REVIEW

Specific Metabolic Characteristics of Women With Former Gestational Diabetes: the Importance of Adipose Tissue

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Summary

Women with a positive history of gestational diabetes mellitus (GDM) face a higher risk of developing type 2 diabetes mellitus (T2DM) and metabolic syndrome later in life. The higher risk of these metabolic complications is closely associated with adipose tissue. In this review, the importance of adipose tissue is discussed in relation to GDM, focusing on both the quantity of fat deposits and the metabolic activity of adipose tissue in particular periods of life: neonatal age, childhood, adolescence, and pregnancy followed by nursing. Preventive measures based on body composition and lifestyle habits with special attention to the beneficial effects of breastfeeding are also discussed.

Key words

Gestational diabetes mellitus • Adipose tissue • Insulin sensitivity • Adipokines • Breastfeeding

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At birth

Our health over the course of life can be to some extent predetermined at birth. In addition to factors like the geographical position of the country where we are born, the socioeconomic status and education of the family with their influence on lifestyle habits, and genetic factors, another such predictor can be body weight at birth. Both low and high birth weight have been well documented to be risk factors for type 2 diabetes mellitus

(T2DM) and features of metabolic syndrome including insulin resistance, hypertension, and dyslipidemia.

Hales *et al.* (1991) demonstrated an inverse relationship between birth weight and risk for T2DM later in life. Subsequently, many studies have contributed to the growing body of evidence that supports an association of low birth weight with high blood pressure and abnormal lipid profiles (Barker *et al.* 1993a, Rich-Edwards *et al.* 1999). These findings demonstrate a negative correlation between the percentiles of birth weight and the risk of various metabolic abnormalities in adulthood, and have led to low birth weight being used as a proxy for suboptimal fetal organogenesis (Ogonowski *et al.* 2014), in line with Barker's hypothesis of fetal programming (Barker *et al.* 1993b). Concurrently, high birth weight has also been found to be linked with an increased risk of insulin resistance and T2DM (McCance *et al.* 1994, Wei *et al.* 2003).

Studies in the past two decades have also presented associations of low and high birth weight with gestational diabetes mellitus (GDM). GDM is a prevalent complication of pregnancy that strongly predicts the later development of T2DM and shares many features of metabolic syndrome (Williams *et al.* 1999, Innes *et al.* 2002, Seghieri *et al.* 2002, Savona-Ventura and Chircop 2003, Claesson *et al.* 2007, Yeung *et al.* 2010). Williams *et al.* (1999) demonstrated that low birth weight women are at increased risk for GDM in white populations, but that in African-American populations, rather high birth weight women experienced an increased risk of GDM. This U-shape distribution, with a greater proportion of GDM women having low as well as high birth weight,

has since been also described by many others (Innes *et al.* 2002, Savona-Ventura and Chircop 2003, Claesson *et al.* 2007). In a large cohort of more than 116,500 Danish mothers, being born premature or with low birth weight for gestational age was associated with an increased risk of GDM and pre-eclampsia, while high birth weight for gestational age was associated with an increased risk of GDM, but with a decreased risk of pre-eclampsia. Importantly, inappropriate weight for gestational age was a more significant risk factor than prematurity *per se* (á Rogvi *et al.* 2012). However, differences have been found between studies on the newborn low/high birth weight limits and the degree of associated risk. For example, in one study, birth weight <2,600 g was associated with a twofold higher risk of the development of GDM in adulthood (odds ratio = 1.89 [95 % CI 1.088-3.285], $p=0.02$), and this association was independent of major confounders such as age, parity, family history of T2DM, and pre-pregnancy body weight (Seghieri *et al.* 2002).

Research studying this issue in the Czech population was published in 2010 and 2015 by our team at the Institute of Endocrinology (Vejražková *et al.* 2010, Vejrazkova *et al.* 2015). A long-term study was undertaken to analyze birth weight in relation to GDM status and to other components of metabolic syndrome in adulthood using more than 600 participants (350 of them with positive history of GDM). The longitudinal design of the study allowed an evaluation of metabolic changes over years, and found that in women with former GDM, birth weight was systematically associated with glucose metabolism. In those born with low birth weight ($\leq 2,900$ g), there was lower peripheral insulin sensitivity persisting more than 5 years after delivery compared to those born with normal or high birth weight (Vejrazkova *et al.* 2015). Furthermore, our analysis of both genders found that high birth weight ($> 3,750$ g) was associated with significantly higher BMI in adulthood, suggesting that large newborns are more likely to retain larger amounts of fat, including visceral fat, which predisposes them to impairments of insulin sensitivity later in life (Vejražková *et al.* 2010).

Childhood

Obesity in children is a significant predictor of obesity in adulthood, and is also a risk factor for numerous complications, including metabolic syndrome, T2DM, and GDM. According to the recent literature,

20 % of obese newborns will become obese children, 40 % of obese children will become obese teenagers, and 80 % of obese teenagers will become obese adults (Trandafir *et al.* 2016).

There is also a great deal of literature devoted to the relationship between maternal GDM and the risk of obesity in children born of these pregnancies. Recently, a large study on 6,909 children born to mothers with GDM concluded that these children were significantly more overweight at an early age (5-12 years) than those born to non-GDM mothers (Hakanen *et al.* 2016). Another large multinational cross-sectional study was carried out on 4,740 children aged 9-11 years (Zhao *et al.* 2016), with maternal GDM shown to be associated with an increased risk of childhood obesity; however, this association was not fully independent of maternal BMI. The odds ratios (multivariably adjusted for factors like maternal age at delivery, gestational age, education, infant feeding mode, sedentary time, sex, birth weight and some others) for children of GDM mothers in comparison with children of non-GDM mothers were 1.53 [95 % CI 1.03-2.27, $p=0.034$] for obesity defined as BMI z-scores $> +2$ SD, and 1.73 [95 % CI 1.14-2.62, $p=0.010$] for central obesity defined as waist circumference $\geq 90^{\text{th}}$ percentile of the NHANES III reference (Zhao *et al.* 2016). After an additional adjustment for current maternal BMI, the positive association was still significant for central obesity, but not for obesity defined by BMI. Therefore, along with maternal GDM, the question of maternal BMI and body fat distribution seems to be very important in predicting the obesity risk in children.

Considering the relationship between maternal GDM and the risk of obesity in children, the opposite issue arises: an association between obesity in childhood and subsequent GDM development in adulthood. That is, to what extent can obesity in girls be predictive for the development of GDM in their pregnancies? In the literature, increased maternal BMI has been stressed as a contributor to the increased incidence of GDM cases. Pre-pregnancy obesity was identified as the most potent predictor of GDM (Solomon *et al.* 1997, Zhang *et al.* 2006, Pirjani *et al.* 2016), with a recent prospective cohort study calculating the odds ratio as 2.74 [95 % CI 1.28-5.88, $p=0.009$] (Pirjani *et al.* 2016). However, prospective studies monitoring obese girls until their pregnancy are absent. Our group evaluated data on the development of obesity in different periods of life including pre-school age, school age and adolescence in a cohort of 580 former

GDM patients and non-GDM women with normal fasting glucose. Out of all the obese women ($\text{BMI} > 30 \text{ kg/m}^2$) in this cohort, 53 % in the GDM group reported obesity already in childhood, compared to only 15 % in the control non-GDM group ($\text{Chi}^2=10$, $p=0.001$; unpublished data). This highly suggests that childhood is a crucial period of life in terms of the ability of excess fat to predispose individuals to metabolic complications later in life. Therefore, it is extremely important to emphasize the importance of obesity prevention in children.

Toward adulthood and pregnancy

The metabolic role of adipose tissue during life

Adipocytes consist of functionally distinct cellular subtypes, with white adipocytes serving as energy storage deposits (apart from many other active functions discussed below) and brown adipocytes serving primarily as energy dissipators producing heat. White and brown adipocytes are also morphologically distinct and their developmental origins are different. Recent studies have revealed a vascular or perivascular localization of white adipocyte progenitors, whereas brown fat shares a developmental origin with the skeletal muscle expressing specific myogenic marker genes (Yang *et al.* 2014). Brown adipose tissue is especially abundant in newborns. Due to their low amount of musculature and inability to shiver, brown fat is of great importance to avoid hypothermia. It is also present and metabolically active in adult humans, but its proportion decreases with age. Of note, heat is generated also outside classical brown adipose tissue deposits in adipocytes termed 'brite' (brown-in-white) or 'beige'. The presence of 'brite/beige' adipocytes correlates with a lean, metabolically healthy phenotype, but causality is not yet clear. White adipose tissue composes as much as 20-30 % of the body weight in non-obese adult women. The initiation and maturation of adipose tissue is a complex process, and an interplay between insulin and growth hormone is essential in its regulation (Zhang *et al.* 2016). After termination of the growth phase in adolescence or early adulthood, adipose tissue continues to play its important role in whole-body energy homeostasis by regulating glucose and lipid metabolism.

Adipose tissue is well known for its endocrine function and for its role in inflammation and the immune response. There is robust evidence suggesting that obesity and low-grade inflammation are major players in the development of insulin resistance. Adipokines such as adiponectin, leptin, resistin and visfatin are secreted by

white adipose tissue, and to a large extent determine the degree of adipose tissue inflammation and thus the predisposition for the development of insulin resistance. It is also noteworthy that lean subjects can develop inflammation-associated insulin resistance (Mehta *et al.* 2010). Under certain circumstances, lean insulin-resistant subjects may have a higher proinflammatory adipokine profile than overweight but insulin-sensitive subjects (Moscavitch *et al.* 2016). However, in most individuals, insulin resistance and obesity coexist and are associated with an increased risk of inflammation and subsequent diabetes.

During pregnancy, adipokines are produced not only by the adipose tissue but also by the placenta. There is evidence to suggest that the placenta substantially contributes to maternal adipokine concentrations (Sartori *et al.* 2016). A dysregulation of placental function related to insulin sensitivity and inflammation was reported in pregnancies with GDM (Valsamakis *et al.* 2010).

Significant adipokines (adipose tissue derived peptide hormones) in relation to GDM

Women diagnosed with GDM show signs of subclinical inflammation with decreased concentrations of **adiponectin**, the endogenous insulin-sensitizing hormone (Heitritter *et al.* 2005). Although adiponectin is expressed in adipose tissue, it paradoxically correlates negatively with obesity. Nevertheless, some studies have found lower adiponectinemia as an adiposity-independent marker of decreased insulin sensitivity in women with former GDM (Vejrazkova *et al.* 2017a). There is strong and consistent evidence showing persistently low adiponectin levels during GDM pregnancies and during follow-up after birth (Bhograj *et al.* 2016, Lekva *et al.* 2017) in comparison with non-GDM women. Furthermore, according to recent observations, low adiponectin in GDM women may represent a risk factor for the future development of metabolic and cardiovascular disease (Lekva *et al.* 2017), as adiponectin may protect against the development of atherosclerosis by inhibiting endothelial inflammation and foam cell formation.

Quite an opposite metabolic effect on insulin sensitivity, subclinical inflammation and cardiovascular risk is observed with the adipokine **leptin**. While adiponectin down-regulates inflammatory mediators like TNF α and interleukin-6, leptin up-regulates them. Leptin is positively associated with body adiposity and insulin resistance (Nasrat *et al.* 2016, Osegebe *et al.* 2016). Its levels increase throughout pregnancy, and a significant

correlation between leptin and the degree of pregnancy-induced insulin resistance was described (Skvarca *et al.* 2013). In GDM women, higher leptinemia was found during pregnancy as well as 8 weeks postpartum compared to non-GDM women (Kautzky-Willer *et al.* 2001). Our group found higher leptinemia in lean former GDM women from one-half to one year after delivery, and this was associated with a higher oGTT-derived postchallenge glycemia, insulinemia, and index of insulin resistance (HOMA-IR) and a lower Cederholm index of insulin sensitivity compared to BMI-matched non-GDM women (Vejrazkova *et al.* 2017a).

Resistin was originally described as a factor contributing to the development of insulin resistance and diabetes in mice and humans; however, there is ongoing debate regarding its exact role in glucose and lipid metabolism. Many authors have reported that circulating resistin levels are increased in obesity (e.g. Sartori *et al.* 2016). Due to its role in the inflammatory response, including in several transcriptional and signaling pathways (resistin stimulates secretion of proinflammatory cytokines such as TNF α and interleukin-6), resistin may mediate the link between energy balance signaling and inflammatory processes. In pregnancy, resistin is highly expressed in the placenta, and plasma resistin levels in pregnant women are higher than in non-pregnant women. It has been hypothesized that placental resistin may have a physiological role in the regulation of maternal glucose by decreasing insulin sensitivity during pregnancy. Accordingly, maternal resistin concentrations have been reported to be higher in GDM women than in non-GDM controls (Noureldeen *et al.* 2014, Kuzmicki *et al.* 2009), although not all studies have confirmed this observation (Lappas *et al.* 2005). Of note, high concentrations of resistin in cord blood suggest that this hormone could be related to the control of fetal energy expenditure and adiposity (Sartori *et al.* 2016).

Visfatin is an endocrine, autocrine, and paracrine peptide with many functions including glycoregulation and immunomodulation. It was identified as a substance produced by lymphocytes acting on inflammatory regulation, and concurrently as a protein involved in β cell maturation (Samal *et al.* 1994). In humans, visfatin is predominantly expressed in visceral adipose tissue and its expression correlates positively with visceral adiposity. In contrast, subcutaneous adipose tissue expresses low levels of visfatin (Araki *et al.* 2008). This may indicate an important link with altered glucose metabolism in visceral obesity, which is known to be

accompanied by insulin resistance in adulthood. Visfatin exerts insulin-sensitizing and insulin-mimetic effects, so it has attracted attention for its possible application in glycemic control (Ahmed *et al.* 2015). Maternal visfatin concentrations in GDM women have been found to be higher compared to non-GDM controls in many studies (Noureldeen *et al.* 2014, Lewandowski *et al.* 2007, Ferreira *et al.* 2011), although contrasting results have also been reported (Telejko *et al.* 2009). Ferreira *et al.* (2011) found increased plasma visfatin levels in pregnant women who subsequently developed GDM, suggesting that visfatin could be a potential biomarker for the prediction of GDM. We also found that visfatin levels were higher in lean former GDM women one-half to one year after delivery, who also showed significantly higher oGTT-derived postchallenge glycemia, insulinemia, and HOMA-IR and a lower Cederholm index of insulin sensitivity compared to BMI-matched control non-GDM women (Vejrazkova *et al.* 2017a).

Pre-pregnancy body weight and weight gain in pregnancy

High pre-pregnancy body weight and excessive gestational weight gain are both associated with an increased risk of the development of GDM (Vidanalage *et al.* 2016, Boriboonhirunsarn 2016). Moreover, both independently contribute to adverse pregnancy outcomes (Zilberlicht *et al.* 2016). In GDM mothers, these conditions were associated with a higher incidence of LGA (large for gestational age) newborns (Miao *et al.* 2017). Furthermore, in a population-based cohort study with more than 3,000 women participating, it was shown that early adult weight gain prior to pregnancy even within the normal BMI range is also an important risk factor for the development of GDM, with a relative risk ranging from 2 to 2.9 compared with women with stable weight during adulthood (Adane *et al.* 2017). Thus, weight gain prevention starting in early adulthood appears to be the best strategy for preventing gestational diabetes in pregnancy. Additionally, maternal obesity and excessive gestational weight gain are independent risk factors of the child's overweight at an early age (Bider-Canfield *et al.* 2017, Hillier *et al.* 2016).

Breastfeeding – the best prevention for both mother and child

Breastfeeding has been shown to decrease risk of the child becoming overweight. In a large cohort of more

than 15,700 mother-offspring pairs, it was demonstrated that breastfeeding for at least 6 months had a significant protective effect against overweightness and obesity in the child that persisted up to 2 years of age (Bider-Canfield *et al.* 2017). In addition to protecting against excessive fat accumulation, breastfeeding also confers protection against childhood infections and, later in life, against cardiovascular disease and T2DM (Victora *et al.* 2016, Aguilar Cordero *et al.* 2015, Martens *et al.* 2016).

Breastfeeding is beneficial not only for the child but also for the mother, especially for mothers previously diagnosed with GDM. Some studies have suggested that lactation is associated with lower blood glucose and insulin concentrations and improved glucose tolerance (Kjos *et al.* 1993, Tigas *et al.* 2002). One of our studies found higher insulin sensitivity (a higher Matsuda index of insulin sensitivity and lower HOMA-IR index of insulin resistance) in lactating women with a positive history of GDM compared to non-lactating GDM women. In this study, better insulin sensitivity in lactating GDM women was associated with lower leptin, resistin and visfatin levels, in line with the current knowledge concerning the metabolic activity of these adipokines (Vejražková *et al.* 2017b). Similarly, breastfeeding is associated with a reduced risk of diabetes among mothers, independently of GDM status or age of the mother (Martens *et al.* 2016). Lactation also has favorable effects on the lipid profile, with lactating women with recent GDM exhibiting higher HDL cholesterol and lower triglycerides compared to non-lactating women (Kjos *et al.* 1993, Gunderson *et al.* 2014, Vejražková *et al.* 2017b). As a consequence, mothers who breastfeed are less likely to suffer from cardiovascular disorders, including hypertension, both in the short term and, importantly, also in the long term, independently of GDM history (Aguilar Cordero *et al.* 2015). Last but not least, breastfeeding also gives protection against osteoporosis (Jiménez-Arreola and Aguilera Barreiro 2015) and against some specific types of cancer such as breast and ovarian cancer (Victora *et al.* 2016).

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Conclusion

In conclusion, our adipose tissue presents a variety of pitfalls throughout our lives, and some periods, especially the prenatal period, childhood and pregnancy, are very important with regard to future health. For instance, in women with former GDM, adipose tissue can dramatically affect the manifestation of T2DM or features of metabolic syndrome. Some of the factors determining how we pass through these periods can be very significantly influenced by our decisions (life-style habits like nutrition and physical activity), some of them are more resistant but still modifiable (body composition), and some can be influenced only to a limited extent (fat tissue distribution) or cannot be influenced at all (birth weight). An important factor with long-term positive impacts on future health that can be easily adopted by the vast majority of mothers, is breastfeeding and its duration. It is thus necessary to provide information to promote breastfeeding and increase awareness about its positive impacts not only on the health of the child, but also on the health of mothers. These benefits of breastfeeding are especially important for GDM mothers, and this natural and accessible intervention may be effective in reducing the risk of developing many metabolic complications including T2DM.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

BMI – body mass index, CI – confidence interval, GDM – gestational diabetes mellitus, HOMA-IR – insulin resistance index (homeostatic model assessment), oGTT – oral glucose tolerance test, NHANES – National Health and Nutrition Examination Survey, T2DM – type 2 diabetes mellitus, TNF α – tumor necrosis factor α .

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