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Influence of MiRNAs in gestational diabetes mellitus development

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ABSTRACT

Gestational Diabetes Mellitus (GDM) is a metabolic disorder that is considered a prediabetes state. According to the International Diabetes Federation every year an increase in the number of women diagnosed with gestational diabetes is being noticed. It is known that GDM can cause many complications during pregnancy and labor. What is more, women with GDM history and their offspring are at risk of developing diabetes in the future. A new factor in the pathogenesis of GDM is epigenetics, which is described as changes in gene expression without directly modifying the DNA sequence. One of its regulating mechanisms is based on microRNA (miRNA). A small non-coding RNA sequence that has an influence on protein formation by suppressing gene expression. A better understanding of the miRNA's function could potentially lead to their usage as potential new biomarkers or treatment targets. In this article we review the most significant miRNA molecules in gestational diabetes.

Key words: gestational diabetes mellitus; GDM; miRNA; epigenetics

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INTRODUCTION

Gestational Diabetes Mellitus

Gestational Diabetes Mellitus (GDM) is a metabolic disorder which is characterized by carbohydrate intolerance first recognized during pregnancy. Despite many years of experimental studies, the pathogenesis of GDM remains unclear. Increased insulin secretion and progressive insulin resistance are physiological phenomena during pregnancy. This occurs due to adipose tissue growth and elevated levels of insulin antagonists such as progesterone, estrogen, prolactin and placental lactogen [1]. Normally, there is an increase of insulin secretion by the pancreatic β-cells to sustain normoglycemia. However, in GDM insufficient insulin compensation is being observed [1, 2]. Risk factors of developing GDM include previous GDM history, maternal obesity or overweight, older age, family history of diabetes mellitus, previous child macrosomia, fetal death or stillbirth history. Currently, an increase in the incidence of GDM is being noted, especially in developed countries. The International Diabetes Federation estimated that almost one in six births are affected by GDM [3, 4].

More than 40 years ago, O'Sullivan JB created the first diagnostic criteria [5] that have been improved over the years. Currently, GDM diagnosis is based on Oral Glucose Tolerance Test (OGTT) with 75 g of glucose dissolved in 300ml of water measured between the 24th and the 28th week of pregnancy. The implementation of these criteria by World Health Organization (WHO) and International Association of the Diabetes and Pregnancy Study Groups (IADPSG) was based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [6] (Tab. 1).

Epigenetics

Epigenetics is a rapidly growing field of science. The term includes any changes in the gene activity without modification in the DNA sequence. It was used for the first

Table 1. Cut-off values for diagnosing gestational diabetes mellitus according to International Association of the Diabetes and Pregnancy Study Groups [6]

International Association of Diabetes and Pregnancy Study Group	
Fasting glucose [mmol/L]	≥ 5.1
1-hour glucose [mmol/L]	≥ 10
2-hour glucose [mmol/L]	≥ 8.5

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time in 1939 in Waddington's paper [7]. For many years now, scientists have been interested in the mechanism of epigenetics and have studied this phenomenon extensively. Furthermore, the development of diagnostic techniques will allow for a more accurate analysis of changes that are not related with changes in the gene sequence. Epigenetic mechanisms operate through the regulation of gene expression as a result of chemical modification of DNA or proteins related to DNA. Thus far, the best known of the mentioned processes are DNA methylation, histone alteration, chromatin modification and a mechanism that uses non-coding RNA sequences (microRNA) [8]. This article will concentrate on the role of microRNA (miRNA) as an epigenetic mechanism in GDM development.

MicroRNA

MiRNA was discovered in 1993 by Rosalind C. Lee, Rhonda L. Feinbaum and Victor Ambros [9] and from that time the state of knowledge has significantly expanded. MiRNA expression occurs in several stages.

The first pathway starts with the DNA transcription catalyzed by RNA polymerase II and III which then forms harpin structure primary-miRNA (pri-miRNA). The pri-miRNA is processed in the nucleus by the RNase III Drosha enzyme into the pre-miRNA. Subsequently, it continues in the cytoplasm with the use of the Dicer enzyme resulting in 19–22 double-stranded miRNA nucleotides. In the next stage the RNA-induced silencing complex (RISC) is being formed. One of the strands degrades and the second takes part in gene transcription regulation.

There is a second pathway — The Mirtron Pathway of miRNA formation. During the splicing process the pri-miRNA is being created and then it follows the same pattern as stated above [10].

For many years it was considered that non-coding sequences of RNA had no significant role. Whereas nowadays it have been proved that that one mRNA may contain many binding locations for different miRNAs and that one miRNA can affect several different genes [10, 11]. The RISC-miRNA complex can interact with the target mRNA, without perfect homology and consequently, inhibit the translation process or lead to the degradation of complementary RNA [12]. The main role of microRNA is the regulation of post-transcriptional gene expression through the mechanisms of mRNA cleavage or deadenylation, leading to the down-regulation of gene expression by [13]. On the other hand, miRNA can possibly promote protein expression. MiRNA can play a role in enhancing the organism's response to stress and can have an impact on many pathological processes [14]. Furthermore, it is known that miRNA can play a role in autocrine or paracrine regulations and it is present in every kind of human fluid.

MIRNAS IN GESTATIONAL DIABETES MELLITUS

One of the first papers assuming the usefulness of a miRNAs in diagnosis of GDM was Zhao C. et al. [15] article. They suggest three miRNAs as an early serum biomarker of GDM, hsa-miR29a, hsa-miR222 and has-miR132 whose level was significantly decreased in GDM compared to the control group. Hsa-miR29a is known as a regulating factor for hepatic gluconeogenesis and a stimulator for insulin secretion by the pancreatic β cells contributing to preventing diabetes development [15, 16]. Meta-analysis conducted by Zhu H. [17] has confirmed the presence of miR-29a and miR-132 in the blood of T2 diabetes patients, whereas upregulation of miR-222 has been noted in the adipose tissue of GDM patients. It is known that estrogen receptor α (Erα) is a target for miR-222, which, when activated, leads to an increase in estrogen concentration and consequently, the inhibition of GLUT4 transporter. That phenomenon leads to estrogen induced insulin resistance [18].

Zhu Y. et al. [19], reported a potential biomarker role of miR-16-5p, miR-17-5p, miR-19a-3p, miR-19b-3p and 20a-5p which were upregulated in the plasma taken from the GDM patients between 16–19th weeks of pregnancy. Cao L.Y. et al. [20], checked those miRNAs in plasma samples of women between 24th–28th weeks of pregnancy when GDM is usually diagnosed. Results confirmed a significant upregulation of miR-16-5p, miR-17-5p and 20a-5p. Moreover, authors proved a positive correlation of those miRNAs and HOMA-IR, one of the indicators of GDM. Data describes the role of miR-16-5p and miR-17-5p in pathogenesis of T2 diabetes. Target genes for miR-16-5p were reported as downregulated genes in T2 diabetes. The miR-17-5p is involved in cell proliferation and is upregulated especially in samples from diabetic patients with vascular complications. So far, there is no data about the role of miR-20a-5p in diabetes development [19, 20]. Surprisingly, Carmen Pheiffer [21] did not show an increased expression of miR-16-5p and 17-5p in his paper. Only miR-20a-5p was upregulated. The difference between those results may be caused by race because Zhu and Cao [19] examined Asian women, whereas Carmen conducted his research in South Africa. MiRNA occurrence is sensitive and can depend on many factors such as BMI, race, nutrition and even sex of the fetus.

More recently, Sebastiani G. et al. [22], reported a miR-330 upregulation in GDM plasma. They found a correlation between miR-330 level and caesarean section rate and pregnancy complications (fetal macrosomia, polyhydramnios and maternal hydronephrosis). Authors suggested that high levels of examined miRNA may predispose to a more severe diabetic phenotype. Proof of miR-330 involvment in GDM pathophysiology are the target genes, CDC42 and E2F1. Both are associated with insulin resistance. CDC42 im-

paired insulin release whereas E2F1 reduced beta-cells proliferation [23, 24].

During pregnancy, an additional source of miRNA is the placenta. Nair S. at al. [25], reported that has-miR-125a-3p and has-miR224-5p were upregulated in chorionic villi and skeletal muscle tissue in GDM. Those RNAs are involved in CD40 and Glypican 4 expression which are associated with body fat composition and insulin resistance (correlation with HOMA-IR). What is more, a glypican 4 has an affinity to insulin receptors and increases insulin signaling [26]. Increased miR-125a-3p level was also described in the liver and the adipose tissue in a diabetic rat model as a molecule involved in insulin resistance development. The target for miR-125a-3p is PI3K, a crucial kinase in PI3K/AKT pathway leading to an increased glucose uptake in skeletal muscle [27].

Human Molecular Genetics published a paper indicating long term effects in the adult offspring of women with GDM. Individuals exposed to maternal diabetes have an increased miR-15a and miR-15b expression in skeletal muscle. These miRNAs may alter the expression of proteins important in insulin signaling pathways and decrease insulin receptors development causing impaired glucose tolerance or even diabetes in the offspring of diabetic women [28]. It testifies that epigenetics could potentially prove a potent diagnostic tool and a treatment option being a chance for a better care for people suffering from GDM and its complications.

SUMMARY

Due to the fact that miRNAs are resistant to RNase and remain stable in tissues and body fluids, even after multiple freeze-throw cycles, changes in their expression may be both sensitive and specific indicators of metabolic disorders like gestational diabetes mellitus (GDM). Furthermore, miRNAs can be collected from peripheral blood, thus rendering miRNAs an easy to collect, minimally invasive diagnostic biomarker [17]. However, changes in the miRNA expression in the blood during hyperglycemia complicated pregnancy have so far been ambiguous and further research needs to be done to create a GDM prediction miRNA profile.

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