

## REVIEW

# The role of obesity and adipose tissue dysfunction in gestational diabetes mellitus

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## Abstract

Gestational diabetes mellitus is defined as diabetes diagnosed in the second or third trimester of pregnancy in patients with no history of diabetes prior to gestation. It is the most common complication of pregnancy. The underlying pathophysiology shares some common features with type 2 diabetes mellitus (T2DM) combining relatively insufficient insulin secretion with increased peripheral insulin resistance. While a certain degree of insulin resistance is the physiological characteristics of the second half of pregnancy, it is significantly more pronounced in patients with gestational diabetes. Adipose tissue dysfunction and subclinical inflammation in obesity are well-described causes of increased insulin resistance in non-pregnant subjects and are often observed in individuals with T2DM. Emerging evidence of altered adipokine expression and local inflammation in adipose tissue in patients with gestational diabetes suggests an important involvement of adipose tissue in its etiopathogenesis. This review aims to summarize current knowledge of adipose tissue dysfunction and its role in the development of gestational diabetes. We specifically focus on the significance of alterations of adipokines and immunocompetent cells number and phenotype in fat. Detailed understanding of the role of adipose tissue in gestational diabetes may provide new insights into its pathophysiology and open new possibilities of its prevention and treatment.

## Key Words

- ▶ obesity
- ▶ adipose tissue
- ▶ gestational diabetes mellitus
- ▶ inflammation
- ▶ adipokines

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## Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder of pregnancy. It is defined as diabetes diagnosed in the second or third trimester of pregnancy in patients with no history of diabetes prior to gestation (ADA 2017). The prevalence of GDM is increasing rapidly worldwide along with the changes in lifestyle, growing incidence of obesity and older age of pregnant women.

It complicates 4–20% pregnancies depending on screening method used, gestational age and the population studied (Hollander *et al.* 2007). Numerous risk factors for GDM development were described. The most important ones include family history of type 2 diabetes mellitus (T2DM) or GDM, especially in the first-degree relatives, previous history of GDM or macrosomic newborn, advanced

maternal age and obesity (Di Cianni *et al.* 2003). GDM is associated with an increased risk of pregnancy complications for both mother and child, including among others cesarean delivery, shoulder dystocia, macrosomia and neonatal hypoglycemia (Metzger *et al.* 2008). Fetal hyperinsulinism due to maternal hyperglycemia results in exaggerated fetal anabolism, growth of the fetal adipose, bone and muscle tissue and subsequent macrosomia. The newborns are prone to neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, respiratory distress syndrome and polycythemia (Hod *et al.* 1991).

In the long term, epigenetic changes induced by *in utero* exposure to maternal hyperglycemia increase the risk of obesity (Desai *et al.* 2013), T2DM (Clausen *et al.* 2009), cardiovascular diseases (Wu *et al.* 2012) and neuropsychiatric morbidity (Nahum Sacks *et al.* 2016). Although the underlying pathogenic mechanism is still unknown, epigenetic changes during fetal life are implicated.

In addition, women with GDM are more than seven times more likely to develop T2DM and approximately 50% of mothers with GDM will develop T2DM within 10 years (Bellamy *et al.* 2009). This makes GDM one of the strongest predictors of T2DM. The risk of developing cardiovascular morbidity later in life is also substantially increased (Sullivan *et al.* 2012). Risk factors and consequences of GDM are summarized in Fig. 1. During pregnancy, significant changes in maternal glucose metabolism occur. Insulin sensitivity typically decreases in the late gestation (Catalano *et al.* 1991). There is a significant increase in basal hepatic glucose production by the third trimester of pregnancy accompanied by a significant increase in basal insulin secretion (Catalano *et al.* 1992). These changes take place on the background of pregestational metabolic status. The underlying pathophysiology of GDM lies in an inability of pancreatic beta-cells to maintain adequate insulin response to increased peripheral insulin resistance. Physiological insulin resistance in the second half of pregnancy thus creates an increased challenge to beta-cells' functional reserve that may unmask inherited or acquired predisposition to impaired glucose metabolism. Increasing evidence from clinical and experimental studies indicates that metabolic and endocrine dysfunction of adipose tissue plays an important role in the pathophysiology of GDM.

## Obesity and pregnancy

Obesity is increasing in prevalence worldwide, and it is associated with adverse short- and long-term health

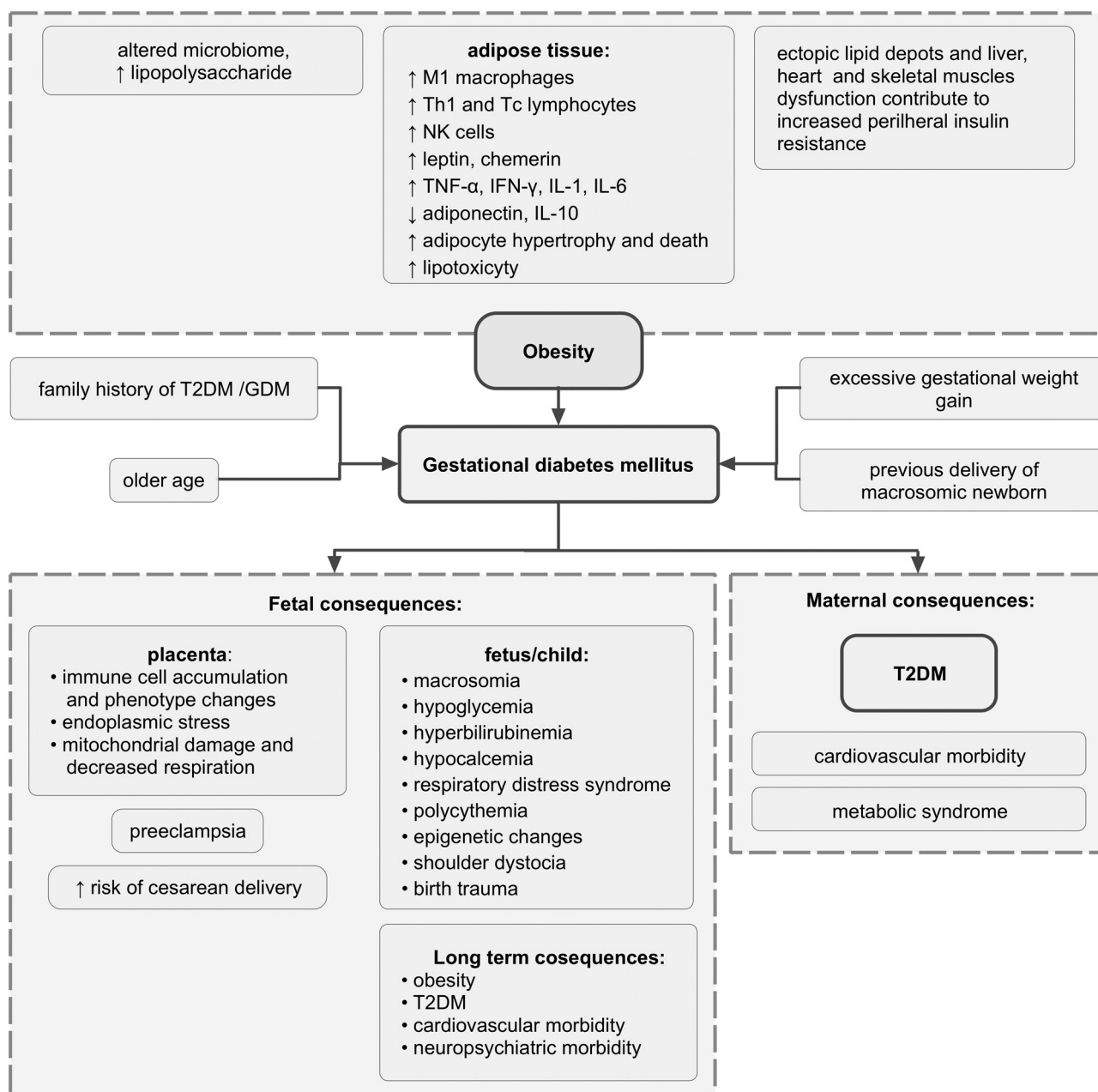
outcomes for the mother and the offspring (Leddy *et al.* 2008, Tenenbaum-Gavish & Hod 2013). It is estimated, that up to 50% of women of reproductive age are either overweight (BMI 25–29.9 kg/m<sup>2</sup>) or obese (BMI >30 kg/m<sup>2</sup>) (Kanagalingam *et al.* 2005). The prevalence of maternal obesity at the beginning of pregnancy is increasing and currently exceeds 16% (Heslehurst *et al.* 2007). Also, the prevalence of childhood obesity rises steadily. In the United States, 8.9% among 2- to 5-year-old children and 17.5% among 6- to 11-year-old children are obese (Ogden *et al.* 2015).

Both prepregnancy obesity and excessive gestational weight gain have been associated with higher risk of adverse pregnancy outcomes, such as macrosomia, GDM, preeclampsia and cesarean delivery (Li *et al.* 2013, Liu *et al.* 2015). The offspring of obese mothers have a higher risk of congenital anomalies and tend to be large for gestational age at birth (Stothard *et al.* 2009, Gaudet *et al.* 2014). Children of obese women, particularly those, who are born large for gestational age, are prone to development of obesity, metabolic syndrome and subsequent increase in cardiovascular morbidity (Whitaker 2004, Drake & Reynolds 2010). Similar to GDM, obese women are also at increased risk of metabolic and cardiovascular disorders later in life (Lavie *et al.* 2009, Pi-Sunyer 2009).

Obesity and GDM are frequently comorbid conditions. The risk of developing GDM is increased three-fold in obese women compared to women with normal BMI (Leddy *et al.* 2008). When coinciding with GDM, obesity and excessive gestational weight gain increase the risk of numerous GDM complications (Berggren *et al.* 2015, Xiong *et al.* 2016). Children of obese women with GDM are more likely to develop obesity and insulin resistance, which can lead to a vicious cycle of metabolic disorders into the next generation. Maternal obesity is an important predictive factor for the development of obesity, cardiovascular disease and T2DM in the offspring (Dabelea *et al.* 2008, Gaillard *et al.* 2014).

## Mechanisms of obesity-induced insulin resistance and disturbed glucose metabolism in pregnancy

Adipose tissue serves not only as the lipid storage depot but is also an active endocrine organ secreting factors that can both improve and impair insulin sensitivity. While subcutaneous adipose tissue accumulation manifesting by gynoid type of obesity does not represent a major metabolic risk, accumulation of visceral adipose tissue in

**Figure 1**

GDM: risk factors and consequences. GDM is associated with an increased risk of pregnancy complications and future metabolic complications for the mother and the offspring. Obesity is one of the major risk factors of gestational diabetes. Prepregnancy obesity is related to the subclinical inflammation in adipose tissue and alteration of the intestinal microbiome. GDM, gestational diabetes mellitus; IFN- $\gamma$ , interferon gamma; IL, interleukin; NK cells, natural killer cells; T2DM, type 2 diabetes mellitus; Tc lymphocytes, T cytotoxic lymphocytes; Th lymphocytes, T helper lymphocytes.

the abdominal region is associated with a greater risk of insulin resistance, cardiovascular diseases, hypertension and T2DM (Samsell *et al.* 2014). Lipid storage capacity of adipose tissue is limited. Once it is exceeded, ectopic lipids are excessively deposited in liver, heart and skeletal muscles, leading to impairment of insulin signaling cascade and impaired glucose uptake (Unger 2003).

Adipose tissue dysfunction eventually leads to local subclinical inflammation that further impairs insulin signaling and increases cardiovascular risk (Boren *et al.* 2013). Adipose tissue dysfunction primarily occurring in visceral adipose tissue is linked to obesity and metabolic syndrome development, and it is a promising subject of research with a potential for treatment of these pathologies

(Bluher 2009). As described in detail below, obesity and T2DM are accompanied by numerous changes in adipose tissue endocrine function and local inflammation. Some of these changes seem to accompany GDM as well (Al-Badri *et al.* 2015). Understanding the role of adipose tissue in GDM, thus, may provide new insights into its pathophysiology, potentially opening new possibilities for its treatment in the future.

## Adipokines and GDM

Numerous human studies established that obesity is associated with alterations of adipose tissue composition and expression profile. The first change characterizing obesity is adipocyte hypertrophy (Jo *et al.* 2009). Persistent adipocyte hypertrophy is connected with adipocyte dysfunction, altered adipocyte expression profile and lipid metabolism resulting in local lipotoxicity, local hypoxia, dysregulation of adipokine production and adipocyte death (Winkler *et al.* 2003, Jernas *et al.* 2006, Hosogai *et al.* 2007, Halberg *et al.* 2008, Veilleux *et al.* 2011). These changes constitute a stimulus for the infiltration of adipose tissue by immune cells, the development of subclinical inflammation and insulin resistance (Cinti *et al.* 2005). Similar to T2DM, the changes of adipokine and cytokine production were also detected during GDM development and progression (Lopez-Tinoco *et al.* 2012).

The healthy adipose tissue of the lean subjects is a primary source of adiponectin. Adiponectin has several positive properties such as stimulation of anti-inflammatory interleukin (IL)-10 and suppression of proinflammatory interferon gamma (IFN- $\gamma$ ) production (Wolf *et al.* 2004). It also improves hepatic insulin sensitivity (Ward *et al.* 2001), reduces TNF- $\alpha$ -stimulated expression of cell adhesion molecules (Ouchi *et al.* 1999) and inhibits lipopolysaccharide inflammatory actions (Ajuwon & Spurlock 2005). While it does not appear to be affected by sex hormones changes during menstrual cycle (Kleiblova *et al.* 2006), it is markedly lowered in obesity (Haluzik 2005). Similar to obese subjects (Haluzik *et al.* 2004), normal-weight women with GDM have decreased adiponectin levels (Ranheim *et al.* 2004), and hypoadiponectinemia could be considered as a predictive marker of GDM development in early pregnancy (Bao *et al.* 2015, Iliodromiti *et al.* 2016). Macrosomia of newborns is also connected with decreased adiponectin, and maternal adiponectin levels are inversely associated with neonatal birth body weight (Sylvén 1993, Arora *et al.* 2003). Interestingly, adiponectin supplementation

restored maternal insulin sensitivity, placental insulin/mTORC1 and peroxisome proliferator-activated receptor alpha signaling, nutrient transport and fetal growth in obese GDM C57BL/6J mice (Aye *et al.* 2015). Women with a history of GDM have lower adiponectin levels even after adjustment for insulin sensitivity or the degree of obesity (Winzer *et al.* 2004). Lower adiponectin concentrations are associated with subclinical inflammation, atherogenesis (Winzer *et al.* 2004) and independently predict future dyslipidemia (Lekva *et al.* 2017). Moreover, high leptin/adiponectin ratio in pregnancy and in particular in patients with GDM is linked to an unfavorable cardiovascular risk profile during follow-up (Lekva *et al.* 2017). Apart from adipose tissue, another potential source of adiponectin is the placenta (Kleiblova *et al.* 2010). Placental adiponectin secretion could be negatively modulated by TNF- $\alpha$ , IFN- $\gamma$ , IL-6 and leptin (Chen *et al.* 2006), but the impact of GDM is unclear due to contradictory data (Chen *et al.* 2006, Mrizak *et al.* 2014).

In opposite to adiponectin, leptin is increased in obese subjects and women with GDM (Kautzky-Willer *et al.* 2001, Krizova *et al.* 2004, Anderlova *et al.* 2006). Early hyperleptinemia is a predictor of GDM risk (Qiu *et al.* 2004), and it precedes the changes in maternal glycemia (Gao *et al.* 2008). Interestingly, mice lacking the suppressor of cytokine signaling 3 gene (*Socs3*) in cells expressing leptin receptors have most of the obesity-induced metabolic changes diminished, resulting in the prevention of leptin and insulin resistance without affecting the ability to carry their gestation to term (Zampieri *et al.* 2015). In general, leptin reduces food intake and increases energy expenditure (Halaas *et al.* 1995) and in contrast to adiponectin, it has rather proinflammatory actions. It can contribute to macrophage recruitment (Gruen *et al.* 2007) along with increased immune cell activation and differentiation (Lord *et al.* 1998, Papathanassoglou *et al.* 2006, Claycombe *et al.* 2008). Leptin levels are partially dependent on ethnicity mirroring higher GDM risk in South Asians compared to Europeans (Sommer *et al.* 2015). Maternal glycemia inversely correlates with methylation rate of the human *LEP* locus, and these epigenetic changes could be associated with future obesity development in the child (Allard *et al.* 2015). Both fetal leptin and leptin produced by placental vascular endothelial cells increase with maternal body weight (Tsai *et al.* 2015a). Leptin is released in a greater amounts from placental tissues compared to amnion and chorion, and basal leptin release is decreased from these tissues and increased from adipose tissue and skeletal muscle in GDM compared to healthy pregnant women (Lappas *et al.* 2005). This is more

pronounced in GDM women treated by insulin than GDM women treated by diet (Lappas *et al.* 2005).

Besides classical adipokines including adiponectin and leptin, several other adipokines were examined in the context of GDM. One of these adipokines is chemerin, which is involved in the regulation of adipocyte development and liver, skeletal muscle and adipose tissue metabolism (Goralski *et al.* 2007, Yang *et al.* 2010). Chemerin is produced by the adipose tissue with significantly higher chemerin mRNA expression found in subcutaneous compared to visceral adipose tissue and in obese compared to lean subjects (Alfadda *et al.* 2012). Circulatory chemerin levels are increased in obesity and T2DM (El-Mesallamy *et al.* 2011), and there is a significant negative correlation between circulating chemerin levels and chemerin mRNA expression in subcutaneous adipose tissue (Alfadda *et al.* 2012). Data in GDM patients are contradictory (Pfau *et al.* 2010, Hare *et al.* 2014, Fatima *et al.* 2017), most probably owing to different diagnostic criteria of GDM and variable sample size and mean BMI of the trial cohorts used. The study comprising the largest sample size reported a seven-fold increase in plasma chemerin levels in women with GDM compared with healthy pregnant controls in the third trimester of pregnancy (Fatima *et al.* 2017). In this study, IADPSG criteria for the diagnosis of GDM were applied. In another study, normoglycemic obese women had higher chemerin levels compared to normal-weight normoglycemic women, and GDM normal-weight women had higher chemerin levels compared to obese GDM women (Li *et al.* 2015). Arterial cord blood chemerin levels were increased with GDM and venous chemerin cord blood levels were higher in children of obese women, and both arterial and venous chemerin levels positively correlated with maternal chemerin at birth (van Poppel *et al.* 2014). Chemerin levels were suggested as a marker of preeclampsia severity and high maternal chemerin is related to adverse neonatal outcomes (Cetin *et al.* 2017). In general, chemerin is associated with obesity, inflammation and insulin resistance (Sell *et al.* 2009) and regulates adipocyte development and metabolic functions (Goralski *et al.* 2007). Moreover, chemerin could have some positive functions due to its protective effect on regulation of nitric oxide signaling. Chemerin inversely correlates with serum nitric oxide synthase levels and increases nitric oxide synthase and protein kinase B levels, decreases TNF- $\alpha$  signaling and vascular cell adhesion molecule 1 expression in human umbilical vein endothelial cells (Wang *et al.* 2015).

Another adipokine, visfatin, was originally considered potentially protective against insulin resistance but its ability to directly bind to the insulin receptor and activate insulin signaling pathway was not confirmed (the original article was hereafter retracted by the authors (Fukuhara *et al.* 2005)). Nevertheless, it has been shown that visfatin is actively produced by macrophages (Svoboda *et al.* 2017), enhances cytokine production in leukocytes and induces leukocyte chemotaxis (Moschen *et al.* 2007). Increased plasma visfatin concentrations were described in overweight/obesity, T2DM and metabolic syndrome (Chang *et al.* 2011). However, the results in GDM are unambiguous. Increased (Krzyzanowska *et al.* 2006, Lewandowski *et al.* 2007) as well as decreased (Chan *et al.* 2006, Haider *et al.* 2007) visfatin levels were described. In addition, no difference in visfatin mRNA expression in subcutaneous adipose tissue, visceral adipose tissue and placenta was observed between GDM and normoglycemic women (Telejko *et al.* 2009). The significance of visfatin in GDM is poorly understood. According to *ex vivo* human and rat studies, visfatin inhibits myometrial contractility even more potently than leptin (Mumtaz *et al.* 2015). Visfatin is also significantly associated with placental sirtuin 1 levels. Sirtuin 1 is a nuclear protein that regulates cell survival, cellular senescence, differentiation, metabolism and inflammation in numerous tissues such as liver, muscle, pancreas, testis, ovary and adipose tissue via heterochromatin formation by deacetylation of histones and non-histone proteins including transcription factors (Shoba *et al.* 2009, Chung *et al.* 2010). Increased visfatin levels potentially prevent a labor-associated decrease of sirtuin 1 leading to post-term delivery in obese women (Tsai *et al.* 2015b). Omentin is an adipokine with insulin-sensitizing action, which is secreted by visceral adipose tissue and decreased in patients with obesity (de Souza Batista *et al.* 2007). Maternal obesity is characterized by decreased omentin-1 levels in maternal circulation, and its levels are lower in non-obese GDM compared to non-obese normoglycemic women (Barker *et al.* 2012). On the contrary, there is no difference between obese GDM and obese normoglycemic women suggesting a role of both GDM and obesity in modulation of omentin levels. Maternal obesity does not affect umbilical cord omentin levels, and placental and adipose tissue omentin-1 expression is not influenced by GDM (Barker *et al.* 2012). Maternal omentin-1 levels inversely correlate with fetal birth weight and fetal ponderal index (Barker *et al.* 2012).

Resistin is an adipokine named after its ability to induce insulin resistance in mice (Steppan *et al.* 2001).

In obese humans, resistin is increased and positively correlated with increased adiposity and inflammation (Vozarova de Courten *et al.* 2004, Piestrzeniewicz *et al.* 2008). Resistin promotes monocyte-endothelial cell adhesion (Manduteanu *et al.* 2010, Hsu *et al.* 2011), induces TNF- $\alpha$  and IL-12 expression in macrophages (Silswal *et al.* 2005) and acts as a modulator of macrophage-foam cell transformation (Xu *et al.* 2006). The results of studies exploring resistin levels in GDM patients are inconsistent. Increased (Chen *et al.* 2007, Kuzmicki *et al.* 2009), unchanged (Lappas *et al.* 2005) and lowered (Megia *et al.* 2008) resistin levels were described in GDM women compared to healthy pregnant women. Moreover, some studies found no correlation between resistin levels and preeclampsia incidence or maternal BMI (Hendler *et al.* 2005). Resistin levels in newborns of GDM mothers did not differ from newborns of normoglycemic mothers (Ng *et al.* 2004). Furthermore, there were no differences in resistin release from human placenta and fetal membranes, neither between subcutaneous adipose tissue nor skeletal muscle obtained from healthy pregnant women and those with GDM (Lappas *et al.* 2005).

Vaspin or visceral adipose tissue-derived serpin (serpin A12) is an adipokine secreted predominantly by visceral adipose tissue. Higher levels of vaspin were found in T2DM and obese subjects (Feng *et al.* 2014). Vaspin levels are associated with circulating leptin, insulin and C-peptide levels and with an amelioration of insulin sensitivity (Handisurya *et al.* 2010). In GDM women, unchanged (Stepan *et al.* 2010, Gkiomisi *et al.* 2013), decreased (Huo *et al.* 2015) and increased (Mm *et al.* 2014, Jia *et al.* 2015) vaspin circulating levels were found. Placental mRNA and protein vaspin levels in the GDM group did not differ from pregnant women with normal glucose tolerance and were inversely correlated to neonatal birth weight in the GDM women (Huo *et al.* 2015). Adipose tissue vaspin mRNA and protein levels are increased in GDM women (Mm *et al.* 2014).

Several new adipokines and factors originating from adipose tissue were described in relation with GDM. One of these factors is fetuin A, also known as  $\alpha$ 2-Heremans-Schmid glycoprotein, which is secreted by the liver and adipose tissue (Jialal *et al.* 2015) and associates with insulin resistance and fat accumulation in the liver (Stefan *et al.* 2006). Besides that, fetuin A contributes to proinflammatory macrophage phenotype (Chatterjee *et al.* 2013). Fetuin A is increased during pregnancy and decreases after delivery (Iyidir *et al.* 2015), and women with GDM have higher fetuin A levels compared to healthy pregnant women suggesting its possible role in

metabolic complications accompanying GDM (Kalabay *et al.* 2002). Furthermore, the dynamics of plasma fetuin A concentrations during pregnancy was altered in patients who develop preeclampsia compared to healthy pregnant women, and it was significantly lower in women with preterm preeclampsia at the time of clinical diagnosis (Chaemsaihong *et al.* 2014). Similarly, adipokine/hepatokine fetuin B is increased in GDM women (Kralisch *et al.* 2017). Increased fetuin B levels were also found in patients with liver steatosis and T2DM. Its administration impaired insulin signaling in muscle and liver in mice (Meex *et al.* 2015).

Changes in adipokine levels in patients with GDM and obesity, respectively, are summarized in Table 1.

### Subclinical inflammation and GDM

Several mechanisms such as local hypoxia, increased adipocyte death and production of proinflammatory cytokines represent potent stimuli for migration of immune cells into adipose tissue (Sun *et al.* 2011). In obese subjects, macrophages and lymphocytes appear to be the most important players in the development of subclinical inflammation (Mraz & Haluzik 2014, Cinkajzlova *et al.* 2017). Macrophages have in general two main polarization states. In lean subjects, M2 or alternatively activated macrophages that have homeostatic functions and contribute to angiogenesis, wound healing and anti-inflammatory IL-10 production are abundant in adipose tissue. In contrast, M1 or classically activated macrophages connected with proinflammatory actions and TNF- $\alpha$  production occur more often in obese subjects (Sica & Mantovani 2012). Nevertheless, both polarization states represent the extremes and more often macrophages with mixed phenotype and mixed cytokine production participate in the progression of subclinical inflammation in adipose tissue (Zeyda *et al.* 2007). Similarly, T lymphocytes have various activation states with anti-inflammatory or proinflammatory functions. In lean subjects, T helper (Th) 2 and T regulatory (Treg) lymphocytes producing IL-10, IL-4, IL-13 and IL-5 with anti-inflammatory actions predominate. In contrast, Th1 and Th17 lymphocytes together with T cytotoxic (Tc) lymphocytes, natural killer (NK) cells providing IFN- $\gamma$  production, proinflammatory actions and cytotoxicity and probably B lymphocytes producing immunoglobulins are more frequently seen in obese subjects (Mills *et al.* 2000, Kang *et al.* 2008, Nishimura *et al.* 2009, McDonnell *et al.* 2012, Joller *et al.* 2014, Madhumitha *et al.* 2014,

**Table 1** Changes in circulating levels of adipokines in patients with gestational diabetes mellitus and obesity (without gestational diabetes).

Adipokine	Gestational diabetes mellitus	Obesity
Adiponectin	↓ (Ranheim <i>et al.</i> 2004)	↓ (Haluzik 2005)
Leptin	↑ (Kautzky-Willer <i>et al.</i> 2001)	↑ (Anderlova <i>et al.</i> 2006)
Chemerin	↑ (Fatima <i>et al.</i> 2017) ↓ (Hare <i>et al.</i> 2014) No change (Pfau <i>et al.</i> 2010)	↑ (Tsai <i>et al.</i> 2015a,b)
Visfatin	↑ (Krzyzanowska <i>et al.</i> 2006, Lewandowski <i>et al.</i> 2007) ↓ (Chan <i>et al.</i> 2006, Haider <i>et al.</i> 2007)	↑ (Chang <i>et al.</i> 2011) –
Omentin	↓ In non-obese (Barker <i>et al.</i> 2012)	↓ (de Souza Batista <i>et al.</i> 2007, Barker <i>et al.</i> 2012)
Resistin	↑ (Chen <i>et al.</i> 2007, Kuzmicki <i>et al.</i> 2009) ↓ (Megia <i>et al.</i> 2008) Unchanged (Lappas <i>et al.</i> 2005)	↑ (Vozarova de Courten <i>et al.</i> 2004, Piestrzeniewicz <i>et al.</i> 2008) No change (Hendler <i>et al.</i> 2005)
Vaspin	↑ (Mm <i>et al.</i> 2014, Jia <i>et al.</i> 2015) ↓ (Huo <i>et al.</i> 2015) No change (Stepan <i>et al.</i> 2010, Gkiomisi <i>et al.</i> 2013)	↑ (Feng <i>et al.</i> 2014)
Fetuin A	↑ (Kalabay <i>et al.</i> 2002)	–
Fetuin B	↑ (Kralisch <i>et al.</i> 2017)	–

Lee *et al.* 2016). Natural killer T (NKT) cells have anti-inflammatory as well as proinflammatory functions dependent on their antigen structure. With respect to adipose tissue, invariant NKT cell expressing CD1d lipid-recognizing antigen and anti-inflammatory actions are mostly described in the context of obesity (Borg *et al.* 2007, Schipper *et al.* 2012).

Immune cells communication is mediated by several routes including production of signaling molecules, self-antigen presentation or by direct cell contacts (Koenen *et al.* 2011, Chatzigeorgiou *et al.* 2013, Wensveen *et al.* 2015, Morris *et al.* 2016). Increased cytokine levels, in particular TNF- $\alpha$  and IFN- $\gamma$  together with IL-1 or IL-6 along with altered adipokine secretion is one of the major reasons for development of subclinical inflammation in adipose tissue as well as on systemic level. Potentially, obesity during pregnancy could be partially responsible for development of pregnancy complications and indirectly contribute to fetal metabolic status.

Importantly, apart from the significance of immune cell accumulation in adipose tissue, their accumulation in placenta very likely plays a role in GDM development in obese pregnant women. Synergic actions of adipose tissue and placenta were demonstrated in a study aimed at the determination of alternatively activated macrophage marker CD163 secretion. Its soluble form sCD163 was suggested as a prognostic marker of low-grade inflammation and T2DM. GDM women and their offspring had elevated sCD163 levels compared to controls, together with increased sCD163 protein concentration and greater amounts of CD163-positive cells in the placenta and adipose tissue (Bari *et al.* 2014).

The placenta contains its own macrophages called Hofbauer cells, which have M2 anti-inflammatory phenotype and protect fetus against pathogen transmission from the mother. However, under proper stimulation, including stimulation by lipopolysaccharide, these cells produce proinflammatory cytokines such as IL-6 and IL-8 (Young *et al.* 2015). This could have important implications as increased lipopolysaccharide levels were reported in obese subjects (Troseid *et al.* 2013) and alterations in placental microbiome were described in women with GDM (Bassols *et al.* 2016). Moreover, higher placental macrophage accumulation, as well as increased placental and macrophage cytokine production, were observed in obese compared to lean pregnant women. Increased placental expression of TNF- $\alpha$ , IL-6 and IL-1 together with increased systemic levels found in women with GDM or preeclampsia suggest a potential placental contribution to systemic inflammation, GDM development and progression (Rinehart *et al.* 1999, Challier *et al.* 2008, Yu *et al.* 2013). Certain roles in macrophage accumulation and inflammatory reactions could be attributed to the proinflammatory cytokine called macrophage migration inhibitory factor, which has pleiotropic immune functions (Nishihira 2000). Migration inhibitory factor concentrations are increased in GDM and its polymorphisms associate with susceptibility to GDM development in pregnancy (Aslani *et al.* 2011, Yilmaz *et al.* 2012). Apart from proinflammatory cytokine production, M1 macrophages represent the potential source of reactive oxide species and nitric oxide (Mantovani *et al.* 2004) that may eventually contribute to the development of adipose tissue (Jang *et al.* 2016) and placental fibrosis

(Pustovrh *et al.* 2000) via mitochondrial dysfunction of preadipocytes and activation of metalloproteinase 9, respectively.

Except for macrophages, lymphocyte populations are also altered during pregnancy and GDM development. According to first murine studies (Dudley *et al.* 1993, Wegmann *et al.* 1993), healthy pregnancy is accompanied by anti-inflammatory Th2 lymphocyte response characterized by anti-inflammatory IL-10, IL-4, IL-13 and IL-5 cytokine production, while proinflammatory Th1 lymphocyte response is downregulated. In humans, a limited number of studies are available. Increased percentage of total lymphocytes and CD8 lymphocytes expressing gamma/delta T receptor have been described in GDM patients along with higher CD8 lymphocytes expressing gamma/delta T receptor and decreased NK cells in circulation in their newborns. Interestingly, percentage of Th (CD4+) cells in circulation was lower in GDM treated by insulin compared to those treated only by diet (Lapolla *et al.* 2005). However, increased mRNA expression of TCR receptor and GATA3 genes in contrast with T-bet factor indicates increased T lymphocytes infiltration in the placenta of GDM patients, which have rather Th2 than Th1 phenotype (Mrizak *et al.* 2014). In the context of cell activation, GDM patients treated by both diet only or by insulin have increased percentage of activated Th (CD4+CD25+) cells, memory T (CD4+CD45RO+) cells and decreased naïve T (CD4+CD45RA+) cells in peripheral blood compared to healthy pregnant women suggesting higher immune activity in GDM compared to physiological pregnancy (Mahmoud *et al.* 2005). Accordingly, increased percentage of costimulatory molecules CD4+ Th and CD8+ Tc cells expressing early activation marker CD69 were described in GDM patients (Pendeloski *et al.* 2015). Importantly, GDM was associated with an elevation of the whole lymphocyte population and with a change of activation status of Th (CD4) and Tc (CD8) lymphocyte proportion (Lapolla *et al.* 2005). By contrast, GDM was not related to alterations in the percentage of anti-inflammatory CD4+CD127low+/-CD25+FoxP3+ Treg cells within the total CD4+ T cell pool (Schober *et al.* 2014). Moreover, the proinflammatory IL-17 cytokine link to Th17 lymphocyte response could have potential deleterious effects. Increased IL-17 levels were found in preeclampsia or other pregnancy-related complications (Fu *et al.* 2014). However, maternal Th17 lymphocyte number is unchanged during pregnancy (Nakashima *et al.* 2010), preeclampsia, GDM or chronic diabetes and so innate lymphoid cells were established as a potential source of IL-17, because of cytokine production shared

with Th lymphocytes (Barnie *et al.* 2015). Furthermore, cell subpopulations belonging to NK cell population in maternal peripheral blood and placenta are altered in GDM women (Chiba *et al.* 2016, Hara Cde *et al.* 2016). These immune cells are characterized by increased TNF- $\alpha$  and INF- $\gamma$  production supporting inflammatory reactions in women with GDM (Chiba *et al.* 2016).

Adipose tissue homeostasis during pregnancy and GDM could also be influenced by endoplasmic reticulum (ER) stress leading to inflammation and increased IL-1 $\beta$  production. ER stress markers were increased in adipose tissue of obese compared to lean pregnant women and higher in adipose tissue of women with GDM compared to BMI-matched normal glucose-tolerant women suggesting a possible contribution of ER stress in the etiopathogenesis of GDM (Liong & Lappas 2015). Interestingly, ER stress in human placenta is triggered by labor and could contribute to the pathophysiology of preeclampsia (Fu *et al.* 2015, Veerbeek *et al.* 2015, Yung *et al.* 2015). Similarly, mitochondrial damage and decreased mitochondrial respiration in trophoblast cells together with the abnormal metabolic flexibility of these cells are associated with GDM and maternal obesity (Mele *et al.* 2014, Muralimanoharan *et al.* 2016). Besides ER stress, mitochondrial damage, insufficient function and changed expression profile of enlarged adipose tissue, obesity is associated with increased levels of free fatty acids (FFAs) with deleterious effects on skeletal muscle, liver and endothelial cells mediated by enhanced insulin resistance (Boden 2008). Similar to obesity and T2DM, GDM is associated with increased FFA levels (Meyer *et al.* 1996, Bomba-Opon 2006), while newborns of GDM women have normal levels possibly due to the lipogenic and antilipolytic activity of the fetus (Bomba-Opon 2006, Jovandarić & Ivanovski 2017). Increased FFA accompanying obesity represents one of the factors potentially responsible for decreased insulin sensitivity and GDM development in pregnancy. In summary, adipose tissue is an active endocrine organ secreting factors with the ability to markedly alter insulin sensitivity. Its dysfunction characterized by changes in expression of numerous adipokines along with adipose tissue inflammation and alterations in adipose tissue immunocompetent cells content and phenotype contributes to development of insulin resistance. These changes were described in both obesity and T2DM and to some extent, similar changes were also observed in GDM. Collectively, these findings suggest an analogous adipose tissue involvement in the pathophysiology of GDM. Further research is needed to elucidate the exact role of adipose tissue dysfunction in the development of GDM



and to pave the way toward interventions targeting the adipose tissue to prevent and/or treat gestational diabetes.

#### Declaration of interest

The authors certify that they have no affiliations with, or involvement in, any organization or entity with any financial or non-financial interest in the subject matter discussed in this review.

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#### Author contribution statement

P Š and A C wrote the manuscript. K A performed a database search for relevant articles under the supervision of A P and M K. M M and M H supervised the manuscript preparation. All authors discussed and commented on the manuscript prior submission.

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