Adipokines in gestational diabetes

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Abstract

Introduction: Gestational diabetes (GDM) is any hyperglycemic condition that has appeared for the first time in previously healthy pregnant women. The incidence varies from 1% to 20% and is constantly increasing. It is associated with an aging population, a sedentary lifestyle, and the increasing prevalence of obesity and type 2 diabetes in society. GDM results in numerous complications for both the fetus and the mother. Adipokines are a group of protein hormones and cytokines that are secreted by adipose tissue. They affect glucose and lipid metabolism, insulin sensitivity, appetite, and immune response. Due to their involvement in these processes, there are more and more reports that adipokines influence the pathomechanism of gestational diabetes.

Material and methods, aim: The literature in the PubMed scientific database published in 2015-2022 was searched using the keywords: gestational diabetes, adipokines. The aim of this review is to present the role of adipokines in the pathomechanism of gestational diabetes as well as their potential role in the detection and treatment of this condition.
Results: The pathophysiology of gestational diabetes is not fully understood. It has been noted that mothers with GDM have elevated levels of leptin. In turn, the level of adiponectin is lower in women with gestational diabetes compared to healthy women. Adipokines such as visphatin, resistin or chimerin are also suspected of a possible role in the pathomechanism of the disease. These reports could lead to the discovery of a biomarker for the rapid detection of GDM.

Conclusions: Gestational diabetes is a common disease in pregnancy, the incidence of which is constantly increasing. Its complications are dangerous for both the mother and her baby. That is why research is important that will allow us to learn about its pathomechanism, to detect it faster, and to prevent it. Studies using adipokines show promising results, hence the urgent need for more randomized, multicentre studies to better understand their role in gestational diabetes.

Keywords: adipokines, gestational diabetes mellitus, obstetrics

Introduction

Gestational diabetes (GDM) is any hyperglycemic condition that has appeared for the first time in previously healthy pregnant women. The prevalence ranges from 1% to 20%, and in some countries as much as 17.8–41.9% (depending on the studied population) and is constantly increasing. It is related to the aging of the population, a sedentary lifestyle, as well as the increasing prevalence of obesity and type 2 diabetes in the society [1, 2]. Women with GDM have a greater risk of gestational hypertension and developing pre-eclampsia. In turn, the fetus is at risk of shoulder dystocia, birth trauma, or premature delivery caused by excessive growth of the fetus. In the future, both the mother and the child are exposed to metabolic and cardiovascular diseases to a greater extent than the general population [3]. Adipokines are a group of protein hormones and cytokines that are secreted by adipose tissue. They produce signaling molecules that are autocrine, paracrine and endocrine active. They affect glucose and lipid metabolism, insulin sensitivity, appetite, and immune response [4]. Changing their expression is a probable cause of low-grade chronic inflammation in obesity [5]. Due to their involvement in these processes, there are more and more reports that adipokines influence the pathomechanism of gestational diabetes.

Material and methods, aim

The literature was searched in the PubMed scientific database published in 2015-2022 using the keywords: gestational diabetes, adipokines. The aim of this review is to present the role of adipokines in the pathomechanism of gestational diabetes as well as their potential role in the detection and treatment of this condition.

Results

The pathophysiology of gestational diabetes is not fully understood. Well-documented risk factors for GDM include advanced maternal age, family history of diabetes, previous GDM, delivery of a macrosomic child, race / non-Caucasian origin, overweight or obesity, and smoking [6]. Its contributing factor is the dysfunction of β cells, which are responsible for the storage and secretion of insulin. This dysfunction is further exacerbated by insulin resistance, which is another element leading to GDM. The available evidence suggests that the amount of adipose tissue before and / or during pregnancy contributes to insulin resistance and the severe complications of GDM associated with it. There is also a dysregulation of adipokine expression, which seems to be an important factor defining and regulating insulin resistance and GDM [7]. Research by C. Powe et al. showed that the insulin secretory response increases significantly in early pregnancy. Circulating hormones can mediate this metabolic adaptation. Identification of mediators of this physiological effect may be of therapeutic value in the treatment of hyperglycemia during pregnancy and beyond [8].
Leptin

Leptin, which is one of the adipokines, is considered the satiety hormone. Leptin resistance and hyperleptinemia are present in GDM. Moreover, placental production of this adipokine is also increased, which facilitates the transport of amino acids across the placenta and causes fetal macrosomia [9].

In the study of S. N. Hinkle, it was noticed that the increase in the amount of free leptin in the 33-39 week of pregnancy was associated with a shorter length of the newborn by 0.55 cm in non-obese women and a longer length by 0.49 cm in obese women. On the other hand, HMW-adiponectin at 33-39 weeks was inversely correlated with the length of the newborn and the thickness of the skin fold in children of obese women [10]. In the study by D. Mazurek et al. it was found that overweight or obesity of the mother and increased plasma leptin concentration may cause excessive fitness of the offspring [11].

Leptin is also positively correlated with the concentration of maternal insulin. Moreover, maternal leptin levels positively correlate with fetal circulating leptin levels, and increased levels of umbilical cord leptin were associated with fetal insulin resistance [12].

It was noticed that the placenta of patients with GDM was characterized by increased expression of receptors for leptin and leptin itself (possible role as a prognostic factor in the first trimester of pregnancy). Increased gene expression for leptin receptors was correlated with the production of pro-inflammatory cytokines, leading to chronic inflammation and leptin production. It is also possible to control fetal homeostasis in response to hyperinsulinemia. Its increased level in umbilical cord blood appears to be dependent on maternal glucose and may be a factor predisposing to obesity in newborns of mothers with GDM [4].

Studies in animal models have shown that leptin is involved in the development and maturation of many organs (heart, brain, kidneys and pancreas). Increased maternal plasma leptin levels are associated with maternal obesity, and decreased fetal plasma leptin levels are correlated with intrauterine growth restriction. Changes in plasma leptin levels during development may be associated with an increased risk of developing many adult diseases including cardiovascular, metabolic and kidney diseases through altered fetal development and organogenesis. In an animal model, it was noticed that after birth, leptin limits the maturation of many organs, and its deficiency restores the body weight of the offspring and improves organogenesis [13].

In the study by M. K. Ozias et al. in the third trimester of pregnancy, the levels of leptin, resistin, visfatin and adiponectin were measured in 17 women with BMI 18.5-24.9 and in 21 patients with BMI 25.0-40.0. Then, the total body and abdominal subcutaneous and visceral tissue weights were measured at 1-3 weeks postpartum. Overweight / obese women had a higher total body fat as well as abdominal subcutaneous fat, but there was no difference in abdominal visceral fat. Women with BMI above normal also had higher levels of leptin and it was associated with total body fat. On the other hand, the amount of resistin correlated with the abdominal fat tissue [14].

In a study by U. Andersson-Hall et al. it has been noted that physical activity during pregnancy can regulate the bioavailability of leptin by increasing the pregnancy-induced increase in sOB-R. This may be especially important in obese women with pre-pregnancy hyperleptinaemia and leptin resistance [15].

A study by C. Ehrhardt et al. showed an association of leptin and IL-6 with pre-pregnancy BMI, thigh circumference, adipose tissue area in the upper arm and the circumference of the upper arm. IL-6 was also connected with total activity. Hence, it is important that the improvement of diet quality and physical activity in women before and during pregnancy, especially overweight and obese women, is addressed [16].

Polyphenolic compounds such as flavonoids are an important bioactive component of plants (fruits, vegetables, legumes, tea). It is reported that in GDM associated with insulin resistance, hyperinsulinemia and hyperleptinemia, flavonoids may reduce the synergistic interaction between insulin and leptin signaling in inflammatory processes. These compounds may also reduce the expression of leptin in the placenta of women with gestational diabetes [17].

Adiponectin

Adiponectin, another adipokine, enhances insulin signaling and fatty acid oxidation, and inhibits gluconeogenesis. Its concentration is reduced in GDM and it has been suggested that it is a factor contributing to this disease regardless of obesity [9].
In the meta-analysis by W. Bao et al. it has been shown that adiponectin levels in the first and early second trimester of pregnancy were lower by 2.25 μg / ml (95% CI: 1.75-2.75), while leptin levels were higher by 7.25 ng / ml (95 % CI 3.27–11.22) among women who developed GDM later than women who did not [18].

Obese women have lower plasma adiponectin levels than normal BMI women throughout pregnancy, and maternal adiponectin is inversely correlated with body fat mass, insulin resistance, glucose production, and fetal growth. This may indicate the role of adiponectin in the regulation of maternal metabolism, placental function and fetal development [12].

The study of E. H. Yeung et al. based on measuring the level of adipokines in the analysis of the dried blood spot noted a relationship with a lower concentration of adiponectin, and preterm labor and SGA (Small for Gestational Age), regardless of the number of pregnancies [19].

Identifying biomarkers that facilitate the early detection of GDM is a public health priority. This will allow for early intervention to normalize blood glucose levels and may prevent complications from gestational diabetes. It is postulated that decreased adiponectin expression during pregnancy may increase insulin resistance in skeletal muscles, leading to decreased glucose uptake, pancreatic beta cell dysfunction, hyperglycemia and the development of GDM. However, the results of the studies are inconsistent and there is a large inter-individual variability in its concentrations. Adiponectin is promising, but more research is needed to establish its clinical potential [20].

Moreover, in a study by X. Chen et al. it has been shown that adipokines may have different concentrations depending on race. It was noticed that African-American women had a higher incidence of both decreased adiponectin and increased resistin levels throughout pregnancy [21].

Other adipokines

There are reports that chemerin is an insulin sensitizer, it may counteract insulin resistance. However, research on this issue is controversial and inconclusive. Some studies show a decline in women with gestational diabetes. In contrast, some authors argue that the overall level of chemerin in women with GDM increases and increases insulin resistance as well as promoting subclinical inflammation. On the other hand, in neonatal patients with GDM, higher arterial blood levels of chemerin were observed, which may reflect a higher proinflammatory status of the fetus. Due to conflicting reports, further research is necessary to obtain reliable conclusions [22].

TNF-α has been found to inversely correlate with insulin sensitivity in women with gestational diabetes. Moreover, TNF-α has been shown to contribute to insulin resistance by impairing insulin signaling by increasing the serine phosphorylation of the insulin receptor substrate (IRS-) 1 and reducing the activity of insulin receptor tyrosine kinase (IR) [23].

Meta-inflammation in the mother, as evidenced by elevated levels of IL-6 and leptin, and low levels of adiponectin, may stimulate placental nutrient transport in obese pregnant women with GDM, leading to fetal hypertrophy. TNF-α level is considered to be a reliable predictor of insulin sensitivity during pregnancy. It also stimulates the transport of nutrients [24].

Visfatin is a compound that promotes adipogenesis and may improve insulin sensitivity in the 2nd and 3rd trimester in normal pregnancy. The role of this compound in the pathogenesis of GDM is also ambiguous. Some researchers observed higher concentrations of this compound in ill women, additionally, visfatin was positively correlated with insulin in the fasting state and with glucose load in the third trimester. It has been suggested that high levels in the first trimester may also be a biomarker of gestational diabetes. However, some studies show a lower concentration of it in GDM. Hence, further research is still necessary [22].

Resistin is a protein that regulates glucose metabolism in mammals. High levels of resistin induce insulin resistance and have a pro-inflammatory effect [25]. Resistin probably has an inhibitory effect on the conversion of adipose tissue, acting as a feedback regulator of adipogenesis and adipose tissue [26].

In a study by E. Francis et al. it was noticed that changes in the concentration of chemerin, sOB-R, adiponectin and HMW-adiponectin from 10-14 to 15-26 weeks of gestation differed between women with gestational diabetes and healthy controls. In early and mid pregnancy, FABP4, chemerin, IL-6, and leptin were positively associated with an increased risk of GDM, while adiponectin and sOB-R were inversely correlated. These results provide a better understanding of the pathogenesis of gestational diabetes and may contribute to future research on GDM prediction [27].

M. Ruszała's review focused on less studied biomolecules. Chemerin and resistin may prove to be promising predictors, as their levels in the saliva of women with gestational diabetes are much higher than in healthy
women. These are promising observations towards the detection of a non-invasive method in the diagnosis of GDM. Among the tested molecules, predictive markers may also include: a high level of FABP4, a high level of one form of osteocalcin (ucOC) and a low level of serum irisin [28].

Conclusions

Gestational diabetes is a common disease in pregnancy, the incidence of which is constantly increasing. Its complications are dangerous for both the mother and her baby. That is why research is important that will allow us to learn about its pathomechanism, to detect it faster, and to prevent it. The most promising substances are leptin and adiponectin. Studies using adipokines show promising results, hence the urgent need for more randomized, multicentre studies to better understand their role in gestational diabetes.

Bibliography


