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MINIREVIEWS

Mechanism underlying the effects of exercise against type 2 diabetes: A review on research progress

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Abstract

Exercise has emerged as one of the important and effective non-drug therapies used for management of type 2 diabetes (T2D) in certain nations. The present report summarizes the latest findings from the research on the beneficial effect of exercise on T2D. The objectives were to provide references for the theoretical study and the clinical practice of exercise-based management of T2D, in addition to identify the limitations of the existing literature, thereby provide direction for future research in this field.

Key Words: Type 2 diabetes; Diabetes; Exercise; Mechanism; Inflammation

Core Tip: Exercise significantly benefits type 2 diabetes (T2D) management by enhancing insulin sensitivity, regulating glucose and lipid metabolism, and reducing inflammation. This review reveals how different exercise types, including aerobic, resistance, and flexibility exercises, contribute to these effects. It also highlights the need for personalized exercise programs to optimize T2D treatment. The article underscores the importance of incorporating exercise into comprehensive care strategies for T2D, pointing towards future research to refine and personalize exercise recommendations for individuals with T2D.

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INTRODUCTION

Diabetes incidence is increasing every year, and the reason is improved living standards, altered lifestyles, and changes in the methods used for food processing. Diabetes has consequently emerged as a global health crisis, contributing enormously to the economic burden, mortality, and disability worldwide[1]. Type 2 diabetes (T2D) accounts for 90%-95% of all cases of diabetes[2], and the number of people with T2D is expected to increase to 556 million by the year 2030[3]. Unfortunately, T2D is incurable and might present with various complications, such as cardiovascular diseases, stroke, kidney failure, and other critical conditions. Moreover, T2D ranks among the diseases with the highest mortality rate worldwide. Patients with T2D have to consume medication for their entire lives, and treatment costs are huge, placing an immense economic burden on the families of these patients while leading to a serious decline in the quality of life of the patients. Therefore, it is imperative to search for effective interventions for this metabolic disease. The objectives of the treatment for T2D should be to facilitate an individualized treatment plan, achieve and maintain optimal blood glucose and metabolism, lipid profile, and blood pressure level, and prevent or delay the development of any chronic complications[4].

In 1935, Joslin, a famous scholar who worked on diabetes, proposed that "physical activity should be regarded as a treatment tool for diabetes". However, the research exploring exercise therapy for T2D was scarce initially. In 1969, the term "exercise prescription" was officially adopted by the World Health Organization, following which the topic of the therapeutic effects of exercise on T2D began attracting considerable attention. Exercise is currently recommended as an important non-pharmacological therapeutic strategy for the management of T2D by certain major national and international guidelines, and is, therefore, considered critical to managing the cases of T2D and achieving and maintaining the desired therapeutic goals and improving the quality of life of the affected patients[5-9]. According to the statement of the American College of Sports Medicine, various kinds of physical activity, inclusive of although not limited to planned exercise, could greatly enhance the health and glycemic management of individuals of all ages with T2D, such as flexibility and balance exercise in adults[5]. Research has demonstrated that different types of exercise allow for intervening in T2D and could even reduce the incidence of diabetic complications *via* different mechanisms. Glucose metabolism, immune inflammation, endothelial function, intestinal flora, and epigenetics have been reported to play significant roles in the beneficial effect of exercise on T2D.

Among the various strategies adopted to combat T2D, exercise has been recognized as one of the most powerful approaches. However, the mechanism through which exercise contributes to diabetes management and prevention remains to be elucidated. In this context, the present review explored the latest findings of the research exploring the mechanism underlying the effect of exercise against diabetes to offer insights that could revolutionize the therapeutic approach adopted to overcome this chronic metabolic condition.

EFFECT OF EXERCISE ON T2D AND THE ASSOCIATED COMPLICATIONS

Studies have demonstrated that exercise effectively prevents the development of T2D and its associated complications by improving insulin resistance, lipid metabolism, and inflammatory reaction[10,11]. In the context of the complications associated with T2D, exercise reportedly improves cardiovascular complications by enhancing the expression of extracellular superoxide dismutase (EcSOD) in skeletal muscles to attenuate oxidative stress, aberrant cell signaling, and inflammation[12]. In addition, progressive resistance training reportedly improved muscle strength in knee extensors and flexors and the motor function of individuals with T2D polyneuropathy[13]. The animal experiments conducted to explore diabetes-induced kidney injury in T2D revealed that treadmill exercise training significantly suppressed the levels of albuminuria, tubulointerstitial fibrosis, inflammation, and oxidative stress in the kidneys of Wistar fatty rats[14].

Multiple exercise training modalities, such as aerobic exercise, resistance exercise, combined exercise, and flexibility training, are recommended by the American Diabetes Association, American College of Sports Medicine, European Society of Cardiology, Belgian Physical Therapy Association, and Exercise and Sports Science Australia[15] (Figure 1).

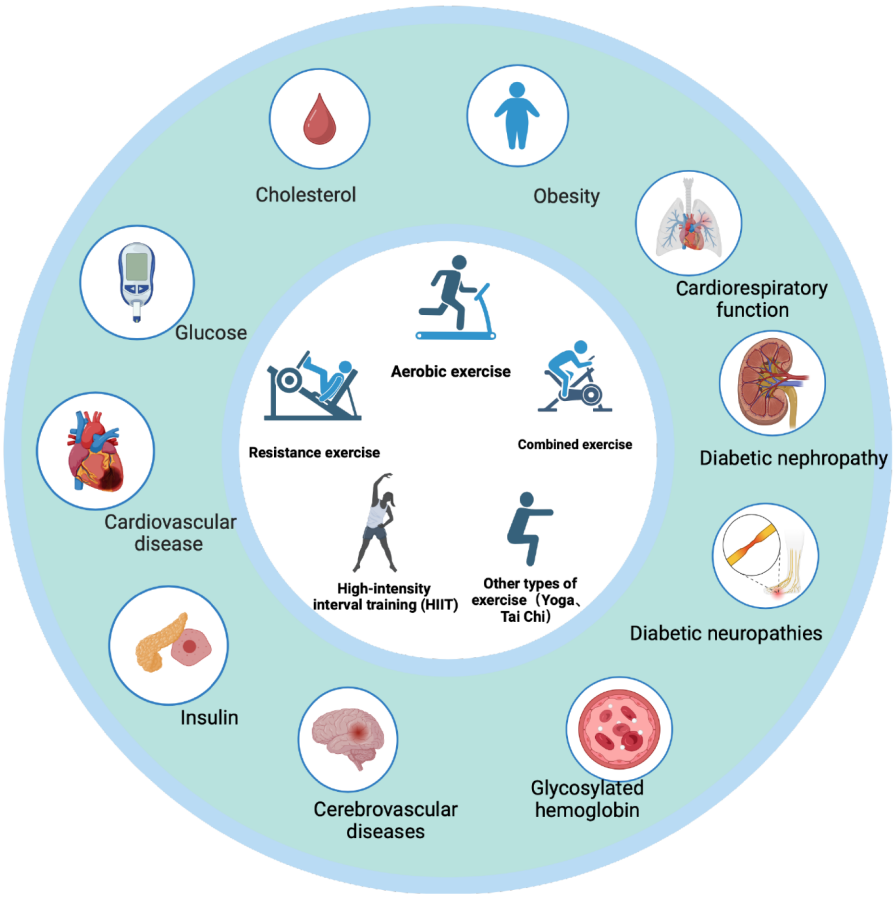

Figure 1 Effects of different types of exercise on type 2 diabetes and the associated complications. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[41].

Aerobic exercise

Aerobic exercise training improves insulin sensitivity in adult T2D patients, while paralleling improved mitochondrial function[16]. An even-day training involving vigorous exercise reportedly improved glycemia in T2D, increased peripheral insulin sensitivity and responsiveness, and inhibited the production of hepatic glucose[17]. Aerobic exercise also improved the control of glycated hemoglobin (HbA1c) levels and increased cardiorespiratory fitness[6].

Resistance exercise

Resistance exercise training reportedly improved strength, bone mineral density, blood pressure, blood lipids, skeletal muscle mass, and insulin sensitivity in adult patients with T2D[5]. According to the guidelines of the American College of Sports Medicine and the American Diabetes Association, resistance exercise training provides optimal benefits for reducing the risk of cardiovascular diseases and minimizing injuries[8]. It has been demonstrated that resistance training exercises improve the control of blood glucose and HbA1c levels[18].

Combined exercise training

A combined aerobic and resistance exercise intervention might be superior to the implementation of either of these modalities separately and is effective in improving the levels of inflammatory, metabolic, and lipid markers in middle-aged and older adults with T2D[19]. The combined practice of aerobic and resistance exercises reportedly led to a greater reduction in the HbA1c levels than that achieved using any of the training modalities alone in adults with T2D[5].

High-intensity interval training

High-intensity interval training (HIIT) is a regimen comprising aerobic training conducted during the 65%-90% VO_2 peak or 75%-95% heart rate peak (HR peak) for a duration of 10 seconds to 4 minutes, followed by 12 seconds to 5 minutes of active or passive recovery.

As a potentially time-efficient modality, HIIT elicits significant physiological and metabolic adaptations. In adults with T2D, one session of HIIT (10 seconds × 60 seconds cycling at approximately 90% HRmax) reduces postprandial hyperglycemia while improving the cardiorespiratory fitness levels and reducing the HbA1c levels and the body mass index (BMI). HIIT also reduces the risk factors for developing cardiovascular diseases, enhances the diastolic function, increases the left ventricular wall mass, enhances the end-diastolic blood volume due to increased stroke volume and left ventricular ejection fraction, and improves the endothelial function[5,20].

Other types of exercise training

Yoga could lead to significant improvements in several indices significant for the management of T2D, including glycemic control, lipid levels, and BMI. A limited set of data suggests that yoga might also lower oxidative stress and blood pressure, enhance pulmonary and autonomic function, mood, sleep, and quality of life, and reduce the consumption of medication in adults with T2D[21]. Tai Chi, on the other hand, could improve glycemic management, balance, and neuropathic symptoms, in addition to enhancing certain dimensions of the quality of life[22].

MECHANISM UNDERLYING THE EFFECT OF EXERCISE AGAINST T2D

Mechanisms revealed through metabolomics

Glucose metabolism: T2D is a chronic metabolic disease characterized by the dysregulation of systemic glucose homeostasis. While the precise etiology of T2D remains to be comprehensively understood, studies have implicated impairments in key glucoregulatory functions in the pathogenesis of this disease. Exercise training, including both aerobic and resistance training, could ameliorate the hyperglycemia associated with T2D by stimulating alterations in skeletal muscle glucose transport and glucose metabolism[23]. Multiple studies have demonstrated that exercise training stimulates alterations in skeletal muscle glucose transport and glucose metabolism by improving the glycolytic capacity of skeletal muscles, decreasing the activity of the hexosamine pathway in skeletal muscles, increasing the glycogen content in skeletal muscles, and stimulating glucose flux *via* the pentose phosphate pathway in skeletal muscles. Owing to the duration of the exercise program, the exercise intensity, and the number of muscle groups stimulated, aerobic exercise may often lead to a pronounced effect on glucose transport and glucose metabolism compared to resistance exercise[24,25] (Figure 2).

Insulin sensitivity and insulin resistance: Insulin was one of the greatest scientific discoveries of the 20th century. Insulin plays a major role in the regulation of glucose in the body and also in the treatment of diabetes. The dominant control of glucose metabolism by insulin occurs under the regulation of complex and highly regulated hormonal and signaling cascades that may exert different and unique effects on skeletal muscles. As the primary tissue involved in insulin-stimulated glucose metabolism, skeletal muscles are a key driver of systemic glycemic control. Skeletal muscles also respond in a unique manner to muscle contraction or exercise with increased sensitivity to the subsequent insulin stimulation. Exercise training sensitizes the skeletal muscles to exhibit a glucose uptake response after insulin stimulation and might activate 5′ adenosine monophosphate-activated protein kinase (AMPK) in the muscles and promote enhanced translocation of insulin-stimulated glucose transporter 4 (GLUT4)[26]. Exercise training of muscle attenuates the subsequent insulin effects in the muscle, including enhanced expressions of muscle GLUT4 and hexokinase and increased mitochondrial capacity, capillarization, and insulin-dependent muscle blood flow[27].

Immune inflammation: Low-grade chronic inflammation *in vivo* is considered one of the pathogeneses of T2D, and pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 reportedly activate intracellular signaling molecules, which then increase the expressions of inflammatory mediators and impair insulin activity through the nuclear translocation of various nuclear factors[28]. A single strenuous exercise stimulates the local muscle tissue to release inflammatory factors such as TNF-α and IL-6 although without releasing these factors into the bloodstream, such that a single strenuous exercise does not exert much effect on the level of systemic pro-inflammatory factors. Long-term regular exercise, however, reduces the basal levels of the corresponding inflammatory factors and causes the body to produce physiological adaptation, such that the levels of inflammatory markers in the entire body are lowered, which then improves the function of pancreatic islets[19].

Lipid metabolism: Cell dysfunction caused by excessive intracellular lipid and ectopic accumulation which is referred to as lipotoxicity, and this phenomenon may subsequently inhibit the insulin signaling pathways, reduce insulin sensitivity, and impact the progression of T2D to a certain degree. It is currently believed that intramuscular lipids do not inherently exhibit lipotoxicity, and rather their metabolic intermediates exhibit lipotoxicity. Intramuscular fat (IMTG) dynamics are disrupted in patients with T2D and its precursor phase, causing the lipophilic intermediates such as diacylglycerol and ceramide to accumulate, and these intermediates then interfere with insulin production. Exercise accelerates the oxidation and conversion of IMTG, and although it increases the levels of intramuscular lipids as well, the reduced levels of lipid intermediates improve insulin function to a certain extent[29,30]. At the same time, patients with T2D have a higher unsaturated intramyocellular fat. Clinical studies have found that patients with T2D can increase contributions of the saturated intramyocellular fatty acid pool through endurance training, adapt to the lipid storage in muscle cells and improve insulin resistance[31].

Endothelial function: Endothelial cells maintain vascular homeostasis, and any imbalance in their physiological function leads to vasoconstriction, possible thrombosis, inflammation, *etc.*, which are the physiological and pathological signs of T2D and are considered important factors for vascular complications in patients with diabetes. Exercise, particularly aerobic exercise and a combination of aerobic and resistance exercises, enhance the vasodilation function[32]. The main mechanism through which exercise produces such changes is as follows: First, exercise increases the intravascular blood flow, enhances the endothelial cell shear force, and increases Nitrogen Oxide (NO) synthesis and bioavailability; next, exercise reduces factors that initiate endothelial dysfunction, such as oxidative stress and reduced expression of pro-inflammatory molecules; finally, exercise restores the function of endothelial progenitor cells, thereby promoting endothelial repair and angiogenesis. Since patients with T2D exhibit a continuous high glucose state in their bodies along with

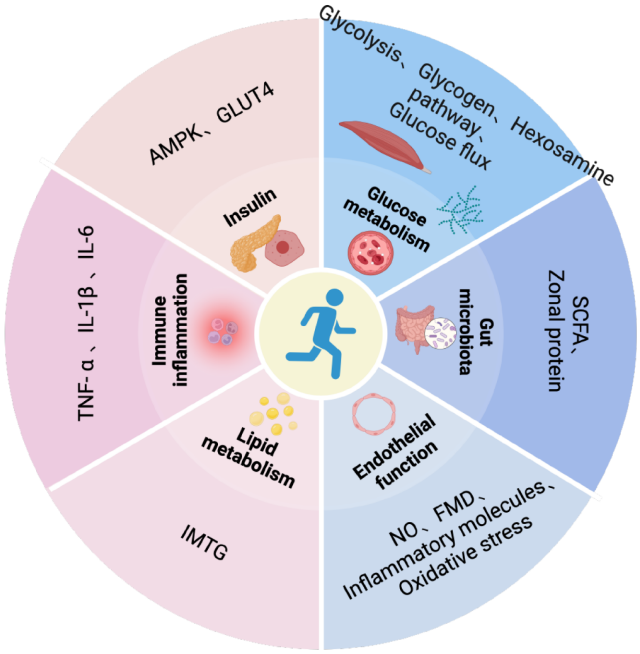

Figure 2 Effects of exercise against type 2 diabetes through reduced insulin resistance, improved insulin sensitivity, increased glucose transport and metabolism, reduced inflammatory response, and regulated lipid metabolism. AMPK: Activated protein kinase; IMTG: Intramuscular fat; FMD: Flow-mediated dilation; SCFA: Short-chain fatty acid; GLUT: Glucose transporter; TNF-α: Tumour necrosis factor alpha; IL: Interleukin. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[41].

the accumulation of advanced glycosylation end products and reactive oxygen species in the circulation, the bioavailability of NO after exercise is lower than that observed in non-diabetic patients. Moreover, the capacity of mobilizing endothelial progenitor cells is weaker in patients with T2D compared to non-diabetic patients. These two factors lead to a lower improvement in flow-mediated dilation (FMD) after exercise in patients with T2D compared to non-diabetic patients. Nonetheless, the FMD of patients with T2D is improved significantly after exercise[33,34].

Gut microbiota composition and the intestinal barrier function: Currently, no definite conclusion has been reached on whether alterations in the intestinal microorganisms in patients with T2D are the cause or the consequence of diabetes. However, it is affirmative that changes in the gut microbiota play an important role in the progression of T2D. The diversity of gut bacteria is decreased in patients with T2D, mainly due to a decrease in the abundance of short-chain fatty acid (SCFA)-producing bacteria. In addition, increased permeability facilitates the entry of inflammatory factors present in the intestine into systemic circulation[35]. The interaction between SCFAs and G protein-coupled receptors increases the secretion of GLP-1, thereby regulating blood glucose levels. The mechanism through which exercise training induces changes in gut microbiota and the intestinal barrier function in patients with T2D remains to be understood, although the reasons for improvement in the internal environment of patients with T2D could include the following: On one hand, exercise training increases the abundance of SCFA-producing bacteria in the intestine, which increases the content of SCFA in the intestine and the blood, thereby partially improving insulin resistance; on the other hand, intestinal zonal protein disrupts the intestinal barrier and increases intestinal permeability, while exercise intervention reduces the concentration of zonal proteins[36,37].

Mechanisms revealed through transcriptomics

Epigenetic mechanisms, including DNA methylation, histone modifications, and RNA-mediated processes, are known to control gene activity and organism development. Disruption of the epigenetic balance could, therefore, lead to various pathologies and contribute to the development of diseases such as T2D (Figure 3). The differential gene expression analysis in the human islets of T2D revealed increased DNA methylation and decreased expressions of INS, PDX1, PPARGC1A, and GLP1R, which are associated with impaired insulin secretion. Meanwhile, high glucose and HbA1c levels could directly increase DNA methylation in these genes. Exercise is thought to partially regulate gene expression and phenotypic outcomes in epigenetics. It has been suggested that alterations in the DNA methylation of genes involved in the AMPK, insulin, and calcium signaling pathways in skeletal muscles after exercise, and these genes include MEF2A, RUNX1, NDUFC2, and THADA, which are reported to be important in T2D and muscles[38].

In addition to methylation, upregulation of the genes involved in insulin function and glucose metabolism, such as fatty acid synthase (FASN), was noted in the skeletal muscles of T2D mice, while the expressions of *LPIN1*, *TBC1D1*, *HK2*, *HMOX1*, *SORBS1*, *PPARGC1A*, and other genes were observed to be downregulated. After exercise intervention, most of the patients with T2D benefited from exercise to a certain extent[39]. The benefits manifested mainly as decreased levels of glycosylated hemoglobin, body fat percentage, and BMI. After exercise, FASN levels decreased in skeletal muscles,

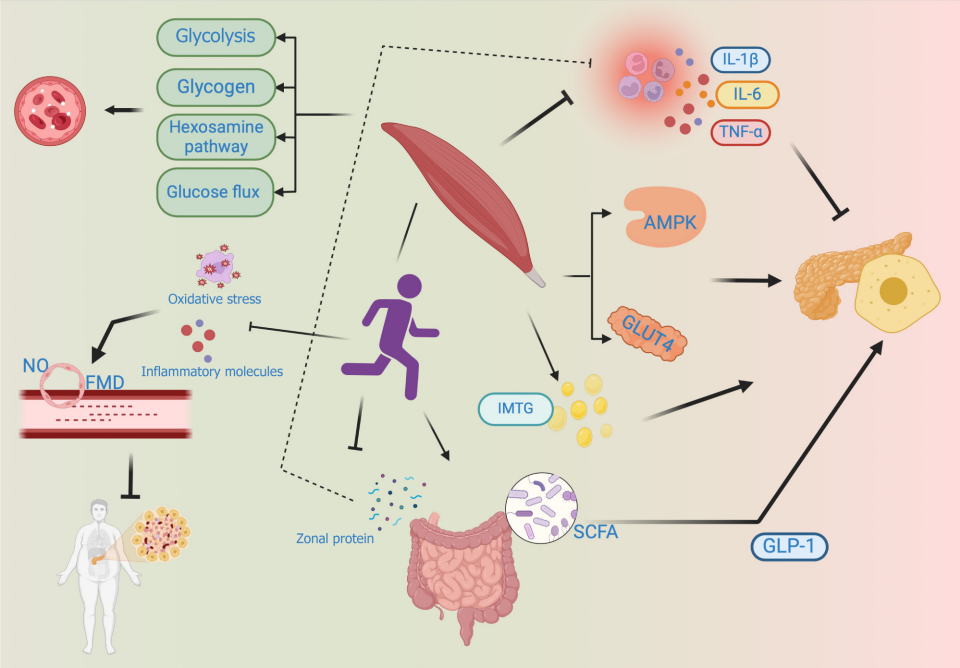

Figure 3 The molecular mechanisms underlying the effect of exercise against type 2 diabetes. AMPK: Activated protein kinase; IMTG: Intramuscular fat; FMD: Flow-mediated dilation; SCFA: Short-chain fatty acid; GLUT: Glucose transporter; TNF-α: Tumour necrosis factor alpha; IL: Interleukin. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[41].

while the levels of LPIN1, TBC1D1, HK2, HMOX1, SORBS1, and PPARGC1A increased. However, certain patients presented no significant decrease in glycosylated hemoglobin and body fat percentage after exercise training. In these patients, the mRNA expressions of PPARα and ELOVL1, which are involved in lipid metabolism, and those of CHKB, CISD2, and FOXO1, which are involved in mitochondrial function, were lower compared to the corresponding levels in responsive patients[40].

CONCLUSION

The understanding of the multifaceted mechanisms through which exercise combats diabetes and its complications is essential for developing effective treatment strategies tailored to individual requirements, emphasizing lifestyle modifications, in addition to medication, as pillars of diabetic care. Numerous studies have demonstrated that exercise could prevent and treat T2D by reducing insulin resistance, improving insulin sensitivity, increasing glucose transport and metabolism, reducing the inflammatory response, and regulating lipid metabolism, among other mechanisms. Exercise might exhibit positive effects on T2D and the associated complications through epigenetic changes as well, although the specific mechanisms underlying such effects are yet to be entirely understood. Significant difficulties remain in issuing personalized exercise prescriptions for different T2D patients in clinical practice. Therefore, future research could include large-scale clinical trials conducted with T2D patients to provide further accurate and efficient guidance for the treatment of these patients.

The clinical evidence of the benefits of physical exercise as a treatment measure for patients with T2D is ample, well-recognized, and widely accepted, and, therefore, deserves to be incorporated into clinical treatment plans. However, several challenges are encountered when the exercise recommendations have to be implemented. The diverse set of exercise modalities available and the inconsistencies in the exercise prescription parameters render it difficult to perform a precise analysis of the dose-response relationship between physical activity and health outcomes. The lack of high-quality evidence regarding the dose-response relationship renders it challenging to recommend measurable and achievable exercise targets in physical activity guidelines. Therefore, exercise prescriptions have to be personalized for individuals according to their habits, preferences, motivations, and tolerance levels, rather than providing generic prescriptions, describing exercise duration, intensity, and frequency based on the clinical testing. Moreover, while exercise has been proven to manage T2D by reducing insulin resistance, improving insulin sensitivity, increasing glucose transport and metabolism, reducing the inflammatory response, and regulating lipid metabolism, it remains unclear whether exercise exerts sustained regulatory effects. These limitations highlight the importance of future research, which could overcome these obstacles by further investigating and elucidating the molecular biology-based mechanisms underlying the effects of exercise against T2D and further comprehensively evaluating the expected type and level-response relationship between exercise and T2D by using more standardized exercise prescription parameters, to realize the full clinical therapeutic effects of exercise. In addition, theoretical demonstration of the effects of exercise therapy against T2D requires further formal evaluation through prospective epidemiological studies.

FOOTNOTES

Author contributions: Peng CJ, Chen S, and Yan SY conducted the original search and wrote the first draft of the paper; Zhao JN and Luo ZW screened the selected articles and contributed to subsequent drafts of the manuscript; Luo ZW, Qian Y, and Zhao GL designed the outline of the manuscript; Qian Y and Chen S generated the original idea of this study and provided suggestions. Luo ZW and Zhao GL, as co-corresponding authors, contributed equally to this article (designed the study), while Peng CJ and Chen S were the co-first authors.

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