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Perspective

Exercise and its role in gestational diabetes mellitus

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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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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

trimester was inversely associated with the risk of developing GDM later in pregnancy [odds ratio (*OR*) = 0.70, 95% confidence interval (*CI*): 0.56–0.88, $P = 0.002$].

Notably, exercise appears to increase adiponectin levels and strengthen adiponectin pathways. A recent study showed that an acute bout of exercise at either a high or low intensity can significantly and immediately elevate serum adiponectin levels, even following 30 min of rest.[26] When investigating the effects of 12-week interval training on plasma levels of adiponectin, Racil et al[27] randomly assigned 34 obese adolescent females to mid-intensity interval training (MIIT), high-intensity interval training (HIIT) or control groups. The results showed that exercise increased plasma adiponectin (pre-intervention *vs.* post intervention, 7.4 ± 1.5 μg/ml *vs.* 9.9 ± 1.5 μg/ml, $P < 0.05$ for HIIT; 6.7 ± 1.0 μg/ml *vs.* 7.7 ± 1.2 μg/ml, $P < 0.05$ for MIIT) and decreased the homeostasis model assessment-estimated insulin resistance (HOMA-IR) index (pre-intervention *vs.* post intervention, 4.4 ± 0.7 *vs.* 3.1 ± 0.4, $P < 0.05$ for HIIT; 4.4 ± 0.6 *vs.* 3.6 ± 0.4, $P < 0.05$ for MIIT). Furthermore, all these changes were markedly more pronounced in the HIIT group. They also found that waist circumference decreased in the exercise group; this may explain how exercise increases adiponectin levels, via exercise-induced weight reduction.

Reducing the inflammatory state

The association between inflammation and insulin resistance is well-documented, particularly in obesity and type 2 diabetes mellitus. Normal pregnancy is characterized by low grade inflammation, once the inflammatory state expands beyond the capacity of pregnant women, GDM may occur. This hypothesis is supported by increased circulating concentrations of inflammatory molecules, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), in GDM pregnancies.[28,29]

TNF-α and IL-6 are major biological markers of inflammation. Plasma levels of TNF-α and IL-6 are thought to have a critical role in the regulation of insulin sensitivity, and they have also been used as insulin resistance markers to some extent.[30] In support of this, one classic study demonstrated that genetic deletion of TNF-α or its receptors significantly reduced insulin resistance and improved insulin signaling transductions in muscle and adipose tissue.[31] Korkmazer[28] evaluated the inflammatory status of pregnant women based on their oral glucose tolerance test and found that, compared with the normal group, the serum concentrations of TNF-α increased significantly in the GDM groups (2.721 [1.325, 4.725] pg/ml *vs.* 0.600 [0.001, 1.762] pg/ml, $P < 0.0001$) and glucose intolerance group (2.125 [0.590, 4500] *vs.* 0.600 [0.001, 1.762] pg/ml, $P = 0.0062$), suggesting that TNF-α was closely associated with pregnancy-associated insulin resistance. A previous study by Hassiakos et al[32] indicated that serum IL-6 concentrations during 11–14 gestational weeks had a predictive effect on the development of GDM later in pregnancy, with an *OR* of 1.85 ($P = 0.003$).

The major mechanism by which TNF-α induces insulin resistance is by promoting serine/threonine phosphorylation of IRS-1 via the c-Jun N-terminal kinase (JNK) and inhibitor of κB kinase β (IKKβ)/nuclear factor-κB (NF-κB) pathway, which effectively blocks IRS-1 from binding to the insulin receptor.[33] IL-6 induces insulin resistance by inhibiting GLUT4 synthesis, as well as increasing the expression of suppressor of cytokine signaling-3 (SOCS-3), which disrupts important factors involved in the insulin signaling pathway, such as IRS-1, IRS-2, PI3K and Akt.[34]

Therefore, controlling the release and activity of TNF-α and IL-6 or other inflammation markers may contribute to a reduction in insulin resistance. The inverse relationship between plasma levels of inflammatory cytokines and exercise has been well-documented. A recent meta-analysis selected studies that evaluated the effects of exercise intervention on inflammatory markers/cytokines in adult patients with type 2 diabetes.[35] The results demonstrated that exercise was associated with a significant decrease in C-reactive protein (CRP) and IL-6 levels.[35] Similar results were published by Akbarpour,[36] who reported that there was no significant difference in CRP of the two groups of obese men before the aerobic training; however, the levels of CRP and IL-6 in the exercise group were significantly lower than those in the control group after 12 weeks of aerobic training.

However, sometimes IL-6 messenger RNA (mRNA) is upregulated in contracting skeletal muscle. And the muscle-derived IL-6 is different from the IL-6 secreted by T cells and macrophages,[37] for it can exert anti-inflammatory effects through its inhibitory effects on TNF-α and stimulatory effects on IL-10.[38] But this response is temporary and mostly triggered during high-intensity and long-duration exercise. Additionally, exercise can also reduce the body's inflammatory state by adjusting the inherent innate immune system, such as by reducing the activation of Toll-like receptor (TLR)

pathway.[39] Besides, weight reduction through exercise decreases the volume and number of adipocytes, which reduces the number of endothelial and macrophage cells that are lodged inside adipose tissue to produce proinflammatory mediators.[40] To date, studies focused on the effect of exercise on inflammation levels during pregnancy have been scarce. Wang et al[41] indicated that recreational exercise before pregnancy, but not during pregnancy, may significantly reduce CRP levels during pregnancy, particularly vigorous exercise.

Upregulating antioxidative capacity

Oxidative stress refers to an imbalance in the body's oxidation and antioxidation mechanisms, such as a disturbance between reactive oxygen species (ROS) and antioxidant defenses. Malondialdehyde (MDA) and 8-isoprostane are the most commonly used markers of ROS.[42] The body utilizes two types of antioxidant defenses; one is an enzymatic antioxidant system, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), whereas the other is a non-enzymatic antioxidant system, which includes vitamin C, vitamin E, glutathione, melatonin, carotenoids, and trace elements copper and zinc.[43] When the generation of ROS overwhelms the functional capacity of antioxidants, oxidative stress emerges and further contributes to various pathological processes, such as type 2 diabetes.

Several studies have indicated that increased oxidative stress observed in pregnancy contributes to the pathogenesis of GDM. Grissa et al[44] assessed serum antioxidant status and lipid peroxidation in women with and without GDM. They found that, compared with non-diabetic pregnant women, women with GDM exhibited decreased levels of vitamin E and SOD and their thiobarbituric acid-reactive substance levels were enhanced, which led them to conclude that GDM patients experience a downregulation of antioxidation. Karacay et al[45] also demonstrated that amplified oxidative status and reduced antioxidant ability may give rise to GDM, based on the finding that MDA (7.8 ± 2.3 nmol/mL *vs.* 6.5 ± 1.9 nmol/mL, $P < 0.001$) levels and advanced oxidative protein product (AOPP) levels (0.30 ± 0.25 μmol/L *vs.* 0.11 ± 0.07 μmol/L, $P < 0.001$) were higher in women with GDM. Thus, treatment with SOD, CAT or other antioxidants may improve insulin resistance.[46]

There is an association between increased oxidative stress and GDM as excessive oxidative stress decreases the phosphorylation of insulin-stimulated Akt, glycogen synthase kinase 3 (GSK-3) and forkhead box O (FOXO) 1α and alters the phosphorylation of MAPKs, including p38, extracelluar signal-regulated protein kinase and JNK, all of which have been reported to contribute to insulin resistance.[46]

Exercise training has been shown to be associated with upregulating antioxidant agents in pregnant women. Specifically, one early study confirmed that regular exercise throughout pregnancy may significantly increase the expression of antioxidant markers, such as SOD, GSH-Px and CAT.[47] Similar results were published by Sankaralingam[48] and Wagey[49] which showed that exercise during pregnancy increased the levels of antioxidant agents in pregnant women. In fact, many other studies that were not confined to pregnant women have also confirmed that aerobic exercise and resistance training can have antioxidant effects.[50,51]

Thus, exercise may be a non-invasive therapeutic option for preventing and managing GDM that can be readily applied to the antenatal population.

Exercise recommendations

As early as 2002, physical activity guidelines issued by the American College of Obstetricians and Gynecologists (ACOG) suggested pregnant women without complications should engage in at least 150 min of moderate-intensity physical activity per week.[52] In 2008, the United States Department of Health and Human Services published the same exercise suggestion and advised that women who performed high-intensity exercise before pregnancy should maintain their original exercise level during pregnancy.[53] Moderate-intensity physical activities in these two guidelines refer to activities that require moderate physical effort that make pregnant women breathe slightly harder and their heart beat a little faster than normal.

However, the prevalence of exercise during pregnancy remains very low throughout the world.[54] This is largely due to the lack of specific recommendations on the type, intensity and duration of exercise during pregnancy, and people's traditional beliefs that pregnancy requires rest and recuperation.[55] In fact, exercise during pregnancy is beneficial to the mothers' and their fetuses' health, such as avoiding maternal excessive weight gain, relieving pregnancy-related depression and irritability, maintaining fetal weight within the normal range, preventing pregnancy complications, and reducing the risk of macrosomia.[56,57] Furthermore, one retrospective study conducted by Mourtakos et al[58] showed that the *OR* of offspring being overweight/obese at the age of 8 after mild exercise during pregnancy, compared to that of a sedentary pregnancy, was

0.77 (95% *CI*: 0.65–0.91). However, studies focusing on the long-term effects of antenatal exercise on maternal and offspring outcomes remain scarce.

As documented in many studies, physical exercise during pregnancy is safe for both the pregnant women and fetus. However, if a pregnant woman has medical complications or contraindications, such as a serious heart or lung disease, premature labor or threatened miscarriage, placenta previa, incompetent cervix or ruptured membranes, she should reduce or prevent exercise.[59] Moreover, before pregnant women begin any type of exercise, they should consult their health provider for an individualized opinion on their exercise program.

Regular aerobic exercise is advised during pregnancy, particularly exercises that involve large muscle groups and have less pressure on joints, such as walking, swimming, stationary cycling, jogging and strength training. On the contrary, exercises that may hit or kick you in the stomach or make you fall should be avoided, for example, contact sports, skiing, horseback riding, gymnastics, scuba or sky diving.[59,60] If pregnant women exhibit symptoms such as dizziness, dyspnea, amniotic fluid leaking or vaginal bleeding, they should immediately stop exercising.[59–61]

Different guidelines have differing suggestions for the intensity of exercise that should be performed during pregnancy; however, most guidelines support moderate-intensity exercise three or more times per week during pregnancy.[59]

Many manners can be used to ensure the safety and intensity of exercise during pregnancy. Firstly, health providers and obstetricians should complete a comprehensive medical evaluation for each pregnant woman before advising them on how to exercise during pregnancy.[60] Secondly, ratings of perceived exertion can be used to evaluate whether an exercise intensity is either too easy or too hard for pregnant women. In addition, from talking with women who are doing exercise, one can elucidate whether the intensity is appropriate for them.[60,61] Thirdly, heart rate calculators that measure the mother's heart rate can also be used to assess the intensity of the exercise based on the target zones for each section. Fetal heart rate monitoring can also be selectively used to ensure the safety of exercise. For women who were sedentary before pregnancy, exercise during pregnancy requires a step-by-step program that should be gradually strengthened. Moreover, pregnant women should wear loose-fitting clothing, keep hydrated and exercise in an environment with an appropriate temperature and humidity.[59]

Conclusion

In conclusion, pregnancy may be a good opportunity for women to maintain or form healthy living habits. This opportunity to improve the mother and offspring's health should be seized, and great importance should be attached to this opportunity, even in the long-term. Exercise during pregnancy has been approved by various studies and should be readily applied to the antenatal population. However, further research is required to specify exercise mechanisms and to further determine the optimal type, duration and intensity of exercise during pregnancy, particularly for women with GDM. Of equal importance, long-term follow-up studies are necessary to determine the impact of exercise during pregnancy on the long-term health of the mother and fetus.

Conflicts of interest

The authors have declared no conflicts of interest.

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