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Physical Exercise as Therapy for Type 2 Diabetes Mellitus: From Mechanism to Orientation

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Abstract
Background: Exercise therapy plays an important role in the prevention and treatment of type 2 diabetes (T2DM). The mechanism of exercise therapy in the improvement of glycolipid metabolism of T2DM is very complex and not completely clear. ***Summary:*** Exercise training improves the whole body metabolic health in patients with T2DM, leading to an increase in glycolipid uptake and utilization, improved insulin sensitivity, optimized body mass index, and modulated DNA methylation, etc. Recent findings support that some cytokines such as irisin, osteocalcin, and adiponectin are closely related to exercise and metabolic diseases. This study briefly reviews the physiological mechanisms of exercise therapy in diabetes and the potential role of these cytokines in exercise. ***Key Messages:*** More high-quality, targeted, randomized controlled studies are needed urgently, from mechanism study to treatment direction, to provide a more theoretical basis for exercise therapy and to explore new therapeutic targets for diabetes.

Introduction

Type 2 diabetes (T2DM) is a systemic metabolic disease, which is characterized by insulin resistance and relative deficiencies in insulin secretion, accounting for more than 90% of all diabetes types. According to a published survey, the prevalence of diabetes in China is up to 11.6%, and the prevalence of prediabetes is as high as 50.1% [1]. Therefore, it has been increasingly recognized as a serious, worldwide public health concern that urgently calls for stronger countermeasures to control and prevent this trend. In the classic diabetes "5 carriages" management, exercise therapy is given more and more

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attention because of its specific accessibility and cost-effectiveness. Regular physical exercise has proved to be effective not only in improving glycemia by lowering insulin resistance and promoting insulin secretion, but also in reducing the risk of cardiovascular disease and obesity in patients with T2DM [2]. However, a detailed mechanism that links physical activity (PA) to T2DM still remains unknown. This review focuses on the progresses made in understanding the mechanism of exercise therapy in regulating glycolipid metabolism disorder and the possible direction of treatment in T2DM mellitus.

Relationship between Exercise Therapy and Glycolipid Metabolism

A large number of randomized controlled trials have demonstrated that exercise can regulate the glycolipid metabolism disorder in T2DM patients effectively, whether aerobic exercise or resistance exercise, or the combination of the 2, which is advantageous to better control the progression of diabetes [3]. A multicenter cross-sectional survey in China has found that glucose metabolism, fat metabolism, blood pressure, and body mass index (BMI) were significantly improved after regular exercise in patients with T2DM. Similarly, the decline in prevalence of diabetes-related chronic complications such as diabetic nephropathy, retinopathy, peripheral neuropathy, peripheral vascular disease, and diabetic foot were reported in patients who had full compliance to exercise [4]. Regular exercise likely plays an important role in the prevention and treatment of T2DM, but how does it work? The mechanisms will be discussed in following sections.

Mechanism of Exercise Therapy to Improve Glucose Metabolism

Increase of Glucose Uptake and Utilization

One of the most well-established mechanisms of insulin resistance in T2DM is the decrease in the expression of glucose transporter 4 (GLUT4) protein in muscle, possibly associated with mitochondrial dysfunction and decreased biogenesis [5]. The translocation of GLUT4 from intracellular to plasma membrane is crucial for glucose uptake in skeletal muscle. This process is usually believed to be insulin-induced. Interestingly, in recent years, researchers have found that regular exercise can also mediate GLUT4 translocation through distinct proximal signaling mechanisms that bypass defects in insulin action [6]. Whether for healthy people, impaired glucose tolerance or T2DM patients, long-term exercise can significantly increase the expression of GLUT-4 protein in the skeletal muscle cells and promote its translocation to the cell membrane, which enhances the ability of skeletal muscle to increase glucose uptake and transport [7]. Endurance exercise has been shown to increase the capacity of mitochondria in skeletal muscle cells, the activity of mitochondrial oxidase, and to regulate the content of lipid in mitochondria, resulting in an improvement of mitochondria function to make a good use of glucose oxidation [8]. There is evidence that expression of peroxisome proliferator-activated receptor γ co-activator-1α (PGC1-α), a marker of mitochondrial biogenesis, was increased in response to the first exercise bout. The cytochrome C oxidase IV protein that reflects in part the enzyme activity was also increased after training [9].

Improvement of Insulin Sensitivity

Muscle tissue is the main target tissue for insulin action. Previous studies found that resistance exercise (strength training) can significantly increase the strength of skeletal muscles and enlarge the cross-sectional area of the quadriceps muscles [10, 11], which result in an increased number of insulin receptor and the improvement of insulin sensitivity. In addition, the beneficial effects of exercise are also studied by amplifying insulin signaling and enhancing the transduction of intracellular signaling pathways. Thus, exercise is likely to facilitate the physiological effects of insulin. In T2DM patients, glucose is taken up by skeletal muscles through 2 major pathways: insulin-dependent and non-insulin-dependent. T2DM is mostly associated with varying degrees of insulin resistance and hypoinsulinism, which causes impairment of insulin-dependent glucose uptake in skeletal muscles. Because normal uptake of glucose can be obtained through the non-insulin-dependent pathway activated by acute exercise, this pathway is becoming another important way of glucose regulation in insulin resistance state [6].

Protection of Pancreatic β-Cells Function

With the increase of exercise intensity and duration of activity, accumulated glucose and lipid are gradually consumed, which can not only relieve the glucotoxicity and lipotoxicity on pancreatic β-cells caused by hyperglycemia and hyperlipidemia in the internal environment, but also reduce the pancreatic inflammation and oxidative stress injury in tissue [12]. By protecting the

residual pancreatic β-cells and promoting the recovery of damaged islet function, the level of endocrine ability on its own may get better or at least not deteriorate. In other words, the pancreatic β-cells, in response to a given exercise stimulus, can increase insulin secretion to regulate glycolipid metabolism and meet the need of daily physical activities. It has been reported that the dosage of exogenous insulin is also reduced to a certain extent after regular exercise. The researchers recruited 105 subjects with impaired glucose tolerance or T2DM who participated in 12–16 weeks of aerobic exercise training (ET), and observed evidence that training-induced changes in insulin secretion, that is, pancreatic β-cell function is critical to improvements in glycemic control [13].

Mechanism of Exercise Therapy to Improve Lipid Metabolism

Increase of Lipid Hydrolysis Oxidation

An increased understanding of the mechanism for exercise-induced lipid metabolism provides evidence for exercise therapy in T2DM. As is known, T2DM is mostly accompanied with varying degrees of abnormal metabolism of blood lipids, mainly with high levels of triglyceride (TG) and low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, which is closely related to cardiovascular disease risk [14]. Exercise therapy is another way of treating diabetes through improving the blood lipid profile. Based on a recent study, aerobic or resistance exercise can promote the secretion of catecholamine in the body and raise hormone-sensitive lipase enzymatic activity, resulting in an acceleration of lipid hydrolysis. The lipid was hydrolyzed into free fatty acids and transferred to the target cell, then oxidized and utilized within mitochondria. What's more, the reduction of intracellular lipid accumulation is also beneficial to alleviate peripheral insulin resistance [15].

Alleviation of Systemic Inflammation

During the past several years, researchers have learned much about the relationship between obesity and systemic inflammation, and demonstrated that the serum concentration of some inflammatory markers, such as cytokines, TNF-α, IL-1β, IL-6, and C reactive protein were significantly higher in obese patients with T2DM than in healthy individuals. Furthermore, it has been observed that there is obvious macrophage aggregation and chemotaxis in fat, liver, and muscle tissues, which confirmed the pathogenesis of obesity-mediated chronic low-grade inflammation in the whole body [16]. In the state of obesity, fatty acids directly activate the Toll-like receptor 4 at the surface of monocytes to trigger systemic inflammation, and then macrophage infiltration is chronically increased in tissue with an up-regulation on the expression of proinflammatory factors [17]. These changes activate various signaling cascades and subsequent inflammatory pathway, eventually leading to the phosphorylation dysfunction of insulin signal transduction protein. The possible mechanisms of exercise on anti-inflammatory effect are as follows: Firstly, regular exercise might decrease the storage of visceral fat and lower the production of proinflammatory cytokines, with an inhibition of inflammatory cells aggregation and infiltration, effectively alleviating systemic inflammation and maintaining normal insulin signaling [18]. Secondly, some anti-inflammatory factors originating from contracting skeletal muscle fibers might be released into the blood during exercise. For example, interleukin-6, which is rapidly rising under the exercise stimulation, involves some changes in cytokine levels (decreases the production of TNF-α and increases interleukin-1 receptor antagonist) to directly take the anti-inflammatory effect [19].

Optimization of BMI and Systemic Condition

Obesity is an important risk predictor for incident T2DM. Exercise can increase the energy consumption and help lose weight, reducing the risk of obesity and T2DM. A few studies have shown that the BMI, abdominal sebum thickness, visceral fat, and waist-to-hip ratio in obese patients have improved after 8–12 weeks of resistance exercise and aerobic exercise [20, 21]. It is worth noting that overweight or obese diabetic patients who are persistent in exercising can not only increase their lean body mass and reduce fat deposit, but also better control the progression of T2DM. Besides, a reduction in burden on the heart and lung following exercise-induced weight loss has clear benefits in the improvement of cardiopulmonary function. A strong relationship between exercise and body immunity has been found; exercise can promote a healthy immune system, leading to decreased disease susceptibility and severity [22]. Exercise can also positively impact patients' psychological states by eliminating general anxiety and stress. In addition, by actively cooperating with the doctor, patients are willing to change some of the unhealthy lifestyle habits and have a better control of blood glucose.

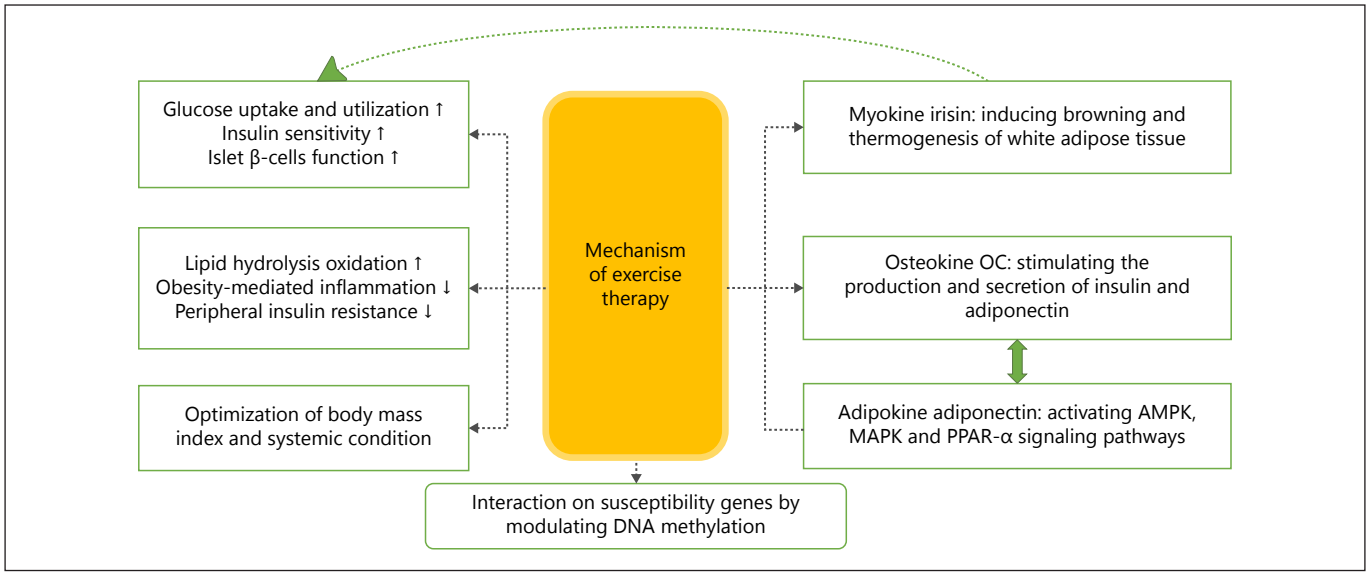

Fig. 1. Overview of the mechanism of exercise therapy in the improvement of glycolipid metabolism and potential role of some cytokines in exercise. AMPK, activated protein kinase; PPAR-α, peroxisome proliferator-activated receptors-α; OC, osteocalcin.

Interaction between PA and Susceptibility Genes

Interestingly, while T2DM risk variants do not interact with PA [23], obesity risk variants do [24]. Many studies demonstrated that PA can attenuate in part the impact of obesity-predisposing gene variants like FTO on BMI or body adiposity index in children, adolescents, and adults [25–27], which revealed the positive effects of PA on high genetic risk subgroups against obesity. Obesity-associated insulin resistance that has been found as a common pathophysiological basis of metabolic diseases is crucial in the development of T2DM. Cauchi et al. [28] have reported that obesity status can interact with the susceptibility to T2DM through modulating insulin action. Based on these findings, it is speculated that an interaction between PA and susceptibility genes may also have a decreased effect on T2DM. Recently, DNA methylation is believed to be a potential epigenetic mechanism to explain the interactions between lifestyle changes and genetic variation [29, 30]. Barrès et al. [31] have observed that decreased DNA methylations in response to acute exercise intervention induced a dose-dependent expression of metabolic genes in human skeletal muscle. Similarly, another important study has shown that chronic exercise also caused hypomethylation of the promoter region for nuclear receptor factor, fatty acid transporter (SLC27A4), and GLUT4 in obese patients with T2DM [32]. The studies presented thus far provide evidence that PA is positively associated with susceptibility genes by modulating DNA methylation, which highlight the role of exercise therapy in improvement of T2DM and obesity.

Advances of Exercise Therapy for T2DM Mellitus: Cytokines

The more recent studies have found that some cytokines such as myokine irisin, osteokine osteocalcin (OC), adipokine adiponectin (ADP), are closely related to diabetes and metabolic diseases. Accumulating evidences indicate the possibility that these cytokines, released by the newly proposed "endocrine organ" like skeletal muscle, skeleton, and adipose tissue, might be hormonal mediators of the whole body effects of exercises. The cytokines might play an important role in regulating energy metabolism, promoting insulin synthesis and secretion, decreasing insulin resistance and so on (Fig. 1). However, the relationship between change of cytokines and physical training, as well as their potential mechanism are not yet clear.

Myokine: Irisin

Discovery of Irisin

Irisin is often considered as a myokine secreted by skeletal muscle during exercise, which was first report-

ed by Boström et al. [33]. It is a newly discovered myokine regulated by PGC1-α, as previously mentioned, a nuclear transcriptional co-activating factor that mediates energy metabolism. The PGC1-α exerts its action on the regulation of intracellular oxidation metabolism, thermogenesis, mitochondria biosynthesis, angiogenesis, skeletal muscle fiber type transformation, and other bioprocesses [34]. Importantly, researchers have found that PGC1-α could promote the expression of FNDC5, the precursor of irisin. FNDC5 is a type III membrane-bound protein in skeletal muscle. After the N-terminal signal peptide of FNDC5 is excised, the remaining peptide is hydrolyzed by enzyme, and secreted as a new polypeptide fragment, namely Irisin [33].

Biological Function of Irisin

The white adipose tissue is the main tissue for body fat storage, while the brown adipose tissue is enriched with mitochondria and specific UCP-1 expression to maintain body's balance of temperature and energy [35]. Some recent studies suggest that irisin might upregulate the UCP-1 expression and increase the mitochondrial density, thereby inducing browning and thermogenesis of white adipose tissue. Thus, these effects lead to be an increase in energy expenditure and an improvement of glucose and lipids homeostasis. Moreover, both in vivo and in vitro experiments have confirmed that irisin has a strong role in inducing the phenotypic transformation of white adipose tissue into brown adipose tissue. However, it is unclear how this happens. Several hypotheses have been proposed that irisin might act on its receptors located on white adipocytes in mice, and then induce phosphorylation of p38 mitogen-activated protein kinase and extracellular signal-regulated kinase signaling pathways, eventually increasing the expression of downstream signaling molecules such as peroxisome proliferator-activated receptors-α, UCP-1, and so on [36]. In terms of irisin and exercise, Shan et al. [37] found that the activity of adenylate activated protein kinase (AMPK) in skeletal muscles may be closely related to the production of irisin, which is involved in exercise-induced AMPK-PGC1-α-FNDC5 pathway activation and the subsequent increase of irisin and UCP1.

Irisin and Exercise

It was initially reported that the plasma concentrations of FNDC5 mRNA and irisin increased significantly after 3 weeks of free wheel running in mice. The mice plasma concentration of circulating irisin was elevated (65%) by Western blotting and other methods. Similar analyses in healthy adult humans who were subjected to a 10-week endurance ET indicated a 2-fold increase in the circulating irisin levels compared to the non-exercised group [33].

Since then, irisin has become a focus for research in the exercise therapy for metabolic diseases. It is well established that the level of circulating irisin was lower in both newly diagnosed T2DM and those suffering from T2DM [38, 39]; however, the correlation between levels of irisin and clinical glycolipid indexes is not consistent.

Different exercise intensity, type, time, and frequency may affect the expression and secretion of irisin. Huh et al. [40] observed that acute exercise had promoted an increase of serum irisin level, rather than chronic exercise, which was possibly due to exercise adaptation. Kim et al. [41] found that resistance exercise significantly increased circulating irisin while aerobic exercise had no effect. Another study reported that the changes in serum levels of irisin are associated with post-exercise duration, with a rising trend following single sessions of endurance exercise and strength training, then after the peak value gradually declined until 24 h [42]. In addition, a recent meta-analysis concluded that fitness level and BMI were identified as important predictive variables for post-exercise irisin concentration [43]. In contrast, a few studies showed that neither acute nor chronic exercise had any influence on FNDC5 and irisin levels in overweight and obese people [44].

To date, there is controversy about the property and origin of irisin. Some scholars believe that irisin can also be produced by adipocytes with a lower expression level than that of skeletal muscle cells. FNDC5 produced by skeletal muscle accounts for about 72% of the total amount in circulation [45]. It has been observed that the secretion of FNDC5/irisin in subcutaneous fat and visceral fat tissue significantly increased within one week after short-term physical training, and gradually decreased after 3 weeks. In obese people, the level of plasma irisin was evidently elevated, but dropped substantially after bariatric surgery, presumably as a result of reduced adipose tissue or improvement of irisin resistance. There are also studies suggesting that levels of serum irisin are positively correlated with BMI, which may partly explain a possible link with the content of skeletal muscle tissue [46]. Therefore, the relevance among irisin, adipose tissue, skeletal muscle tissue, and even other organs remains to be further explored.

Osteokine: OC

Discovery of OC

OC is a non-collagen protein, synthesized and secreted by osteoblasts. OC is a straight chain polypeptide consisting of 49 amino acid residues. The level of serum OC can generally reflect the activity of osteoblasts, thus OC is also considered a marker of bone formation and bone turnover. In 2007, Lee's team found that bone could also be involved in systemic metabolism as an endocrine organ [47].

Biological Function of OC

So far, the physiological function of OC has not been fully elucidated. Early studies suggested that OC primarily maintained the normal mineralization rate of bone and regulated bone resorption. In the acidic environment typical of bone resorption, OC is converted into undercarboxylated osteocalcin (UcOC) that exert a hormonal action [48]. Animal studies first found that mice knocked out of the OC gene became obese with metabolic abnormalities such as impaired glucose tolerance, reduced insulin secretion, decreased insulin sensitivity, and elevated TGs [47]. Ferron et al. [49] reported that daily injections of recombinant OC in mice fed a high-fat diet resulted in an increase of glucose tolerance and insulin sensitivity, which provided new insights into the therapeutic potential of OC in T2DM and obesity. The endocrine function of bone-derived UcOC is mainly in 2 ways. First, once released in the systemic circulation, UcOC combines with its receptor and directly stimulates pancreatic β-cells to synthesize and secrete insulin. Second, UcOC can improve insulin sensitivity and energy expenditure by increasing the ADP expression in adipose tissue and mitochondrial biogenesis in skeletal muscle, and by regulating the expression of PGC1-α in glucose and lipid metabolisms [50, 51]. With regard to the relationship between exercise and OC, one point of view is that acute exercise enables increased secretion of serum UcOC [52], as a consequence of the increase in bone resorption and bone turnover, ultimately causing bone loss [53]. The possible reason for multiplying OC after exercise is a need for adaptive movement of muscle fibers [54]. For example, it is conducive to the utilization and uptake of glucose and fatty acids for ensuring nutrient supplies of muscle fibers during acute exercise. In other words, the reactive increase of OC reflects a capacity of exercise tolerance [55]. However, there is also another voice that long-term exercise does not have a significant effect on OC because exercise may prevent bone loss and promote an increase in bone mineral density (BMD) by inhibiting bone resorption [56]. Consequently, there is no change or even a decrease of bone-active hormones with the intervention of chronic exercise.

OC and Exercise

In recent years, more and more clinical studies have also confirmed that there is a link between OC and some glucose and lipid metabolism indicators [57]; the OC concentration was negatively correlated with fasting plasma glucose, TG, glycosylated hemoglobin, BMI, body fat rate (BF%), and insulin resistance index. It is important to note that OC concentration was significantly decreased in patients with T2DM and metabolic syndrome [58, 59], implying that OC may have a positive regulation function on glucose and lipid metabolisms. A study in obese individuals has shown that the levels of serum carboxylated OC and insulin sensitivity are significantly improved after acute exercise compared to their levels at rest-control sessions [52]. Similarly, in another study, the content of serum OC increased significantly after 8 weeks of aerobic training, which gives a possibility that chronic exercise might also have a certain effect on OC [58]. On the contrary, it has been shown that 6-month chronic exercise in obese older adults did not have a significant impact on serum UcOC [60]. What's more, long-term ET caused a decrease in serum OC and attenuated weight loss-induced reduction in hip BMD [56]. In short, the results of studies on the effects of exercise on OC have not been conclusive. The latest study found that mice injected with exogenous OC had an increase and recovery of exercise tolerance, indicating that OC signaling molecules may play an important role in reversing age-related decline of exercise tolerance [55]. The discovery of OC may open a new and exciting field in the treatment for diabetes and related complications such as osteoporosis in the future.

Adipokine: ADP

Discovery of ADP

ADP is an adipose-derived secreted factors or adipokine, exclusively synthesized and released by adipocytes, and plays a clear regulatory and functional role linked to many pathophysiological processes such as energy metabolism, anti-inflammation, and anti-atherosclerosis and more [61]. In addition, ADP is positively correlated with insulin sensitivity by enhancing the insulin activity [62]. Much evidence have confirmed that ADP levels in the plasma and adipose tissue are obviously decreased in obese and diabetic patients compared to healthy individuals. These observations are consistent with the previous findings in animal experimental models of diabetes [63].

Biological Function of ADP

Human ADP receptors are mainly expressed on skeletal muscles and liver. After ADP binds to its receptor, the biological effects of ADP on insulin sensitivity seem to be mediated by its ability to activate AMPK, MAPK, and peroxisome proliferator-activated receptors-α signaling pathways, resulting in an increase of fatty acid oxidation and glucose uptake in muscle tissue, as well as an inhibition of gluconeogenesis in the liver [62]. In addition, ADP can also promote the production of endothelial nitric oxide to exert anti-atherosclerotic effects by improving the vascular dysfunction and inhibiting vascular inflammation [64, 65]. With the deepening of research, it has been found that osteoblasts can express ADP and its receptors, and it can be concluded that ADP may be a key factor in metabolic bone disease [66]. In vitro studies have shown that ADP may regulate bone resorption and bone formation by affecting the proliferation and differentiation of osteoclasts and osteoblasts. A number of clinical observational studies have shown that ADP levels is negatively correlated with BMD, suggesting that it might be a negative regulator of bone metabolism [67], nevertheless, it still remains controversial in the study of human body. Thus, the interaction between ADP and OC on bone metabolism and glycolipid metabolism and the mechanism therein are unclear yet, which need to be further studied for a better understanding.

ADP and Exercise

In the past 10–15 years, the results of research on the effects of exercise on ADP have been inconsistent. A recent meta-analysis indicated that exercise, particularly aerobic exercise, significantly increased the ADP levels compared to no exercise as well as control in overweight and obese individuals [68], consistent with the finding in T2DM [69]. However, some studies is contrary to the results presented before suggested that the plasma ADP levels were not altered after 12 weeks' combined training in overweight and obese children [70]. Another similar study also showed that there is no change in ADP in inactive men who carried out a sports-based exercise intervention [71]. Intriguingly, the exercise mode may lead to different effects on the expression of ADP. It was observed that ADP concentrations presented a diverse change in response to acute and chronic exercises, and short- (<12 weeks) and long-term training (≥12 weeks) showed contrasting results [72]. In China, a study on 24 weeks of moderate-intensity exercise interventions for obese type 2 diabetic patients also revealed that plasma ADP levels as well as increased insulin sensitivity elevated significantly [73]. ADP as an adipokine may be strongly associated with total fat, fat distribution, and catabolism, presumably owing to the influence of complex weight changes after exercise, leading to great differences in ADP levels.

Conclusion

As described earlier, exercise therapy plays an important role in the prevention and treatment of T2DM with multiple complicated mechanisms. The discovery of cytokines such as irisin, OC, and ADP has brought about a novel insight that they may be crucial hormonal mediators of exercise therapy for diabetes and metabolic diseases, but the exact mechanism is still unclear. There is also discrepancy in the relationship between physical training and changes of cytokine levels. The major reasons for this discrepancy may be due to the differences in study populations, methods, detection techniques, and sample sizes. In addition, most of the subjects investigated are healthy young people, overweight or obese people. Studies on T2DM patients in China and abroad are lacking. Therefore, more high-quality, targeted, and innovative researches are needed urgently, from mechanism study to treatment direction, to provide a more scientific basis for the formulation of personalized exercise regimen and to bring new hope in exploring new targets for diabetes treatment in the future.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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