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The relationship between adipose tissue-derived hormones and gestational diabetes mellitus (GDM)

Związek hormonów pochodzących z tkanki tłuszczowej z cukrzycą ciążową (GDM)

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Abstract

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance of varying severity with onset or first recognition during pregnancy. The prevalence of GDM is growing rapidly worldwide, resulting in numerous and serious complications for both mother and foetus. Two major metabolic disorders, insulin resistance and β cells dysfunction, are currently linked to the pathogenesis of GDM, although the cellular mechanisms involved in the development of GDM are not yet completely understood. Increasing evidence from clinical and experimental studies indicates that adipose tissue dysfunction, characterised by abnormal production of adipokines, is an essential factor linked to insulin resistance and GDM. To date, several adipose tissue-derived hormones have been identified, including leptin, adiponectin, resistin, visfatin, apelin, retinol-binding protein 4 (RBP-4), vaspin, and omentin. The relationship of leptin and adiponectin to insulin resistance in GDM is relatively well documented, but the molecular mechanisms by which these hormones affect insulin resistance are not yet fully known. The other aforementioned adipokines appear to be also important players in the pathophysiology of GDM, although their precise function in this complex process remains to be established.

The aim of this article is to review the literature concerning the relationship between the above-mentioned adipokines and GDM, and to clarify their role in the pathophysiology of GDM. **(Endokrynol Pol 2014; 65 (2): 134–142)**

Key words: *adipokines; adiponectin; gestational diabetes mellitus (GDM); leptin; omentin; RBP-4; resistin; vaspin; visfatin*

Streszczenie

Cukrzyca ciążowa (GDM) jest definiowana jako nietolerancja glukozy, która po raz pierwszy wystąpiła lub została wykryta w czasie ciąży. Zachorowalność na GDM szybko wzrasta na świecie, prowadząc do licznych i poważnych powikłań zarówno u matki, jak i płodu. Dwa główne zaburzenia metaboliczne, czyli oporność na insulinę i dysfunkcja komórek β, biorą udział w patogenezie GDM, jednak komórkowe mechanizmy prowadzące do jej rozwoju nie są jeszcze do końca poznane. Wyniki badań klinicznych i eksperymentalnych wskazują, że dysfunkcja tkanki tłuszczowej, charakteryzująca się nieprawidłową produkcją adipokin, jest istotnym czynnikiem związanym z GDM. Do tej pory zidentyfikowano kilka hormonów wytwarzanych przez tkankę tłuszczową, w tym leptynę, adiponektynę, rezystynę, wisfatynę, apelinę, białko wiążące retinol 4 (RBP-4), waspinę i omentynę. Spośród nich stosunkowo dobrze udokumentowany jest związek leptyny i adiponektyny z insulinoopornością w GDM, ale molekularne mechanizmy działania obydwu hormonów w tym procesie nie są jeszcze całkowicie wyjaśnione. Pozostałe wyżej wymienione adipokiny wydają się być również istotnymi czynnikami w patofizjologii GDM, chociaż ich dokładna funkcja w tym kompleksowym procesie pozostaje niejasna. Celem niniejszego artykułu był przegląd istniejącej literatury dotyczącej związku między wyżej wymienionymi adipokinami i GDM oraz wyjaśnienie ich roli w patofizjologii GDM. **(Endokrynol Pol 2014; 65 (2): 134–142)**

Słowa kluczowe: *adipokiny; adiponektyna; cukrzyca ciążowa (GDM); leptyna; omentyna; RBP-4; rezystyna; waspina; wisfatyna*

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Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance of varying severity with onset or first recognition during pregnancy. It affects 1–14% of all pregnancies, depending on racial/ethnic group and the diagnostic test employed [1]. However, the recently published report by the International Association of Diabetes in Pregnancy Study Groups (IADPSG), which used new recommendations for the diagnosis of GDM, has revealed GDM prevalence to be as high as 17.8% [2]. In Poland, 3.4% of pregnant women develop GDM [3].

Gestational diabetes mellitus causes numerous and serious short- and long-term complications for both mother and foetus. In the short term, mothers with GDM are at increased risk of delivering a macrosomic infant or developing preeclampsia [4], whereas their offspring are prone to neonatal hypoglycaemia, hyperbilirubinemia, hypocalcaemia, respiratory distress syndrome, and polycythemia [5]. In the long term, GDM women are at mark-

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edly increased risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease after pregnancy, and their offspring are at risk for the development of obesity and abnormal glucose metabolism during childhood, adolescence, and adulthood [6].

To date, a large number of risk factors associated with GDM development have been identified, including previous history of GDM or impaired glucose tolerance, ethnicity, family history of GDM or T2DM (especially in first-degree relatives), advanced maternal age, previous history of macrosomic baby or of stillbirth or of baby with congenital abnormality, pregnancy-induced or pre-existing hypertension, other insulin-resistant conditions (for example, metabolic syndrome or polycystic ovary syndrome), smoking during pregnancy, high parity, and obesity [6]. In respect of obesity, clinical and epidemiological studies indicate that this metabolic disorder is a major modifiable risk factor for GDM development. As estimated, the risk of developing GDM is 3.56-fold and 8.56-fold higher in obese and severely obese pregnant women, respectively, compared to normal-weight pregnant women [7]. In the context of the global epidemic of obesity, it should be emphasised that there is also a rapidly growing number of obese patients among pregnant women, who are at increased risk of developing GDM.

Two major metabolic disorders, insulin resistance and β-cells dysfunction, are involved in the pathogenesis of GDM, although the cellular mechanisms involved in its development are not yet completely understood. Accumulating evidence indicates that adipose tissue plays a key role in the pathophysiology of GDM since it is not only the main site of lipid storage but also an endocrine organ responsible for synthesis and secretion of various bioactive molecules, collectively called adipokines or adipocytokines. It is now accepted that adipose tissue dysfunction, characterised by abnormal production of adipokines, represents a pathophysiological link between obesity and diabetes [8]. In this context, changes in the expression and secretion of several adipose tissue-derived hormones have been observed in GDM patients, including leptin, adiponectin, resistin, visfatin, apelin, retinol-binding protein 4 (RBP-4), vaspin, and omentin. In this review, we discuss the roles of these adipokines in GDM, based on recent findings in this area.

Leptin

Leptin, encoded by the *ob* gene, is a 16-kDa-peptide hormone comprising 167 amino acids. It is produced predominantly in adipocytes, although its presence has also been detected in other tissues, including placenta, ovaries, mammary epithelium, bone marrow, and lymphoid tissues [9]. Leptin is considered as an essential factor in energy homeostasis since it regulates food intake and energy expenditure via leptin receptors (ObRs) in the central nervous system (CNS), mainly localised in the hypothalamus. To date, at least six ObR isoforms (i.e. ObRa, ObRb, ObRc, ObRd, ObRe, and ObRf) produced by alternative RNA splicing of the *db* gene have been identified, but only four of them are present in humans: the long (ObRb), short (ObRa and ObRc), and secretory (ObRe) splice variants [10]. Of these, the ObRb receptor is believed to be the most important isoform participating in the transduction of intracellular signals [11]. The primary signal transduction pathway of leptin is the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling (JAK/STAT signalling), although other important intracellular signalling routes mediating leptin effects have also been found, including phosphatidylinositol-3-kinase (PI3K), AMP-activated protein kinase (AMPK), and mitogen-activated protein kinase (MAPK) [11].

Leptin level is low in lipodystrophic mice with severe insulin resistance and its administration into these animals restores insulin sensitivity [12]. However, adipocyte leptin expression and its plasma circulating level are raised in both obese patients [13, 14] and obese animal models (except the leptin-deficient *ob/ob* mouse), regardless of whether the obesity is caused by genetic defects, hypothalamic lesions, or brown adipose tissue deficiency [15–17]. Additionally, exogenous leptin administration into obese patients does not cause weight loss, suggesting that obese humans are resistant to the effects of leptin [18]. The limited leptin transport across the blood-brain barrier and/or suppression of the leptin signalling pathways in leptin-responsive hypothalamic neurons have been proposed to be attributal to the leptin resistant state in human obesity [19].

Interestingly, leptin mRNA expression is higher in subcutaneous than omental adipocytes and the subcutaneous-to-omental ratio of leptin mRNA expression is markedly higher in women than men [20]. Thus, adipose tissue distribution and mass, as well as gender, appear to be important factors determining plasma leptin concentration, although other factors influencing leptin secretion have also been identified, including fasting or energy restriction, tumour necrosis factor α (TNF-α), glucose, fatty acids, insulin, cortisol, and catecholamines [21].

Since leptin receptor isoforms are present in muscle, liver, adipose tissue, and pancreas, numerous studies have revealed direct effects of leptin on glucose and lipid metabolism as well as insulin secretion in these peripheral tissues, independently of CNS. In skeletal muscle, leptin stimulates basal, but not insulin-stimulated, glucose uptake through the PI3K-dependent pathway

[22]. Additionally, leptin prevents the accumulation of lipids in muscle tissue by stimulating fatty acid oxidation through activating AMPK and, in turn, suppression of the activity of acetyl coenzyme A carboxylase (ACC). Thus, AMPK is considered to be a main mediator of leptin action on fatty-acid metabolism in muscle [23].

In isolated hepatocytes, leptin affects glucose metabolism by significant reduction of glucose production from different gluconeogenic precursors (i.e. glycerol, L-lactate, L-alanine, and L-glutamine) [24] and this effect appears to be mediated by PI3K-dependent activation of phosphodiesterase 3B (PDE3B) [25]. Leptin, at physiological concentrations, acts through an intracellular signalling pathway similar to that activated by insulin in isolated hepatocytes [25]. Leptin activation of PI3K rather than AMPK is required for the lipid-lowering effect of leptin in liver [26].

The relation between leptin and insulin sensitivity in adipocytes is inconclusive so far. There have been studies showing no effect of leptin on glucose transport, lipoprotein lipase activity, and insulin action in cultured rat adipocytes and 3T3-L1 adipocytes [27], whereas some others have demonstrated that leptin, at an elevated concentration, is able to down-regulate insulin signalling in adipose cells, leading to the inhibition of insulin-stimulated glucose transport in adipocytes [28]. Therefore, further studies are needed to clarify these findings.

Leptin can also directly affect pancreas function through inhibiting β-cell insulin secretion and several mechanisms engaged in this process have been proposed, including (i) reduction of proinsulin mRNA level in pancreatic β-cells under high glucose concentrations, (ii) suppression of glucose transport into β-cells, (iii) PI3K-dependent activation of PDE3B that leads to a reduction of cAMP level and, in turn, inhibition of protein kinase A (PKA) involved in the regulation of Ca^{2+} channels and exocytosis, and (iv) inhibition of the phospholipase C (PLC)/protein kinase C (PKC) pathway [29].

A growing number of studies in pregnancies complicated by GDM have strongly supported the relationship of hyperleptinaemia with GDM [30–33]. Although the reasons behind this are not yet known, leptin secretion by adipocyte in the presence of increased estrogen [34] or/and by placenta [35] is possible. The role of leptin in the pathophysiology of GDM has been proposed by Chen et al. [31] who revealed significantly higher plasma leptin concentration in GDM women compared to normal glucose tolerant (NGT) subjects, which subsequently significantly decreased after delivery reaching a level comparable to the NGT group. It should be noted that besides elevated plasma leptin concentration in diabetic pregnancy, there is also data showing either decreased or unchanged plasma level of this adipokine [36, 37].

The relevance of leptin as a predictor of GDM risk has been implied by Qiu et al. [38] who demonstrated that hyperleptinaemia, independent of maternal adiposity, in early pregnancy is associated with an increased risk of GDM later in pregnancy and that each 10 ng/mL increase in leptin concentration is associated with a 20% increase in GDM risk.

Particular attention has focused on placenta, where leptin is also synthesised and secreted into both the maternal and foetal circulation [35]. Placental leptin is identical to that from adipose tissue regarding size, charge, and immunoreactivity. However, its gene has an upstream enhancer and therefore leptin expression can be regulated differently in both tissues [39]. Placenta contains long and short leptin receptor isoforms that are co-localised with leptin to the syncytiotrophoblast at the maternal interface [39], suggesting a potential autocrine or paracrine effect of leptin on placental function.

There are conflicting reports in respect of placental leptin expression during GDM with its either up-regulation [40–42] or down-regulation [36, 43]. The reasons for these discrepancies are currently unclear, although differences in the material used for testing, i.e. placenta versus tissue explants containing non-trophoblast cells producing paracrine mediators that may affect leptin release, are taken into account [43]. On the other hand, it cannot be excluded that increased expression of the soluble leptin receptor in placentas of GDM women that is capable of binding leptin with a high affinity may limit its accessibility to the transmembrane receptor, leading to a reduction of the release of leptin from GDM placentas [43].

Adiponectin

Adiponektin (AdipoQ), also known as adipocyte complement-related protein of 30 kDa (Acrp30) and gelatin binding protein of 28 kDa (GBP28), is a 244-amino acid protein with high structural homology to complement C1q [44] as well as TNF-α [45]. AdipoQ is produced almost exclusively by white adipose tissue and it occurs in three oligomeric forms: a low-molecular-weight trimer, a middle-molecular-weight hexamer, and a high-molecular weight (HMW) 12- to 18-mer [46]. Two receptors for Adipo Q, namely AdipoR1 and Adipo2, with different tissue distributions have been identified so far. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 expression predominates in liver [46].

AdipoQ is believed to be an insulin-sensitising factor involved in the regulation of glucose and lipid metabolism in insulin-sensitive tissues, mainly in liver and muscle, in both humans and animals. A connection of low AdipoQ level with the development of insulin

resistance has been found in mouse models of both obesity and, paradoxically, lipoatrophy. In humans, plasma AdipoQ level is reduced in T2DM [47] and it is more closely related to whole body insulin sensitivity than to adiposity [48]. With regard to the involvement of AdipoQ in lipid metabolism, it has been observed that this adipokine inversely correlates with triacylglycerol (TG) level and positively correlates with plasma HDL-cholesterol concentration [49–51].

Although the insulin-sensitive action of AdipoQ is complex and incompletely defined so far, the existing evidence suggests that it works by AdipoR1 and AdipoR2 receptors stimulating fatty acid oxidation in both muscle and liver as well as activating glucose uptake in muscle and reducing gluconeogenesis in liver through AMPK [52]. Additionally, AdipoQ may activate peroxisome proliferator-activated receptor α (PPARα), leading to an increased fatty-acid oxidation and subsequently decreased TG content in liver and skeletal muscle, thereby increasing insulin sensitivity (Fig. 1) [46].

AdipoQ may also improve insulin signal transduction via an increase of tyrosine phosphorylation of insulin receptor in skeletal muscle [53].

A number of factors regulating AdipoQ expression or secretion have been identified both *in vitro* and *in vivo*. Among them, the insulin-sensitising thiazolidinediones (TZDs), i.e. agonists of peroxisome proliferator-activated receptor γ (PPARγ) that as transcriptional factor modulates insulin resistance as well as fat cell differentiation, and adipogenesis, have been shown to enhance the expression and secretion of AdipoQ in diabetic patients [54, 55]. Thus, PPARγ activity seems to be closely related to AdipoQ production. According to this, carriers of the rare dominant negative mutations in the PPARγ gene have very low or undetectable plasma AdipoQ concentration [55]. Moreover, both TNF-α and IL-6 may reduce human adipocyte AdipoQ mRNA expression resulting in insulin resistance [56].

Numerous independent studies have associated hypoadiponectinaemia with GDM. Cseh et al. [57] demonstrated a significant inverse correlation between maternal AdipoQ level and increased BMI, fasting C-peptide concentration, and C-peptide/glucose ratio in pregnant women with GDM, while others found reduced adipocyte AdipoQ expression as well as its decreased plasma concentration in GDM women, independently of obesity [58, 59]. Low AdipoQ level in normal weight GDM women may result from its down-regulation in placenta, which is considered as another source of this adipokine [60]. It has been demonstrated that AdipoQ is expressed in human term placenta, primarily in the syncytiotrophoblast, and its expression, along with AdipoR1 and AdipoR2 receptors, is differently regulated by

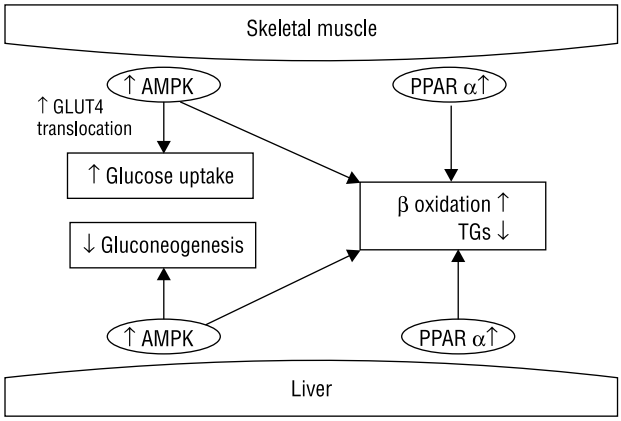

Figure 1. *AdipoQ-mediated regulation of glucose and lipid metabolism in liver and skeletal muscle. AMPK — AMP-activated protein kinase; GLUT4 — glucose transporter type 4; PPARα — peroxisome proliferator-activated receptor α; TGs — triacylglycerols; ↑ increase; ↓ decrease*

Rycina 1. *Udział AdipoQ w regulacji metabolizmu glukozy i lipidów w wątrobie i mięśniach szkieletowych. AMPK — kinaza białkowa aktywowana przez AMP; GLUT4 — transporter glukozy typu 4; PPARα — receptory aktywowane proliferatorami peroksysomów α; TGs — triacyloglicerole; ↑ wzrost; ↓ obniżenie*

TNF-α, IFN-γ, IL-6, and leptin, suggesting the significance of AdipoQ in adapting energy metabolism at the materno-foetal interface [60]. Surprisingly, Lappas et al. [43] did not detect differences in the release of AdipoQ from placenta obtained from normal and GDM complicated pregnancies. These results are currently difficult to explain, and therefore further studies are needed in this field.

Besides the association of hypoadiponectinaemia with insulin resistance during GDM, a relationship between its reduced concentration and β-cell dysfunction in GDM women has also been reported [61]. Thus, AdipoQ appears to be a factor linking insulin resistance to β-cell dysfunction in the pathogenesis of diabetes.

Interestingly, plasma AdipoQ level negatively correlates with GDM development among women in the first trimester of pregnancy [62], implying that its concentration in the bloodstream in early pregnancy could be a predictor of GDM development. Additionally, plasma AdipoQ level is reduced in women with previous GDM, independently of the prevailing insulin sensitivity or the degree of obesity [63].

Resistin

Human resistin is a 12.5 kDa cysteine rich peptide that is predominantly expressed in peripheral blood mononuclear cells (PBMCs), macrophages and bone marrow cells, whereas its expression is low in mature adipocytes [64].

In mice, resistin is up-regulated in both genetic and diet-induced obesity and its circulating level is decreased by TZDs [65]. Additionally, administration of anti-resistin antibody into the diet-induced obese mice decreases blood glucose level and improves insulin sensitivity in these animals [65]. From these findings, it has been concluded that this hormone links obesity to insulin resistance and diabetes. According to this hypothesis, resistin is involved in glucose metabolism, thereby it could contribute to hepatic insulin resistance. It has been observed that resistin decreases insulin receptor and glycogen synthase activity and increases the activity of glycogen phosphorylase, leading to an attenuated glycogenesis and an enhanced glycogenolysis in liver [66]. However, subsequent studies have failed to confirm the association of high resistin expression with obesity and increased insulin resistance in various rodent models of obesity and diabetes, implying that the expression of resistin may be differentially regulated among these animal models [64].

In humans, there is disagreement in respect of the pathogenic role of resistin in the development of insulin resistance and obesity. Several studies have supported a positive correlation between obesity, insulin resistance and elevated plasma resistin concentration [67, 68], whereas others did not find such an association [69, 70]. Therefore, further well-designed human studies are needed to precisely determine the potential involvement of resistin in the pathophysiology of obesity and diabetes. Since resistin expression is high in immune cells, it is possible that it may play a role in insulin resistance through effects on inflammation.

Human resistin is also present in placental tissue, mainly in trophoblastic cells [64], but its physiological and pathophysiological roles in human normal and complicated pregnancies are unclear. It has been demonstrated that plasma resistin concentration is higher in GDM women than NGT pregnant women and non-pregnant women [71], and that it correlates with plasma IL-6 concentration, but not insulin level, in diabetic subjects. These results suggest that alterations in insulin sensitivity in GDM patients could be mediated by inflammatory pathways, in which resistin appears to be involved. In another study, plasma resistin concentration was also significantly elevated in GDM subjects compared to NGT controls and it was independently associated with markers of adiposity (BMI, plasma leptin), TGs, and creatinine [72]. Besides the positive correlation between plasma resistin level and GDM [71], there are studies demonstrating its either decreased [73] or unchanged [74] concentration in diabetic pregnant women. A recent meta-analysis concerning the relationship of resistin with GDM revealed no difference in plasma resistin level between GDM subjects and control pregnant women [75]. However, these findings should be treated with caution due to considerable heterogeneity among analysed studies [75]. Thus, it is clear that further studies are required to understand the accurate pathophysiologic role of resistin in human diabetic pregnancy.

Visfatin

Visfatin, also known as pre-B cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (NAMPT), is a 52 kDa protein produced mainly by the visceral adipose tissue in both humans and mice [76]. Visfatin has been shown to mimic insulin effects by binding to the insulin receptor, but in another site than insulin, and to reduce plasma glucose level in mice [76]. These findings suggest that visfatin could play a regulatory role in glucose homeostasis [76]. Indeed, secretion of visfatin by adipocytes *in vitro* in response to glucose exposure as well as its increase in plasma of human subjects after glucose administration has been reported [77].

Although the exact pathophysiologic role of visfatin is not fully elucidated, there are studies showing the association of elevated visfatin concentration with T2DM. Chen et al. [78] demonstrated higher circulating visfatin level in T2DM patients compared to normal subjects. Furthermore, some polymorphisms in the visfatin gene may play a role in determining T2DM susceptibility, possibly by modulating chronic, low-grade inflammatory responses that significantly affect insulin resistance [79]. There is evidence supporting the immunoregulatory effects of visfatin. Moschen et al. [80] reported that in human monocytes, visfatin up-regulates the production of several proinflammatory cytokines such as IL-6, TNF-α, and IL-1β. Moreover, treatment of human foetal membranes with recombinant human visfatin markedly increases levels of the aforementioned cytokines [81].

There are no consistent results regarding plasma visfatin level in diabetic pregnant women and its association with GDM. For example, Krzyzanowska et al. [82] reported markedly higher plasma visfatin concentration in GDM women compared to NGT pregnant controls; however, there was no relationship between visfatin and fasting plasma glucose, plasma insulin, insulin resistance, and BMI. Elevated plasma visfatin concentration in GDM women has also been demonstrated by others [83, 84]. Lewandowski et al. [83] revealed positive correlations of plasma visfatin levels with concentrations of both fasting and post-glucose-load insulin in GDM women in the third trimester of pregnancy. Ferreira et al. [84] reported an increased plasma visfatin level in the first trimester of pregnancy in women who developed GDM, suggesting that visfatin could be a potential biomarker for predicting GDM. In contrast, a reduced plasma visfatin level, by approx. 25%, was

detected in women of Chinese origin with GDM compared to healthy pregnant controls [85]. Moreover, there was a significant negative correlation between plasma visfatin concentration and first trimester BMI as well as maternal age [85]. The reasons for these discrepancies are currently unknown, although differences in study design, including the number of subjects, gestational age, and differences in BMI might explain, at least partially, the differences among the aforementioned studies. Therefore, more restrictive controlled human studies are needed to define the significance of visfatin in diabetic pregnancy.

Apelin

Apelin is expressed and secreted by both human and mouse adipocytes and its production is increased four-fold upon differentiation of fat cells [86]. To date, several active apelin forms have identified, including apelin-36, -17, and -13 as well as the pyroglutamated isoform of apelin-13, which is produced by a post-translational modification of glutamine to pyroglutamine at the *N*-terminus [87]. Apelin acts through a specific G protein coupled receptor named APJ, which is expressed in both peripheral tissues and CNS [87].

It has been shown that insulin regulates the expression and secretion of apelin through the PI3K and PKC pathways in mice as well as in murine and human adipocytes [86]. Moreover, an increased plasma apelin level has been observed in obese and hyperinsulinaemic humans, implying that the rise in plasma insulin could promote higher plasma apelin concentration in these subjects [86].

The connection between apelin and T2DM has been postulated. A raised apelin level has been found in both non-obese patients with impaired glucose tolerance or T2DM and morbidly obese patients with T2DM [88, 89]. Recently, Dray et al. [90] disclosed a markedly increased plasma apelin level in T2DM subjects that positively correlated with insulin concentration, glycaemia, and the percentage of glycated haemoglobin. In contrast to these findings, a reduced plasma apelin level was found in patients with newly diagnosed and untreated T2DM [91].

Very few studies have aimed at evaluating the significance of apelin in GDM. Aslan at al. [92] reported a markedly higher maternal plasma apelin level in GDM patients compared to control pregnant women, which positively correlated with its cord blood level. By contrast, Telejko et al. [93] demonstrated no association between plasma apelin concentration or apelin/APJ mRNA expression and GDM. Thus, the relationship of this novel adipokine with the pathophysiology of GDM remains to be elucidated.

Retinol-binding protein 4 (RBP-4)

RBP-4 is a 21 kDa protein synthesised in hepatocytes and adipocytes that participates in the metabolism of retinol as its carrier in the bloodstream. Yang et al. [94] demonstrated increased plasma RBP-4 level in insulin-resistant mice and humans with obesity and T2DM, which stimulates hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) and impairs insulin signalling in muscle, suggesting that RBP-4 might contribute to the pathogenesis of T2DM [94]. Graham et al. [95] supported this hypothesis showing the existence of a correlation between increased plasma RBP-4 level and the magnitude of insulin resistance in subjects with obesity, impaired glucose tolerance, or T2DM and in non-obese, non-diabetic subjects with a strong family history of T2DM. However, this correlation remains controversial since no change in plasma RBP-4 level has been detected in subjects who developed insulin resistance [96].

There are no consistent results on plasma RBP-4 level in normal pregnancy. Ueland et al. [97] reported a significant increase in fasting RBP-4 from early to late pregnancy, and this change was associated with a decline in insulin sensitivity. In contrast, Inoue et al. [98] demonstrated that RBP-4 level tended to decrease after early gestation with no obvious difference between mid- to late-gestation. Reports on circulating RBP-4 in GDM have also yielded conflicting results. There exist studies showing increased [99], decreased [100], or even unaltered [101] plasma concentration of this adipokine during pregnancy complicated by GDM. Therefore, the precise role of RBP-4 in normal human pregnancy and GDM remains to be clarified.

Vaspin

Vaspin, belonging to the serine protease inhibitor family, is a novel 392–395 amino acid adipokine that was identified in visceral white adipose tissue of obese, diabetic Otsuka Long-Evans Tokushima fatty (OLEFT) rats [102]. In this experimental animal model, visceral vaspin expression and its plasma level were decreased with worsening of diabetes and body weight loss [102]. Vaspin has also been demonstrated to improve glucose tolerance and insulin sensitivity in diet-induced obese rodents and may also normalise altered expression of genes relevant to insulin resistance [102].

In human adipose tissue, vaspin mRNA expression was undetectable in lean individuals (BMI < 25), whereas it was fat depot specific in obese subjects [103]. Visceral vaspin mRNA expression positively correlated with BMI and percentage body fat and negatively correlated with plasma glucose concentration at 2-h oral glucose tolerance test (OGTT). Subcutaneous vaspin mRNA expres-

sion negatively correlated with waist-to-hip ratio, fasting plasma insulin concentration, and glucose infusion rate during steady state of euglycaemic-hyperinsulinaemic clamp. It has been suggested that induction of vaspin mRNA expression in human adipose tissue might represent a compensatory mechanism associated with obesity, insulin resistance, and T2DM [103].

Vaspin is also present in human placenta, where its expression increases gradually during pregnancy, reaching the highest level at the end of gestation [104]. Vaspin expression predominates in cytotrophoblasts and syncytiotrophoblasts during the first trimester, whereas its presence is exclusively limited to syncytiotrophoblasts in the third trimester [104]. Food restriction increases placental vaspin expression, implying its regulation by energy status in placenta [104].

To date, the role of vaspin in normal pregnancies remains poorly understood. Giomisi et al. [105] reported a lower plasma vaspin level in pregnant women than non-pregnant controls that negatively correlated with their lipid parameters (total cholesterol, TGs, LDL-cholesterol), implying that vaspin might be used as a surrogate marker of lipid metabolism in pregnancy. Additionally, plasma vaspin level positively correlated with adiponectin in pregnant and non-pregnant women, but was not correlated with BMI, serum insulin level, or the quantitative insulin sensitivity check index (QUICKI) in both groups, suggesting that vaspin cannot serve as a biomarker of insulin resistance in either pregnant or non-pregnant women [105].

Little is also known about the significance of vaspin in GDM. Stepan et al. [106] showed no significant difference in circulating vaspin concentration between GDM women and normal pregnancy. Furthermore, there was no correlation between vaspin level and parameters of insulin sensitivity or lipid metabolism in pregnant subjects. Recently, Gkiomisi et al. [107] revealed a similar reduction in vaspin level from the second trimester to postpartum in women with and without GDM. Interestingly, vaspin positively correlated with insulin, the homeostasis model assessment-insulin resistance (HOMA-IR) and TGs, and negatively correlated with QUICKI in GDM women in the third trimester of pregnancy, but not in the second trimester or postpartum [107]. Additionally, insulin treatment did not change vaspin level in GDM patients, suggesting that exogenous administration of insulin does not affect the adipokine [107]. Taken together, more research is needed to define the physiological and pathophysiological significance of vaspin.

Omentin-1

Omentin-1, also named intelectin-1, is a novel 34 kDa visceral fat depot-specific adipokine. Its gene is located in the 1q22-q23 chromosomal region, which is considered to be linked to T2DM in various populations [108, 109]. Thus, omentin could be a candidate gene for T2DM susceptibility in humans. Indeed, it has been demonstrated *in vitro* that treatment with recombinant omentin-1 enhances insulin-stimulated glucose uptake in human subcutaneous and omental adipocytes, implying its beneficial effect on insulin sensitivity [110]. Moreover, several clinical studies have revealed reduced plasma omentin level in obese patients as well as patients with T2DM or polycystic ovary syndrome that negatively correlates with BMI, fasting insulin, and HOMA-IR [111–114].

Recently, Barker et al. [115] demonstrated that human placenta also secretes omentin-1 and its release from placenta is markedly higher than from omental adipose tissue. In that study, omentin-1 level was higher in the first trimester than in the second trimester of pregnancy, suggesting increased omentin-1 clearance in the later stages of pregnancy or reduced secretion from maternal adipose tissue. Additionally, there was no difference in omentin-1 level between 28 weeks gestation and seven weeks postnatal. In respect to GDM, it has been shown that maternal omentin-1 level is significantly lower in non-obese GDM women compared to non-obese NGT women, whereas it is not different between obese GDM and obese NGT women [115]. In addition, maternal obesity or GDM does not affect cord plasma omentin-1 level [115]. Further experimental studies are required to understand the role of omentin-1 in GDM.

Conclusions

GDM is a highly complex process involving multiple factors which the identification as well as determination of the molecular mechanisms by which these factors participate in the pathophysiology of GDM is currently a serious challenge [116]. In recent years, considerable progress has been made in respect of the involvement of adipose tissue-derived hormones in the pathophysiology of GDM. Although the significance of leptin and adiponectin is relatively well characterised in glucose and lipid metabolism in diabetes, the molecular mechanisms by which these adipokines potentially exert their effects on insulin action are not completely defined and require further studies. Additional clinical studies are also needed to clarify discrepancies between findings in rodent models and humans in respect of resistin dysregulation in diabetic patients.

Given that the list of molecules identified as adipokines has grown over recent years, more well-controlled human studies should be performed to define whether or not dysregulation of newly discovered adipokines such as visfatin, apelin, RBP-4, vaspin, and omentin directly contribute to the pathophysiology of GDM.

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