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# The Role of Adipocyte Mediators, Inflammatory Markers and Vitamin D in Gestational Diabetes

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## 1. Introduction

Gestational diabetes mellitus (GDM) usually reveals itself in the latter half of pregnancy and it is identified by carbohydrate intolerance of variable severity.

The presence of GDM has implications for both the mother and the baby. Perinatal morbidity includes macrosomia, hypoglycemia, hyperbilirubinaemia and respiratory distress syndrome which lead to the subsequent complications (Hod et al., 1991). Long term outcomes for the offspring may include obesity and diabetes independent of genetic factors (Silverman et al., 1995; Van Assche et al., 1992, 2001). For the mother there is an increased risk of overt type 2 diabetes later in life (Mestman, 1987; O'Sullivan, 1989). Both type 2 diabetes and gestational diabetes have common pathogenic mechanisms where pregnancy tends to expose disease in those women who are at risk of developing type 2 diabetes later in life. Similar to all forms of hyperglycemia, GDM is characterized by insulin levels that are inadequate to proper insulin requirement (Metzger et al., 2007). The pathogenesis of GDM has not been clearly defined. The most common hypothesis is that GDM is caused by decreasing insulin sensitivity and increasing anti-insulin hormones that are secreted by the placenta during pregnancy, such as human placental lactogen, prolactin, glucocorticoid and progesterone (Xue-lian et al., 2008).

It has become increasingly evident that endocrine/metabolic hormones such as leptin, adiponectin, resistin, proinflammatory mediators including C-reactive protein (CRP) are strongly linked with abnormal carbohydrate metabolism.

In recent times a number of first trimester studies have shown association of different biomarkers with the development of GDM. These include elevated serum or plasma C-reactive protein (Wolf et al., 2003), lower sex hormone-binding globulin (Thadhani et al., 2003), increased placental growth factor (Ong et al., 2004) and elevated leptin (Qiu et al., 2004) and decreasing of adiponectin concentration.

Some studies have recommended that Vitamin D deficiency could play a role in pathogenesis of gestational diabetes.

This chapter will focus on the studies about the role of adipocytes mediators, proinflammatory factors and vitamin D in gestational diabetes.

## 2. Adipocyte mediators

It is becoming obvious that adipose tissue is not just a storage for extra energy but that it secretes a number of biologically active peptides as a group named adipocytokines that control glucose and fatty acid metabolism (Youn et al., 2004). These peptides have similar properties with cytokines, and so referred to as "adipocytokines", e.g. leptin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), adiponectin and resistin. These adipocytokines may influence activity of other tissues (Nedvidkova et al., 2005).

### 2.1 Adiponectin

#### 2.1.1 Adiponectin structure

Adiponectin is a 244-amino-acid-long polypeptide that regulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin is exclusively secreted from adipose tissue into the circulation and is very plentiful in plasma relative to other hormones. Adiponectin concentrations ranging from 5 to 30 mg/ml and accounting for approximately 0.01% of total plasma protein. Females have higher levels of plasma concentration than males (Díez & Iglesias, 2003).

Adiponectin was first identified in mice as a transcript overexpressed in preadipocytes (Lara-Castro et al., 2007) differentiating into adipocyte (Matsuzawa et al., 2004). The human homologue was recognized as the most abundant transcript in adipose tissue. As opposed to anticipation, in spite of being produced in a fat tissue, adiponectin was found to decline in obesity (Díez & Iglesias, 2003; Nedvídková et al., 2005; Ukkola & Santaniemi, 2002). This down regulation has not been clearly described. The gene was localised to chromosome 3p27, a region highlighted as affecting genetic vulnerability to obesity and type 2 diabetes. Supplementation by varying forms of adiponectin improved control of insulin, blood glucose and triglyceride levels in mouse models.

Berberlin, a herbal folk medicine, has been shown to increase adiponectin expression which partly explains its advantageous effects on metabolic disturbances (Choi et al., 2009).

A reduction in adiponectin expression is associated with insulin resistance in animal models. Administration of adiponectin has been accompanied by a reduction in plasma glucose and an increase in insulin sensitivity. In addition, thiazolidinediones, drugs that increase insulin sensitivity by stimulation of the peroxisome proliferator-activated receptor- $\delta$ , increase plasma adiponectin and mRNA levels in mice.

A recent study has shown that phosphorylation and levels of the hormone are conversely correlated with body fat proportion in adults although the association in infants and young children is less clear. The hormone plays a role in the inhibition of the metabolic disturbance that may end in type 2 diabetes (Ukkola & Santaniemi, 2002), obesity, atherosclerosis (Díez & Iglesias, 2003), non-alcoholic fatty liver diseases (NAFLD) and independent risk factors for metabolic syndrome (Renaldi et al., 2009). Levels of adiponectin are decreased in diabetics compared to non-diabetics. Weight loss significantly increases circulating levels (Coppola et al., 2009).

Adiponectin automatically self-associates into larger structures. Initially, three adiponectin molecules bind together to form a homotrimer. The trimers continue to self-associate and form hexamers or dodecamers. Like the plasma concentration, the relative levels of the higher-order structures are sexually dimorphic, where females have increased proportions of the high-molecular weight forms.

Adiponectin exerts some of its weight reduction effects via the brain. This is similar to the action of leptin, but the two hormones perform complementary actions, and can have additive effects (Nedvídková et al., 2005).

### 2.1.2 Metabolic effect of adiponectin

Adiponectin affects glucose flux through decreasing gluconeogenesis and increasing glucose uptake (Díez & Iglesias, 2003; Nedvídková et al., 2005; Vasseur et al., 2003). Adiponectin has a role in lipid catabolism (Vasseur et al., 2003) by  $\beta$ -oxidation and triglyceride clearance (Nedvídková et al., 2005). The other metabolic effects of adiponectin are protection against endothelial dysfunction and improvement of insulin sensitivity and weight loss, and control of energy metabolism (Vasseur et al., 2006). Adiponectin has also another effects, including putative insulin-sensitising, anti-atherogenic and anti inflammatory characteristics (Berg et al., 2002; Ukkola & Santaniemi, 2002).

Consistent with the low circulating levels of adiponectin observed in type 2 diabetes, adiponectin concentration is contrarily related to both insulin resistance and central adiposity (Arita et al., 1999; Weyer et al., 2001). Low baseline adiponectin concentration can predict the subsequent development of insulin resistance although elevated baseline levels have been shown to be protective against the succeeding development of type 2 diabetes (Daimon et al., 2003; Lindsay et al., 2002; Snehalatha et al., 2003; Spranger et al., 2003). Recognition of gestational diabetes mellitus helps in identification of populations of young women at high risk of developing type 2 diabetes. Therefore, reduction in serum adiponectin levels in GDM may be comparable to type 2 diabetes.

### 2.1.3 Adiponectin and GDM

Some studies exhibited hypoadiponectinemia in pregnant women with gestational diabetes. A cross sectional study of 180 women in their third trimesters illustrated gestational diabetic women had more hypoadiponectinemia compared with normoglycemic controls after adjustment for covariates including insulin resistance. This study showed adiponectin concentration is an independent correlate of beta cell function in late pregnancy. Adiponectin was correlated with insulin secretion-sensitivity index (ISSI). ISSI was positively correlated with adiponectin and negatively correlated with GDM and IGT. Therefore, adiponectin may play a principal role in mediating insulin resistance and beta cell malfunction in the development of diabetes (Rentakaran et al., 2005). To determine whether adiponectin relate to the postpartum metabolic disturbance linking GDM with type 2 diabetes a cohort study was done on 487 pregnant women in pregnancy and at 3 months post partum. This study demonstrated adiponectin was related to postpartum insulin sensitivity and hypoadiponectinemia in pregnancy predicts postpartum insulin resistance, beta cell dysfunction and fasting glycaemia, and hence may be relevant to the pathophysiology relating GDM with type 2 diabetes (Rentakaran et al., 2010). To investigate level of adiponectin and metabolic factors in women with gestational diabetes a cross sectional study was done. The result of this study showed the level of adiponectin was lower in gestational diabetes and adiponectin correlates negatively with insulin resistance in homeostasis model assessment-insulin resistance (HOMA-IR) (Altinova et al., 2007). To evaluate whether adiponectin is a predictive factor for gestational diabetes mellitus (GDM) and is appropriate as a screening test for GDM a study was done and the results

demonstrated that adiponectin was an independent predictor for GDM. For GDM screening, adiponectin was not as strong a predictor as GCT. In any case, adiponectin could be used to rule out pregnant women at low risk of GDM (Weerakiet et al., 2006). In a cross sectional study serum level of adiponectin in GDM women and impaired glucose test and normal pregnant women was compared. This study showed the serum adiponectin level in gestational diabetes was significantly lower than the impaired glucose test and control groups and a negative correlation between prepregnancy BMI and adiponectin (Soheilykhah et al., 2009). In another study, class A2 and B gestational diabetes are associated with a suppressed level of adiponectin (Thyfault et al., 2005). To investigate changes in serum adiponectin during pregnancy and postpartum and assess its relationship with insulin resistance as measured by homeostasis model assessment (HOMA-IR) a study was done and revealed adiponectin was lower in gestational diabetes than in control groups during pregnancy and a significant post reduction in adiponectin was observed in maternal adiponectin after delivery indicating a significant placental contribution to adiponectin production (Vitoratos et al., 2008). The result of the another study identified weight gain as the strongest factor associated with declining  $\beta$  cell compensation for insulin resistance in Hispanic women at high risk for type 2 diabetes. Such effects may be mediated through at least two mechanisms: alteration in adipokine levels and increasing insulin resistance (Xiang et al., 2010). A prospective, nested case control study showed adiponectin concentration in early pregnancy was significantly lower in women with GDM than controls (4.4 vs. 8.1), approximately 73% of women with GDM, compared with 33% of controls, had adiponectin concentration less than 6.4 $\mu$ g/ml. After adjustment for confounding, women with adiponectin concentration in early pregnancy, less than 6.4 $\mu$ g/ml, experienced a 4.6-fold increased risk of GDM as compared with those with higher concentrations (Williams et al., 2004). Postpartum follow-up showed that women developing metabolic syndrome had significantly lower adiponectin and resistin concentration during pregnancy. Nonetheless, after adjustment for age, prepregnancy BMI, logistic regression analysis did not show independent relation between adiponectin and resistin with development of postpartum metabolic syndrome (Hosseini-nezhad et al., 2010). To evaluate plasma adiponectin levels, insulin resistance and glucose tolerance in women with gestational diabetes mellitus and in normal pregnancies adiponectin measurement were performed two times as in 28–31 weeks of pregnancy and at 3 months after delivery. Insulin resistance was calculated by the homeostasis model assessment. This study demonstrated decreased adiponectin levels in GDM do not normalize instantaneously following the delivery. The difference is more apparent in adiponectin levels than in HOMA-IR (Cavit et al., 2007). Low plasma adiponectin concentration was associated with GDM in another study and adiponectin mRNA levels in adipose tissue biopsies from GDM subjects were reduced (Ranheim et al., 2004). Concentration of adiponectin may change before the appearance of the abnormal glucose level during pregnancy (Xue-lian et al., 2008). To identify potential biomarkers for impending gestational diabetes that appear in the plasma before impaired glucose tolerance a prospectively study was done and the results demonstrated a significant difference in insulin and adiponectin concentration at 11 weeks gestation and, compared to control groups, women with gestational diabetes exhibited elevated plasma insulin and reduced plasma adiponectin at 28 weeks gestation. Bivariate logistic regression analysis showed that both insulin and adiponectin were associated with subsequent development of gestational



diabetes. Based upon this study (Georgiou et al., 2008) the predictive threshold values for GDM at 11 weeks are  $>25\mu\text{U/ml}$  insulin and  $<3.5\mu\text{g/ml}$  adiponectin. This study confirmed the another survey (Williams et al., 2004) that a low blood concentration of adiponectin early in pregnancy is associated with increased risk of subsequent GDM.

In summary the results of case control and prospective studies demonstrated association of low adiponectin and GDM.

## 2.2 Leptin

### 2.2.1 Leptin structure

Leptin, a protein product of the obese (ob) gene with a 16 KDA molecular weight, is made of 167 amino acids (Hui-lan et al., 2004). It is a circulating hormone that is expressed plentifully in the adipose tissue. Leptin is also produced by non adipose tissue including the stomach, intestine and the placenta in humans (Masuzaki et al., 1997) and acts on the receptors of the hypothalamus to decrease food intake and increase energy consumption (Zhang et al., 1994). Leptin is encoded by the obesity gene. It signals to the brain when there has been enough eating to sustain body weight. It has been exhibited that laboratory mice have a mutation on the ob gene which inhibits the function of leptin causing the mice to become morbidly obese. In addition mutation in the gene that codes the leptin receptor causes obesity in the mice. Mutations in the ob gene affect expression of leptin, which in turn can cause obesity, infertility, and diabetes in lab mice (Zhang et al., 1997). It is hypothesized that alteration in the human ob gene causes some serious cases of early-onset obesity. Other less severe kinds of human obesity are considered not to be caused by mutation, but by changing in regulation or resistance to the action of leptin (Flier et al., 1995). Diminished production of leptin or fewer receptors may also be responsible for those who are overweight but not obese. It seems that the appropriate amount of leptin has to be present in the central nervous system to leptin act as weight lowering in human obesity (Zhang et al., 1997).

### 2.2.2 Leptin action

Homeostatic regulation of body weight depends on the capacity of the brain to sense and respond to changes in peripheral energy supplies. Insulin receptors were recognized in the brain and concentrated in the hypothalamus. These receptors have binding and signaling properties like peripheral insulin receptors. Leptin and insulin enter the brain and act on special hypothalamic neurons to prevent food intake and alter appetite. Leptin raise energy expenditure by regulating of neurotransmitters. (Porter et al., 2002). The evidence shows that insulin and leptin also act on the hypothalamus to control glucose production from the liver via stimulation of the autonomic nervous system. Thus, communication between leptin, insulin and significant hypothalamic neurons is necessary for normal energy balance and glucose homeostasis, deregulation of which will lead to obesity and type 2 diabetes. Indeed, in many forms of obesity, hypothalamic leptin and insulin resistance develops in which leptin and insulin are less effective in causing anorexia and decreased body weight. Some studies propose that leptin also has a specific effect on the regulation of whole body glucose homeostasis (Al-Dahhri et al., 2002; Ceddia et al., 2002). Numerous metabolic studies have shown a positive association between direct and indirect measures of adiposity with plasma leptin concentrations. Plasma leptin concentration correlated with BMI, percent of body fat and plasma insulin in both overweight/obese and normal weight and decreased after sustained weight loss (Havel et al., 1996).

### 2.2.3 Leptin and gestational diabetes

The increased risk of GDM with increasing maternal plasma concentration of leptin is biologically plausible and is likely accounted for by diverse molecular and biochemical pathways in multiple tissue. Leptin has been shown to regulate peripheral glucose homeostasis through its action in skeletal muscle and its effects on hepatic gene expression of the gluconeogenic enzymes and phosphoenolpyruvate carboxykinase (Rossetti et al., 1997). In addition, leptin has been shown to directly modulate glucose handling in skeletal muscle by promoting fatty acid oxidation. Investigators have postulated that leptin induced insulin resistance may be secondary to glucose flux via the hexosamine pathway (Mueller et al., 1998). Although the pathophysiology of hyperleptinemia in GDM is unknown, it is clear that leptin has numerous actions on target tissues and is involved in regulation on several endocrine pathways. Although the biologic action of leptin primarily mediated through interactions with receptors expressed in the hypothalamus, leptin receptors are widely distributed across other tissues including the lungs, liver, kidney, pancreas, heart and the placenta (Chen et al., 1999; Hoggard et al., 1997; Kieffer et al., 1996; Schulz et al., 2000). This wide distribution of leptin receptors portends the peptide diverse influence on neuroendocrine, cardiovascular and reproductive functions. Leptin is correlated with a series of endocrine parameters including insulin, insulin-like growth factors, hemoglobin A1c and sex hormone-binding globulin

In pregnant women with changes in maternal fat stores and glucose metabolism, leptin increases (Schubring et al., 2000). Maternal leptin concentration increases 2 to 3 times above the non-pregnant concentration with the peak around 28 weeks of gestation (Schubring et al., 2000). The serum leptin level relates to body weight, body mass index, fat accumulation of the pregnant woman, fetal growth and development and fetal fat deposits. In recent years, it was considered that leptin is associated in pregnancy-induced hypertension syndrome, fetal intrauterine growth retardation and gestational diabetes. Increasing maternal plasma leptin levels may result from an upregulation of adipocyte leptin synthesis in the presence of increasing insulin resistance and hyperinsulinemia in the second half of pregnancy (Laivuori et al., 2000; Rossetti et al., 1997). Investigators have shown that leptin directly affects whole body insulin sensitivity through regulating the efficiency of insulin-mediated glucose metabolism by skeletal muscle (Cohen et al., 1996) and by hepatic regulation of gluconeogenesis (Rossetti et al., 1997). Some evidence suggests that leptin has an acute inhibitory effect on secretion of insulin (Ceddia et al., 2002). Large epidemiological studies have shown that plasma leptin concentrations were positively associated with insulin resistance in men and non-pregnant women (Donahue et al., 1999).

Available data suggest a complex relation between leptin and glucose homeostasis in humans. Two teams of investigators have studied maternal leptin concentrations in GDM women and the related published results are conflicting. On the other hand, the available data do not explain whether the alterations in leptin concentrations are the cause or result of the metabolic disturbances, such as hyperglycemia, that are essential to GDM. In addition, the severity of any possible association of GDM risk with different concentrations of leptin was not assessed in either study (Festa et al., 1999; Kautzky-Willer et al., 2001). In a case-control study reported that maternal third-trimester plasma leptin concentrations were higher in GDM women compared with the control group (24.9 versus 18.2 ng/mL;  $P=0.001$ ) (Kautzky-Willer et al., 2001). Such a relation was also found in other study. (Vitoratus et al., 2000) Hyperleptinemia, independent of maternal adiposity, in early pregnancy appears to be predictive of an increased risk of GDM later in pregnancy. After adjusting for maternal

prepregnancy adiposity and other confounders, women with leptin concentrations of 31ng/ml or higher experienced a 4.7-fold increased risk of GDM as compared with women who had concentrations of 14.3ng/ml or lower. Each 10-ng/ml increase in the leptin concentration was associated with a 20% increase in GDM risk (Qiu et al., 2004). Serum leptin level is correlated with glucose tolerance during pregnancy (Liu et al., 2003). In a case-control study, at 28 weeks of gestation, fasting serum concentration of leptin, insulin and homeostatic model assessment index were measured in three groups, GDM, IGT, and normal control, and compared them with each other. This study demonstrated that the serum leptin level was significantly higher in women with GDM than in the two other groups ( $p = 0.03$ ). In women with GDM and IGT, leptin was significantly positively related with insulin and homeostatic model assessment index ( $r = 0.221$ ,  $p = 0.03$ ) and ( $r = 0.246$ ,  $p = 0.03$ ), respectively. (Soheilykhah et al., 2011)

In a case-control study, noted that maternal third trimester leptin concentrations were significantly lower in GDM cases as compared with controls after adjusting for possible confounding factors such as BMI and insulin concentrations (Festa et al., 1999). Concentration of leptin increased before the appearance of the abnormal glucose level during pregnancy (Xue-lian et al., 2008). Some studies evaluated the relationship between leptin concentration and insulin resistance. Leptin concentration was positively associated with insulin level and HOMA index (Maghbooli et al., 2007). A positive and significant correlation between the maternal leptin and fasting insulin levels (Liu et al., 2003) and also has shown that leptin predicts the development of GDM independent of maternal BMI and other risk factors. The findings of Kautzky-Willer et al are generally consistent with the Different reports. (Kautzky-Willer et al., 2001 ,Lappas et al., 2005 Qiu et al., 2004).

Several possible explanations are suggested for the disparities in the existing studies. The study design and the confounding factors such as the time of blood sampling (whether blood samples were collected before, after, or during labor) and maternal factors, including whether women were treated with medication or diet before blood was collected for leptin determination might account for differences. Moreover, variations in population characteristics and status of glycemic control could also account for some of the observed differences in the study results.

In summary, the results of different studies from experimental, clinical, and epidemiological investigations suggest that leptin is an important mediator of glucose homeostasis in pregnancy (Qiu et al., 2004) and measurement of leptin alone, or combined with the assessment of other risk factors, may help identify women at risk of developing GDM.

## 2.3 Resistin

### 2.3.1 Resistin structure

Insulin resistance is strongly associated with obesity, but even among obese subjects insulin sensitivity is different. Recently, a new adipocyte hormone, resistin, was identified, shown to decrease insulin-mediated glucose uptake, and shown to be increased in obese mice

Resistin, also known as adipose tissue-specific secretory factor, is a cystein-rich protein that in humans is encoded by the *RETN* gene (Wang et al., 2002). Resistin was discovered to be produced and released from adipose tissue to provide endocrine functions likely involved in insulin resistance. This thought initially developed from studies exhibiting that serum resistin levels increase with obesity in several species (humans, rats, and mice). (Yamauchi et al., 2003; Gabriely et al., 2002; Steppan et al., 2001). Resistin is also produced by several



other tissues, including the hypothalamus, pituitary and adrenal glands, pancreas, gastrointestinal tract, myocytes, spleen and white blood cells

The role of resistin in obesity and insulin resistance in humans is controversial.

### 2.3.2 Resistin action

Resistin causes insulin resistance and glucose intolerance in mice. Serum resistin levels will rise with increased adiposity, particularly central obesity (Degawa-Yamauchi et al., 2003; Vendrell et al., 2004). Conversely, serum resistin levels decrease with lowering adiposity following medical treatment (Valsamakis et al., 2004). The level of tissue resistin is decreased by insulin, cytokines such as tumour necrosis factor,  $\alpha$  endothelin-1 and increased by growth and gonadal hormones, hyperglycaemia, interleukin-6 and lipopolysaccharide (Adeghate, 2004). Animal study exhibited that resistin gene expression and protein levels are regulated in parallel with glucose and insulin during fasting and feeding. Many researchers have shown positive correlations between resistin levels and insulin resistance. Thus resistin has been suggested to link obesity with type 2 diabetes (Hirosumi et al., 2002; Rajala et al., 2004; Silha et al., 2003; Smith et al., 2003). This discovery is further confirmed by studies which verified a direct correlation between resistin levels and subjects with type 2DM (Asensio et al., 2004; Fujinami et al., 2004; McTernan et al., 2003; Steppan et al., 2001). With the finding that resistin was at least in part a cause of the insulin resistance and T2DM, medications which specifically lead to decreased serum resistin in T2DM subjects were developed (Tjokropawiro, 2006). The level of circulating resistin is decreased by the anti-diabetic drug such as rosiglitazone and increased by obesity. Administration of the anti resistin antibody decreases blood sugar and improve insulin action in mice with diet induced obesity. Treatment of normal mice with recombinant resistin impairs glucose tolerance and decreases insulin action. Insulin stimulated glucose uptake by adipocyte is increased by neutralization of resistin and is reduced by resistin treatment (Steppan et al., 2001). Because resistin is identical to a protein which had a role in allergic pulmonary infiltration, the effect of resistin in inflammation was studied and these researches demonstrated association of resistin with other physiological systems such as inflammation and energy homeostasis (Adeghate, 2004; Stumvoll & Häring, 2002; Vendrell et al., 2004).

### 2.3.3 Resistin and gestational diabetes

Resistin is expressed in human placenta and has been supposed to play a role in regulating energy metabolism in pregnancy. Resistin protein expression in placental tissue was much higher than that in subcutaneous adipose tissue in normal human abdomen, pregnant abdomen and thigh. It was indicated that resistin protein can be secreted from human placental tissue. Resistin might be one of the factors that lead to pregnant physiological insulin resistance and GDM (Yongming et al., 2006). Resistin is secreted by the placenta during human pregnancy (Sagawa et al., 2002). Serum resistin levels are not different among non-pregnant women and women in the first and second trimesters of pregnancy. Serum resistin increases by the third trimester (Chen et al., 2005). Resistin is detectable at 20 weeks of gestation. In newborns, resistin concentrations were two to three-fold higher than those reported in adults regardless of sex, birth weight, pattern of growth or metabolic state of the mother (Yongming et al., 2006). Resistin gene expression is found in placental tissues during pregnancy (Yura et al., 2003) and it has been supposed that it could be involved in the pathogenesis of the insulin resistance state found in the second half of pregnancy and in the

development of gestational diabetes. Resistin levels were significantly higher in normal pregnant women than in nonpregnant controls and showed a negative correlation with gestational age. Resistin was detected in the umbilical venous blood in fetus from 20 to 41 weeks of gestation. Detection of high levels of resistin in cord blood during gestation is consistent with a regulatory action of these adipokines on tissue differentiation and foetal growth (Cortelazzi et al., 2007). Recent reports have measured the level of resistin during pregnancies complicated by gestational diabetes with inconsistent results (Cortelazzi et al., 2007, Chen et al., 2007). The result of a study showed resistin level in gestational diabetes was lower than normal pregnancy (Megia et al., 2008). This result is inconsistent with other study that demonstrated serum resistin concentration was significantly higher in women with GDM than in controls before delivery and the serum levels of resistin significantly decreased after delivery in both the GDM group and controls. The serum level of resistin was different on days 1 and 3 but not by day 5 after delivery (Chen et al., 2007). The serum resistin levels were higher in the 1st, 2nd and 3rd trimesters of pregnancy and higher in GDM than in control groups and hyperresistinemia may also be associated with the pregnancy-induced insulin resistance (Palik et al., 2007). The discrepancy of these findings is unclear, but may be related to different populations of the studies, the type of study or the time of sampling during pregnancy.

### 3. Inflammatory mediators (C-reactive protein)

#### 3.1 C-reactive structure and actions

C-reactive protein (CRP) is a sensitive marker of systemic infection and is widely used in clinical settings (Kushner I & Rzewnicki, 1994). CRP was first detected in 1930 by Tillet and Frances (Tillett & Francis, 1930), who identified a substance that formed a precipitate when combined with polysaccharide C of streptococcus pneumonia in the sera of patients acutely infected with pneumococcal pneumonia. Subsequently, it was found that this reaction was not unique to pneumococcal pneumonia but could be found with a variety of the other acute infections. This was early evidence of the body's chemical response to inflammatory states and led to characterization of other so called acute phase proteins (Abernathy & Avery, 1941). CRP is normally present in low levels in serum but increase rapidly and dramatically in response to a variety of infectious or inflammatory conditions (Ballou & Kushner, 1992). Since its discovery, CRP has been studied as a screening device for occult inflammation, as a marker of disease activity and as a diagnostic tool (Pepys, 1981). Recently, more rapid and accurate methods of quantifying CRP have led to a new interest in its value in clinical medicine (Palosuo et al., 1986) although low-grade inflammatory states not originated from infections and atherosclerosis have also been associated with an increase in CRP levels. For instance, obesity is linked to chronic subclinical inflammation as manifested by mild increases in CRP cytokines and adipocytokines and is the principal risk factor for type 2 diabetes. In addition, patients with increases in CRP are at risk of myocardial infarction and peripheral arterial disease (Engström et al., 2003; Ford, 1999; Ridker et al., 2000; Tracy et al., 1997; Yudkin et al., 1999). Elevated serum concentration of acute-phase proteins, exhibiting chronic subclinical inflammation, has been associated with insulin resistance syndrome in men and non-pregnant women (Festa et al., 2000; Han et al., 2002; Pradhan et al., 2002; Ridker et al., 2003). The molecular basis for the association between the inflammation and diabetes related to the action of cytokines such as interleukin-6 and tumor necrosis factor (TNF)- $\alpha$  which lead to

insulin resistance and stimulate the acute phase inflammatory response (Fernandez-Real et al., 2001; Kern et al., 2001; Mohamed-Ali et al., 1998; Vozarova et al., 2001).

### 3.2 C-reactive protein and GDM

Some evidence supports the theory that chronic inflammation might be a risk factor for developing type 2 diabetes (Freeman et al., 2002; Pradhan et al., 2001; Taniguchi et al., 2002; Thorand et al., 2003). Inflammation may have a role in the pathogenesis of diabetes, suggesting that inflammatory markers may identify patients at risk of diabetes. The issue was investigated in a subset of women (1584 who developed diabetes and 2193 who were normal after 6 years). Women with diabetes had higher median baseline level of interleukin-6 (IL6), high sensitivity CRP and tumor necrosis factor alpha receptor 2 compared with control. Two markers (IL6 and CRP) were significantly associated with diabetes risk in all ethnic groups (Liu et al., 2007). Similar results were obtained in the women's health study (Pradhan et al., 2001) and the nurse health study (Hu et al., 2004). In a population-based study in Mexico City, serum CRP was a predictor of the metabolic syndrome and type 2 diabetes in women but not in men (Han et al., 2002). Among middle aged men in Germany those with a serum CRP in the highest quartile  $\geq 2.91$  ng/ml had an increased risk of type 2 diabetes compared with men in the lowest quartile ( $\leq 0.67$  ng/ml) (RR 2.7, 95% CI 1.4-5.2) (Thorand et al., 2003). Epidemiological studies have shown that CRP predicts incident type 2 diabetes and increased cardiovascular disease. In healthy middle-aged women, or young men, CRP levels were associated with a three-fourfold increased risk of developing diabetes (Buchanan, 2001; Kjos & Buchanan, 1999).

Very limited attention has been given to the role of inflammation in the etiology of gestational diabetes a condition that is biochemically and epidemiologically similar to type 2 diabetes (Kjos & Buchanan, 1999). The second and third trimesters of pregnancy represent a physiological type of insulin resistance (Kautzky-Willer et al., 1997). Insulin resistance is associated with dysfunction of endothelial and inflammation as well as increase production of cytokines by adipose tissue (Baallethofer et al., 2000). Limited available data suggest that pro-inflammatory cytokines may be predictive of GDM (Winkler et al., 2002; Kirwan et al., 2002).

Some studies have measured CRP at various gestational ages in pregnant women and found inconsistent results regarding the association between inflammatory markers and the incidence of GDM and the interdependence with the degree of adiposity (Retnakaran et al., 2003; Wolf et al., 2003, 2004). The interpretation of the results was influenced by coexistence of hypertension, preeclampsia, and different race groups or small sample size in some studies. The result of a study demonstrated women with GDM had significantly higher CRP serum levels than normal pregnant women at 37-38 weeks of gestation but at the time of OGTT (24-28 weeks of pregnancy) there was not any significant difference between the two groups (Leipold et al., 2005). This report is inconsistent with the findings of the Massachusetts General Hospital obstetric maternal report, where increased CRP concentration was shown in the first trimester (10 weeks of gestation) and the association between GDM and CRP depended primarily on coexisting obesity (Wolf et al., 2004). The result of another study demonstrated that CRP concentration is not affected by GDM until the end of the second trimester of pregnancy (Retnakaran et al., 2003). In the third trimester, however, these results suggest an up-regulation of inflammatory markers by GDM resulting in elevation of CRP concentration at the end of pregnancy in women with GDM. In a prospective nested case control study Wolf et al found that CRP concentration in the first

trimester predicted the development of GDM in the pregnancy. In this study risk of developing GDM among women in the highest CRP tertile compared with the lowest tertile was 3.2 (95% CI 1.2-8.8), after adjusting for age, race, smoking, parity, blood pressure and gestational age at CRP sampling. The risk of developing GDM among women in the highest compared with the lowest tertile was 3.6 (95%CI 1.2-11.4), when BMI was included in the model; however, the association between increased CRP and GDM was reduced (odds ratio for the highest compared with the lowest tertile 1.5 (95% CI 0.4-5.51). Therefore, this association is mediated in part by increasing BMI (Wolf et al., 2003) and pregestational obesity as the most prominent risk factors of GDM (Wolf et al., 2003).

Another prospective study was done to examine the association between CRP and GDM risk. Women were recruited before 16 weeks gestation and were followed until delivery. This study demonstrated elevated CRP was associated with GDM risk. After adjustment of maternal prepregnancy BMI, family history of diabetes and nulliparity, women with CRP in the highest tertile experienced a 3.5-fold increased risk of GDM (95% CI 1.2-9.8) as compared with those in the lowest tertile. The association between CRP and GDM was evident when analyses were restricted to lean women (BMI<25kg/m<sup>2</sup>). Lean women with CRP ≥5.3mg/l had a 3.7-fold increased risk of GDM (95%CI 1.6-8.7) as compared with women with CRP < 5.3mg/l. This study concluded systemic inflammation is associated with an increased risk of GDM and this association is independent of maternal prepregnancy adiposity (Qiu et al., 2004). Serum CRP in gestational diabetes and pregnant control women was evaluated and showed CRP was positively related with fructose amine hemoglobin A1c, triglyceride and BMI. This study concluded CRP plays a role in pathogenesis of GDM (Li et al., 2010). The association of sex hormone-binding globulin, high sensitive C-reactive protein and fasting glucose and insulin in the late first trimester and early second trimester of pregnancy with the diagnosis of gestational diabetes were also evaluated. In this study sex hormone-binding globulin was lower and high-sensitive CRP was higher among women who subsequently developed gestational diabetes. Multivariate analysis suggested that sex hormone-binding globulin measurement was the best predictor of GDM (Smirnakis et al., 2007). A 180 healthy pregnant women undergoing oral glucose tolerance testing in the late second or early third trimester were evaluated. Based on OGTT and prepregnancy BMI, participants were divided to 4 groups: (1) normal OGTT and BMI<25kg/m<sup>2</sup>; (2) normal OGTT and BMI >25; (3) impaired glucose tolerance, and (4) GDM. This study showed CRP level was higher in overweight women with normal OGTT, followed by GDM, impaired OGTT groups and lean normal GTT. This study demonstrated that maternal CRP are not related to GDM, but rather correlate significantly with prepregnancy obesity (Rentakaran et al., 2003).

## 4. Vitamin D

### 4.1 Vitamin D structure and actions

Vitamin D, or calciferol, is a group of lipid soluble substance with a four-ringed cholesterol backbone. Human obtained Vitamin D from exposure to Sunlight, their diet and from dietary supplement. Ultraviolet light convert provitamin D to vitamin D<sub>3</sub> (cholecalciferol) in the skin and afterwards Vitamin D<sub>3</sub> was bounded by vitamin D binding proteins (DBP) and transported via blood to target organs for metabolism and activity. Vitamin D hydroxylate to form 25-hydroxy-vitamin-D (25OHD) in the liver. Hydroxylation of 25-hydroxy-vitamin-D to 1, 25-dihydroxy-vitamin D occurs in the mitochondria of the proximal tubules of the kidney. This form of vitamin D (1,25(OH)<sub>2</sub>-vitamin D) is the physiologically active form. The



renal production of 1,25-dihydroxy-vitamin D is regulated by plasma parathyroid hormone and serum calcium and phosphorus levels. Vitamin D increases calcium and phosphorus absorption from the gut and reabsorption from the kidneys and increases plasma concentration of these elements. As such, the main effect of vitamin D is maintenance of mineral homeostasis and regulation of bone remodeling (Holick et al., 2006) .

Vitamin D deficiency is defined when the level of 25-Hydroxyvitamin D is less than 20 ng/ml (50 nmol/l). Level of 25-29 ng/ml can be considered to indicate a relative insufficiency of vitamin D and a level of 30 ng/ml or more indicate sufficient vitamin D. Vitamin D intoxication is observed when serum level of 25-hydroxyvitamin D are greater than 150 ng/ml (Dawson et al., 2005).

Vitamin D deficiency or resistance is caused by different mechanisms including reduced of vitamin D access due to insufficient dietary vitamin D, fat malabsorptive disorders, and/or lack of photoisomerization, Impaired hydroxylation of vitamin D by the liver and kidney to produce 25-OH vitamin and 1,25(OH)<sub>2</sub>-vitamin D respectively and end organ insensitivity to vitamin D metabolites.

#### 4.2 Vitamin D deficiency and diabetes

Some human and animal studies have shown a relationship between diabetes type 1 and vitamin D deficiency. Vitamin D deficiency make predispose subjects to type 1 and type 2 diabetes, and receptors for its activated form 1, 25-dihydroxy-vitamin D have been recognized in beta cells and immune cells. Vitamin D deficiency impairs insulin synthesis and secretion in humans and animal models of diabetes and some investigations suggested that vitamin D deficiency has a role in the development of type 2 diabetes. Epidemiological studies recommended a link between vitamin D deficiency in early life and the subsequently onset of type 1 diabetes. In some populations, type 1 diabetes is associated with certain polymorphisms within the vitamin D receptor gene. In studies in non obese diabetic mice, pharmacological doses of 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, or its structural analogues, have been shown to delay the onset of diabetes, mainly through immune modulation. Vitamin D deficiency may, therefore, be included in the pathogenesis of both types of diabetes. (Luong et al., 2005; Mathieu et al., 2005). Vitamin D supplementation could improve or prevent diabetes. This effect may be due to immunomodulatory action of vitamin D. (Stene et al., 2000; Eva, 1999).

There was less data about the association between vitamin D and type 2 diabetes. Some evidences show the role of vitamin D in insulin secretion, for example the presence of vitamin D receptors in  $\beta$  cells and the vitamin D-binding proteins in pancreatic tissue and the association between specific allelic variations in the vitamin D receptor and vitamin D-binding protein genes with glucose tolerance and insulin secretion have further supported this hypothesis. The mechanism of action of vitamin D in type 2 diabetes is thought to be mediated not only through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, but also through a direct action on pancreatic beta-cell function (Palomer et al., 2008). Vitamin D deficiency decreases insulin secretion without changing in glucagon secretion. The effects of a vitamin D deficiency on insulin and glucagon secretion was obtained in isolated perfused rat pancreas by radioimmunoassay of the secreted proteins. Throughout a 30-minute times of perfusion with glucose and arginine, pancreases from vitamin D-deficient rats showed a 48 percent reduction in insulin secretion compared to that for pancreases from vitamin D-deficient rats that had been resupplied with vitamin D. Vitamin D status had no effect on pancreatic glucagon secretion. This result,



along with the previously demonstrated presence in the pancreas of a vitamin D-dependent calcium-binding protein and cytosol receptor for the hormonal form of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub>, indicates an important role for vitamin D in the endocrine functioning of the pancreas. The data demonstrated a positive correlation of 25(OH)D concentration with insulin sensitivity and a negative effect of hypovitaminosis D on function of  $\beta$  cell. Subjects with hypovitaminosis D are at higher risk of insulin resistance and the metabolic syndrome. Vitamin D repletion in early stages of experimental dietary vitamin D deficiency and in vitamin D deficiency subjects improves glucose intolerance and increases insulin secretion. Some studies demonstrated that vitamin D supplementation increased insulin secretion in response to an oral glucose load in patients with type 2 diabetes but not in patients with established type 2 diabetes (Chiu et al., 2004; Inomata et al., 1986; Orwoll et al., 1994; Gedik & Akalin, 1986). Some evidence indicates that vitamin D increases insulin secretion from  $\beta$  cells by increasing intracellular calcium concentration through nonselective voltage-dependent calcium channels. The main effect of vitamin D on insulin secretion is acquired from conversion of proinsulin to insulin. Calcium is principal not only for insulin exocytosis but also for cell glycolysis (Boucher, 1998). Vitamin D also activates protein biosynthesis in pancreatic islets. Vitamin D deficiency reduces insulin secretion and action. Variation in the vitamin D receptor or vitamin D-binding protein causes glucose intolerance.

Vitamin D increases cellular glucose absorption either directly or by increasing insulin sensitivity. Vitamin D may directly or indirectly regulate  $\beta$  cell function and secretion by binding 1,25 dihydroxy vitamin D to  $\beta$  cell vitamin D receptors and controlling the balance between the extracellular and intracellular  $\beta$  cell calcium pools (Norman et al., 1980).

Vitamin D can promote insulin sensitivity by stimulating the expression of insulin receptors and enhancing insulin responsiveness for glucose transport. It also regulates extracellular calcium and thus establishes normal calcium inflow through cell membranes and an adequate intracellular cytosolic calcium pool, which is necessary for the insulin-mediated intracellular process in insulin responsive tissues (Draznin et al., 1988).

#### 4.3 Vitamin D deficiency and gestational diabetes

Data about vitamin D as a risk factor for GDM is sparse. Pregnant women with diabetes are known to be more vitamin D deficient compared with normal pregnant women (Bikle, 1992). Intravenous administration of vitamin D to pregnant women with gestational diabetes transiently decreases fasting glucose; however, the level of insulin also decreases (Rudnicki & Molsted-Pedersen, 1997). Vitamin D deficiency was associated with a 2.66-fold increase in GDM risk and each 5 ng/ml decrease in 25-hydroxy D concentrations was related to a 1.29-fold increase in GDM risk (Zhang et al., 2008). Another study demonstrated that the serum concentration of vitamin D during 24-28 weeks of pregnancy in gestational diabetes was lower than normal groups (Maghbooli et al., 2007; Soheilykhah et al., 2009). Women with GDM had a 2.66 fold increased risk of vitamin D deficiency (25-hydroxy D < 15 ng/ml) compared with control group (Soheilykhah et al., 2009). Maternal hypovitaminosis was reported in diabetic pregnancies in Spain and fasting glycaemia decreased with vitamin D supplementation (Farrant et al., 2008). Vitamin D, insulin and proinsulin were measured at 30 weeks gestation in another study. This study demonstrated that vitamin D insufficiency is common in mothers but is not associated with gestational diabetes. There was no association between maternal 25(OH)D and gestational diabetes. In this study mothers with hypovitaminosis D, higher 25(OH)D concentrations were associated

with lower 30-min glucose concentrations and higher fasting proinsulin concentrations (Farrant et al., 2009). Clifton-Bligh et al. showed mean serum 25(OH)D concentration in pregnant women was negatively correlated with fasting plasma glucose, fasting insulin and insulin resistance as calculated by homeostasis model assessment. The association between fasting glucose and log-transformed 25OHD concentration was of borderline significance after accounting for ethnicity, age and body mass index in multivariate analyses. The odds ratio of gestational diabetes in women with 25OHD < 50 nmol/L did not reach statistical significance (1.92, 95% confidence interval 0.89-4.17) (Clifton-Bligh et al., 2008).

In another study total prevalence of vitamin D deficiency (<25 nmol/L) was 70.6% in pregnant women. Prevalence of severe vitamin D deficiency (<12.5) in GDM patients was higher than in normoglycaemic pregnancies. These results show that a positive correlation of 25(OH) vitamin D concentrations with insulin sensitivity and vitamin D deficiency could be a confirmative sign of insulin resistance (Maghbooli et al., 2007). Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring (Chiu et al., 2003). In Finland, 10,366 children who were given 2000 IU of vitamin D<sub>3</sub> per day during their first year of life were followed for 31 years. The risk of type 1 diabetes was reduced by approximately 80% (relative risk, 0.22; 95% CI, 0.05 to 0.89) (Hypponen et al., 2001). Among children with vitamin D deficiency, the risk was increased by approximately 200% (relative risk, 3.0; 95% CI, 1.0 to 9.0). In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome (Chiu et al., 2004). Another study demonstrated that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D (Pittas et al., 2006). 4000 IU vitamin D was administered for 6 months to women with vitamin D less than 50 nmol/L and median serum 25(OH)D<sub>3</sub> increased significantly and insulin resistance and fasting insulin decreased (Von Hurst et al., 2010). In summary the result of different studies show high prevalence of vitamin D deficiency in pregnant women and most of these findings demonstrated the relationship between vitamin D status and glucose tolerance in pregnancy.

## 5. Conclusion

Early diagnosis of gestational diabetes prevents maternal and fetal complications. Recently a number of studies illustrated association of various biomarkers with subsequent development of GDM. These metabolic mediators are known to be produced in the intrauterine environment. Some studies demonstrated that decreased level of adiponectin and increased level of leptin and resistin preceded the onset of diabetes in pregnancy.

Some investigations also have been shown association between C-reactive protein and risk of GDM. Some researches exhibited maternal vitamin D concentration inversely related to fasting glucose and insulin concentration and vitamin D deficiency was associated with increasing risk of GDM.

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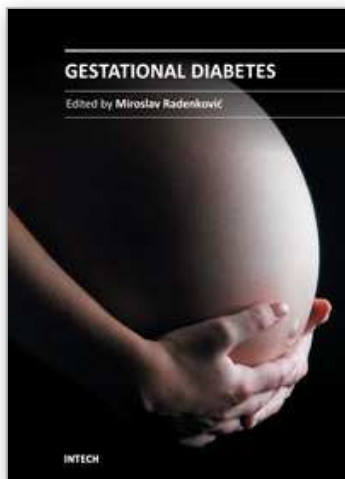
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## **Gestational Diabetes**

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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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