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The role of new adipokines in gestational diabetes mellitus pathogenesis

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ABSTRACT

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Explanation of the GDM pathogenesis is important due to preventing gestational complications. During pregnancy there are significant changes in maternal metabolism. Many of these changes are influenced by different adipokines produced in the placenta and adipose tissue. The exact role of adipokines in the pathogenesis of GDM remains still unknown. Several adipokines have been analysed throughout gestation and their levels have been suggested as biomarkers of maternal–perinatal outcomes. Some of them have been postulated as significant in the pathogenesis of pregnancy complications like GDM.

This report aims to review some of the recent topics of adipokine research that may be of particular importance in pathophysiology and diagnosis of gestational diabetes mellitus. *Because of manuscript length limitations*, after thorough literature review and in view of the recent evidence, we focus on the one of the most well-known adipokine: adiponectin, and not so well-studied: nesfatin-1, chemerin, ghrelin, and CTRP 1.

Key words: gestational diabetes mellitus, adiponectin, nesfatin-1, chemerin, ghrelin, CTRP 1

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first detected during pregnancy. It is the most common metabolic disorder of pregnant women. The frequency of GDM may range from 5 to 20% of all pregnancies, depending on the population studied and the diagnostic tests employed. GDM represents one of the major problems in perinatal medicine because women with GDM have an increased risk for prenatal morbidity and significantly elevated risk for type 2 diabetes mellitus (T2DM) in later life [1].

Explanation of the GDM pathogenesis is important due to the possibility of preventing gestational complications. The underlying pathophysiological mechanism of GDM is believed to be the composition of decreased insulin sensitivity of the mother before pregnancy and insufficient insulin response during pregnancy. Pregnancy is associated with progressive insulin resistance. During each trimester there are some physiological mechanisms that increase food intake, promotes the adipogenesis and energy storage for the high metabolic requirements of pregnancy and lactation. Many of these maternal metabolic changes during gestation are influenced by different adipokines produced in the placenta and adipose tissue. It has been observed that adipokines cause insulin resistance in normal pregnancy but the exact role of adipokines in the pathogenesis of GDM remains unknown. Several adipocytokines have been analysed throughout gestation and their levels have been postulated as biomarkers of maternal–perinatal outcomes, some of them with pathophysiological significance [2].

This report aims to review the recent topics of adipokine research: adiponectin, nesfatin-1, chemerin, ghrelin and complement C1q tumor necrosis factor related proteins 1 (CTRP 1) that might be of particular importance in pathophysiology and diagnosis of gestational diabetes mellitus.

Because of manuscript length limitations, after thorough literature review and in view of the recent evidence, we focus on the one of the most well-known adipokine: adiponectin,

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and not so well-studied: nesfatin-1, chemerin, ghrelin, and CTRP 1. Also, in our laboratory and clinical studies we will analyse the concentration of this adipokines and we will try to find the correlation between this adipokines levels and possible clinical application of this measurements in prediction of GDM.

ADIPONECTIN

Adiponectin is a 244-amino-acid-long polypeptide hormone representing adipokines family which modulates different biological processes. Adiponectin is known to be produced not only by adipose tissue but also within the intrauterine environment and stimulates the glucose uptake in skeletal muscles and decreases the hepatic glucose synthesis [3].

Levels of the adiponectin are inversely correlated with body fat percentage, fasting glucose and insulin concentration, and insulin resistance in adults. It is believed that circulating adiponectin levels are increased during caloric restriction. The adiponectin concentration is decreased in obese and/or type 2 diabetic patients. The inverse correlation between the adiponectinemia and abdominal obesity, and the strong positive correlation between the adiponectin levels and the insulin sensitivity has been described [4]. It has been proved that the adiponectin expression is inhibited by pro-inflammatory cytokines, hypoxia, oxidative stress and all of them are typically observed in obese patient. Adiponectin can reduce ectopic fat storage by stimulating lipid oxidation and decreasing adipose tissue lipolysis. Intravenous injection of recombinant adiponectin in rodent models of insulin resistance improved normal insulin sensitivity [5].

The study of Mazaki-Tovi et al. has revealed that the adiponectin levels during 1st, 2nd and 3rd trimester were comparable and were significantly higher than in puerperium. Authors noticed that despite the increasing insulin resistance as pregnancy progresses, there were no significant changes in the adiponectin levels. This may signify that the regulation of the adiponectin release during gestation is altered. The elevated gestational adiponectin levels could be in accordance with the postulated increased "adiponectin resistance" during pregnancy [6]. It has not been confirmed whether the placenta is the source of adiponectin [3, 6]. Low maternal adiponectin levels and decreased insulin sensitivity may facilitate the glucose transport to the fetal circulation and be responsible for macrosomia. Adiponectin can be detected in fetal circulation after 24th week and the level tends to increase as pregnancy progresses. The fetal adiponectin levels have been found to be significantly higher than those in the mother [7].

Adiponectin is adipokine, which relation to GDM was the most widely studied but the results of research are not unambiguous. It has been published that adiponectin levels decrease in GDM patients when compared to healthy ones and there are also some studies indicating that the levels of adiponectin do not differ in GDM and normal pregnancy. Cortelazzi et al. have found that the circulating adiponectin levels were decreased in patients with GDM as compared to pregnant controls independent of pre-pregnancy body mass index (BMI) and the insulin sensitivity [8]. Bao et al. have showed in their meta-analysis that concentration of adiponectin was significantly lower in first and early second trimester in pregnant woman who later had diagnosed with GDM. This reduction of adiponectin levels may be correlated with the developing of GDM through decreased insulin sensitivity and anti-inflammatory capability. It has been published that the risk of GDM is 5-6 times higher in women with low adiponectin levels when compared to women with high levels [9]. An association between significantly decreased concentration of adiponectin and beta cell dysfunction during pregnancy has been found what may suggest the use of adiponectin as an early predictor of the GDM development [10].

NESFATIN-1

Nesfatin-1 is a 82 amino acid peptide derived from the previously described protein nucleobindin-2 (NUCB2), that is encoded by the NUCB2 gene. Nesfatin-1 is secreted by peripheral organs and tissues (pancreas, duodenum, stomach, adipose tissues) and nervous system. Nesfatin-1 has significant impact on carbohydrate metabolism by inhibiting glucagon release and has a glucose-dependent insulinotropic effect. The level of nesfatin increases after feeding. Nesfatin-1 has been shown to regulate the hunger and satiety sensations, body weight and is expressed in several regions of the hypothalamus playing the main role in controlling food intake [11]. Nesfatin-1 has a big impact on blood glucose levels and endogenous nesfatin-1 concentration is changed in diabetes. The significant reduction in the fasting plasma nesfatin-1 levels in T2DM and PCOS patients has also been noticed. It might be related to impaired insulin sensitivity and suggests that nesfatin-1 could be inhibited by hyperglycemia, hyperinsulinemia and insulin resistance [12]. There are only a few studies, which showed decreased level of nestafin-1 in the pregnant woman with GDM [13, 14]. Kucukler et al. have observed that nesfatin-1 level was lower and insulin concentration was higher in GDM group than in control one. The negative correlation has been found between nesfatin-1 levels and weight, BMI, the glucose concentration fasting and at first hour level of the 50 g OGTT and with homeostasis model assessment of insulin resistance (HOMA-IR). The positive correlation between nesfatin-1 and insulin concentrations have been showed. These observations may be suggestive of a role of nesfatin-1 in the pathophysiology of GDM. Therefore,

when nesfatin-1 involvement in GDM pathogenesis is clear, its assessment may be useful as early biomarker of GDM development [14].

Aslan et al. have been revealed that nesfatin-1 levels were lower in patients with GDM compared with healthy ones. The cord blood nesfatin-1 levels were similar in the GDM and control groups and maternal serum nesfatin-1 levels correlated strongly and positively with their respective cord blood concentrations [13]. Su et al. have been suggested that the reduction of nesfatin-1 level in serum of pregnant patients and the decrease of its insulinotropic effect lead to dysregulation of insulin release in GDM patients [15]. In addition, they have also reported that the intravenous injection of nesfatin-1 suppresses hyperglycemia in ob/ob mice by increasing insulin action. Therefore, nesfatin-1 could act as anti-diabetic factor in pregnant women with GDM [15]. Another study has found the increased levels of nesfatin-1 in fetuses of mothers with GDM. It was well established that these fetuses have been exposed to high glucose concentrations in utero. Thus, it may be hypothesized that the adverse hyperglycemic intrauterine environment in GDM patients could result in increased fetal nesfatin-1 levels in comparison to the control group. Nevertheless, in neonates of GDM mothers glucose dysregulation after birth was not observed, probably due to balancing mechanisms involving endogenous insulin secretion [12].

CHEMERIN

Chemerin, also known as retinoic acid receptor responder protein 2 (RARRES2), is a 14 kDa protein secreted in an inactive precursor as prochemerin and is activated through fragmentation of the C-terminus by inflammatory and coagulation serine proteases. Chemerin is a novel adipokine playing an essential role in adipocyte differentiation and insulin signalling. Chemerin and its receptor, chemokine-like receptor 1 (CMKLR1, or ChemR23) are higly expressed and secreted in various tissues, especially white adipose tissue, and they are thought to play an important role in inflammation and metabolic complications associated with obesity [16]. Chemerin levels are increased in obesity and it is connected with numerous components of the metabolic syndrome. The increased concentration of chemerin observed in obese patient is postulated to play an important role in the development of type 2 diabetes as an effect of dysregulation of the important physiological processes regulated by chemerin [16]. Fatima et al. have analysed the levels of adipokines (including chemerin) and their relations to the clinical phenotypes of GDM and the fetal growth parameters. Level of chemerin was seven folds higher in study group versus control one. The adipokines (chemerin, IL-18 and leptin) had positive correlation with fasting blood glucose concentration, HOMA-IR, fetal weight, and negative correlation with quantitative insulin

sensitivity check index (QUICKI). The higher chemerin levels were identified in 96% cases. In conclusion, authors have suggested that the high chemerin and leptin levels seen in GDM may play a role in the development of insulin resistance through a subclinical inflammation [17]. Li et al. have noticed that serum chemerin in obese normal glucose tolerant (NGT) group and normal-weight-GDM group was significantly higher than that of normal weight NGT group. There was no significant difference of CMKLR1 (encoding the receptor of chemerin) mRNA expression between normal weight NGT and normal weight GDM group [18].

Van Poppel and colleagues analysed concentration of chemerin in arterial and venous cord blood in infants of GDM and non-GDM patients, in their mothers at the beginning of the third trimester and at delivery and in amniotic fluid of GDM patients. In GDM group increased concentration of chemerin in fetal arterial cord blood were found but the difference in venous cord blood were not observed. Chemerin level in venous cord blood was higher in infants of obese women. Arterial and venous levels were associated with maternal chemerin levels at birth, and also chemerin level in arterial blood was correlated with GDM status [19].

Pfau et al. have reported that maternal serum chemerin concentrations were not significantly different in GDM patients as compared to control group. Chemerin level significantly and positively was correlated with HOMA-IR and serum levels were highest in patients in the third tertile of HOMA-IR [20]. Ademoglu and colleagues have noticed that serum chemerin levels were significantly higher in subjects with GDM than in healthy pregnant controls. Fasting insulin concentration was similar in both groups. In multiple linear regression analyses, chemerin was significantly correlated with BMI, HbA1c, HDL-cholesterol, triglyceride, insulin levels and HOMA-IR [21].

The impact of maternal obesity and GDM on maternal chemerin concentrations has been analysed, and no effect was revealed. However, chemerin levels were significantly higher in cord plasma from obese women. There was no effect of GDM on maternal and cord chemerin concentrations, and on the release of chemerin from placenta and adipose tissue [22].

Lehrke et al. have noticed the increased chemerin levels during third trimester of pregnancy. They suggested that it might be related to proinflammatory conditions due to high levels profile of mediators of inflammation such as TNF-alfa, resistin or IL-6 [23].

GHRELIN

Ghrelin is a 28-aa Ser3 acylated peptide called "hunger hormone" which regulates glucose homeostasis by altering insulin secretion and is also involved in the regulation of both glycogenolysis and gluconeogenesis. In animal studies,

the elimination of ghrelin improves the diabetic phenotype with significantly increased insulin secretion, improved glucose tolerance and decreased fasting glucose level [24]. Ghrelin is secreted from the gastrointestinal tract and plays an important role in the regulation of eating behaviour through appetite modulation and the regulation of body weight [25]. It has been suggested that ghrelin and obestatin are significant in GDM pathophysiology based on the comparing of their measurement after and before delivery [26]. The increased fasting serum ghrelin level in the 2nd trimester may be associated connected with weight gain during pregnancy [24].

Baykus et al. observed that serum ghrelin, obestatin and preptin levels were statistically higher in GDM and physiological pregnancy in the puerperium when compared to the pregnancy period. The positive correlation was found between ghrelin and preptin, and preptin and insulin in the GDM group [26]. A negative regulatory feed-back mechanism between resistin, TNF-alpha and ghrelin could be also postulated. It could be a risk factor for developing gestational diabetes mellitus. The decreased ghrelin concentration has been found in pregnant women compared to postpartum levels. In pregnant patients with type 1 diabetes and lactating mothers with GDM, serum ghrelin concentrations were found to be lower than those of the control group. Aydin et al. have also observed that mothers with GDM have a significant lower (more than two-fold) serum ghrelin level [27]. Another study has shown that ghrelin levels were lower in diabetic pregnant women, although pre-term birth appeared to reverse this trend in GDM group. The concentrations were lower in pregnant women with diabetes and HbA1c of < 6.5%. It has been suggested that ghrelin is involved in the adaptation to the caloric imbalance in GDM patients and may play a similar role in pregnancy-related complications, since high ghrelin concentrations may be vital for normal fetal development [28].

Riedl et al. have observed that whereas basal ghrelin concentrations are suppressed during pregnancy, the downregulation of ghrelin by glucose uptake is markedly reduced [29]. They have suggested that this suppression is not caused by the reduced insulin sensitivity in pregnant patient. They found no correlation between plasma ghrelin and pregestational BMI or weight gain during pregnancy. In conclusion, authors have noticed that both in the fasting state and suppressed ghrelin plasma concentrations are significantly lower during pregnancy, but fasting ghrelin level is not related to insulin sensitivity. Thus, the suppression of ghrelin throughout whole pregnancy appears to have other reason and/or purpose [29].

The decreased umbilical cord ghrelin levels have been observed in women with GDM. The negative correlation between cord blood ghrelin concentration and birth weight was also found [30]. It has been revealed that fasting plasma glucose during pregnancy and in puerperium, and post--partum C-peptide and ghrelin levels were significant risk factors for the development of type 2 diabetes in women with previous GDM. Lappas et al. have suggested that C-peptide and ghrelin might be potential biomarkers in the prediction of type 2 diabetes in patient with a history of GDM [31].

CTRP 1

Complement C1q tumor necrosis factor related proteins (CTRPs) is the family of proteins characterized by a common TNF alpha–like globular domain. Currently, 15 members are identified [32]. CTRP 1 is a member of the CTRPs group comprising family characteristic collagen and TNF-like domains and exhibit marked expression in vessel wall. The structural homology of CTRP1 and adiponectin has been described, but expression of CTRP1 is unlike adiponectin. CTRP 1 is mainly expressed in adipose tissue and derived mostly from stromal vascular cells composed of adipose-tissue macrophages, preadipocytes and endothelial cells. Its expression is markedly higher in fatty tissue of *db/db* mice and Zucker diabetic fatty *(fa/fa)* rats [33].

It is believed that abnormal synthesis and secretion of CTRP 1 change glucose metabolism by causing insulin resistance in adipose tissue, liver and skeletal muscles. Specific CTRP 1 receptor has not been yet described but animal studies showed that the injection of CTRP 1 was sufficient to decrease blood glucose levels and increase energy input required by activating protein kinase (AMPK) signalling cascade in the skeletal muscles [32].

Although several animal experiments have postulated CTRP1 as an important regulator of glucose metabolism and insulin sensitivity, the clinical observations in humans are still poorly characterized [34]. Recent studies have indicated that the circulating levels of CTRP 1 were significantly increased in subjects with metabolic syndrome [35]. It has been revealed that serum CTRP 1 concentrations were markedly higher in subjects with T2DM comparing to the healthy subjects and serum CTRP 1 levels were correlated with the insulin secretion and sensitivity in this both groups. Thus, the elevation of serum CTRP 1 levels in T2DM patients may reflect a self--protective mechanism in response to the incorrect glucose metabolism [34]. Serum CTRP 1 concentrations in healthy subjects were also associated with fasting insulin levels and basal insulin secretion (HOMA-%B), suggesting that serum CTRP 1 levels are dependent on insulin secretion in healthy human subjects [35]. Xin et al. showed that circulating CTRP 1 levels are elevated in T2DM patient and independently correlated with T2DM risk factors including BMI, fasting blood glucose levels, HbA1c, LDL cholesterol, and TNF-α [36]. Han et al. demonstrated higher circulating CTRP 1 levels in prediabetes/type 2 diabetes group than in control one. These levels are positively correlated with HOMAR-IR, fasting blood

glucose concentration, age and BMI. T2DM and GDM have similar pathogenesis, so circulating the test for CTRP1 might be useful as diagnostic test for GDM [37]. However, the limited data addressing the use of CTRP 1 as a diagnostic test in GDM are available and further studies are necessary.

CONCLUSIONS

Gestational diabetes mellitus affects a significant number of women during pregnancy. GDM is characterized by altered concentrations of different adipokines. The exact significance of adipokines in the pathogenesis of GDM remains unclear. Several adipokines have been analysed throughout gestation and their levels have been assessed in healthy and complicated pregnancies but the final settlement over their usefulness as predictive biomarkers of abnormal glucose metabolism is still to be elucidated.

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