDM in our study, can also indicate that high levels of iron in the blood of pregnant mothers may be important in setting

the stage for GDM, regarding the causes and reasons mentioned above.

Also, in a large prospective study recently conducted in women with a history of GDM who were generally treated with prophylactic iron, long-term post-pregnancy iron supplementation concurrent with GDM, was significantly associated with an increased risk of type 2 diabetes [27].

Insulin resistance indices

The role of insulin in stimulating glucose uptake in muscle and adipose tissue and inhibiting gluconeogenesis in the liver to maintain glucose homeostasis have been proven. Insulin sensitivity (IS) is a concentration of insulin that is needed to produce half of its maximum effect. In contrast, the decrease in responsiveness to the metabolic effects of insulin is called "insulin resistance" (IR), which plays an important role in the process of developing metabolic syndrome [11].

Although there are many time-consuming and costly methods for evaluating IR (such as "Euglycemic Clamp" and "Insulin Suppression Test"), these methods are not applicable in medical diagnostic laboratories [28]. In contrast, there are simpler methods for investigating IR that use fasting glucose and fasting insulin, we used the same methods in this study.

Many studies have shown that IR screening is very helpful in predicting the incidence of diabetes 10-20 years before diabetes begins [12].

One of the most important indices widely used in diverse populations for IR evaluation is the homeostasis model (HOMA-IR) [29, 30].

In our study, the HOMA-IR difference in diabetic and healthy mothers was statistically significant (*P-value <0.001*) and it appears that this index may be an important indicator in determining IR in pregnant women even several weeks before routine screening for GDM (24-28 week of pregnancy).

However, the HOMA-B index did not show a significant difference (*P-value <0.001*) between the GDM and NGT groups, and it can be said that HOMA-B cannot be considered a valuable indicator in GDM screening.

The association between different glucose clamp studies has been performed by Katz et al; they found that there was a significant relationship between QUICKI and the IS clamp (r=0.78) [15, 30]. QUICKI in our present was significantly different between GDM and NGT groups (*P<0.001*). Good correlation with results of standard euglycemic clamp method and its possibility to be used in early screening of GDM diagnosis for all pregnant women can make this index as a valuable criterion for IS and IR assessment.

Mean HOMA-IR of 2.2 to 3.2 has been reported by Kwak for Korean women with a history of GDM [31] that is not significantly different from the values obtained in the Sae Jeong Yang study (mean HOMA-IR of 2.3 in GDM participants) [32].

Two indices FBS/fasting insulin (G/I) and 1/insulin in diabetic mothers were significantly lower than the healthy mothers (*P <0.001*).

Therefore, evaluating IR levels can be useful in assessing the likelihood of diabetes, especially in people who have not yet had abnormal glucose tolerance or diabetes [33].

Kirwan et al. attempted to predict IS in women before and during pregnancy by investigation on IS using the OGTT and calculation of fasting glucose/insulin levels simultaneously and found that the OGTT test was significantly better in the estimation of IS in pregnant women than G/I [34].

As noted, increased ferritin levels were significantly correlated with all indices of insulin resistance and sensitivity (except HOMA-B). In interpreting this result, it can be concluded that a significant increase in the level of insulin secretion in people with GDM and/or a relative increase in fasting blood glucose in these individuals may be related to their plasma ferritin level. Ferritin is not only a protein for storing iron, but it is also an acute-phase protein in inflammatory conditions of the body.

Pregnant women with GDM are in much more critical condition than healthy pregnant women, and although increased ferritin levels in women with GDM than normal pregnant women can be considered a natural issue but may also indicate a pathophysiological relationship between the level of plasma ferritin and glucose homeostasis in the blood. The relationship between the important HOMA-IR index and serum iron level in diabetic pregnant mothers compared to healthy pregnant women is evidence of this claim.

Lack of significant association between plasma ferritin and HOMA-B index may indicate that increased ferritin does not necessarily cause pancreatic tissue damage in patients with GDM.

On the other hand, the serum iron level in this study was not significantly correlated with any of the indices of IR and IS, except HOMA-IR. Sharing a significant relationship with HOMA-IR between ferritin and serum iron levels may indicate that an increase in iron content (whether in the form of storage or plasma) can play an important role to induce IR in peripheral tissues.

Conclusion

Increased serum iron and ferritin levels can have a positive effect on insulin resistance in peripheral tissues, through various mechanisms whose molecular basis has not yet been elucidated. This is more important in pregnant women that have naturally varying degrees of insulin resistance. Pregnant

women are potentially at risk for gestational diabetes and some risk factors can lead them to this disease. In addition to those risk factors, elevated plasma iron levels in these individuals may increase the risk of developing gestational diabetes due to an increase in insulin resistance. It is therefore recommended that pregnant women who do not have a clear indication of iron intake, not to be treated with iron supplements.

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