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Pro-Inflammatory Cytokines, Lipid Metabolism and Inflammation in Gestational Diabetes Mellitus as Cause of Insulin Resistance

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1. Introduction

Gestational diabetes mellitus (GDM) is a glucose intolerance of varying severity with onset or first recognition, during pregnancy that complicates 2–4% of pregnancies (Ben-Haroush et al 2004, American Diabetes Association 2005, NICE Guidelines 2008). Both patients with GDM, and their offspring, have greater risk of developing type 2 diabetes later in life (Damn 1998). There is a close relationship between GDM and prediabetes state in addition to the risk of future deterioration in insulin resistance and ultimate development of overt type 2 diabetes mellitus (Kjos et al 1999). Diabetes in pregnancy is increasing and therefore it is important to raise awareness of the associated health risks to the mother, the growing fetus, and the future child. Perinatal mortality and morbidity is increased in diabetic pregnancies through increased stillbirths and congenital malformation rates (Canadian Diabetes association 2003, HAPO 2008, RCOG SAC 2011). These are mainly the result of early fetal exposure to maternal hyperglycaemia. In the mother, pregnancy may lead to worsening or development of diabetic complications such as retinopathy, nephropathy, and hypoglycaemia (Ali and Dornhorst 2011). Although glycaemic control is important in reducing microvascular complications due to diabetes in pregnancy, it has not reduced the rate of congenital anomalies, macrosomia and other adverse outcomes (Canadian Diabetes Association 2003). This may be as a result of our lack of understanding of the epidemiology and pathogenesis of GDM (Omu et al. 2010), especially the role of inflammation, cytokines and lipid metabolism.

1.1. The main objectives of this review are to draw attention to

- a. The epidemiology, genetics and immunological basis of GDM

- b. Elucidate the effect of lipid metabolism and lipid peroxidation, oxidative stress on antioxidant gene expression and other inflammatory cytokines.
- c. Investigate the role of risk factors including obesity and adipokines like adiponectin, leptin and tumor necrosis factor alpha, acute phase proteins like C-reactive protein (C-RP), IL-6 and plasminogen activation inhibitor -1 (PAI-1) and proinflammatory Cytokines and the mechanisms involved in the pathogenesis.
- d. Highlight the role of intervention strategy in the prevention of progression of GDM to type 2 Diabetes Mellitus and alteration of Maternal effects of GDM

2. Epidemiology of gestational diabetes mellitus

Gestational diabetes has been recognised as a heterogenous disorder of glucose intolerance (Kjos et al 1999, Metzger et al 2010, and Omu et al 2011). Unfortunately, comparisons of frequencies of GDM among various populations is difficult because, there are differences in screening programmes and diagnostic criteria (Butte 2000, Ben-Haroush et al 2004, Buchanan et al 2007). There is an urgent need to develop and unify appropriate diabetic diagnostic and prevention strategies and address potentially modifiable risk factors such as obesity.

2.1. Diagnostic criteria of gestational diabetes mellitus (GDM)

Historically, the diagnosis of gestational diabetes mellitus (GDM), like diabetes mellitus in general, has been by measuring the fasting plasma glucose level and performing an oral glucose tolerance test (OGGT) with the threshold as shown in Table 1. In 2010, the American Diabetic Association added haemoglobin A1c (Hb A1c) as a diagnostic tool for individual with type 2 diabetes mellitus with a threshold fixed at 6.5 % for diagnosis. It was however, not recommended for use in GDM.

	mg/dl	mmol/L
100g glucose load		
Fasting	95	5.3
1 hour	180	10.0
2 hour	155	8.6
3 hour	140	7.8
75 g glucose load		
Fasting	95	5.3
1 hour	180	10.0
2 hour	155	8.6

Table 1. Diagnosis of Gestational Diabetes Mellitus (GDM)

For diagnosis of GDM, 2 values in each diagnostic group must be met or exceeded (ADA 2011).

According to the NICE guidelines No 63 (2008), screening for GDM using fasting plasma glucose, random blood glucose, glucose challenge test and urinalysis for glucose, should not be recommended. Instead a 2 hour 75 g OGTT should be done at 24-28 weeks of gestation.

2.2. Non-genetic factors

Ethnicity, old age, family history, obesity and high fat diet and sedentary lifestyle, represent some important non-genetic identifiable predisposing factors for GDM, and in the absence of risk factors, there is low incidence of GDM. Ethnicity has been proven to be an independent risk factor for GDM (Dooley et al 1991, Weerakiet et al. 2004) which varies in prevalence in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group. Women with an early diagnosis of GDM, in the first half of pregnancy, represent a high-risk subgroup, with an increased incidence of obstetric complications, recurrent GDM in subsequent pregnancies, and future development of Type 2 diabetes (Ben-Housah et al 2004, Buchanan et al 2007). There is a strong association between Gestational Diabetes Mellitus and women with diagnosed Polycystic Ovary Syndrome (PCOS) (Weerakiet et al 2004, Lo et al 2006). The prevalence of GDM is increasing worldwide because of the obesity epidemic and the increasing sedentary lifestyle and the attractive high caloric intake and need for insulin for glycaemic control (Bray et al 2003, Hedley et al 2004, Callagher et al 2008, Kulie et al. 2011, WHO 2011).

2.3. Postpartum diabetes mellitus

Gestational Diabetes Mellitus increases the risk of developing Type 1 and Type 2 diabetes mellitus. Risk estimates for type 2 Diabetes is 17 to 68 percent within 5-16 years after pregnancy (O'Sullivan 1991, Hanna et al. 2002, Ben-Housah et al 2004). The risk factors for postpartum diabetes include islet autoantibody positivity, insulin requirement during pregnancy, Obesity (Lauenborg et al 2004) and strong family history.

2.4. Genetics of GDM

GDM is considered to result from interaction between genetic and environmental risk factors. Women with mutations in MODY (Maturity onset diabetes of the young) genes often present with GDM. Genetic predisposition to GDM has been suggested given the occurrence of the disease within family members. GDM is reported to be often present in women with mutation of MODY gene mutations (Lapolla et al 1996, Ferber et al. 1999, Watanabe et al 2007). Candidate susceptibility gene variants have been suggested to increase the risk of GDM. These genes include glucokinase (GCK), HLA antigens, insulin receptor (INSR), insulin-like growth factor-2 (IGF2), insulin gene (INS-VNTR), plasminogen activator inhibitor 1 (PAI-1), potassium inwardly rectifying channel subfamily J, member 11 (KCNJ11), hepatocyte nuclear factor-4a (HNF4A) (Love-Gregory and Permutt 2007). Identification of the possible underlying genetic factors and mechanisms of the pathogenesis may contribute to the individualization of both prevention and treatment of complications for the mother and fetus (Lambrinoudaki et al 2010). Furthermore, it may improve options to prevent GDM and the complications for the mother and child (Shaath and Groop 2007). During pregnancy, pancreatic cells should by

necessity, expand and produce more insulin to adapt to the needs of the pregnancy and the growing baby. Hepatic Growth Factor (HGF) which interact with a surface receptor called c-Met. HGF/c-Met pathway signaling, plays a key role in increasing insulin secretion during pregnancy. The mechanisms in the maternal β -cells adaptation during pregnancy include maternal β -cell hyperplasia by lactogens and HGF/c-Met (Ernst et al 2011). Loss of HGF/c-Met Signaling in Pancreatic β -Cells leads to incomplete Maternal β -Cell Adaptation and Gestational Diabetes Mellitus (Demirci et al 2012).

3. Lipid metabolism and gestational diabetes mellitus

3.1. Lipid and lipoproteins

Hyperlipidemia is a common comorbidity among patients with diabetes mellitus (Anger et al 2011, Koukkou et al 2011). A recent study has found an association between cholesterol intake and GDM (Gonzalez-Clemente et al. 2007). In the placenta, expressions of key proteins involved in de novo lipid synthesis are affected by changes in maternal metabolism (hypercholesterolemia and GDM) that may subsequently affect fetal development and result in asymmetric macrosomia. In addition, impaired placental function gives rise to significant increases in LDL, Apo-B-100 and triglyceride in maternal serum with increased levels of fatty acid synthase (FAS) and SREBP-2 expression and inflammatory cytokines (IL-1 β and TNF- α) in placenta (Marseille-Trembley et al 2008). This may give rise to trend towards an increased risk of cardiovascular disease (Gonzalez-Clemente et al. 2007).

3.2. Free fatty acids

Free fatty acids (FFA) are the main circulating lipid fuel. FFA released from visceral depot appear to serve as a marker of systemic insulin resistance and associated increases in cardiovascular risk (Sivan et al 1999, Catalano et al 2002, Jensen 2006). This has been attributed to apoptosis of pancreatic beta cells through pathway involving caspase and ceramide as a mechanism underlying FFA induced impairment of beta -cell function (Turpin et al 2006). Hyperglycaemia and elevated FFA may act synergistically in causing damage to beta cells (El-Assaad et al 2003) and decreases ability of insulin to suppress free fatty acids with advancing gestation with GDM (Darmady and Postle 1982). In a recent report, Schaefer and Colleagues (2011) demonstrated higher free fatty acids in the cord blood of those neonates from mothers with gestational diabetes, indicating their enhanced placental transport and/or enhanced lipolysis as a result of decreased insulin responsiveness (Kautzky-Willer et al 2003).

3.3. Effects of lipid peroxidation

The markers of lipid oxidation, especially malondialdehyde (MDA) increased with hyperglycaemia (Davi et al. 2005). Lipid peroxidation is a crucial process generated naturally in the body, mainly by the effect of several reactive oxygen species such as hydroxyl radical, hydrogen peroxide and superoxide. These reactive oxygen species readily attack the polyun-

saturated fatty acids of the fatty acid membrane, initiating a self-propagating chain reaction (Hanachi et al. 2009). The destruction of membrane lipids and the end-products of such lipid peroxidation reactions cause cell damage. Enzymatic (catalase, superoxide dismutase) and nonenzymatic (vitamins A and E) natural antioxidant defense mechanisms exist; however, these mechanisms may be overcome, causing lipid peroxidation to take place. Lipid peroxidation has been implicated in disease states such as atherosclerosis, asthma, Parkinson's disease, kidney damage and preeclampsia (Mylonas and Kouretas 1999, Veskoukis et al 2012)

3.4. Effect of lipid metabolism on neonatal outcome

The development of diabetes in pregnancy induces a state of dyslipidemia, characterized by a high triglyceride concentration (Koukkonen et al 1996,) and associated with disturbance of fetal development with modification of key features of placental function (Marseille-Tremblay 2008). GDM patients with macrosomic fetuses are associated with higher lipid and lipoprotein concentrations than in control patients (Mersouk et al. 2000).

8-Isoprostane is a product of lipid peroxidation that can be used as a measure of free radical exposure or injury. Periventricular-intraventricular hemorrhage, necrotizing enterocolitis, chronic lung disease and retinopathy of prematurity have been referred to as oxygen radical diseases (ORD) because they are thought to be related to excess oxidant stress relative to antioxidant defenses in premature infants (Weinberger et al 2006). Umbilical cord venous, but not arterial, 8-isoprostane levels are associated with mortality and the development of one or more of the ORD. In a study, serum triglyceride, total cholesterol, and LDL-c concentrations were higher in the SGA neonates than in AGA neonates, whereas high-density lipoprotein cholesterol concentrations were similar, suggesting a limited ability to clear intravenous lipids in SGA infants (Arends et al 2005). These findings are in agreement with many previous studies in adults and children that show that low birth weight was significantly associated with a less favorable lipid profile (Mortaz et al 2001). Hyperinsulinemia is known to enhance hepatic very-low-density lipoprotein synthesis, which may contribute to increased plasma triglycerides and LDL-c levels. Resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated triglyceride and LDL-c levels. (Barker et al 1993).

3.5. Adipose tissue as an endocrine organ

The discovery of leptin in the mid-1990s has focused attention on the role of proteins secreted by adipose tissue (Wang et al 2004). Leptin has profound effects on appetite and energy balance, and is also involved in the regulation of neuroendocrine and immune function. Sex steroid and glucocorticoid metabolism in adipose tissue have been implicated as a determinant of body fat distribution and cardiovascular risk. Other adipose products, include other adipokines such as adiponectin, proinflammatory cytokines such as TNF-alpha and IL-6, C-Reactive Protein, complement factors (Cipollini et al 1999, Coppack 2001) and components of the coagulation/fibrinolytic cascade like plasminogen activation inhibitor-1 (PAI-1), that may mediate the metabolic and cardiovascular complications associated with obesity and insulin resistance (Ahima and Flier 2000, Hutley and Prins 2005, Jensen 2006).).

4. Immunology of gestational diabetes

Pregnancy represents a distinct immunologic state in the fetus that acts as an allograft to the mother, needing protection against potential rejection. There is some evidence that inflammation and activated innate immunity is associated with the pathogenesis of Type 2 Diabetes (Pickup 2004), but this needs confirmation, especially in GDM.

4.1. Humoral reactivity in pregnancy

The placental HLA-G proteins facilitate semiallogeneic pregnancy by inhibiting maternal immune responses to foreign (paternal) antigens via their actions on immune cells is now well established, and the postulate that the recombinant counterparts of these proteins may be used as powerful tools for accommodating the fetus and prevent immune rejection (Hunt et al 2005). Humoral immune-reactivity does not change much during pregnancy, with the exception of lowered immunoglobulin G concentration at late phase, probably explained by placental transport. Regarding cellular immunity, the reduction, elevation, and lack of variation in the number of different lymphocytic populations, have been reported (Mahmoud et al 2005, 2006).

4.2. Autoimmune GDM

Multiple autoimmune disturbances may be manifested during pregnancy (Leiva et al 2008). Ferber and Associates (1999) have demonstrated that women with GDM who have islet autoantibodies at delivery or develop IDDM postpartum have HLA alleles typical of late-onset type 1 diabetes, and that both HLA typing and islet antibodies can therefore predict the development of postpartum IDDM. Freinkel et al. (1986) first proposed what may be defined as autoimmune GDM; that GDM entails genotypic and phenotypic diversity which may include patients with slowly evolving type 1 diabetes (Mauricio and Leiva 2001, Lapolla et al 2009). There is current consensus that autoimmune GDM is a heterogeneous condition that accounts for 10% of all Caucasian women diagnosed with GDM (Mauricio et al 1996). As a high-risk group for type 1 diabetes, women with previous autoimmune GDM may be candidates for potential immune intervention strategies (Mauricio et al 2001).

4.3. Cellular immune response and gestational diabetes

There is a significant increase in the absolute number of total and activated (CD3+HLA-DR+) T lymphocytes and a significant increase in the absolute number and percentage of suppressor/cytotoxic T lymphocytes (CD8) and NK lymphocytes (CD57) in GDM patients compared with normal pregnant controls (Mahmoud et al. 2006). Concerning frequency for HLA A, B, C, DR antigens in the GDM population, only Cw₇ was found to be significantly increased and A₁₀ significantly decreased in comparison with controls (Lapolla et al 1996). When compared with healthy pregnant women, both GDM cohorts showed higher percentages CD4+CD25+ ($P < 0.05$), CD4+CD45RO+ ($P < 0.05$) and CD4+CD29+ (Mahmoud et al 2005).

5. The placenta is a target of cytokines: maternal and fetal influences

There is a robust cytokine network in the placenta with diverse pathogenesis and effects on the development of the fetus.

5.1. Bidirectional nature of cytokine at the fetal-maternal interface

Subpopulations of T helper lymphocytes (CD3+/CD4+) can be classified as either T helper 1 (Th1) or T helper 2 (Th2) cells depending on their cytokine profiles. Th2 cells selectively produce interleukins (IL)-4, IL-5, IL-6, IL-9, IL-10 and IL-13, and are involved in the development of humoral immunity against extracellular pathogens but inhibit several functions of phagocytic cells. In contrast to this, Th1 cells produce interferon- γ (IFN- γ), IL-2 and tumour necrosis factor- α (TNF- α) and evoke cell-mediated immunity and phagocyte-dependent inflammation (Mosmann et al 1989, Mosmann and Moore 1991, Romagnani 2000). Cytokines are mainly produced by cells of the immune system, NK cells, and macrophages in response to an external stimulus such as stress, injury, and infection. Adipose tissue represents an additional source of cytokines, making possible a functional cooperation between the immune system and metabolism (Guerre-Miller 2004, Radaelli et al. 2005).

5.2. The role of adipokines and other inflammatory markers

Research has recently focused on a group of substances produced mainly by adipose tissue called adipokines, this group includes, among others, adiponectin, leptin, Retinol-Binding Protein-4 (RBP-4), and resistin. These substances as well as other inflammatory mediators (CRP, IL-6, PAI-1, TNF- α) seem to play an important role in glucose tolerance and insulin sensitivity dysregulation in women with GDM (Thyfault et al 2005, Defalu 2009). There are two main pathways leading to GDM and T2DM: insulin resistance and chronic subclinical inflammation. Insulin resistance is caused by the inability of tissues to respond to insulin and the deficient secretion of insulin by pancreatic beta cells (Vrachnis et al 2012). Inflammatory processes have a robust contribution to the pathogenesis of dysglycemia condition and acute phase inflammatory response is a risk factor for T2DM and cardiovascular disease [Pickup et al. 2004]. Obesity has a role in the development of both T2DM and GDM through chronic subclinical inflammation, low-grade activation of the acute phase response, and dysregulation of adipokines (Yudkin et al 1999, Greenberg et al 2002). Increased levels of inflammatory agents during and after pregnancy have been reported in patients with GDM, while increased body fat has been strongly associated with inflammation and adipocyte necrosis, hypoxia, and release of chemokines which cause macrophages to infiltrate adipose tissue. Macrophages secrete cytokines which activate the subsequent secretion of inflammation mediating agents, specifically interleukin-6 (IL-6) and C-reactive protein (CRP) (Festa et al 2000). Other molecules such as Plasminogen Activator Inhibitor 1 (PAI-1) and sialic acid lead to dysregulations of metabolism, hyperglycemia, insulin resistance, and diabetes. These are a group of substances that are produced mainly in the adipose tissue. The group includes leptin, adiponectin, tumor

necrosis factor alpha (TNF- α), retinol-binding protein-4 (RBP-4), resistin, visfatin, and apelin. These molecules are involved in a wide range of physiological processes including lipid metabolism, atherosclerosis, blood pressure regulation, insulin sensitivity, and angiogenesis, while they also influence immunity and inflammation. Their levels in pathologic states appear increased, with the exception of adiponectin which shows decreased levels (Vrachnis et al 2012).

5.3. Adiponectin

Since the discovery of adiponectin in 1994 by Jeffrey M. Friedman (Zhang et al 1994), more than 20 members of the adiponectin family have been identified (Klein et al 2002, Housa et al 2006). Adiponectin is a 30-kDa protein that is synthesized almost exclusively by adipocytes. It exists in three major oligomeric forms: a low-molecular-weight trimer, a middle-molecular-weight hexamer and high-molecular-weight (HMW) 12- to 18-mer adiponectin. It is an insulin-sensitizing and stimulates glucose uptake in skeletal muscle and reduces hepatic glucose production through AMP-activated protein kinase [Zavalza et al 2008]. Circulating adiponectin levels are reduced in patients with GDM as compared to healthy pregnant controls. Adiponectin mRNA is downregulated in placental tissue, while circulating adiponectin concentrations are decreased postpartum in women with a history of GDM. It also possesses antiatherogenic and anti-inflammatory properties [Chandran et al 2003, Wiecek et al 2007]. The levels of adiponectin decrease as visceral fat increases [Cnop et al 2003, Weyer et al 2001, Hotta et al 2000, Shondorf et. al 2005] in such conditions as central obesity, insulin resistance, and diabetes mellitus. Reduced adiponectin levels have notably been associated with subclinical inflammation [Retnakaran et al 2003]. It has been shown that adiponectin levels begin to decrease early in the pathogenesis of diabetes, as adipose tissue increases in tandem with reduction in insulin sensitivity [Hotta et al 2001]. Hypoadiponectinemia has also been associated with beta cell dysfunction [Musso et al 2005, Retnakaran et al 2005], while it has additionally been linked to future development of insulin resistance and type 2 diabetes mellitus, in the development of which adiponectin appears to have a causative role (Stefan et al 2002). As such, adiponectin may play a key role in mediating insulin resistance and beta cell dysfunction in the pathogenesis of diabetes (Retnakaran et al 2004, Retnakaran et al 2005). Retnakaran and Associates (2005) have demonstrated that adiponectin concentration is an independent correlate of pancreatic beta cell function in late pregnancy.

5.4. Leptin

Leptin is a 16-kDa protein hormone that is known to play a key role in the regulation of energy intake and energy expenditure and in a number of physiological processes including regulation of endocrine function, inflammation, immune response, reproduction and angiogenesis. The main function of leptin in the human body is the regulation of energy expenditure and control of appetite. Indeed, lack of leptin in mice with a mutation in the gene encoding leptin, or absence of functional leptin receptor (*db/db* mice) results in obesity and many associated metabolic complications such as insulin resistance [Ceddia

et al 2002)]. Leptin is a key molecule in obesity and it is predominantly produced by white adipose tissue [Harvey and Ashford 2003]. Circulating leptin is actively transported through the blood-brain barrier and acts on the hypothalamic satiety center to decrease food intake. Serum level of leptin reflects the amount of energy stored in the adipose tissue and proportional to body fat mass [Fruhbeck 2006], i.e. increased in obese and decreased after several months of pronounced weight loss [Moschen et al 2009, Hegyi et al 2004]. Thus, it increases insulin sensitivity by influencing insulin secretion, glucose utilization, glycogen synthesis and fatty acid metabolism, regulates gonadotrophin releasing hormone secretion from the hypothalamus and activates the sympathetic nervous system. Leptin acts via transmembrane receptors (OB-R), which belong to the class I cytokine receptor family, such as the receptors of interleukin-2 (IL-2), IL-3, IL-4, IL-6, IL-11, IL-12, granulocyte colony-stimulating factor (G-CSF) or leukemia inhibitory factor (LIF). OB-Rb has full signaling capabilities and is able to activate the JAK/STAT pathway, the major pathway used by leptin to exert its effects [Cirillo et al 2008]. It has receptors on many other cell types such as adipocytes, osteoclasts, endothelial cells, lung and kidney cells, mononuclear blood cells, muscle, endometrial and liver cells [Hegyi et al 2004].

5.5. Association between leptin and TNF-alpha and insulin resistance

Placental leptin mRNA production is upregulated by tumour necrosis factor (TNF) α and interleukin (IL)-6. Most studies have found increased leptin concentrations in GDM. Moreover, hyperleptinaemia in early pregnancy appears to be predictive of an increased risk to develop GDM later in pregnancy independent of maternal adiposity (Hotamistigil et al 1993, Das 2002, Kirwan et al 2002,). The human placenta expresses virtually all known cytokines including tumor necrosis factor (TNF)- α , resistin, and leptin, which are also produced by the adipose cells (Qasim et al 2008, Rabe et al. 2008). The discovery that some of these adipokines as key players in the regulation of insulin action suggests possible novel interactions between the placenta and adipose tissue in understanding pregnancy-induced insulin resistance, which is evident in gestational diabetes mellitus (GDM) (Winzer et al 2004).

5.6. Inflammatory mediators in diabetes mellitus

Gestational diabetes mellitus is characterized by an amplification of the low-grade inflammation already existing in normal pregnancy (Retnakaran et al 2010). This hypothesis is supported by increased circulating concentrations of inflammatory molecules like TNF α and IL-6 in GDM pregnancies. TNF α is one of the candidate molecules responsible for causing insulin resistance. Comparison of the placental gene expression profile between normal and diabetic pregnancies indicates that increased leptin synthesis in GDM is associated with a higher production of proinflammatory cytokines, e.g. IL-6 and TNF α causing a chronic inflammatory environment that enhances leptin production (Pickup et al 2000, Winkler et al 2002, Gao et al 2008). Thus, compared with normal pregnant women, placental leptin expression in patients with GDM is increased. Conversely, leptin itself

increases production of TNF α and IL-6 by monocytes and stimulates the production of CC-chemokine ligands. Elevated leptin concentrations in turn amplify inflammation

6. Link between inflammation and insulin resistance

In 1876 Ebstein asserted that sodium salicylate could make the symptoms of diabetes mellitus totally disappear. Similarly, in 1901 Williamson found that “sodium salicylate had a definite influence in greatly diminishing the sugar excretion”(Shoelson 2002, Shoelson et al 2006, Cefalu 2009). Increased levels of markers and mediators of inflammation and acute-phase reactants such as fibrinogen, C-reactive protein (CRP), IL-6, plasminogen activator inhibitor-1 (PAI-1), sialic acid, and white cell count correlate with incident T2D (Sternberg et al 1992, Bo et al 2005, Kim et al. 2008). Markers of inflammation and coagulation are reduced with intensive lifestyle intervention. This was confirmed in the diabetes prevention program (DPP Research Group 2005). Experimental evidence have also confirmed that adipose tissue–derived proinflammatory cytokines such as TNF- α could actually cause insulin resistance (Wolf et al 2003, Dandona et al 2004, Hu et al 2004, Heitritter et al 2005). Hotamisligil and colleagues (1993, 1994) and Karasik and Colleagues (1993) first showed that the proinflammatory cytokine TNF- α was able to induce insulin resistance. The concept of fat as a site for the production of cytokines and other bioactive substances quickly extended beyond TNF- α to include leptin, IL-6, resistin, monocyte chemoattractant protein-1 (MCP-1), PAI-1, angiotensinogen, visfatin, retinol-binding protein-4, serum amyloid A (SAA), and others (Dandona et al 2004). Adiponectin is similarly produced by fat, but expression decreases with increased adiposity. While leptin and adiponectin are true adipokines that appear to be produced exclusively by adipocytes, TNF- α , IL-6, MCP-1, visfatin, and PAI-1 are expressed as well at high levels in activated macrophages and/or other cells (Baer et al 1998). Sites of resistin production are more complex; they include macrophages in humans but both adipocytes and macrophages in rodents. TNF- α , IL-6, resistin, and other pro- or antiinflammatory cytokines appear to participate in the induction and maintenance of the subacute inflammatory state associated with obesity (Thyfault et al 2005). MCP-1 and other chemokines have essential roles in the recruitment of macrophages to adipose tissue. These cytokines and chemokines activate intracellular pathways that promote the development of insulin resistance and T2D (Wu et al 2002, de Victoria et al. 2009).

6.1. Mechanisms of insulin resistance by pro-inflammatory cytokines

The JNK (also referred to as SAPK) and p38 MAPKs are members of the complex superfamily of MAP serine/threonine protein kinases. This superfamily also includes the ERKs (Lewis et al 1998). In contrast to ERKs (also referred to as MAPKs), which are typically activated by mitogens, JNK/SAPK and p38 MAPK are known as stress-activated kinases. This can be attributed to the fact that the activities of these enzymes are stimulated by a variety of exogenous and endogenous stress-inducing stimuli including hyperglycemia, ROS, oxidative stress, osmotic stress, proinflammatory cytokines, heat shock, and UV irradiation (Tibbles et al 1999). Many of the more typical proinflammatory stimuli simultaneously activate JNK and

IKK β pathways, including cytokines and TLRs (Seger and Krebs 1995). Concordantly, genetic or chemical inhibition of either JNK or IKK β /NF- κ B can improve insulin resistance. The several mechanisms have been postulated to explain how obesity activates JNK and NF- κ B. These can be separated into receptor (Lowes et al 2002) and nonreceptor pathways (Tamura et al 2002). Proinflammatory cytokines such as TNF- α and IL-1 β activate JNK and IKK β /NF- κ B through classical receptor-mediated mechanisms that have been well characterized (Shen et al 2001, Tournier et al 2001). JNK and IKK β /NF- κ B are also activated by pattern recognition receptors, defined as surface proteins that recognize foreign substances. These include the Toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE). Many TLR ligands are microbial products, including LPS and lipopeptides (Tamura et al 2002).

6.2. Transcription versus phosphorylation in the pathogenesis of insulin resistance

JNK is a stress kinase that normally phosphorylates the c-Jun component of the AP-1 transcription factor, but to date there are no known links between this well-established transcriptional pathway and JNK-induced insulin resistance. JNK has been shown to promote insulin resistance through the phosphorylation of serine residues (Shen et al 2001, Tournier et al 2001). Insulin receptor signaling that normally occurs through a tyrosine kinase cascade is inhibited by counterregulatory serine/threonine phosphorylations.

6.3. IKK β signaling pathway and insulin resistance

Unlike JNK, IKK β does not phosphorylate IRS-1 to cause insulin resistance but causes insulin resistance through transcriptional activation of NF- κ B. Increased lipid deposition in adipocytes leads to the production of proinflammatory cytokines, including TNF- α , IL-6, IL-1 β , and resistin, which further activate JNK and NF- κ B pathways through a feed-forward mechanism (Hou et al 2008). In addition to the cytokines, there is upregulated expression of transcription factors, receptors, and other relevant proteins including chemokines that recruit monocytes and stimulate their differentiation into macrophages.

Cytokines and chemokines produced locally include MCP-1 and macrophage inflammatory protein-1 α (MIP-1 α), MIP-1 β , MIP-2, and MIP-3 α . T cell activation leads to expression of IFN- γ and lymphotoxin; macrophages, endothelial cells, and SMCs produce TNF- α ; and together these stimulate the local production of IL-6 in the atheroma

6.4. Oxidative stress and activation of JNK and NF- κ B pathways

In addition to proinflammatory cytokine and pattern recognition receptors, cellular stresses activate JNK and NF- κ B, including ROS and ER stress. Elevated glucose cause oxidative stress through (1) increased production of mitochondrial reactive oxygen species (ROS), (2) Non-enzymatic glycation of proteins, (3) Glucose autooxidation (Elevated free fatty acids (FFA) and beta oxidation (Tibbles et al 1999, Evans et al 2002, Lewis et al 2002, Muoio et al. 2008). Systemic markers of oxidative stress increase with adiposity, consistent with a role for ROS in the development of obesity-induced insulin resistance, (Ozdemir et al 2005). One potential mechanism is through the activation of NADPH oxidase by lipid accumulation in the adipocyte.

cyte, which increases ROS production. This mechanism was shown to increase the production of TNF- α , IL-6, and MCP-1, and decrease the production of adiponectin (Barbour et al 2007). Consistent with this, the antioxidant *N*-acetyl cysteine can reduce ROS and improve insulin resistance in a hyperglycemia-induced model (Pieper et al 1997, Ozkiloglu et al 2006). Lipid accumulation also activates the unfolded protein response to increase ER stress in fat and liver. ER stress has been shown to activate JNK and subsequently, lead to serine phosphorylation of insulin receptor substrate-1 (IRS-1), but as with all of the stimuli, ER stress similarly activates NF- κ B (Evans et al 2002)

7. Health implications of cytokines, lipid metabolism, inflammation and GDM

The triad of cytokines, lipid metabolism and inflammation are hooked together by a biological thread of oxidative stress and pathogenetic end-point of insulin resistance. Oxidative stress inhibits expression of Pax 3, a gene that is essential for neural tube closure, and possibly congenital cardiac anomalies which have been associated with uncontrollable diabetes in pregnancy before and in early pregnancy (Chang et al 2003). The association between GDM and macrosomia is real, with a secondary effect of increased cesarean section and increased risk of postpartum genital infection and development of overt type 2 diabetes mellitus. The markers of inflammation, dyslipidemia, oxidative stress and endothelial dysfunction may provide additional information about a patient's risk of developing cardiovascular disease and hypertension. This may provide new attractive targets for drug development.

8. Intervention strategies

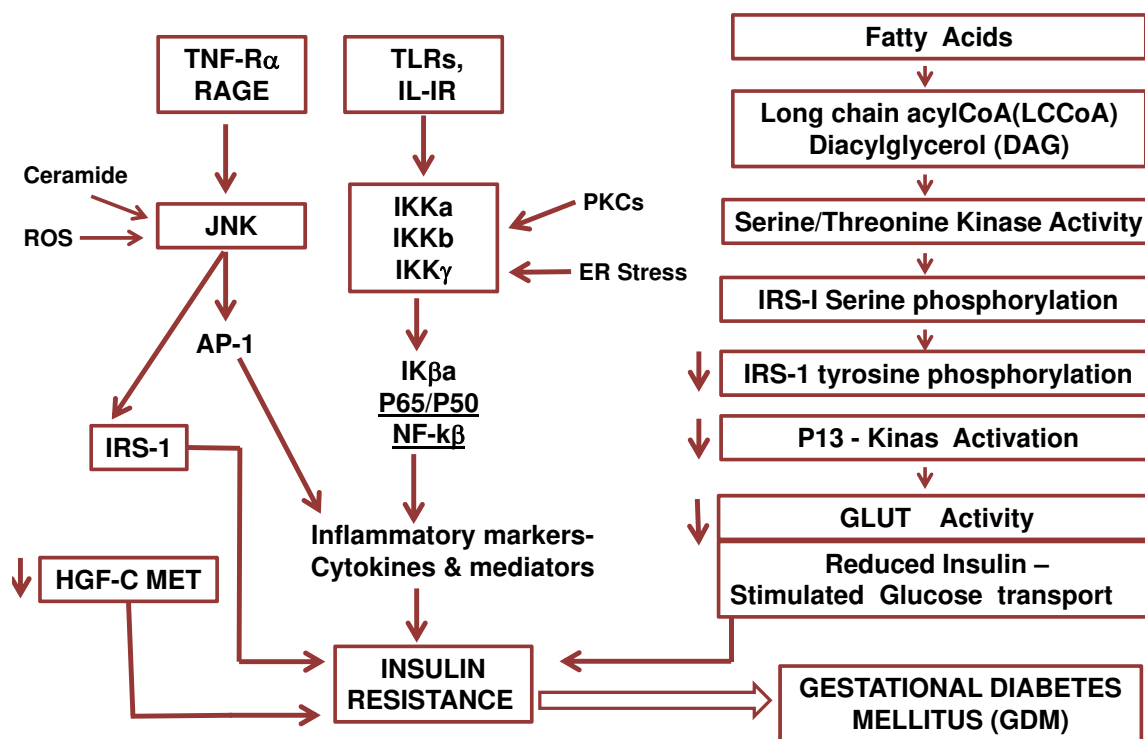
GDM offers an important opportunity for the development for testing and the implementation of clinical strategies in diabetic prevention (Volpe et al 2007). The main objective should be to improve insulin sensitivity and prevent diabetes mellitus.

8.1. Lifestyle modification

Lifestyle modifications have been shown to be successful in decreasing the progression to T2DM in several populations, including American, Finnish and Asian, so it seems rational to consider similar interventions in women with a history of GDM (An Empowered Based Diabetic Prevention 2011). The ACOG (2003), RCOG Guidelines (2011), NICE Guidelines (2009) and the ADA (2005) all recommend that women at increased risk for T2DM should be counseled about the benefits of diet, exercise, and weight reduction and/or maintenance in an effort to prevent the development of T2DM as part of preconception care.

8.2. Breast-feeding

Breast-feeding is associated with reduced blood glucose levels and a reduced incidence of T2DM among both women with a history of GDM and women in the general population. Lactation has also been associated with postpartum weight loss, reduced long-term obesity risk, and a lower prevalence of the metabolic syndrome (O'Reilly et al 2003).



References: Shoelson et al 2006, Qatanani et al 2007, Savage et al 2007)

Figure 1. Mechanisms of Insulin Resistance and Gestational diabetes Fatty acid metabolites (long-chain acyl-CoA [LCCoA] and diacylglycerol [DAG]) trigger a serine/threonine kinase cascade and protein kinase C, to induce serine/threonine phosphorylation. This inhibits IRS-1 binding and activation of PI 3-kinase and insulin signalling with resultant reduced insulin-stimulated glucose transport. Obesity-associated changes in secretion of adipokines and inflammatory IKKβ and NF-κβ and JNK pathways through ligands for TNF-α, IL-1, Toll and AGE receptors, intracellular stresses like Reactive oxygen species, Ceramide and PKC isoforms. These factors modulate insulin signalling, through activation of NF-κβ and cause insulin Resistance(Shoelson et al 2006, Qatanani et al 2007, Savage et al 2007,)

8.3. Pharmacologic interventions

Insulin is the drug to use, especially in GDM. Drugs with anti-inflammatory and vascular effects have future potential of being used in interventions aimed at reducing the enormous cardiovascular burden associated with Type 2 diabetes (Ziegler 2005). Use of sodium salicylate (Aspirin) (Hostamistigil et al 1993, Karasik et al 1993) has the concerns with high dose and possible side-effect of peptic ulceration. The use of antioxidant E and C reduces embryopathy in animal model (Cederberg) and in human with use of N-acetyl Cysteine has beneficial effects (Ozkilic et al 2006).

9. Concluding remarks

Recent advances in the understanding of carbohydrate metabolism during pregnancy, suggest that preventive measures should be aimed at improving insulin sensitivity in women with strong risk factors of developing GDM. The mechanisms involved in the pathogenesis of insulin resistance and Gestational Diabetes Mellitus are summarized in Figure 1. Further research is needed to elucidate the mechanisms and consequences of alterations in lipid metabolism during pregnancy (Marseille-Tremblay et al 2008). Inflammation-induced insulin resistance is certainly increasing in parallel with the epidemic of obesity. Strategies for reducing this trend should be part of the Public Health initiatives.

9.1. Future directions

There is need for genetic studies especially from the Human Genome to identify those with candidate genes for diabetes and epigenetic factors that may affect gene expression and predisposition to inflammation. It should be possible to directly target inflammation with pharmacological interventions to treat and/or prevent insulin resistance and T2D and modulate risk for CVD and other metabolic conditions. In addition to anti-inflammatory drugs such as NF- κ B inhibitors and IL-1 receptor antagonists already known to improve inflammatory and glycemic parameters, should have utility to block the prolonged exposure to inflammatory danger signals may further enhance the metabolic and cardiovascular outcome of obese patients. Early recognition and management of women predisposed to develop T2DM is crucial in the development of primary health care strategies, modification of lifestyle, and dietary habits significantly to prevent or delay of insulin resistance and development of glucose intolerance.

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