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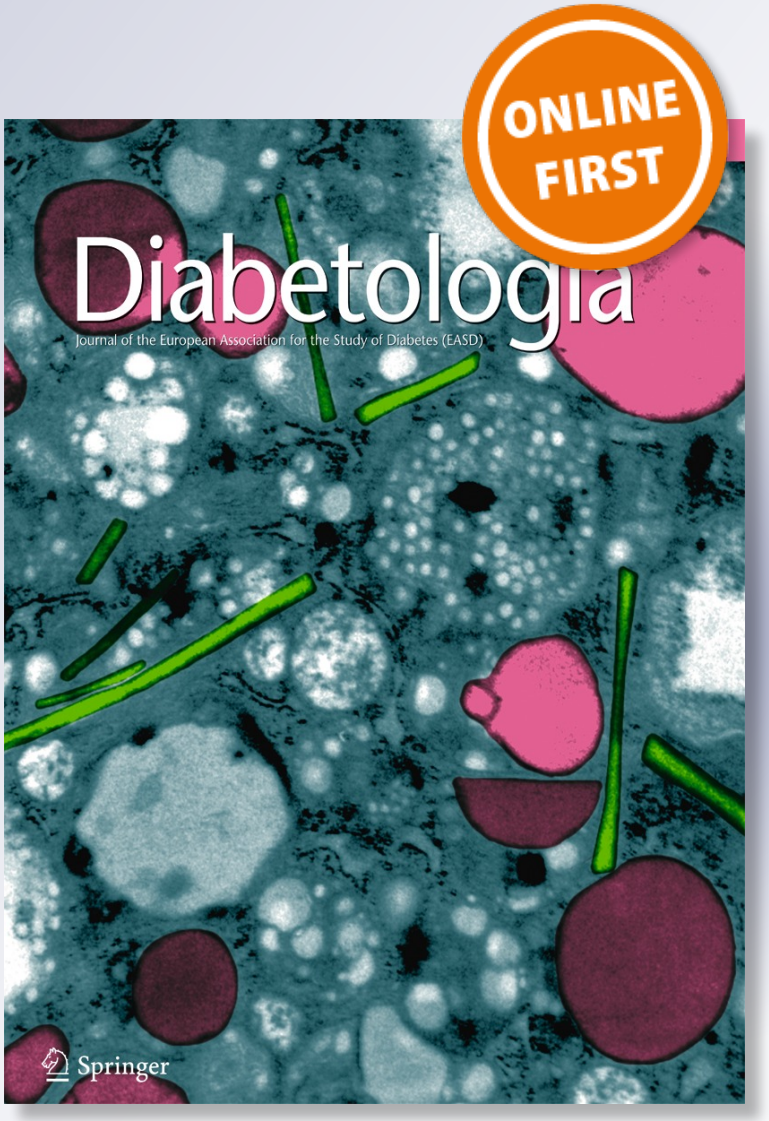

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COMMENTARY

Placental endoplasmic reticulum stress and acidosis: relevant aspects in gestational diabetes

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Abstract In this issue, Yung and colleagues (doi: 10.1007/s00125-016-4040-2) report endoplasmic reticulum stress in the placenta of patients with gestational diabetes mellitus. With the use of a trophoblast-like cell line, these authors identify putative mechanisms involved in, and treatments to prevent the induction of endoplasmic reticulum stress. Here, the relevance and possible implications of these findings and areas for further research are discussed.

Keywords Endoplasmic reticulum stress · Gestational diabetes mellitus · Glycolysis · Oxidative stress · Placenta

Abbreviation
GDM Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a prevalent disease with adverse consequences for the mother, the placenta, the fetus and the newborn, both perinatally and in the long-term [1]. With the aim of identifying pregnant women at risk of adverse outcomes in offspring, such as fetal macrosomia, The International Association of Diabetes and Pregnancy Study Groups (IADPSG) guidelines recommend cut-off values for fasting blood glucose of 5.1 mmol/l for GDM diagnosis [2]. The reduction in the cut-off value of blood glucose concentration for GDM diagnosis, and other factors including the association with obesity and the intrauterine programming of metabolic diseases are leading to a global increase in the number of GDM patients who receive dietary and/or medical interventions to achieve blood glucose control during pregnancy [3]. However, it is increasingly recognised that blood glucose levels should not be the only clinical focus in GDM pregnancies, and that diverse irregularities are evidenced in individuals with GDM who have well controlled blood glucose levels, such as those reported in the placenta in this issue of *Diabetologia* [4].

In this article, Yung and colleagues are the first to report placental endoplasmic reticulum stress in participants with GDM [4]. Since this work evidences mild placental endoplasmic reticulum stress in individuals who had achieved good blood glucose control, it is possible that more severe endoplasmic reticulum stress affects the placenta of GDM patients with poor metabolic control. Of note, the placenta is an endocrine organ with a short life-span and a very active role as a producer and secretor of protein hormones and cytokines [5]. Thus, the placenta is likely to be highly susceptible to endoplasmic reticulum stress, as highlighted by the authors [4].

The resultant unfolded protein response, which is activated to restore endoplasmic reticulum homeostasis under stressing conditions, leads to reduced protein translation and increased synthesis of chaperone proteins. Since an efficient unfolded protein response prevents apoptosis, this pathway may be linked to reduced apoptotic pathway activation, as evidenced in GDM placentas, which are associated with placental and fetal overgrowth [6]. Taking this into account, an effective unfolded protein response may constitute a marker for adverse placental function in the presence of good metabolic control. Whether serum chaperones are altered in GDM patients under good and poor metabolic control, as a result of placental endoplasmic reticulum stress and consequent restoration activities deserves to be further evaluated.

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Previous studies have identified increased concentrations of the chaperone, human CCAAT/enhancer-binding protein homologous protein (hCHOP), in umbilical vein endothelial cells from GDM participants [7] and in adipose tissue from pregnant women with GDM [8]. The identification of placental endoplasmic reticulum stress and unfolded protein responses in GDM patients is relevant in the search for new biomarkers of adverse intrauterine programming. Indeed, there is clear evidence that impaired placental growth and function are related to the induction of fetal adaptations that would lead later to diseases in the offspring [9–11]. Considering the relationship between endoplasmic reticulum stress, oxidative stress, angiogenesis and the induction of a proinflammatory environment, efforts to understand the role of these processes during development would improve our understanding of the intrauterine programming of adult diseases [12, 13].

On the other hand, in order to characterise hyperglycaemic effects on endoplasmic reticulum stress, Yung and colleagues generate a new trophoblast-like cell line denominated BeWo-NG, which has the main trophoblast characteristics but is adapted to be cultured under glucose concentrations of 5.5 mmol/l [4]. This is interesting since most cell lines are adapted to be cultured under 11 mmol/l glucose concentrations: hyperglycaemic conditions that impair the evaluation of response to glucose challenge. As a consequence, the studies performed by these authors allow for the identification of not only hyperglycaemia-induced endoplasmic reticulum stress, but also hyperglycaemia-induced acidosis in trophoblast cells, leading to the conclusion that increased lactate concentrations were the cause of the endoplasmic reticulum stress observed in these cells [4]. In agreement with this, in a recent study Muralimanoharan and colleagues found increased lactate dehydrogenase in the placentas of GDM participants, highlighting the relevance of increased anabolic pathway activation, and its relationship with mitochondrial dysfunction, in GDM placentas [14]. Mitochondrial dysfunction is closely related to oxidative stress, which affects GDM placentas [12]. Interestingly, Yung and colleagues showed that endoplasmic reticulum stress in trophoblast-like cells cultured under hyperglycaemic conditions was not only reduced by protein chaperones, but also by vitamins C and E; vitamins C and E were able to prevent the increase in lactate, as well as the acidosis induced by the 10 mmol/l and 20 mmol/l glucose concentrations [4].

These studies have clinical implications and encourage further research in the search for an antioxidant that prevents placental alterations in GDM pregnancies. Importantly, the results obtained thus far point to anaerobic glycolysis as a basic mechanism that can be highly relevant in the damage induced by maternal diabetes, in the placenta and consequently in the developing fetus. Understanding the interrelationship between endoplasmic reticulum stress, oxidative stress and increased anaerobic metabolism may contribute to the understanding of the adverse placental and fetal outcomes in GDM.

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References

1. Ashwal E, Hod M (2015) Gestational diabetes mellitus: where are we now? Clin Chim Acta 451:14–20
2. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG et al (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 33:676–682
3. Sacks DA, Hadden DR, Maresh M et al (2012) Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care 35:526–528
4. Yung HW, Alnæs-Katjavivi P, Jones CJP et al (2016) Placental endoplasmic reticulum stress in gestational diabetes: the potential for therapeutic intervention with chemical chaperones and antioxidants. Diabetologia, doi: 10.1007/s00125-016-4040-2
5. De Bonis M, Torricelli M, Severi FM, Luisi S, De Leo V, Petraglia F (2012) Neuroendocrine aspects of placenta and pregnancy. Gynecol Endocrinol 28(Suppl 1):22–26
6. Belkacemi L, Kjos S, Nelson DM, Desai M, Ross MG (2013) Reduced apoptosis in term placentas from gestational diabetic pregnancies. J Dev Orig Health Dis 4:256–265
7. Farias M, Puebla C, Westermeier F et al (2010) Nitric oxide reduces SLC29A1 promoter activity and adenosine transport involving transcription factor complex hCHOP-C/EBPalpha in human umbilical vein endothelial cells from gestational diabetes. Cardiovasc Res 86:45–54
8. Liong S, Lappas M (2015) Endoplasmic reticulum stress is increased in adipose tissue of women with gestational diabetes. PLoS One 10, e0122633
9. Higa R, Jawerbaum A (2013) Intrauterine effects of impaired lipid homeostasis in pregnancy diseases. Curr Med Chem 20:2338–2350
10. Barker DJ, Thornburg KL (2013) Placental programming of chronic diseases, cancer and lifespan: a review. Placenta 34:841–845
11. Jansson T, Powell TL (2013) Role of placental nutrient sensing in developmental programming. Clin Obstet Gynecol 56:591–601
12. Lappas M, Hiden U, Desoye G, Froehlich J, Hauguel-de Mouzon S, Jawerbaum A (2011) The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxid Redox Signal 15:3061–3100
13. Sobrevia L, Salsoso R, Fuenzalida B et al (2016) Insulin is a key modulator of fetoplacental endothelium metabolic disturbances in gestational diabetes mellitus. Front Physiol 7:119
14. Muralimanoharan S, Maloyan A, Myatt L (2016) Mitochondrial function and glucose metabolism in the placenta with gestational diabetes mellitus: role of miR-143. Clin Sci (Lond) 130:931–941