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Iron Biomarker in Gestational Diabetes Pathogenesis

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Abstract

Gestational diabetes mellitus (GDM) is observed to be associated with increased perinatal morbidity and mortality. Screening for glucose intolerance during pregnancy provides an opportunity to offer management to those women diagnosed with gestational diabetes mellitus after first trimester. Elevated iron stores may induce diabetes through a variety of mechanisms, including oxidative damage to pancreatic beta cells, impairment of hepatic insulin extraction by the liver, and interference with insulin's ability to suppress hepatic glucose production. Raised Serum Ferritin could be related to the occurrence of long term complications of diabetes, both micro vascular and macro vascular. Iron affects glucose metabolism and glucose metabolism impinges on several iron metabolic processes. Iron overload decreases insulin sensitivity and cause earlier complications in diabetes mellitus. Iron plays a direct and causal role in diabetes pathogenesis mediated both by cell failure and insulin resistance. Iron also regulates metabolism in most tissues involved in fuel homeostasis, with the adipocyte in particular serving an iron-sensing role.

Keywords: Pregnancy; Diabetes; Gestational diabetes mellitus; Serum ferritin; Biomarkers

Background

Gestational diabetes mellitus (GDM) is a disturbance in glucose metabolism, which is diagnosed during pregnancy and affects pregnant women [1]. The incidence of gestational diabetes has been increasing the last 20 years [2]. The longitudinal changes in carbohydrate metabolism during gestation are integral to a successful pregnancy outcome for both mother and fetus. Therefore, prevention of any disease particularly non-communicable diseases includes four steps that include primary prevention, post primary prevention, secondary prevention and tertiary prevention [3]. The steps are taken after diagnosing some form of abnormal glucose tolerance like impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) are called post primary prevention. There are two components for the development of any disease, the genetic and the environmental factors. Of the two, there are evidences to establish the fact that the intra uterine environment plays a vital role in the development of diabetes. Intrauterine exposure to hyperglycemia during the critical period of fetal development programs the development of pancreas [4] relatively and affects insulin secretion function. Further maternal hyperglycemia has a direct effect on the fetal pancreas and is associated with the increased susceptibility to future diabetes in the infant. Women with a history of gestational diabetes mellitus as well as their children are at increased risk of future diabetes, predominantly type II diabetes [5]. During pregnancy, there is a significant alteration in glucose homeostasis secondary to the complex hormonal changes and increased metabolic demands of gravid uterus, its contents, and the mother [6]. The rise in the hormones includes estrogen, progesterone [7], human placental lactogen and cortisol that alters this metabolism is largely responsible for the altered homeostasis [8]. Gestational diabetes mellitus is the most common metabolic abnormality of carbohydrate metabolism of pregnancy occurring in 1-14% of the patients depends on a population. Criteria for diagnosis of gestational diabetes mellitus could define as carbohydrate intolerance of any degree with onset or first recognition during pregnancy. Diagnosis of gestational diabetes mellitus is important to identify both infants at risk of adverse outcomes and women at risk of subsequent development of diabetes. In addition to fetal demise [9], gestational diabetes mellitus has been linked to the complications of large for gestational age, macrosomia, birth trauma such as increased maternal lacerations and neonatal shoulder dystocia, increased need for operative interference and neonatal metabolic disorders such as hypoglycemia, hyper bilirubinemia and disordered calcium balance [10]. The occurrence of gestational diabetes mellitus may go unrecognized throughout pregnancy unless complications arise and some of these may occur late. Because gestational diabetes mellitus is associated with adverse effects on the pregnancy and a significant number of patients subsequently develop overt diabetes, it is important to screen for the condition. Ferritin, the major iron storage protein, plays a key role in iron metabolism [11,12]. Serum ferritin concentration provides an indirect estimate of body iron stores because it is highly correlated with bone marrow iron. Ferritin is also a positive acute-phase reactant and increases in the presence of various acute or chronic disease conditions [11,12]. Elevated serum ferritin levels have been found in many chronic inflammation–related diseases. Recent studies among healthy individuals and non pregnant women have shown positive associations of moderately elevated serum ferritin levels with risk factors for cardiovascular diseases (CVDs) [13,14]. Studies also showed a significant relation between higher serum ferritin levels and insulin resistance syndrome and risk of type 2 diabetes [15-17]. However, data are conflicting about whether elevated serum ferritin is an independent risk factor for diabetes and whether higher levels reflect inflammation or increased iron stores [10,13-15].

Gestational diabetes mellitus (GDM) increases the risk of macrosomia and perinatal morbidity and mortality for the fetus, while presaging a long-term risk of development of type 2 diabetes for the mother [16,17]. The mechanisms involved in the development of GDM are not completely understood. It is increasingly being recognized that there is a systemic inflammation in GDM, as indicated by higher levels of serum C-reactive protein (CRP) and/or interleukin-6 [18,19]. Inflammation is usually associated with obesity because adipocytes from adipose tissue can secrete pro inflammatory cytokines [20]. In pregnant Chinese women, serum ferritin concentration was higher in women with impaired glucose tolerance and GDM [21,22], but it is not clear if this increase reflected inflammation or excess iron stores. Data are not available on the relationship between serum ferritin and the risk of GDM in comparable U.S. populations. Thus, the objective of this study is to determine whether there is a relationship between serum ferritin concentration and the risk of GDM in pregnant women whether elevated serum ferritin reflected inflammation (CRP) or increased iron stores in gravidas who developed GDM. The amount of iron that would have to be absorbed to satisfy the gestational needs should be 4–5 mg/d during the second trimester and 6–7 mg/d during the third trimester.

Significance of Biomarkers in GDM

Screening for glucose intolerance during pregnancy provides an opportunity to offer management to those women diagnosed with gestational diabetes mellitus especially in first and second trimester of pregnancy. However, there is a need to diagnose gestational diabetes early to minimize exposure of the developing foetus to suboptimal conditions and prevent prenatal complications. The purpose of this study is to identify potential biomarkers for impending gestational diabetes that appear in the plasma before impaired glucose tolerance. Biomarkers play an integral part in conducting clinical trials and treating patients. In most instances, they help medical practitioners, researchers, and regulatory officials make well-informed, scientifically sound decisions. However, in clinical studies, there is often uncertainty in how much weight to place on biomarker results versus clinical outcomes. This uncertainty emanates from opposing goals of the drug approval process. On one hand, the process must ensure that all therapeutics test is safe and that the benefits outweigh the risks. On the other hand, the process should allow therapies to be accessible to patients as quickly as reasonably possible. Judicious use of biomarkers in the drug development process can bring these goals into alignment. More efficient discovery and use of biomarkers in the development of anti diabetic drugs will depend on advancing our understanding of the pathogenesis of diabetes and especially its macro vascular and other complications in pregnancy. Serum ferritin level is highly associated with GDM independently of BMI the mid-pregnancy ferritin level is not a prognostic factor for pregnancy morbidity or subsequent impaired glucose tolerance after delivery, and fasting plasma glucose values at the time of diagnosis of GDM are the most important prognostic factors for glucose concentration in an early postpartum oral glucose tolerance test. serum ferritin concentrations during diabetic pregnancy reflects insulin resistance, and also the risk of subsequent development of postpartum impaired glucose tolerance and overt DM but serum ferritin level in case of GDM alters the development of fetus in many ways.

Iron and Diabetes Risk

Iron overload is a risk factor for diabetes. The link between iron and diabetes was first recognized in pathologic conditions—hereditary hemochromatosis and thalassemia—but high levels of dietary iron also impart diabetes risk. Iron plays a direct and causal role in diabetes pathogenesis mediated both by cell failure and insulin resistance. Iron also regulates metabolism in most tissues involved in fuel homeostasis, with the adipocyte in particular serving an iron-sensing role. The underlying molecular mechanisms mediating these effects are numerous and incompletely understood but include oxidant stress and modulation of adipokines and intracellular signal transduction pathways.

Pregnancy Outcome with Increased Iron Status and Stores

Randomized trials of iron prophylaxis during pregnancy have demonstrated positive effects on reducing low haemoglobin and hematocrit, and increasing serum ferritin, serum iron and other measures, including bone marrow iron [23,24]. A recent study of iron containing supplement utilization from NHANES, 2008–2011 showed that 72% of pregnant and 69% of lactating Women used iron supplements during the month before they were surveyed. However, median consumption of supplemental iron was in excess of the tolerable upper limit of 45 mg/d in pregnant (58 mg/d) and lactating women (57 mg/d) [25]. Overall, -15% of reproductive age women, pregnant and no pregnant alike, who took iron supplements, had or were being treated for anemia within the past 3 months. Thus, there is a potential concern that some women who are not anemic may be taking large doses of supplemental iron during pregnancy. It has been suggested that such use may build up the mother's iron stores and increase blood viscosity so that utero-placental blood flow is impaired or that the excess iron intake could cause other toxic reactions [26]. In addition to their work on anemia, Scanlon and colleagues considered high levels of haemoglobin during the 1st and 2nd trimesters [9]. They found that high haemoglobin was associated with an increased risk (5%–79%) of small for gestational age (SGA) births, but not with preterm delivery. Levels that were 1SD unit or more above the mean marked the threshold for increased risk and were equivalent to 131 g/L at week 12 and 126 g/L at week 18. Likewise, Zhou et al. [24] examined high haemoglobin along with anemia. During the 1st trimester women with hemoglobin levels exceeding 130 g/L showed no increase in the risk of SGA births but had a 2-fold increases in preterm delivery and infant low birth weight. There were few such women and increased risks were usually not statistically significant. Failure of hemoglobin to fall below 105 g/L was associated with increased risk of poor outcome in a multiethnic sample of gravidas from England [27]. In the stratum of women whose lowest hemoglobin was between 126–135 g/L, there was a greater than 2-fold increase in preterm delivery and low birth weight and at the highest level, when hemoglobin remained above 145 g/L, there was a 7-fold increase in risk of low birth weight and 5-fold increases in risk of preterm delivery. Hemminiki and Rimpela carried out a clinical trial of selective versus routine iron supplementation in 2912 Finnish women [28-30] to determine whether routine supplementation with iron (100 mg elemental iron from at least 16 wk gestation to delivery) in non anemic women increased risk of high maternal haemoglobin and poor fetal growth. Women randomized to the selective group received iron supplements only when hematocrit fell below 30% or haemoglobin below 100 g/L on 2 consecutive visits after week 33. In comparison to selective gestation supplementation,

routine supplementation with iron halted the decline in hematocrit by week 20 and did not alter infant birth weight, whereas duration was increased significantly (0.2 wk). Interestingly, in both routine and non routine groups, a high hematocrit was negatively correlated with birth weight and placental weight; this correlation was first detected during the 1st trimester [23]. A recent study from the Netherlands, wherein a cohort of 240 women was monitored from before conception to delivery, underscores this point. Gravidas with an early pregnancy fetal loss had a less profound decline in hematocrit from before conception to 10 wk post LMP [24]. Thus, factors that underlie an adverse pregnancy outcome (poor plasma volume expansion, increased blood viscosity) may give rise to high maternal haemoglobin rather than use of iron supplements. Iron stores that are elevated for pregnancy are associated with preterm delivery, preeclampsia and gestational diabetes mellitus. Women with ferritin levels that are elevated for the 3rd trimester of pregnancy (41 ng/mL) have a greatly increased risk of preterm and very preterm delivery that has been attributed to intrauterine infection [25,26]. Another plausible mechanism for high ferritin levels is failure of the maternal plasma volume to expand. In Camden, increased IDA and lower levels of folate were found in women who went on to have high 3rd trimester ferritin. In the 3rd trimester the situation reversed, thus implicating plasma volume expansion [26]. Ferritin production also is increased with infection and inflammation as part of the acute phase response. In the presence of infection, macrophages produce inflammatory cytokines that generate reactive oxygen species, releasing free iron from ferritin [31].

Iron, Maternal Diabetes, and Oxidative Stress

Iron supplementation during pregnancy increases maternal iron status during pregnancy including hemoglobin, serum iron, MCV, transferrin saturation, and serum ferritin. Reactive oxygen species are products of oxygen. When brought into contact with a transition metal that is capable of changing valence, such as iron, (Fe(II)-Fe(III)) a very reactive free radical, the hydroxyl radical is formed from oxygen via the Fenton Reaction. These free radicals have the potential to damage cells, organs, and tissues in the body [32]. Oxidative stress over time is now thought to be a component of the processes of aging, cancer, and the development of cardiovascular disease. 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 insulin [33]. It is difficult for reproductive age women to become iron overloaded because of blood loss with menstruation. However, moderately elevated iron stores also increase the risk of type 2 diabetes [34]. 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 ethnicity. High levels of ferritin were a risk factor for the development of gestational diabetes mellitus (GDM) in pregnant women. Non anemic gravidas from Hong Kong who developed GDM during the course of pregnancy were compared with control without anemia or diabetes selected at random from the at-risk population. Unadjusted concentrations of serum ferritin, iron, transferrin saturation, and the post-natal hemoglobin were significantly higher at 28–31 wk gestation in cases with GDM compared with controls [35]. In Camden, use of iron supplements increased serum ferritin concentrations. At entry to care and in the 3rd trimester, gravidas who took iron were significantly more likely to be in the highest quintile of serum ferritin. At entry the likelihood of being in the highest quintile was increased by 44% (OR: 1.44, 95%) and in the 3rd trimester it was increased 2-fold (OR: 2.01, 95% CI 1.48-2.74). We were able to detect an association between maternal serum ferritin and gestational diabetes using data from 1023 gravidas from Camden. Controlling for potential confounding variables (age, BMI, parity, ethnicity, smoking, iron supplement use), we found a 2-fold increase in risk of GDM for women in the highest quartile of serum ferritin at entry (AOR 2.32; 95% CI 1.06–5.08) and nearly a 3-fold increase in the 3rd trimester (AOR 2.9; 95% CI 1.27-6.95) [36]. This positive relation suggests that iron stores may play a role in the development of GDM, a precursor of type 2 diabetes mellitus. Supplementation with iron clearly augments iron status and iron stores. Whether supplementation with iron during pregnancy increases oxidative stress by adding to iron stores and creating a temporary iron surplus has been little studied. Because an increase in oxidative stress is part of normal pregnancy, routine iron supplementation in women who were not iron depleted or deficient might also contribute to or exacerbate oxidative stress.

Cytochrome P450 monooxygenases are a superfamily of heme-thiolate proteins which are involved in the biotransformation of endogenous compounds such as steroids, fatty acids, vitamins, bile acids, leukotriens, thromboxanes and prostaglandins. It is demonstrated to produce reactive oxygen species (ROS) such as superoxide radical and hydrogen peroxide. These ROS produced by the P450 system may serve as precursors for the generation of other oxidants. The heme moiety of cytochrome P450 system therefore may serve as an intracellular source of iron capable of catalyzing free radical reactions. Maternal Diabetes can alter the ROS production which will influence many physiological pathways during pregnancy.

Serum Ferritin and Cardiovascular Disease

In 1981, Sullivan [37] proposed that body iron stores are positively related to coronary heart disease (CHD) risk. The theory was that production of free radicals that subsequently modify low density lipoprotein cholesterol was important in the development of atherosclerosis and that iron helps to catalyze the oxidation reactions that produce free radicals [38,39]. Since the 1992 publication of data from Finland showing a positive relation between serum ferritin and risk of acute myocardial infarction in men [40], there has been considerable interest in this theory. The accumulated epidemiologic evidence has been inconsistent, but most studies do not support the theory [38-42].

Studies have varied in their design and the measure of stored body iron used. Serum ferritin is regarded as the best biochemical measure of body iron stores [43]. Most of the cross-sectional and case-control studies used serum ferritin, and a few found a significant association. However, because the disease itself and changed behavior due to disease influence serum ferritin levels, these study findings are not as useful as those from prospective studies. Eight prospective studies have been reported, and two found a significant association, one with CHD in a Finnish study and one with an ultrasound measure of atherosclerosis in an Italian study [44]. Most of the prospective studies had a short follow-up, few provided results for women, and few involved more than 100 cases. In addition, despite the iron theory relating to atherosclerosis in general, few studies have examined serum ferritin in relation to other forms of cardiovascular disease such as stroke. Given the inconsistency and limitations of previous studies, it is surprising that there have been suggestions for changes to dietary recommendations and a suggestion of phlebotomy as a means of

lowering iron levels [45,46]. Clearly, further long-term prospective studies are needed.

Potential Molecular Mechanisms for Iron Regulation and Glucose Metabolism

The mechanisms underlying the effects of altering tissue iron on metabolism are just beginning to be understood. Given the many effects in multiple tissues already described and the involvement of iron and heme in processes as diverse as glucose and fat oxidation, hypoxia sensing [47], CO and NO sensing, transcriptional regulation [48], generation of reactive oxygen species, and regulation of hormone levels, the effects of iron are likely to be protean. Furthermore, the effects will have dose thresholds that will differ across the range.

In patients who have had an episode of unstable coronary artery disease, levels of inflammation markers such as acute-phase proteins, C-reactive protein, and fibrinogen tend to be higher, which is the result of an increase in the risk of cardiovascular disease. Fibrinogen plays a key role in both coagulation cascade and platelet aggregation, which is a determinant of plasma viscosity. Free radical species are important agents in both myocardial ischemic and reperfusion injuries. Superoxide is capable of releasing iron from ferritin, and the released iron can cause hydroxyl formation from H_2O_2 . Most of the ferritin is found in the liver cells, spleen and bone marrow. It is also found in the heart, pancreas and kidney. Human serum contains a small but significant quantity of ferritin. Serum ferritin levels are affected by age and sex. In normal individuals, ferritin levels are slightly higher at birth and decrease during childhood until puberty. After puberty, body iron storage in males increases progressively with a proportional rise in serum ferritin, whereas serum ferritin levels are lower and more stable in females the during reproductive period. Ferritin levels only increase after the menopause. Literally, may the difference in hemorheological properties in female blood is caused by the increased concentration of younger red blood cells(RBCs) and the reduced population of older RBCs. Higher viscosity, increased RBC aggregation and decreased RBC deformability are observed in male compared with female blood. The Oxygen Delivery Index (a ratio of hematocrit levels to blood viscosity) is significantly lower in the male population. There is also a higher risk of cardiovascular disease due to decreased oxygen delivery, increased RBC aggregation and by steroids during stress could be the cause of increased serum ferritin levels following AMI. There is a hypothesis that iron depletion improves vascular dysfunction in type 2 diabetic patients with high ferritin concentrations [49]. The relationship between inflammation and insulin resistance has long been accepted. Insulin resistance is also associated with atheromatous risk factors, such as central obesity, hyperinsulinemia, hyperglycemia and hypertriglyceridemia.

Serum Ferritin – A Risk Factor in Type 2 Diabetes Mellitus

Ferritin has been known as an index for body iron stores and also as an inflammatory marker. In some epidemiological studies, serum ferritin was the second strongest determinant of blood glucose (after BMI) in regression models and the third strongest determinant of serum insulin (after BMI and age). Its concentration also correlated positively with plasma triglycerides and apolipo protein B concentrations, and negatively with HDL2 cholesterol. It was then hypothesized that serum ferritin could be a marker of insulin resistance. The probable correlation between ferritin and DM was considered first in 1993 by Kayet al., after which other studies were focused on this subject. In 1999 a survey by Ford and his colleagues in United States on 9486 diabetic adults determined high levels of ferritin in diabetics. Another study by Kwant8 on the prevalence of C282Y mutation of hemochromatosis gene, determined the higher prevalence of this mutation in type 2 DM that could be considered as an evidence for some relationship between these two disorders. Fernandez in 1998 studied the relationship between serum ferritin and the results of glucose tolerance test and insulin sensitivity in healthy subjects. In this study the correlation between serum ferritin and diastolic blood pressure, HDL, glucose area under the curve and insulin sensitivity suggest that serum ferritin could be a marker of insulin resistance. Such results have also been reported by Kim et al. There are different theories regarding the role of ferritin in DM. Pancreatic damage due to some degree of subclinical hemochromatosis has been considered at least in some cases of diabetes. Others have determined ferritin just as a marker of pancreatic inflammation, and some have referred to it as a marker for insulin resistance as mentioned above. Fernandez et al, studied the effect of ferritin reduction by bloodletting on insulin sensitivity and HbA1c levels in diabetic patients. In this study the positive effect of ferritin reduction on blood glucose control was used for confirmation of the probable role of ferritin in DM pathogenesis but, the use of bloodletting may affect total hemoglobin level and HbA1c as well, so the use of HbA1c as a marker of blood glucose control has not been appropriate. Recently some studies have investigated the effect of chelator agents such as Desferal on the control of diabetes mellitus. There are different results in this regard. Some studies have determined a higher level of ferritin in people who are high risk for atherosclerosis. Since insulin resistance has been considered as the basic factor in the pathogenesis of atherosclerosis12 higher ferritin in atherosclerotic patients can be due to insulin resistance. Poorly controlled patients of DM have hyperferritinemia which co-relates with diabetic retinopathy, diabetic nephropathy and vascular dysfunction. Jiang et al. [34] have reported elaboration of hydroxyl radical in iron overload which causes cell damage and leads to insulin resistance. Deferroxamine, a chelating agent with antioxidant properties improve fasting blood glucose in chronically transfused patients of thalassemia major support this hypothesis. Recently, it has been suggested that transferrin and iron induce IR of glucose transport in adipocytes. Some studies found a positive correlation between increased SF and poor glycemic control reflected by higher HbA1C, supporting the findings of Eschwege et al. DyMock et al. [32] reported influence of the increased body iron stores on diabetic nephropathy and vascular dysfunction. In patients with increased SF glycemic control is poor and there is vascular damage. Insulin resistance has been documented by Ralpha & Fronzo [48] in such patients.

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