Iron status in women with and without gestational diabetes mellitus

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Abstract

Objective: Gestational diabetes mellitus (GDM) affects approximately 7% of all pregnancies. Pregnancy, mostly because of the mitochondria-rich placenta, is a condition that favors oxidative stress. A transitional metal, especially iron, which is particularly abundant in the placenta, is important in the production of free radicals. Also, studies have shown that free radicals have a role in GDM. As there are little data about iron status in GDM, this study was performed to compare iron status in GDM and control group.

Research Design and Methods: In this case-control study, 34 women with diagnosed GDM were compared with 34 non-GDM women in the control group at 24–28 weeks of pregnancy in terms of iron status, including ferritin, serum iron, total iron-binding capacity (TIBC), hemoglobin (Hb), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH).

Results: In this study, concentration of serum ferritin, iron, transferrin saturation and hemoglobin, MCV, and MCH was significantly higher in the GDM group and TIBC was significantly lower in this group (P<0.05). No significant association was observed with the other variables including familial history of diabetes and GDM.

Conclusion: Our findings indicate an association between increased iron status and GDM. The role of iron excess from iron supplementation in the pathogenesis of GDM needs to be examined.

Keywords: Gestational diabetes mellitus; Serum ferritin; Serum iron

1. Introduction

Pregnancy is a condition that favors oxidative stress mostly because of the mitochondria-rich placenta. Transitional metals, especially iron, which are particularly abundant in the placenta, are important in the production of free radicals (Casanueva & Viteri, 2003; Halliwell & Gutteridge, 1999). It is increasingly recognized that iron influences glucose metabolism, even in the absence of significant iron overload. In the general population, body iron stores are positively associated with the development of glucose intolerance, Type 2 diabetes (Barbieri et al., 2001; Medalie, Papie, Goldbourt, & Herman, 1975) and gestational diabetes mellitus (GDM) (Lao & Tam, 1997). Tissue iron stores contribute to produce and amplify the injury caused by free radicals as well as to modulate various steps involved in the inflammatory lesion (Fernandez, Lopez, & Wifredo, 2002). Lachili et al. (2001) found that administration of an iron supplement with vitamin C during the third trimester of pregnancy increased the measures of maternal iron status. An indicator of oxidative stress from lipid peroxidation, plasma thiobarbituric acid reactive substances (TBARS) was significantly increased in the 27 supplemented women compared with controls (Lachili et al., 2001).

In rats, both iron deficiency and excess result in free-radical mitochondrial damage (Srigiridhar, Nair, Subramaniam, & Singotamu, 2001). Estimates of gestational iron requirements and the proportion of iron absorbed from different iron supplemental doses suggest that, with present supplementation schemes, the intestinal mucosal cells are constantly exposed to unabsorbed iron excess and oxidative stress (Abraham, Yardley, & Wu, 1999).
Many studies have shown that high as well as low maternal antenatal hemoglobin (Hb) concentrations are associated with increased pregnancy complications and adverse outcome (Knottnerus, Delgado, Knipschild, Essed, & Smits, 1989; Murphy, O’Riordan, Newcombe, Coles, & Pearson, 1986), which include low birth weight, small-for-gestational-age newborns, preterm birth, increased prenatal mortality, and pre-eclampsia (Rasmussen & Oian 1993; Steer, Alam, Wadsworth, & Welch, 1995), but none had included GDM as one of the outcomes. Recently, some studies have shown that high hemoglobin concentration is an independent risk factor for GDM (Lao, Chan, Tam, & Ho 2002; Lao & Ho 2000). Another study demonstrated that maternal Hb concentration of 13 g/dl in the first antenatal visit is an independent risk factor for GDM (Graham, Ryall, & Wise, 1980). However, in studies performed in men, Hb was significantly related to the incidence of diabetes (Medalie, Papier, & Herman, 1974). Also in women, Hb was positively and significantly related to fasting glucose and glucose intolerance (Harlan, Harlan, Landis, & Goldstein 1978; Medalie et al., 1974; Rao, 1987; Rao & Morghom, 1984). Therefore, the association between high Hb with glucose intolerance may represent a universal phenomenon and may be independent of sex or pregnancy status. Accumulating evidence suggests a link between body iron excess and insulin metabolism (Fernandez et al., 2002). Studies have shown an association between serum ferritin and one or more metabolic syndrome features (Fernandez et al., 1998; Festa, D’Agostino, Tracey, & Haffner, 2002; Piperno et al., 2002; Williams, Poulton, & Williams, 2002). Moreover, a syndrome characterized by hepatic iron overload associated with insulin resistance features unrelated to genetic hemochromatosis has been described (Mendler et al., 1999; Moirand et al., 1997). Frequent blood donations have been demonstrated to reduce postprandial hyperinsulinemia in healthy volunteers, to improve insulin sensitivity, and to constitute a protective factor for the development of Type 2 diabetes (Ascherio, Rimm, Giovannucci, Willett, & Stampfer, 2001). In one study, women with high levels of ferritin (107 ng/ml) were nearly three times more likely to develop Type 2 diabetes over a 10-year interval, independent of other risk factors (Scholl, 2005). Increased serum ferritin concentration, which is associated with insulin resistance and diabetes in the general population (Fernandez et al., 1998; Tuomainen et al., 1997), has also been recently reported in GDM (Lao et al., 2002; Lao et al., 2001). All these observations suggest that iron is more intimately linked to human pathophysiology than previously thought. This study was performed to compare iron status in women with gestational diabetes mellitus and non-GDM women.

2. Patients and methods

In this case-control study, 34 women with diagnosed GDM (according to ADA criteria) (ADA, 2007) were compared with 34 non-GDM women in the control group.
at 24–28 weeks of pregnancy in terms of iron status. Among patients referred to Yazd obstetric clinics, women with GDM (diagnosed by a 100-g oral glucose load; two or more of the plasma glucose values should be met or exceeded for a positive diagnosis) (ADA, 2007) were selected consecutively. The control group was selected by performing an initial screening test in 24–28 weeks. A 1-h glucose challenge test was done as interpreted by the original ADA criteria and matched with the GDM group referred to Yazd obstetric clinics, women with GDM and BMI. Excluded were women with other causes of anemia such as thalassemia trait, chronic diseases, and infections.

Maternal iron status was examined at 24–28 weeks of pregnancy. The serum was aliquoted and sorted for the batch assay of serum ferritin (Immunoradiometric Assay by Kavo shyark Ferritin IRMA [125] kit) and serum iron and transferrin (measured as the total iron binding capacity with the calorimetric method) (Fig. 1). Transferrin saturation was calculated as serum iron divided by the total iron binding capacity (serum iron/TIBC).

Informed consent was obtained from all subjects and the research had the approval of the institutional review board and ethics committee of Yazd University of Medical Sciences and was carried out in accordance with the Declaration of Helsinki.

3. Statistical analysis

For statistical analysis, categorical variables were compared with the independent samples T-test and Mann–Whitney test. Continuous variables that are normally distributed were expressed as mean±S.D. Statistical calculation was performed using a commercial computer package (Statistical Package for Social Sciences for Windows version 13.0; SPSS, Inc.).

4. Results

In this study, 34 GDM women were compared with non-GDM groups. Our results showed that the mean Hb was significantly higher in the GDM group than in the control group (13.39±1.1 vs. 11.75±1.4 g/dl) (P<.0001) (Table 1).

There were significant differences in the mean serum iron between the two groups (100.44±22.09 vs. 56.85±23/03 μg/dl) (P<.0001) (Table 1). When mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were analyzed, they were all significantly higher in the GDM group (85.34±10.8 vs. 77.69±6.46 fl) (46.94 vs. 22.06 pg) (P=.001) (Table 1).

The mean TIBC was 383.09±30/55 μg/dl in the GDM group and was 457.79±58.20 μg/dl in the control group (according to P=.0001). Also, the mean transferrin saturation was significantly higher in the GDM group (26.49±5.94%) than in the control group (12.77±5.67%) (P=.0001). We found significant differences between the two groups in serum ferritin (73.34±31.73 vs. 41.55±28.31 ng/ml) (P<.0001). No significant association was observed with the other variables including familial history of GDM and diabetes.

5. Discussion

Our findings show that iron status in women with GDM was significantly higher than in the control group. Many studies have shown that increased iron stores in the general population have been associated with increased incidence of diabetes (Ford & Cogswell, 1999; Salonen, Tuomainen, Nyyssonon, Lakka, & Punnonen, 1998). These observations suggest that one prerequisite for the association between increased Hb and diabetes is the presence of at least an adequate, if not excessive, iron store in the individual.

Measurement of Hb concentration has become a standard laboratory test in pregnancy. Maternal Hb concentration reflects not only maternal nutritional status but also the degree of hemodilution, both of which would impact pregnancy outcome as reflected by the relationship between high and low Hb concentration with adverse pregnancy outcome (Scholl & Hediger 1994). In a case-control study in Chinese women with a body mass index (BMI) of more than 26 kg/m2, it was shown that those who developed impaired glucose tolerance, with the 2-h glucose value of the 75-g oral glucose tolerance test between 8.0 mmol/L (144 mg/dL) and 10.9 mmol/L (196 mg/dL), during pregnancy had significantly increased hemoglobin concentration compared with BMI-matched controls (Lao & Ho 2000). Indeed, in the same population, the incidence of GDM in women with iron-deficiency anemia was not only lower than that in the nonanemic women, but it was also significantly lower than that in women with thalassemia traits (Lao & Pun, 1996). In our study, Hb concentration was significantly higher in the study group, which confirms other studies.

In a prospective observational study of 762 nondiabetic Chinese women with singleton pregnancies, recruited at 28–30 weeks, the group in the highest hemoglobin quartile (more than 13 g/dl) had a significantly higher incidence of GDM (18.7% vs. 10.9%, P=.007), as well as greater age, weight, and serum ferritin and iron concentrations (Lao et al., 2002).

MCV is a robust index of maternal iron status in women without hemoglobinopathies (Godfrey, Redman, Barker, & Osmond, 1991; Tam & Lao, 1999). In our study, MCV level
in the study group (85.34±10.8 fl) was significantly higher than in the control group (77.69±6.46 fl).

In a prospective study, 401 pregnant women without anemia and diabetes mellitus were recruited at the time of oral glucose tolerance test (OGTT) at 28–31 weeks’ gestation for the study of serum ferritin, iron, and transferring concentration. GDM was diagnosed in 97 of the 401 women recruited. Compared with the 194 controls, there was no difference in the weight, BMI, and third trimester hemoglobin, but concentration of serum ferritin, iron, transferrin saturation, and postnatal hemoglobin were significantly higher (Lao et al., 2001). In another study on 1023 women, a twofold increase in risk of GDM was found for women in the highest quartile of serum ferritin at entry and nearly a threefold increase in the third trimester (ADA, 2004). This positive relation suggests that iron stores may play a role in the development of GDM, a precursor of Type 2 diabetes mellitus. Little is known about the relationship between anemia with diabetes or GDM. A study in the Chinese population has found that there was no apparent difference in the incidence of GDM between anemic and nonanemic women (Lao & Ho, 2000); however, when the type of anemia was further analyzed, women with iron deficiency anemia had about one-half the incidence of GDM compared not only with nonanemic women but also with women with anemia due to thalassemia trait (Lao & Pun, 1996). In a retrospective case-control study, 242 women with iron deficiency anemia were compared with 484 nonanemic women matched for year of birth; the prevalence of GDM is reduced in iron deficiency anemia (Lao & Ho, 2004).

In another study at the time of routine screening for anemia and GDM at 28–30 weeks of gestation, there were 60 patients with gestational impaired glucose tolerance (GIGT) and none had frank GDM. There was no difference in the hematological indexes or serum iron and TIBC values, but serum ferritin level was significantly increased in the GIGT group, when compared with control subjects (Lao & Tam, 1997). In our study, in addition to ferritin serum, iron and transferring saturation was also significantly higher probably because of frank GDM. There was this hypothesis that high iron stores in GDM women could be due to nutritional improvement in pregnant women (Lao & Ho, 2004), in addition, excess iron can affect insulin synthesis and secretion, and enhance oxidation of lipids which in turn decreases glucose utilization in muscles and increase gluconeogenesis in liver, thus leading to liver mediated insulin resistance. Accordingly, further studies are needed to show the role of increased maternal iron status from prophylactic iron supplementation and nutritional improvement in the development of GDM.

6. Conclusion

Our results suggest that iron status in women with GDM was significantly higher than in the control group. As iron is administrated during pregnancy, the role of iron excess from iron supplementation in the pathogenesis of GDM needs to be examined.

References


