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Chronic Diseases and Translational Medicine 2 (2016) 208–214

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Perspective

Exercise and its role in gestational diabetes mellitus

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Received 15 January 2016

Available online 20 December 2016

Abstract

Gestational diabetes mellitus (GDM) refers to diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes. GDM is a common medical complication in pregnancy that has been rapidly increasing worldwide. GDM is associated with both short- and long-term health issues for both mothers and offspring. Consistent with type 2 diabetes, peripheral insulin resistance contributes to the hyperglycemia associated with GDM. Accordingly, it is important to identify strategies to reduce the insulin resistance associated with GDM. To date, observational studies have shown that exercise can be a non-invasive therapeutic option for preventing and managing GDM that can be readily applied to the antenatal population. However, the relevant mechanisms for these outcomes are yet to be fully elucidated. The present review aimed to explain the potential mechanisms of exercise from the perspective of reducing the insulin resistance, which is the root cause of GDM. Exercise recommendations and opinions of exercise during pregnancy are briefly summarized.

Keywords: Exercise; Gestational diabetes mellitus; Insulin resistance; Pregnancy

Gestational diabetes mellitus (GDM) refers to diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes.[1] Consistent with type 2 diabetes, peripheral insulin resistance contributes to the hyperglycemia associated with GDM. Global prevalence of GDM has been reported to be as high as 16.1%,[2] whereas GDM prevalence in China is up to 17.5%.[3] GDM is associated with long- and short-term health issues for both the offspring and the mother. Specifically, women with GDM are more likely to have shoulder dystocia and caesarean section, while the fetuses of women with GDM have a significantly increased risk of excessive intrauterine growth and neonatal hypoglycaemia.[4] Furthermore, both GDM pregnant women and their offspring exhibit an elevated risk of type 2 diabetes, obesity and metabolic syndrome in the future.[5,6] Accordingly, it is important to identify strategies to reduce the insulin resistance associated with GDM for the health of women and future generations.

Investigators have reported that exercise improves glucose homeostasis[7] and has an important role in the prevention and treatment of type 2 diabetes in non-

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2016.11.006

pregnant individuals.[8] Given the similar pathogenesis of GDM and type 2 diabetes, attention has been focused on the association between exercise and GDM, indicating that exercise is a promising strategy that may be readily applied to the antenatal population. To date, observational studies have shown that women who are active before and during pregnancy have a significantly lower risk of developing GDM.[9,10] In addition, studies that have administered an exercise intervention in women with GDM have demonstrated improved blood glucose control.[11] Furthermore, American Diabetes Association (ADA) and the International Federation of Gynecology and Obstetrics (FIGO) both recommended that lifestyle management including physical activity should be the first choice in the treatment of GDM.[12] However, the relevant mechanisms for these outcomes are yet to be fully elucidated. The present review aimed to outline the potential role of exercise in reducing insulin resistance, which is the root cause of GDM.

Potential role of exercise

Compensation for defects in the insulin signaling pathway

Insulin stimulates glucose uptake by binding to its cell-surface receptor and activating a complex downstream pathway, which promotes the phosphorylation and activation of a series of downstream signaling proteins and enzymes, including insulin receptor substrates (IRS), phosphatidylinositol-3-kinase (PI3K), protein kinase B (PKB or Akt), Akt substrate and atypical protein kinase C (aPKC).[13] Specifically, after the Akt substrate is phosphorylated, glucose transporter isoform 4 (GLUT4), which acts as the direct and key enzyme in stimulating glucose uptake, will localize to the membrane in order to function.[14] Then, the whole process of insulin stimulating glucose uptake is completed. Any defects within this insulin signaling cascade are associated with insulin resistance, although reduced IRS-phosphorylation is the most prominent.

Exercise provides an alternative pathway of glucose uptake to insulin activated transport. The muscular contraction associated with exercise activates 5′-adenosine monophosphate activated protein kinase (AMPK),[15] which in turn induces phosphorylation of TBC1 domain family, member 4 and 1 (TBC1D4 and TBC1D1) in the key serine/threonine residues,[16] thus, enhancing the representation of GLUT4 at the cell surface membrane so as to stimulate glucose transport. Besides, exercise can also directly increase the biogenesis of GLUT4.[17] Simultaneously, exercise can strengthen insulin signaling, particularly at the distal step of the insulin PI3K cascade via the activation of Akt substrate of 160 kDa (AS160) and aPKC.[18] All of these steps are essential to the translocation and docking/fusion of GLUT4 to the plasma membrane.

In support of the potential role of exercise to compensate for defects in the insulin signaling pathway, studies have reported changes in exogenous insulin requirements and glycemic control after a period of regular exercise during pregnancy.[19,20] For example, after a 6-week period of moderate exercise, the number of GDM patients who required exogenous insulin administration reduced significantly.[19] In another pilot study, GDM patients achieved lower levels of fasting and 1-h capillary plasma glucose following a 6-week walking program, which included 3–4 sessions a week. In addition, these women with GDM required significantly fewer units of insulin per day than women with GDM who were sedentary during pregnancy.[20]

Changing adipokine profile

Exercise can also reduce insulin resistance by changing an individual's adipokine profile.[21] Adipose tissue is now well-established as both an energy storage organ and an important endocrine organ, as it can secrete several proteins, such as adiponectin, leptin, resistin and visfatin.[22] All these proteins are considered to have roles in the pathogenesis of insulin resistance. For example, the binding of adiponectin to its receptor provokes the activation of AMPK, p38 mitogen-activated protein kinase (MAPK), peroxisome proliferator-activated receptor-α (PPAR-α), *Ras*-associated protein Rab5, PI3K and Akt, which in turn allows adiponectin to exert its insulin-sensitizing actions, such as inhibiting the gene expression of gluconeogenic enzymes, upregulating IRS expression, and increasing glucose uptake.[23]

The correlation between adiponectin and GDM is well-established, with low adiponectin concentrations typically believed to markedly increase the risk of developing GDM. For example, Doruk et al[24] found that serum adiponectin was significantly reduced in women with GDM at 24–28 gestational weeks, compared with women who had normal glucose tolerance. Furthermore, adiponectin was demonstrated to be negatively correlated with glucose ($r = -0.263$, $P = 0.013$) and hemoglobin A1c (HbA1c) ($r = -0.274$, $P = 0.01$). Moreover, Lain et al[25] demonstrated that maternal adiponectin in the first