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Health-Boosting Effects of Aerobic Exercise Training and Berberine on Diabetes: A Brief Overview

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Abstract

Type 2 diabetes is one of the most important metabolic disorders that affect lifestyle. Accordingly, studies have shown that lifestyle changes, especially increasing daily physical activity, can prevent diabetes and help people with the disease through various mechanisms. On the other hand, the use of medicinal plants due to having various phytochemical compounds, each of which has healing properties, can be considered a helpful method in preventing and treating diabetes complications. One of the phytochemical compounds used as an effective substance in the treatment of diabetes is an alkaloid called Berberine. Berberine has been used in traditional medicine to lower blood glucose, and new studies in both in vivo and in vitro conditions have confirmed the diabetic effect of Berberine. Receiving increased energy metabolism, increased glucose and fatty acid uptake by peripheral tissues, improving lipid profile, reducing inflammatory mediators, increasing antioxidant capacity are common mechanisms that aerobic exercise and Berberine exert their beneficial effects in diabetes. In the present study, the effect of aerobic exercise, Berberine, and its combination on diabetes markers have been investigated considering the beneficial effects of aerobic exercise and Berberine in diabetes.

Keywords: Aerobic Exercise, Berberine, Type 2 Diabetes

1. Context

Proven reduction of daily physical activity is one of the most important causes of chronic diseases (1, 2). Physical activity is one of the most important factors regulating homeostasis, and reducing it can disturb the body's internal balance through various mechanisms and accelerate the disease. The importance of physical activity in maintaining and developing health is that the World Health Organization and the American College of Sports Medicine have published dedicated guidelines for its implementation in all age groups (3, 4).

Lee et al. (2012) showed that 9% of premature deaths result from insufficient daily physical activity. On the other hand, cardiovascular disease, type 2 diabetes, and breast and colon cancer are statistically higher in inactive people (5). In their review study, Pederson and Saltin (2015) stated that physical activity as a therapeutic measure has a significant effect in the treatment of 26 chronic diseases (6). In this regard, Barker and Eickmeyer (2020) pointed to physical activity as a helpful treatment for chronic diseases (7). Researchers believe that if physical activity as a treatment method can prevent and treat diseases, then as a drug, the appropriate dose should be selected and used based on each person's level of physical fitness (8).

However, one crucial point must be considered. Most of the diseases that physical activity can have a therapeutic effect on metabolic or related diseases, the leading cause of inactivity. For example, diseases that have no origin related to daily physical activity cannot be expected to be cured by physical activity. Although physical activity in all diseases can improve the person's general health and create more appropriate conditions for the person, physical activity in these diseases does not cure the disease. For example, physical activity in type 2 diabetes, fatty liver, and dyslipidemia has a therapeutic effect, but it cannot cure MS, AIDS, and autoimmune diseases. Therefore, as Stephanie and Galanti (2017) introduced physical activity as a treatment and suggested the appropriate dose for each person to be influential (8), he also pointed out that this drug may have a thera-

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peutic effect on the disease. Do not have. This approach can lead to a better understanding of the role and effectiveness of physical activity as a health-promoting measure.

On the other hand, in recent years, attention to drugs of natural origin, especially medicinal plants, in maintaining and developing health has increased significantly. In many countries, such as Iran, China, and India, where the diversity of plant growth is abundant, the use of medicinal plants in the treatment of diseases is widespread in them and both at the level of people and the level of academic studies, special attention is paid to the use of these plants in the follow-up and treatment of diseases, especially chronic diseases. Medicinal plants have therapeutic effects on many diseases due to their abundant phytochemical compounds. Generally, phytochemicals are divided into six main categories based on their structure and chemical properties, including carbohydrates, lipids, phenolics, terpenoids and alkaloids, and other nitrogen-containing compounds (9). Studies show that each plant has healing properties due to the content of phytochemicals in it. These properties include anti-tumor and anticancer effects (10, 11), cardiovascular protection (12), inhibition of dyslipidemia (13), hypoglycemia (14), antioxidants (15), anti-inflammatory (16), and other health-enhancing benefits. However, it should also be noted that medicinal plants, contrary to popular belief, are chemical compounds that can cause poisoning and endanger users' health. Therefore, the use of medicinal plants should be done with caution and should be accurately prescribed by experts and based on the person's characteristics.

In recent years, much attention has been paid to the health benefits of Berberine alone and in combination with physical activity. Berberine is an alkaloid compound found in the roots, rhizomes, stems and bark of *B. vulgaris* and many other plants such as *Hydrastis canadensis*, *Berberis aristata*, *Coptis chinensis*, *Coptis japonica*, *Phellondendron amurense* and *Phellondendron chinense* Schneid (17). There is much evidence about the therapeutic effects of this phytochemical compound, which doubles its importance in treating diseases (18). Therefore, this study discusses the anti-diabetic, neurogenic, antioxidant, and anti-inflammatory effects of aerobic physical activity and Berberine as a phytochemical substance in the form of a brief review.

2. The Effect of Aerobic Exercise on Type 2 Diabetes

Aerobic exercise is one of the most common exercise programs for preventing and treating type 2 diabetes. It has been reported that even one week of aerobic exercise can improve insulin sensitivity in people with type 2 diabetes (19). Nevertheless, the intensity of activity is a determining factor for the effectiveness of exercise. Medium to vigorous aerobic exercise has the most excellent effect on insulin sensitivity (20); however, physical exercises can affect glycemic index according to energy consumption. Interval training (21) and a combination of aerobic and resistance training in obese and overweight people can be reported to have positive effects on insulin resistance (22). However, low-intensity exercise also improves sensitivity in people with type 2 diabetes (23).

Regarding the effect of physical exercise on diabetes, researchers believe that any type of muscle contraction can affect insulin resistance and peripheral glucose uptake. Even inactive contractions, such as whole-body vibration, can reduce glycosylated hemoglobin and resistance in diabetics (24). Researchers have shown that regular exercise causes various changes in gene levels and the expression of proteins involved in blood glucose uptake and oxidation in skeletal muscle. Some of these proteins are in the insulin signaling pathway in skeletal muscle, referred to as PI3K, AKT, and GLUT-4 (25). The result of these changes is a decrease in blood glucose and the resulting disorders in other tissues.

On the other hand, aerobic exercise affects glucose uptake and oxidation pathways, increases fatty acid oxidation in the liver and skeletal muscle (26, 27), and improves diabetes-induced dyslipidemia (26). Since high FFA, LDL, TG, and cholesterol along with low HDL is one of the causes of atherosclerosis and non-alcoholic fatty liver in diabetic patients, increased fatty acid oxidation and improved dyslipidemia in aerobic exercise is one of the reasons for reducing the risk of heart attack, and fatty liver development is non-alcoholic.

A well-established health threat in diabetes is the development of systemic inflammation (27, 28). In diabetes, the production and release of inflammatory mediators are significantly increased and cause many physical problems (29). Regular aerobic exercise has been reported to reduce the production of proinflammatory cytokines, especially TNF-alpha and IL-6, and to reduce chronic inflammation due to type 2 diabetes (30-32). Numerous mechanisms to justify the anti-inflammatory effects of exercise. Aerobics in diabetes has been suggested, the main of which is to reduce white adipose tissue mass and change the secretion of proinflammatory mediators, especially IL-6, adipokines, and TNF-α, as well as reduce the permeability of macrophages in the M1 family and increase the perme-

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ability of macrophages in the M2 family. The tissue is adipose (33, 34).

Obesity and diabetes are associated with the development of oxidative stress (35). Oxidative stress plays a role in the development of obesity-related diseases. Oxidative stress caused by obesity causes pathological disorders such as insulin resistance, cardiovascular complications, sleep disorders, asthma, oncological problems, reproduction, rheumatological problems, and liver failure (36). Aerobic exercise can reduce inflammation in diabetic conditions and reduce oxidative stress, thereby mitigating the detrimental effects of diabetes on health (37-39). A review of the existing literature shows that regular aerobic exercise alters the oxidative homeostasis of cells and tissues by reducing the basal level of oxidative damage and increasing resistance to oxidative stress, and reducing tissue damage caused by free radicals (40-42).

Aerobic exercise leads to positive regulation of antioxidant defense mechanisms in various tissues. The increase in oxidative stress levels during activity seems to be the primary mechanism for strengthening the enzymatic antioxidant defense system. ROS production increases relative to rest time in the low to medium range (41). This increase in tissue damage significantly affects the tissues because it increases the amount of ROS in physiological amounts, and the amount of ROS production in this type of activity is not in pathological amounts. Thus, increasing ROS production due to aerobic exercise can be inducing particular adaptations such as Increased antioxidant/oxidative damage repairing enzyme activity induces increased resistance to oxidative stress and strengthens the enzymatic antioxidant defense system.

On the other hand, overproduction of ROS is usually associated with destructive tissue effects. As mentioned, ROS production increases transiently over time. Nevertheless, studies show that ROS in active people is lower than inactive people under the baseline. Also, in these people, the prevalence of diseases related to oxidative stress is lower than inactive counterparts. Evidence suggests that regular physical activity reduces oxidative damage to the brain, liver, kidney, skeletal muscle, and heart tissue (43, 44).

On the other hand, a strong negative correlation was observed between plasma TBARS levels as an indicator of lipid peroxidation and VO2 max level, which indicates that high physical fitness has a protective role against oxidative stress (45). Overall, the results of studies in diabetic conditions show that in both animal and human studies, regular physical activity reduces oxidative stress, and since many diabetic disorders are caused by oxidative stress, the good effects of physical activity on diabetes can be justified on the basis of reduced production of free radicals (46).

3. The Effect of Berberine on Disorders Caused by Type 2 Diabetes

The therapeutic effects of chloride or berberine sulfate have been well established (45, 47). Like physical activity, Berberine can lower blood glucose and reduce the complications of diabetes through various mechanisms. Evidence suggests that Berberine can positively affect the course of diabetes by affecting cellular signaling pathways (48). The hypoglycemic and hypolipidemic effects of Berberine have led to the introduction of plants rich in this phytochemical as a drug of natural origin for the management of diabetes (49).

Evidence suggests that Berberine improves the metabolic status of diabetes by affecting a range of metabolic processes, including reducing insulin resistance, activating AMPK, modulating intestinal microbiota, reducing gluconeogenesis in the liver, and increasing glycolysis in peripheral tissues (50). Usually, in diabetes, hepatic glucose production is one of the primary sources of high blood sugar. In diabetes, the process of gluconeogenesis in the liver is uncontrollably activated and disrupts blood glucose regulation. There is evidence that Berberine can inhibit gluconeogenesis as one of the main mechanisms of liver glucose production by regulating the function of beta cells. Berberine can also increase glucose uptake by increasing glycolysis (51). Berberine can also reduce abnormal levels of plasma hormones such as glucagon-like peptides (1 and 2), insulin-stimulating polypeptides, and pancreatic polypeptides (52).

Berberine can stimulate L cell proliferation by increasing glucagon and prohormone invertase synthesis and GLP-1 secretion in diabetic rats (53). Accordingly, Berberine can regulate glucose by stimulating the secretion of GLP-1 in the intestine. Accordingly, according to the proposed mechanisms, glucose reduction due to berberine intake can be justified.

The hypolipidemic effects of Berberine have been confirmed in several clinical trials with subjects with hyperlipidemia, type 2 diabetes, and hepatic impairment. Summarizing the results of these studies shows a 25% decrease in LDL-C and TG (54-56). Berberine is so effective in lowering serum lipids that Kong et al. have identified it as a new serum lipid-lowering drug (54).

On the other hand, Berberine can reduce the production and secretion of a set of cytokines/proinflammatory

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mediators (IL-6, IL-1β, and TNF-α) in both serum and tissue surface. Berberine appears to reduce the inflammatory process by inhibiting the NF-κB signaling pathway and activating the SIRT1 pathway (57-59).

Berberine has been studied as a powerful antioxidant in both healthy and diabetic individuals. The inhibitory effect of Berberine on oxidative stress has been investigated both in vitro conditions of cells cultured in high glucose medium (40) and in vivo conditions. In both conditions, the diabetes model is induced, and the antioxidant effect of Berberine is shown (60-63).

4. Simultaneous Effect of Aerobic Exercise and Berberine on Diabetes Indices

In the past few years, some researchers have conducted studies to determine the simultaneous effect of these two interventions on diabetes markers, considering the positive effects of aerobic exercise as well as the health-promoting effects of Berberine. The rationale for these studies stems from the fact that both aerobic exercise and Berberine reduce the adverse effects of diabetes through similar mechanisms and may be more effective than inducing exercise alone and Berberine alone at the same time. After six aerobic exercises with berberine chloride, decreased renal tissue apoptosis has been reported in streptozotocin-induced diabetic rats (64). A similar finding was observed regarding the simultaneous effect of aerobic exercise and Berberine on the inhibitory apoptosis of induction of diabetes in cardiac tissue. In this study, proapoptotic indices increased due to the induction of diabetes. Both aerobic and Berberine training decreased BAX gene expression and increased BCL-2 expression. The rate of change was more significant in the group receiving concomitant Berberine and aerobic exercise (65). Decreased fasting glucose along with a significant decrease in TNF-α and IL-6 circulating concentrations in streptozotocin-induced diabetic rats after receiving berberine chloride and aerobic exercise has been reported by Ramezani et al. (2019). In line with previous studies, aerobic exercise and Berberine chloride enhanced each other's effects on lowering fasting glucose and inflammatory mediators. Another finding of this study showed a dose-dependent effect of Berberine (66). The simultaneous effect of aerobic exercise and berberine chloride in studies with human subjects has also been investigated.

Ghorashi et al. (2019) studied the effect of circular exercise and Berberine on lipid profile in overweight, obese men. In the present study, subjects performed circular exercises with Berberine for eight weeks and three sessions per week. Both exercises, Berberine, and the combination of exercise and Berberine significantly reduced total cholesterol, triglycerides, and LDL. The rate of change in the combination of exercise and berberine group was more than in other groups (67).

5. Conclusions

Decreased physical activity and poor nutrition patterns are the leading causes of chronic diseases. Aerobic exercise is one of the essential non-pharmacological strategies to control metabolic diseases, especially diabetes. Regular aerobic exercise reduces the accumulation of glucose and fatty acids by increasing the uptake of glucose and fatty acids by peripheral tissues, especially skeletal muscle, and their oxidation. On the other hand, reducing inflammatory mediators and oxidative stress is another beneficial effect of aerobic exercise in diabetes. On the other hand, herbs with mechanisms similar to physical activity can reduce the destructive effects of diabetes. Decreased intestinal glucose uptake, reduction of inflammation, and oxidative stress are beneficial effects of Berberine in diabetes, which have very beneficial effects in diabetes management. Since aerobic exercise and berberine chloride reduce the adverse effects of diabetes on health by similar mechanisms, it seems theoretically logical that these two interventions enhance their positive effects on diabetes. Studies have shown that this is the case and the combination of aerobic exercise and berberine chloride with enhancing the effects of each other is an excellent way to control the complications of diabetes.

Footnotes

Authors' Contribution: Mohammad Ali Azarbayjani planned and coordinated the study. Maghsoud Peeri, Parvin Farzanegi, and Seyed Ali Hosseini analyzed the data and prepared the manuscript. Hossein Heidari performed the sample collection, identified and enrolled all participants, and collected all the clinical data. All authors critically reviewed the manuscript and approved the submitted version.

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