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The Roles of Adipose Tissue and Inflammation in Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with first onset or first identification in pregnancy. It is one of the most common complications of pregnancy with a prevalence ranging from 3% to upwards of 16% depending on the screened population and whether a 1 or 2-step screening algorithm is utilized. Its occurrence has historically been predominantly attributed to pro-diabetogenic placental hormone secretion. However, there is emerging evidence to indicate that its mechanistic underpinnings are more complex; similar to type 2 Diabetes Mellitus (T2DM), adipose tissue dysfunction and associated inflammation may be key etiologic factors for the development of GDM. In support of this view, women with a history of GDM are at high risk of subsequent T2DM development and their offspring at increased risk of obesity and metabolic syndrome across their life span. With immediate and long term consequences of GDM on mother and offspring, etiologic understanding that can inform therapeutic and preventative targets is essential. This review article explores the existing literature as it relates to associations of GDM with expansion of adipose tissue depots, secretion of adipose derived biologically active factors, and inflammation and inflammatory related substances.

Keywords: Gestational diabetes mellitus; Inflammation; Adipose tissue; Cytokines; Adipokines; Adipocytokines

Introduction

Pregnancy is a unique physiological condition where weight gain, in accordance with Institute of Medicine pre-pregnancy BMI-specific recommendations, is expected [1]. Some gained weight is attributable to fetus, placenta, amniotic fluid and increased blood volume (~15 pounds); the majority of remaining weight is associated with accumulated adipose tissue (AT), necessary for fetal growth support and subsequent postpartum neonatal support through lactation. Normal pregnancy physiology is characterized by a state of insulin resistance, which has been thought to result in the channeling of maternal nutrients towards support of the growing fetal-placental system. However, despite universal placental production of pro-diabetogenic hormones and the existence of an insulin-resistant or carbohydrate-intolerant state, only a fraction of non-pregestational diabetic women additionally experience pancreatic β-cell insufficiency such that they develop gestational diabetes mellitus (GDM). Thus, in addition to placental hormone secretion, other pregnancy-associated factors must contribute to the development of GDM. In this context, pregnancy-associated adipose tissue expansion, which can enhance insulin resistance and induce inflammation, could be an important risk factor.

GDM is defined as carbohydrate intolerance with onset or first recognition in pregnancy [2]. The American College of Obstetrician and Gynecologists recommends screening all non-pregestational diabetic pregnant women for GDM with medical history, clinical risk factors and/or 2-step laboratory testing [2]. When 2-step laboratory testing is utilized, the first step screening evaluation is usually done between 24-28 weeks gestation with venous blood evaluated 1 hour following a 50g glucose load. A second subsequent diagnostic evaluation is necessary if screening results exceed either a cut-off of 135 or 140 mg/dl, depending on practice protocols. GDM is diagnosed if a failed screening test is followed by a 3 hour 100g diagnostic oral glucose tolerance test in which 2 or more values from the fasting or subsequent 3 postprandial hourly values equal or exceed indicated thresholds by either Carpenter or Coustan or National Diabetes Data Group criteria [2]. A 1-step approach to GDM diagnosis using a 75g oral glucose tolerance load, with a 2 hour postprandial evaluation, has been proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) based on data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [3] and has been adopted by most non-US countries.

Epidemiologic studies show that the prevalence of GDM is strongly correlated with the prevalence of Type 2 Diabetes Mellitus (T2DM) in a population, with significant differences noted in rates amongst racial and ethnic groups [2]. The prevalence by 2-step screening ranges from ~3-8% [4], whereas the 1-step approach results in ~16% of the population being diagnosed with GDM [5]. These prevalence rates make GDM one of the most common complications of pregnancy.

GDM most often resolves immediately following birth. However it is subsequently associated with T2DM development; in some populations this rate is up to a 50% incidence within 5 years postpartum [6]. Mothers with GDM history have a 7-fold increased risk of developing T2DM [7] and there is evidence that up to one-third of women with T2DM have a GDM history [8]. These findings suggest that women with GDM represent individuals with higher inherent

T2DM risk prior to pregnancy. However, the mechanistic underpinnings that determine differences between the subgroup of women who develop GDM and those who do not are not clear. Understanding of these differences is essential given associations of GDM with maternal T2DM and cardiovascular sequelae, and offspring risk of obesity and metabolic syndrome across the life span [9-13].

Pregnancy, Adipose Tissue and T2DM

The development of T2DM has been strongly associated epidemiologically with weight gain. Moreover, a causal relationship between weight gain and insulin resistance was inferred from classical studies in which healthy lean individuals became insulin resistant upon experimental over-nutrition [14]. Additionally, the adipose tissue of mice subjected to a short-term high fat diet, contain enlarged adipocytes that display insulin resistance [15]. Thus, adipocyte hypertrophy during weight gain can directly cause insulin resistance.

Adipocyte hypertrophy may cause insulin resistance through various mechanisms. First, the limited capacity of hypertrophied adipocytes to store additional fat can result in ectopic fatty acid accumulation, triggering lipotoxicity and inflammation in multiple tissues [16-18]. The finding that liver fat content in obese women with previous GDM is strongly associated with insulin resistance, more than any other measures of body composition [19], is consistent with impaired capacity of adipose tissue to sequester fat in individuals developing GDM. Additionally, differences in plasma fatty acid profiles between women with and without GDM suggest similar alterations of fatty acid metabolism in GDM as compared to T2DM [20,21].

In addition to producing lipotoxic fat accumulation in peripheral tissues as a result of limited storage capacity, enlarged adipocytes themselves can secrete pro-inflammatory factors, triggering macrophage infiltration, adipose tissue damage, and a further limitation in adipose tissue storage capacity. Multiple studies have found that expansion of VAT is accompanied by macrophage infiltration and inflammation, which may contribute to the development of non-pregnancy related IR [22]. The evidence for chronic inflammation in pregnancy and its association with GDM development is reviewed below.

Importantly, increased adipose tissue mass can be generated with minimal adipocyte hypertrophy through the process of hyperplasia, where an increase number of adipocytes, rather than the enlargement of existing adipocytes, enables fat storage. Hyperplasia in visceral and subcutaneous adipose tissue depots correlates with decreased risk of lipid, glucose and insulin abnormalities [23]. It is possible that subcutaneous adipose tissue is inherently better able to undergo hyperplasia, as multiple studies indicate that increased weight associated with subcutaneous AT (SQAT) expansion decreases non-pregnancy related IR odds by 48% [24], while weight gain associated with VAT expansion increases the odds by 80%. The differential risk accompanying expansion of different depots is also seen in GDM, where ultrasonography evaluation of SQAT and VAT mass at 12 weeks gestation has identified increased risk of abnormal glucose tolerance in women with VAT depth above the upper quartile, but risk was not related to SQAT [24]. The differential risk conferred by fat accumulation in SQAT or VAT depots during gestation could explain the paradox that the association between gestational weight gain and GDM is less consistent [1] than the overall association between BMI, obesity and body fat percentage [25,26] with GDM development. Thus, an individual whose gestational weight gain occurs as SQAT hyperplasia would be at much lower risk of GDM that one with VAT hypertrophy, despite equal net fat accumulation.

Biomarkers of AT Associated Inflammation in GDM

Evidence for the role of inflammation in GDM is supported by studies that find individuals with GDM having increased leukocyte counts [27] and altered adipocytokine and inflammatory biomarker profiles, similar to non-pregnant individuals with T2DM. In some cases, these changes in adipocytokines and inflammatory profiles persist for years beyond pregnancies complicated by GDM [28-32] lending further credence to similar etiologic underpinnings of GDM and T2DM, with adipose tissue function as a major component of risk. Here we summarize the evidence for a role in GDM of adipose tissue-related mediators implicated in the pathogenesis of insulin resistance and inflammation.

Adiponectin

Adiponectin is an adipocytokine with anti-inflammatory and insulin-sensitizing properties. Adiponectin levels are lower in T2DM [33] in direct contrast to other cytokines like TNFα, IL-6 and leptin that are elevated with T2DM [34].

Plasma adiponectin concentrations have been reported to be similar in normal pregnant women as compared to non-pregnant controls. However in most [35-40] but not all studies [41,42] adiponectin plasma concentrations are consistently lower in GDM compared to control gravidas [35-38,40,42,43] even when evaluated early in gestation [39,42], late gestation [43], and after controlling for BMI [37-39] and weight gain [38] among other factors. Moreover, fetal adiponectin levels, measured in umbilical cord blood, demonstrate lower values in those born to GDM as opposed to non-diabetic mothers [36]. Adiponectin concentrations in women developing GDM, are negatively correlated with prepregnancy BMI [37,39,41], BMI at time of sampling [37,41], and triglycerides [37], whereas levels in normal glucose tolerant gravidas are only negatively correlated with triglycerides [37]. These data suggest that adipose tissue in women developing GDM is qualitatively different from that in normoglycemic gravidas, independent of quantitative differences in accumulation reflected in BMI.

Interestingly, while adiponectin is considered to be produced almost exclusively by adipose tissue in humans, it is also produced by placental syncytiotrophoblasts in pregnancy [44]. Given the varied sources of adiponectin during gestation, the cause of decreased circulating adiponectin in GDM is unclear. To address this question, the culture medium of explanted placenta, fetal membranes, and maternal SQAT and skeletal muscle has been analyzed. While this medium contains detectable amounts of immunoreactive adiponectin, no difference in release has been noted in adiponectin between GDM and control gravidas [45]. Nevertheless, lower adiponectin mRNA levels in SQAT in GDM as compared to control gravidas has been reported [41], suggesting that adipose tissue is the main contributor to the difference in circulating adiponectin. Consistent with this notion is the findings of no difference in adiponectin placental gene expression between GDM and control gravidas [46]. However, a contribution of placental adiponectin cannot be ruled out, as several studies have shown modulation of placenta adiponectin receptors, adiponectin gene expression, and secretion by cytokines (e.g. TNFα, IFN-γ, IL-6 and leptin); and this modulation has been reported to vary with GDM

in some studies [44]. Taken together, evidence suggests that impaired capacity of SQAT to secrete adiponectin may be a risk factor for GDM.

Leptin

Leptin, an adipokine, is secreted predominantly by adipose tissue and acts both centrally and peripherally to regulate energy intake and expenditure. Leptin has well-established connections with obesity, and functions to increase insulin sensitivity by regulating insulin secretion, glycogen synthesis, glucose utilization, and fatty acid metabolism [47]. Leptin is additionally involved in a number of other physiologic processes including regulation of endocrine function, inflammation, immune response, reproduction, and angiogenesis [47]. Leptin serves a critical role in pregnancy as it is involved in implantation, production of trophoblast cells, regulation of placental growth, and amino acid uptake stimulation [48]. Pregnancy is considered a leptin resistant state with serum concentrations elevated even in early pregnancy suggesting that the increase is not related to maternal weight gain nor derived from adipose tissue exclusively [49]. Leptin levels are higher in pregnant as compared to non-pregnant women [50,51], increasing until approximately 28 weeks gestation and then decreasing to non-pregnant levels almost immediately postpartum [52]. Leptin and leptin receptor expression through mRNA and protein have been identified in human placenta [53,54], with increased expression of leptin noted in GDM placentas compared to controls [55-57]. When considering the culture medium of explanted placenta, amnion and choriodecidua, detectable levels of immunoreactive leptin are higher in control pregnancies as compared to GDM; however, this situation is reversed in maternal tissues (adipose tissue and skeletal muscle) where higher detectable levels are found in the GDM pregnancies with a gradient of higher levels in insulin versus diet-managed gestational diabetic gravidas [45].

Women with GDM have been demonstrated to have higher serum values of leptin during pregnancy [35,42,43,51,58-63] and subsequently postpartum compared to controls [51,58,64]. However these results are not consistent across studies as others report decreased [65] and non-different [40,64,66,67] leptin levels in pregnancy, and decreased or non-different [61] levels postpartum. Umbilical cord blood [68,69] and amniotic fluid [70] leptin levels have also been reported as higher in GDM compared to control pregnancies, with the difference in cord blood no longer evident when adjusting for neonatal body composition.

Studies have indicated that differential leptin levels are better explained by maternal BMI as opposed to diabetes status [71] and that there is a positive correlation for leptin with prepregnancy and pregnancy BMI [51,58,65], and maternal weight gain [51]. Other studies demonstrate continued differences even after controlling for maternal prepregnancy BMI or adiposity and note a linear trend in GDM risk with increasing maternal plasma leptin concentrations [63].

The preponderance of evidence indicates that elevated serum leptin levels are associated with GDM risk. Whether the leptin is adipose tissue or placentally derived is unclear although there is significant evidence supporting contribution from both tissue sources. One possible function of increased leptin levels in pregnancy is to mobilize maternal fat stores to increase transplacental support of the growing gestation. Increased levels in the fetal tissue support this and also lend support to the concept of intergenerational exposure and thus cycles of obesity and cardiometabolic dysfunction. One possible hypothesis linking higher leptin to GDM risk is that the combination of fat mobilization due to elevated leptin with diminished adipocyte storage capacity may contribute to lipotoxicity in peripheral tissues and enhance GDM risk.

cRP

C-reactive protein is an acute phase reactant blood protein that is elevated in conditions of inflammation. Retnakaran et al found that systemic cRP levels correlate with prepregnancy BMI but not glycemic status in overweight/obese and lean gravidas with varying degrees of impaired glucose tolerance [72]. Bo et al. reported that cRP is significantly higher in GDM women compared to normal weight women, but not significantly different from overweight/obese normal glucose tolerant subjects at 24-28 weeks and 32-36 weeks gestation; after adjusting for BMI, no significant correlation remaine [73]. Similarly, Wolf et al. noted increased GDM risk in subjects in the highest cRP tertile compared to the lowest but this association was attenuated upon controlling for BMI [74] and Rota et al noted similar findings along with a strong association with glycemic parameters and gestational weight gain [75]. Alternatively, Qiu et al. confirmed a positive association of increased cRP with GDM risk with an association persisting for women in the highest cRP tertile, even after controlling for maternal prepregnancy BMI, T2DM family history, and nulliparity, compared to those in the lowest tertile, with a notable 3.5-fold increased GDM risk [76]. Thus, the predominance of evidence points to a strong association with cRP and BMI, which is maintained during pregnancy. However, an independent association between cRP and GDM risk independent of BMI seems less well supported.

TNFα

TNFα is an inflammatory cytokine secreted by both AT [77] and the placenta [77,78] with the vast majority of placentally derived TNFα released into the maternal circulation [78]. TNFα secretion is associated with adipose tissue expansion and has been implicated in the pathogenesis of IR. Systemic TNFα increases over the course of normal pregnancy [73,78]. Its levels are inversely correlated with insulin sensitivity even after adjusting for BMI [78] such that it is an independent predictor of insulin sensitivity in pregnancy [73]. Elevated systemic levels of maternal TNFα are found in GDM gravidas compared to normal glucose tolerant gravidas [35,37,42,73,79,80] and non-pregnant women [81]. While this relationship between TNFα levels and insulin sensitivity persists after controlling for BMI, it should be noted that in GDM women, prepregnancy BMI is the most predictive indicator of TNFα concentrations with additional variance explained by BMI at time of sampling and triglyceride concentrations [37]. The source of increased circulating TNFα in GDM is unclear, as placenta, SQAT and VAT explants product TNFα, and increasing glucose concentration stimulate production [77]. However, basal release of TNFα from placenta, SQAT and pyrmadalis skeletal muscle has not been shown to be different in normal versus GDM gravidas [82] and TNFα placental gene expression has not been identified as being different between GDM and control gravidas [46]. While identifying the source of increased TNFα in GDM is required, the available evidence suggests that adipose tissue may be a major source.

IL-6

IL-6 is a cytokine with both pro- and anti-inflammatory properties that is secreted by T-cells and macrophages. Although IL-6 is not secreted by adipocytes specifically, adipose tissue expansion can be accompanied by macrophage infiltration and this infiltration results in elevated IL-6 levels that have been associated with elevated BMI [83]

IL-6 has been identified as a potential mediator linking obesity and IR development in the non-pregnant state, [22] in particular accompanying VAT expansion. The role of IL-6 in GDM has been less well explored. Release of IL-6 from placenta, SQAT and pyrmadalis skeletal muscles in-vitro has not been shown to be different in normal versus GDM gravidas [82]. However, several studies have found increased serum levels of IL-6 in GDM compared to control gravidas in the mid to third trimester [84-86], at delivery [35], and persisting postpartum [86], independent of BMI [85,86]. The source of IL-6 in GDM is likely to be adipose tissue as IL-6 gene expression is increased in the SQAT of GDM gravidas compared to controls [46]. Moreover, no difference has been found in placental expression of IL-6 between normal and GDM [46]. Thus, in contrast to cRP, but similarly to TNFα, IL-6 production by adipose tissue is associated with GDM risk independent of BMI.

Omentin-1

Omentin-1 is an adipokine detectable in human plasma [87] that is associated with enhanced insulin-stimulated glucose uptake by both subcutaneous and visceral adipocytes [88]. It is a depot-specific secretory protein produced by stromal vascular cells of omental visceral AT with its mRNA predominantly expressed in omentum and nearly undetectable in subcutaneous AT [88]. In non-pregnant humans, omentin-1 is inversely correlated with BMI, waist circumference, leptin levels, and IR [87]. Similarly, maternal prepregnancy obesity is associated with lower maternal plasma omentin-1 levels, as well as with lower omentin-1 gene expression in both placenta and AT; cord blood levels are unaffected by maternal obesity [89]. Interestingly, in non-obese gravidas the levels of omentin are lower in those with GDM compared to those with normal glucose tolerance; while these results might suggest that lower levels of omentin might increase the risk of insulin resistance, the lower levels of omentin seen in obese gravidas without GDM suggest that this adipokine per se does not determine insulin sensitivity in pregnancy [89]. Moreover, neither cord blood levels, nor placental or AT expression of omentin-1 are altered in GDM [89]. Nevertheless, the observed decreased levels of omentin in normal weight individuals with GDM may be important in that they reflect qualitative differences in VAT functionality of gravidas at higher risk of GDM.

Resistin

Resistin was discovered in mouse studies as an adipokine capable of impairing glucose tolerance by decreasing insulin sensitivity and by increasing plasma glucose concentration. [90] However, subsequent studies have shown that in humans, resistin is mostly secreted by macrophages [91]. Serum levels are increased in normal pregnancy [36,84,92,93] and studies have found a negative correlation between serum resistin and advancing gestational age [36] and others noting an increase with advancing trimesters [92,93]. Studies have measured resistin levels in GDM pregnancies compared with uncomplicated pregnancies with inconsistent results including increased values [84,93,94], decreased values [95] and no difference [36,96] Levels decrease postpartum in both GDM and non-diabetic pregnancies [94,95] Moreover, there is no difference in umbilical cord blood resistin levels in GDM versus control pregnancies [96].

The culture medium of explanted placenta, fetal membranes and maternal SQAT and skeletal muscle have detectable levels of immunoreactive resistin; however no difference in resistin release in culture medium [45] or in resistin placental gene expression [46] has been noted between GDM and control gravidas. No effect on explant incubation (placenta, fetal membranes, maternal AT and skeletal muscle) with LPS, IL-6, IL-8 or TNFα has been demonstrated on resistin release [45]. Thus, the role of resistin in GDM seems less significant than other adipose tissue associated cytokines.

Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 is secreted mainly by endothelial cells with contributions from other tissues including adipose tissue; it inhibits serine proteases (tissue plasminogen activator and urokinase) resulting in fibrinolysis inhibition. PAI-1 is increased in various disease states including obesity, metabolic syndrome, and diabetes, and is associated with increased thrombosis risk in persons with these conditions. PAI-1 plays a critical role in insulin resistance outside of pregnancy [97]. Pregnancy is a well-known prothrombotic condition with PAI-1 levels increased in pregnant as compared to non-pregnant women. Amongst women with GDM, their PAI-1 levels are higher than age-matched pregnant controls [80,98]. The role of PAI-1 in GDM development is further supported by homozygosity for the 5G allele being associated with normal glucose tolerance in pregnancy [99]. Elevated PAI-1 levels are positively correlated with markers of subclinical inflammation, artherogenesis, hypoadiponectemia, and are associated with concern for or development of early postpartum impaired glucose tolerance, overt DM, and cardiovascular disease [29,32,100,101].

Retinol binding protein 4 (RBP4)

RBP4 is produced predominantly by hepatocytes and adipose tissue. Insulin-resistant mice and humans with obesity and T2DM have elevated RBP4 levels, and a causal relationship between RBP4 and insulin resistance has been suggested [102]. Serum RBP4 levels increase from late second to third trimester in subjects with GDM with 33 week gestational age levels positively correlating with mean blood glucose, hemoglobin A1c (HgbA1c) values and cord blood insulin values [103]. GDM diagnosis and HgbA1c levels are related to these 33 week RBP4 levels [103]. In GDM, RBP4 mRNA expression in AT is significantly increased in comparison to control subjects [104].

Summary

Although the exact pathophysiology leading to GDM development remains unclear, there are significant similarities to T2DM development. The role of adipose tissue expansion, in particular the ability of SQAT and VAT to accommodate fat storage with hyperplastic rather than hypertrophic expansion may be a pivotal factor determining GDM risk. The differential contribution of adipose tissue depots to insulin resistance during pregnancy is not clear, but a significant literature base outside of pregnancy suggests that this is an important area of investigation. Studies to date regarding the inter-relationships between weight, weight gain, IR, adipocytes, inflammation and angiogenesis have been conducted almost exclusively in animal models and non-pregnant humans. Here we reviewed the relatively limited literature base that addresses potential adipose tissue and inflammatory contributions to GDM development. The findings in these studies are consistent with an important role of adipose tissue in producing pro-inflammatory factors in pregnancy, but more work needs to be done to define the sources of inflammatory cytokines and define whether they play a causal role in GDM, and whether they operate inter-generationally to determine metabolic disease risk of both mothers and babies. Pregnancy is an important screening opportunity for both maternal and fetal health and disease;

Elucidating underlying mechanisms that lead to GDM will enhance the possibility of early intervention and even prevention of inter-generational metabolic disease risk.

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