Can J Diabetes xxx (2017) 1–9

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

# Expression of Glucose Transporter Proteins in Human Diabetic Placenta

Paweł Jan Stanirowski MD [a,*], Dariusz Szukiewicz MD, PhD [b], Monika Pazura-Turowska MD [a], Włodzimierz Sawicki MD, PhD [a], Krzysztof Cendrowski MD, PhD [a]

[a] *Department of Obstetrics, Gynecology and Oncology, II Faculty of Medicine, Medical University of Warsaw, Mazovian Bródno Hospital, Warsaw, Poland*
[b] *Department of General and Experimental Pathology with Centre for Preclinical Research and Technology (CEPT), II Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland*

ARTICLE INFO

*Article history:*
Received 4 February 2017
Received in revised form
18 April 2017
Accepted 24 April 2017

*Keywords:*
fetal macrosomia
gestational diabetes mellitus
glucose transporter
placenta
pregestational diabetes mellitus

ABSTRACT

Gestational diabetes mellitus and pregestational diabetes mellitus constitute carbohydrate metabolism disorders, which, if not diagnosed and adequately treated, lead to serious and often life-threatening pregnancy complications. According to a recently formulated hypothesis, some diabetes-related complications, such as fetal macrosomia, may be the result of disturbances in the transplacental transport of nutrients—in particular, excessive maternal-fetal glucose transfer. Throughout pregnancy, glucose flux across the placenta is mediated by the group of facilitative glucose transporters (GLUT), the expression of which in different placental compartments is the precondition for effective glucose uptake from maternal blood and its subsequent transfer to the fetal circulation. In diabetes-complicated pregnancies, the location, expression and activity of glucose transporters are modified to an extent that results in alterations in the maternal-fetal glucose exchange, potentially leading to an excessive supply of energy substrates to the fetus. This paper reviews the literature on the expression and activity of glucose transporter proteins—GLUT-1, GLUT-3, GLUT-4, GLUT-8, GLUT-9 and GLUT-12—in the human placenta, with a special focus on diabetes-complicated pregnancy. The characteristics of transporters in conditions of maternal normoglycemia and modifications occurring in the diabetic placenta are summarized, and the factors responsible for the regulation of the expression of selected isoforms are described. Finally, the impact of alterations in the placental expression of the aforementioned members of the GLUT family on intrauterine fetal development in pregnancies complicated by diabetes mellitus is discussed.



*Mots clés :*
macrosomie fœtale
diabète sucré gestationnel
transporteur de glucose
placenta
diabète sucré prégestationnel

RÉSUMÉ

Le diabète sucré gestationnel et le diabète sucré prégestationnel sont des anomalies du métabolisme des glucides qui, si elles ne sont pas diagnostiquées et adéquatement traitées, mènent à des complications de grossesse qui sont sérieuses et qui menacent le pronostic vital. Selon une hypothèse récemment formulée, certaines complications liées au diabète telles que la macrosomie fœtale peuvent résulter des perturbations dans le transport transplacentaire des nutriments, particulièrement le transfert excessif du glucose entre la mère et le fœtus. Tout au long de la grossesse, le flux transplacentaire du glucose est médié par la famille des facilitateurs du transport de glucose (GLUT), dont l'expression dans les différents compartiments placentaires est la condition préalable à une absorption efficace du glucose provenant du sang maternel et à son transfert subséquent à la circulation fœtale. Lors de grossesses compliquées d'un diabète, la localisation, l'expression et l'activité des transporteurs de glucose sont modifiées à un point tel qu'elles entraînent des altérations dans les échanges du glucose entre la mère et le fœtus, qui pourraient mener à un approvisionnement excessif en substrats énergétiques du fœtus. Le présent article porte entre autres sur une revue de la littérature sur l'expression et l'activité des protéines de transport du glucose—GLUT1, GLUT3, GLUT4, GLUT8, GLUT9 et GLUT12—dans le placenta humain et souligne plus particulièrement la grossesse compliquée d'un diabète. Nous résumons les caractéristiques des transporteurs lors d'un état de normoglycémie chez la mère et les modifications placentaires associées au diabète, et décrivons les

* Address for correspondence: Paweł J. Stanirowski, MD, Mazovian Bródno Hospital, Kondratowicza 8, 03-242 Warsaw, Poland.
*E-mail address:* stanirowski@gmail.com

1499-2671 © 2017 Canadian Diabetes Association.
The Canadian Diabetes Association is the registered owner of the name Diabetes Canada.
http://dx.doi.org/10.1016/j.jcjd.2017.04.008

facteurs responsables de la régulation de l'expression de certaines isoformes. En conclusion, nous discutons des conséquences des altérations de l'expression placentaire des membres de la famille des GLUT ci-dessus sur le développement intra-utérin du fœtus lors de grossesses compliquées d'un diabète.



## Introduction

Both gestational diabetes mellitus (GDM) and pregestational diabetes mellitus (PGDM) constitute carbohydrate metabolism disorders, which, if not diagnosed and adequately treated, lead to serious and often life-threatening pregnancy complications. Occurring more frequently in obstetric population GDM is defined as diabetes or a prediabetic state with the onset or first recognition during pregnancy. It is estimated that roughly 2% to 7% of all pregnancies are affected by GDM, and in some ethnic groups, the prevalence may be as high as 12% to 14% (1,2). In contrast, PGDM is diagnosed in 0.4% to 0.5% of pregnant women among whom nearly 75% of cases are type 1 insulin-dependent diabetes (3,4).

A multitude of complications during pregnancy qualify all women with diabetes and their offspring to the group of high obstetric and neonatal risk. The confirmed relationship between diabetes and fetal malformations, macrosomia, pregnancy-induced hypertension and shoulder dystocia has been commonly observed in clinical practice and contributes to an increase in the rate of miscarriages, stillbirths, preterm deliveries, perinatal trauma and caesarean sections (3–6). Altogether this results in a significantly increased perinatal mortality rate among neonates of mothers with diabetes (3,4). According to a recently formulated hypothesis, some diabetes-related complications, such as fetal macrosomia, may be the result of disturbances in the transplacental transport of nutrients—in particular, excessive maternal-fetal glucose transfer (7,8).

During intrauterine development, the lack of endogenous glucose production in the fetus results in strict fetal dependence on maternal supplies. The placenta, which due to its location acts as a buffer between maternal and fetal circulation, plays the pivotal role in the process of glucose transfer. Among numerous factors determining placental glucose transport capacity, the maternal-fetal glucose concentration gradient, the intensity of placental metabolism and blood flow and the expression and activity of specific glucose transporters constitute the most relevant (9–12). However, it is the latter factor that is subjected to the greatest degree of regulation, and is one of the key elements which are impaired in diabetic patients.

Beginning from the mid-1980s, glucose transporters belonging to the glucose transporter (GLUT) family were the subject of intensive research, which proved them to be the proteins responsible for facilitative, gradient-compliant and sodium-independent hexose transfer (13–17). Further studies revealed that apart from glucose, galactose and fructose, GLUT transporters are also involved in the transfer of noncarbohydrate substrates, such as glucosamine, myoinositol and urate (18–20). It is commonly accepted that the main reason for such a wide substrate specificity combined with different kinetics, location and expression of the transporters in human tissues is the need to provide an energy supply adapted to the individual requirements of the cells. In the placenta, various functions performed by the trophoblast, villous stroma or vascular endothelium contribute to the fact that changes in the expression of GLUT proteins may influence the efficacy of the maternal-fetal glucose exchange and, as a consequence, fetal growth.

Of 14 GLUT isoforms discovered so far, the following have been detected in the placenta: GLUT-1, GLUT-3, GLUT-4, GLUT-8, GLUT-9 and GLUT-12 proteins and the mRNA of GLUT-10 and GLUT-11 (21–28). However, it was only with respect to the first of the listed isoforms that the available data facilitated the determination of its possible role in the exchange of glucose between the mother and the fetus. GLUT-1, being a ubiquitous transporter isoform, is present in the majority of tissues and is therefore considered primarily responsible for glucose transfer in humans (29–31). Second in the list and characterized by one of the highest affinities for glucose, GLUT-3 protein is abundantly expressed in tissues exhibiting high energy demand, whereas the location and activity of GLUT-4 and GLUT-12 transporters are closely dependent on insulin stimulation (32–34). Finally, GLUT-9 is one of the most recently discovered isoforms, which apart from glucose, is also known to transport fructose and urate (20,30). Such diverse characteristics of GLUT proteins imply that an analysis of the expression and activity of glucose transporters in the placenta may produce significant insight into the processes leading to the formation of certain diabetic complications. Apart from fetal macrosomia, increased fetal adiposity and cardiomegaly are examples of pathologies related to maternal hyperglycemia in which an understanding of the mechanisms responsible for transplacental glucose transport disturbances may facilitate the development of future interventions.

This paper reviews the literature on the expression and activity of the glucose transporter proteins GLUT-1, GLUT-3, GLUT-4, GLUT-8, GLUT-9 and GLUT-12 in the human placenta with a special focus on diabetes-complicated pregnancy. The characteristics of transporters in conditions of maternal normoglycemia and modifications occurring in the diabetic placenta are summarized, and the factors responsible for the regulation of the expression of selected isoforms are described. Finally, the impact of alterations in the placental expression of the aforementioned members of the GLUT family on intrauterine fetal development in pregnancies complicated by diabetes mellitus is discussed.

## GLUT 1

Isolated from erythrocytes in 1977 and later cloned from the HepG2 hepatoma cell line, GLUT-1 is a ubiquitous transporter isoform present in the majority of human tissues (13,35). Apart from erythrocytes, the greatest expression of GLUT-1 is found in the brain and cells of blood-tissue barriers (29–31). Because of its sequence homology and structural similarity together with GLUT-2, GLUT-3, GLUT-4 and GLUT-14, it belongs to class I of the facilitative glucose transporters family.

In the placenta, GLUT-1 is present in the vascular endothelium and cytotrophoblast and is the primary isoform found in the syncytiotrophoblast (Table 1) (11,21,36–44). Quantitative analyses revealed that the levels of the protein increase during pregnancy and reach maximum concentrations in the third trimester (37,41). In the syncytiotrophoblast alone, which is the direct barrier between the maternal and fetal circulation, isoform expression is asymmetric and higher in the externally facing microvillous membrane (MVM) as compared to adjacent to fetal vessels basal membrane (BM) (11,36). Although the mechanisms responsible for asymmetric GLUT-1 expression in the syncytium remain to be discovered, observed differences in transporter distribution have led to the assumption that the BM—in which the content of protein is approximately 3 times lower than in the MVM–may act as a rate-limiting step in transsyncytial glucose transport (45). The proposed hypothesis was later confirmed in a study using BeWo choriocarcinoma cells as an equivalent of syncytiotrophoblast, in which an inhibition of transporters in the BM resulted in a significant reduction of transepithelial glucose transfer (46). It is important to note that similar results were not observed after selective inhibition of the