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Review Article

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Research Progress on Anti-inflammatory Effects and Possible Mechanisms of Exercise in Gestational Diabetes Mellitus

Lesha Wang[1], Zhaoxia Liang[2*]

[1]*Obstetrical Department, The Fourth Affiliated Hospital, International Institutes of Medicine, Zhejiang University School of Medicine, China.*

[2]*Obstetrical Department, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China.*

[*]Corresponding Author
Zhaoxia Liang, Department of obstetrics, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou 310006, China.

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Abstract

Gestational diabetes mellitus (GDM) is a common pregnancy complication affecting maternal and fetal outcomes, and chronic low-grade inflammation is closely related to its pathogenesis. Exercise is one of the effective solutions for the prevention and treatment of GDM. In recent years, many studies have reported the anti-inflammatory effect of exercise. This paper summarizes the research progress of the anti-inflammatory effect of exercise on GDM and its possible mechanism, in order to deepen the understanding of GDM exercise.

Keywords: Exercise, Inflammation, Gestational Diabetes Mellitus, Mechanism

Introduction

Gestational diabetes mellitus (GDM) is defined as diabetes discovered or diagnosed for the first time during pregnancy, excluding pregnant women with diabetes diagnosed before pregnancy, and some GDM patients can recover to normal after delivery [1]. Given the different diagnostic criteria in different countries, the global epidemiology of GDM is still unknown, but the study has reported that the average prevalence of GDM in various regions of China is 17.5%, and there is a clear upward trend [2]. Pregnant women with GDM are prone to complications and adverse pregnancy outcomes such as gestational hypertension syndrome, premature delivery, and macrosomia [3, 4]. However, GDM is a multifactorial disease affected by genetic and environmental factors, and its pathogenesis has not yet been fully clarified.

In recent years, with in-depth research on the pathogenesis of GDM, it has been found that in addition to insulin resistance and glucose intolerance, persistent chronic low-grade inflammation and pro-inflammatory immune system responses induced by high glucose are also closely related to the pathogenesis of GDM [5, 6]. Appropriate and reasonable exercise therapy is currently recognized as one of the effective solutions for the treatment of GDM, because exercise not only has a direct hypoglycemic effect but also has a long-term anti-inflammatory effect [7, 8]. This paper summarizes the research progress on the anti-inflammatory effect of exercise in GDM and its possible mechanism, hoping to deepen the knowledge and understanding of exercise therapy for GDM, to provide guidance and help for the clinical treatment of GDM in the future.

GDM and Inflammation

Chronic low-grade inflammation (also known as systemic inflammation) is a chronic, subclinical, nonspecific, persistent inflammatory state. Although the pathogenesis of GDM is not fully understood, chronic low-grade inflammation is recognized as one of the influencing factors of its occurrence, and it is a key pathogenic mechanism of other metabolic disorders including type 2 diabetes.

It has been reported that there is systemic inflammation in pregnant women with GDM [9,10], and the levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-1β in the blood circulation of GDM pregnant women are increased compared with normal pregnant women [10,11]. Pan et al. have also found that M1 pro-inflammatory macrophages aggregated in the placental tissue of pregnant women with GDM [12]. It has also been reported that the NLR family pyrin domain-containing protein 3 (NLRP3) inflammasome is also related to the pathogenesis of metabolic diseases such as GDM and type 2 diabetes mellitus [13].

The increase of inflammatory factors can also destroy the function and activity of islet β cells, promote the development of insulin resistance, and finally aggravate the body's glucose metabolism disorder. TNF-α can reduce the expression of glucose transport-

er type 4 (GLUT4) in adipose tissue and skeletal muscle, and its pro-inflammatory activity plays an important role in the apoptosis of islet β cells [14]. IL-6 impairs the phosphorylation of insulin receptor and insulin receptor substrate-1 by inducing the expression of SOCS-3, a potential inhibitor of insulin signaling, leading to insulin resistance [15]. The nuclear factor-κB (NF-κB) signaling pathway can interact with IL-6 and TNF-α to form a positive feedback pathway and aggravate the inflammatory response. This inflammatory activation mechanism can in turn drive insulin resistance and promote the development of GDM [16]. Studies have shown that IL-1β in pancreatic β cells is activated and binds to interleukin-1 receptor type I (IL-1RI). Then, through the involvement of MYD88 and NF-κB, various other pro-inflammatory mediators are recruited and the expression of insulin receptor substrate-1 is reduced at the ERK-dependent transcriptional level and ERK-independent post-transcriptional level [17]. There is also evidence that IL-1β is involved in pancreatic β-cell injury [18].
The above studies all suggest that the inflammatory response, which involves the secretion of inflammatory factors, the activation of inflammasomes, and the aggregation of inflammatory cells, is a crucial link in the pathogenesis of GDM.

The Anti-Inflammatory Effects of Exercise

Studies have shown that regular exercise can prevent and treat the occurrence and development of chronic diseases closely related to chronic low-grade inflammation, such as cardiovascular disease, and its mechanism may be related to the anti-inflammatory effect of exercise [19, 20]. Long-term regular exercise can reduce the levels of pro-inflammatory factors such as IL-6 and TNF-α in the body, while increasing the levels of anti-inflammatory factors such as IL-6, IL-10, and IL-15 [21]. Animal experiments suggest that regular exercise induces the phenotype of macrophages to change from M1 macrophages to M2 macrophages, inhibits inflammatory macrophages from infiltrating adipose tissue, and reduces the inflammatory response of adipose tissue [22, 23]. While vigorous exercise also elicits an increase in the pro-inflammatory cytokines TNF-α and IL-1β, it is largely counteracted by anti-inflammatory cytokines, resulting in an overall anti-inflammatory response [24]. It must be mentioned that excessive exercise leads to an increase in pro-inflammatory cytokines, which further induce chronic inflammation [25-27]. Therefore, proper exercise may be an inexpensive and effective way to prevent and treat GDM through its anti-inflammatory effect. Studies have highlighted the beneficial role of exercise in the prevention and treatment of GDM, but the exact mechanism of the benefit of exercise on GDM is not fully understood.

Possible Mechanisms of Exercise against Inflammation

Anti-inflammatory mechanism of exercise in adipose tissue

According to statistics, between 1999-2000 and 2017-2018, the prevalence of obesity and severe obesity among adult women in the United States increased significantly [28].Being overweight and obesity are one of the major risk factors for GDM, and the risk of GDM in overweight or obese women is about three times higher than in normal-weight women [29]. Several mechanisms have been proposed to explain the pathogenesis of GDM, including the secretory release of pro-inflammatory cytokines and stimulation of placental inflammation in the maternal and fetal circulation [30].

Both cell and animal experiments show immune and inflammatory responses in obesity. The specific mechanism is that the accumulation of adipose tissue reduces the blood flow of subcutaneous and visceral adipose tissue, resulting in the impairment of local tissue oxygen supply, macrophage infiltration and increased expression of pro-inflammatory factor genes [31, 32]. The increase of chronic low-grade inflammation caused by obesity will further affect insulin resistance and accelerate the occurrence and development of GDM [33, 34]. Exercise training can increase the volume of skeletal muscle vasculature and tissue blood flow, improve local tissue effective blood flow and oxygen delivery, and reduce the accumulation of fatty acids and lipids in the blood caused by diabetes [35-37]. Wang J et al.confirmed that in a mouse model of type 2 diabetes, exercise can reduce inflammation and oxidative stress in perivascular adipose tissue and improve endothelial vascular function [38]. We can speculate that exercise also has anti-inflammatory effects and anti-inflammatory mechanisms in GDM similar to those in type 2 diabetes. In addition, with the occurrence of obesity and the accumulation of adipose tissue in the body, the number of classical activated macrophages (M1 type) increases and the number of alternative activated macrophages (M2 type) decreases [39,40]. M1 macrophages mainly produce IL-6, TNF-α and other pro-inflammatory factors, while M2 macrophages mainly produce anti-inflammatory factors, which hinder the occurrence of inflammatory reactions mediated by M1 macrophages. Experiments on mice fed a high-fat diet [22, 23] suggest that regular exercise induces the phenotype of macrophages to change from M1 macrophages to M2 macrophages, inhibits inflammatory macrophages from infiltrating adipose tissue, and reduces the inflammatory response of adipose tissue. Silveira et al. proposed that exercise-trained mice had a higher proportion of M2 macrophages than sedentary mice [41]. It is not difficult to speculate that reasonable exercise training can promote the transformation of adipose tissue macrophages into M2 type, reduce the secretion of pro-inflammatory factors such as TNF-α and IL-6, improve the body's insulin resistance and islet β-cell function, and alleviate the progress of GDM.

As we all know, adipose tissue is an endocrine organ that can secrete various pro-inflammatory and anti-inflammatory adipokines, including pro-inflammatory adipokines such as leptin and anti-inflammatory factors such as adiponectin. Leptin is one of the most extensively studied pro-inflammatory adipokines involved in the development of obesity and its complications. Leptin promotes the activation of the transcription factor NF-κB, which stimulates pro-inflammatory genes [42]. Obesity-induced hyperleptinemia stimulates monocytes and helper T cells to produce pro-inflammatory cytokines such as TNF-α and IL-6, and inhibits the production of anti-inflammatory cytokine IL-4 [43, 44]. As an anti-inflammatory adipokine, adiponectin is a regulator of macrophage

polarization, which stimulates the expression of M2 macrophages and attenuates the expression of M1 macrophages, thus playing an anti-inflammatory role [45]. Adiponectin can inhibit the secretion of TNF-α, MCP-1 and IL-6, while increasing IL-10 , polarization to M2 and reducing β-cell apoptosis [46]. Several studies have established that exercise can lower serum leptin and increase adiponectin levels [47-49].

In summary, exercise may reduce adipose tissue inflammation by alleviating adipose tissue hypoxia, promoting macrophage phenotype switching, inhibiting the secretion of pro-inflammatory cytokines, and regulating the level of adipokines, thereby improving the occurrence and development of GDM.

Exercise Promotes Release of Anti-inflammatory Factors in Skeletal Muscle

During exercise, skeletal muscle, as an endocrine organ, can produce a variety of muscle cytokines, among which IL-6, IL-10 and IL-15 can exert anti-inflammatory effects.

IL-6

IL-6 is the first cytokine detectably released from skeletal muscle in the circulation during exercise. Myogenic IL-6 increases with increased exercise and leads to an exponential increase in circulating IL-6 [50]. The anti-inflammatory effects of exercise are mediated in part through IL-6. Although IL-6 is generally regarded as a pro-inflammatory cytokine, there is evidence that myogenic IL-6 has anti-inflammatory effects [51]. This may be because the pro-inflammatory effect of IL-6 is mediated by the soluble IL-6 receptor, whereas its anti-inflammatory effect is mediated by the membrane-bound receptor Gp130 [52]. IL-6 plays an anti-inflammatory role through the inhibition of TNF-α. It is known to all that IL-6 can inhibit TNF-α production in cultured human monocytes and monocytic cell lines [53]. It is consistent with findings that TNF-α levels were elevated in anti-IL-6-treated mice [54]. In human experiments, endotoxin increased TNF-α levels, and exercise and infusion of IL-6 both inhibited endotoxin-induced TNF-α production [55]. Meanwhile, IL-6 can induce anti-inflammatory cytokines such as IL-10 and IL-1Ra [56]. IL-1Ra limits IL-1β signaling and helps protect pancreatic β cells from IL-1β-mediated destruction [57]. Mauer et al. also found that IL-6 signaling is an important determinant of alternate activation of macrophages SS [58]. IL-6 limits the expression of inflammatory cytokine genes under inflammatory conditions and enhances the responsiveness of macrophages to IL-4, thereby limiting the transition of macrophages to a pro-inflammatory M1 phenotype and ultimately reducing inflammation and insulin resistance associated with inflammation.

IL-10

IL-10 is also one of the typical anti-inflammatory cytokines. IL-10 inhibits the synthesis of proinflammatory cytokines, chemokines, MHC class II molecules, and adhesion molecules in monocytes/macrophages, thereby limiting effector T-cell responses [59]. The beneficial effects of IL-10 on insulin resistance are largely related to its inhibition of pro-inflammatory cytokine production, especially TNF-α [60]. Wang et al. [38]found that 8 weeks of treadmill exercise increased IL-10 levels in perivascular adipose tissue of diabetic mice in the exercise group compared with non-exercise diabetic mice. Arthiese Korb et al. reported that plasma IL-10 levels were increased in patients with type 2 diabetes after 12 weeks of exercise in two settings (in a swimming pool and on a land track) [61]. Another study pointed out that the concentration of IL-10 increased after high-intensity exercise [62]. It can be seen that IL-10 is involved in the anti-inflammatory response of exercise to a certain extent.

IL-15

Regular exercise can reduce visceral fat accumulation and thus play an anti-inflammatory effect, which may be achieved through myokines, such as interleukin-15 which is upregulated in muscles after exercise [63]. IL-15 can induce a decrease in triglyceride synthesis, inhibit triglyceride storage, thereby reducing adipose tissue mass, and can also regulate the amount of abdominal adipose tissue [64]. In addition, IL-15 may help reduce or even inhibit the negative effects of TNF-α in patients with chronic inflammation and may improve tissue insulin sensitivity, especially in skeletal muscle [64]. This effect was confirmed in experimental studies in a mouse model of diet-induced obesity [65]. In this study, increasing IL-15 production by viral vectors improved insulin sensitivity and suppressed weight gain in mice.

Therefore, it is not difficult to see that exercise may improve insulin resistance by promoting the release of anti-inflammatory factors such as IL-6, IL-10, and IL-15 from skeletal muscle, thereby alleviating the occurrence and development of GDM.

Exercise Strategies for Gestational Diabetes

Reasonable exercise plays an important role in preventing GDM, improving blood sugar and insulin resistance, and has a profound impact on the pregnancy outcome of GDM and the long-term health of mothers and infants. The American College of Sports Medicine proposes that regular exercise at any stage of pregnancy (pre-pregnancy, first trimester, and third trimester) can help prevent GDM and weight gain during pregnancy [66]. Several studies have shown that both aerobic and resistance exercise can lower fasting and postprandial blood sugar [67-71]. Exercise during pregnancy can also prevent postpartum obesity and type 2 diabetes in women with GDM [66], improve offspring insulin sensitivity, and reduce the risk of offspring obesity, type 2 diabetes, and cardiovascular disease [72]. Widely accepted forms of exercise during pregnancy include aerobic and resistance exercises. The appropriate exercise prescription for pregnant women who exclude exercise contraindications is at least 5 days a week, 30 minutes of moderate-intensity exercise every day, and individual adjustments are made according to the doctor's guidance. Exercise intensity can be assessed by heart rate, the Brog Exercise Intensity and Perception of Exercise Scale, or a talk test. If the heart rate of pregnant women reach-

es 40%,~59% of the heart rate range (the calculation method is 220-age), or the Berg scale reaches 13-14 points (a bit difficult), it indicates moderate-intensity exercise, and normal communication during the conversation test indicates that the exercise intensity is appropriate. Pregnant women who lacked exercise before pregnancy should start with low-intensity exercise during pregnancy. Although the safe upper limit of exercise intensity has not been determined, pregnant women who have long-term high-intensity exercise before pregnancy can continue to do high-intensity exercise depending on the situation, but they should be alert to the signal to stop exercise, avoid high fever and maintain adequate calorie intake. If pregnant women experience discomfort such as vaginal bleeding, abdominal pain, muscle weakness, calf pain and swelling, dyspnea, dizziness, chest pain, frequent fetal movement, they should stop exercising immediately, and start exercising again under the guidance of a doctor after excluding contraindications. In addition, for GDM patients receiving insulin or other hypoglycemic drugs, it is necessary to adjust drug dosage and carbohydrate intake according to their blood sugar control during exercise therapy to prevent hypoglycemia during and after training.

Conclusion

Chronic low-grade inflammation is closely related to the occurrence and development of GDM. Reasonable and regular exercise training can alleviate the inflammatory response and improve GDM to a certain extent. Appropriate exercise therapy is basically effective, cheap, and easy to implement as a method for the treatment of GDM, and no obvious side effects have been found for pregnant women. As a means of treating GDM, it has important clinical application value. This paper clarifies the possible mechanism of the anti-inflammatory effect of exercise and provides the basis and suggestions for the clinical use of exercise therapy in the treatment of GDM. However, elucidating the specific anti-inflammatory mechanism of exercise prevention and treatment of GBM is still an in-depth topic, and future larger-scale and higher-quality research are needed to prove it.

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