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The Egyptian Journal of Internal Medicine (2023) 35:58
https://doi.org/10.1186/s43162-023-00247-8

The Egyptian Journal of Internal Medicine

REVIEW

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A step in the right direction: exploring the effects of aerobic exercise on HbA1c reduction

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Abstract

Diabetes has become a serious health concern for the global population. An estimated 643 million people will have type 2 diabetes mellitus by the year 2030. A sedentary lifestyle is one of the important risk factors along with obesity, hypertension, and diet. Exercise improves blood glucose levels and reduces glycosylated hemoglobin (HbA1c). Physical aerobic exercise utilizes energy stored in the form of ATP and helps to burn stored fat. The process of muscular contraction during a physical workout controls the mechanisms responsible for improving blood glucose levels. These involve complex pathways that ultimately increase the uptake of blood glucose, improve insulin sensitivity and blood flow, and optimize the functioning of the endocrine pancreas. An overall reduction in HbA1C can be achieved through the interplay of all these pathways.

Keywords Aerobic exercise, HbA1c, Diabetes mellitus, GLUT-4

Introduction

Diabetes is a serious, chronic disorder that affects 422 million people worldwide, and is directly responsible for 1.5 million deaths annually [1]. According to the International Diabetes Federation, an estimated 643 million people will be living with T2DM by 2030 and 783 million by 2045 [2]. Approximately 37.3 million people in the US have diabetes, out of which 28.7 million are diagnosed with the disease [3]. The non-modifiable risk factors for diabetes are family history, race or ethnic background, age, and gestational diabetes. The modifiable factors include obesity, physical inactivity, lipid levels, blood pressure, smoking, alcohol, diet, and stress [4]. The mechanisms involved in the pathophysiology of diabetes mellitus (DM) are a reduction in insulin sensitivity, in addition to the subsequent development of beta cell dysfunction [5]. The average plasma glucose level over the past two to three months can be calculated by the hemoglobin A1c measurement (HbA1c). The objective of diabetes treatment is to provide an individualized treatment plan, that consists of education, glycemic control, lowering cardiovascular risk, and monitoring for microvascular complications, to achieve and maintain optimal blood glucose, lipid, and blood pressure levels that delay chronic complications. It typically involves prescribing lifestyle modifications and/or medication. Some worldwide organizations have advocated for physical activity as a significant non-pharmacological therapy option for the management of T2DM [6]. WHO describes physical activity as bodily movements produced by skeletal

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muscles that require energy expenditure, which includes movements during leisure time, for transport to get to and from places, or as part of a person's work [7]. Exercise is a form of physical activity that entails structured, repetitive, and planned body movement for the purpose of maintaining or enhancing one or more physical fitness components [8]. There are various forms of exercise, like endurance or aerobic exercise, which improve mental health and wellbeing and assist in maintaining a healthy body weight; strengthening or resistance training to build muscle strength; combined aerobic and exercise training; and high-intensity interval exercise [9]. Reduced mortality rates have been linked to enhanced muscular and cardiorespiratory fitness [10].

According to The American College of Sports Medicine (ACSM), Aerobic exercise is any form of physical activity that involves utilizing large muscles, can be performed continually, and adds rhythm to it [11]. The recommendations made for physical activity and exercise by the American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) emphasize frequency, intensity, and modality to positively improve glycemic management [12]. Any form of physical activity (PA) can cause an increase in the absorption of glucose into active skeletal muscles through insulin-independent mechanisms [13]. Reduction in blood glucose levels is closely correlated with the length and intensity of the exercise, as improvements in systemic and potentially hepatic insulin sensitivity can remain for 2–72 h post-activity [14]. Moderate-intensity aerobic exercise includes brisk walking, gardening, dancing, etc. Vigorous-intensity exercise includes swimming, fast walking, jogging, running, cycling, etc. [15]. For maximum benefit on a patient's health, current recommendations on exercise duration are at least 150 min of moderate aerobic activity, 75 min of vigorous aerobic activity, or a combination of the two, each week [16] (Table 1). In individuals with T2DM, short-term aerobic exercise training increases insulin sensitivity in tandem with increased mitochondrial activity [17]. Through enhanced insulin-stimulated glucose uptake and reduction of hepatic glucose production, vigorous aerobic exercise training for a week may improve glycemic control, as can be evaluated by HbA1c, without lowering body weight [18]. Physical activity has been proven to show efficacious benefits in reducing HbA1c levels, but there are only a few studies that implicate the optimal exercise recommendations. The objective of this article is to provide a succinct summary of the latest research on how aerobic exercise affects HbA1c levels and to examine the possibility of using the findings as a treatment strategy (Fig. 1).

Pathophysiology

Aerobic exercises like cycling, running and swimming are dependent on the energy produced by the utilization of adenosine triphosphate (ATP) which is synthesized in the process of oxidative phosphorylation in the mitochondria and results in the production of ATP [19, 20]. Exercise causes activation of the sympathetic system which helps to maintain homeostasis during increased cardiovascular, respiratory, and metabolic demands [20]. The plasma levels of cortisol, epinephrine, norepinephrine, and dopamine increase with exercise and return to basal levels after the cessation of exercise. Insulin sensitivity is improved with long term aerobic exercise and can affect HBA1c levels through the involvement of various mechanisms [20].

Role of GLUT-4

GLUT-4 belongs to the family of glucose transporters which are primarily present in the skeletal muscles, adipose tissue, and myocardial tissue [21]. GLUT-4 is mainly stored within the cells until stimulated to move to the plasma membrane [21]. Once embedded into the plasma membrane, they facilitate the uptake of glucose into the cells. The stimulus causing GLUT-4 translocation to the plasma membrane could be insulin mediated or non- insulin mediated [21]. The latter causes GLUT-4 translocation via contraction of skeletal muscles during exercise allowing glucose to move into the cells. The exact mechanism of contraction induced GLUT-4 translocation is complex involving the role of multiple mediators such as AMP-kinases (AMPK), nitric oxide, and calcium [22, 23]. Skeletal muscle contraction activates AMPK which inhibits AS-160 (an inhibitor of GLUT-4 translocation) by phosphorylation. This results in the disinhibition of GLUT-4 resulting in their translocation to the plasma membranes [21, 22]. As more and more

Table 1 Aerobic Exercise

Aerobic exercise	Moderate intensity	Vigorous intensity
Examples of activity	Brisk walking, bicycling slower than 10 miles/hr on level terrain, active forms of yoga, gardening, and dancing (ballroom)	Hiking uphill, running, aerobic dancing, cycling 10 miles/hr or more
HRmax (heart rate maximum)	55- 74%	75–95%
Duration of exercise	Minimum of 150 min/week	Minimum of 75–150 min/week

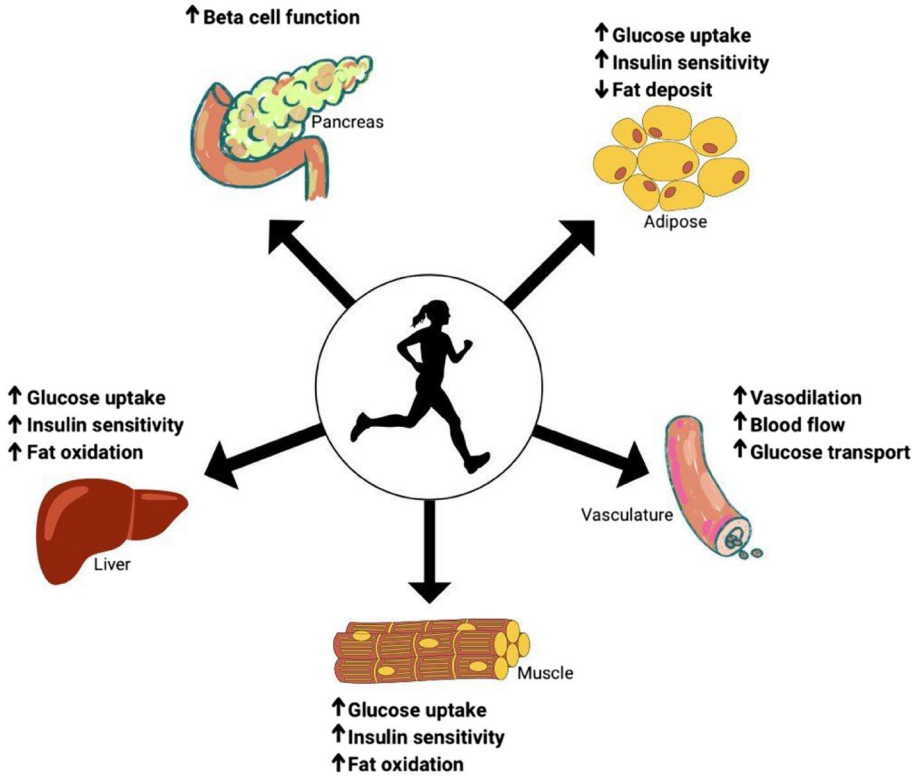

Fig. 1 Physical Activity

GLUT-4 are recruited to the plasma membranes and T-tubules, the glucose uptake capacity of skeletal muscles is enhanced [24].

Improving insulin sensitivity

Insulin resistance is associated with the decreased synthesis of nitric oxide and increased levels of asymmetrical dimethylarginine (an endogenous NO synthase inhibitor) [25]. However, exercise increases the production of nitric oxide by restoring the levels of cGMP and blood nitrite and decreasing circulating levels of asymmetrical dimethylarginine and oxidative stress [25]. This, in turn, results in increased angiogenesis and glucose utilization hence improving insulin sensitivity.

The production of pro-inflammatory cytokines like IL-6 and TNF- alpha causes impairment in insulin signaling. Adipose tissue is involved in the generation and release of these pro-inflammatory mediators. Exercise over a period, causes a reduction in adipose tissue and hence decreases the production of pro-inflammatory cytokines. Exercise also increases the circulating levels of anti-inflammatory cytokines such as IL-4 and IL-10 [25, 26]. Therefore, an overall reduction of inflammation induced by exercise improves insulin signaling and consequently increases insulin sensitivity. Hyperinsulinemia is known to increase the sympathetic nervous (SNS) system by both acting centrally and affecting the baroreceptor reflex [27]. Chronically activated SNS is responsible for sympathetic effects on the cardiovascular system like hypertension and vascular remodeling. Exercise on the other hand improves the baroreceptor reflex and blunts the SNS. This in turn decreases the vascular tone. Angiogenesis due to persistent aerobic exercise along with improved vascular function increases the microcirculation in the muscles and as a result, increases glucose uptake [28].

Increased beta cell mass

Several proteins including signaling molecules and transcription factors are found to increase during exercise. These proteins regulate beta cell proliferation directly or indirectly. For instance, it is found that the levels of pancreatic and duodenal homeobox 1 (PDX1), a transcription factor within the islets of Langerhans, increase with exercise. PDX1 is required for pancreatic development, beta cell proliferation, and insulin gene transcription [29]. Molecules like ERK1/2 and cAMP responsive element binding protein (CREB) are signaling proteins involved in beta cell development, function, and survival. ERK1/2 regulates the activity of transcription factors and

CREB potentiates insulin/insulin-like growth factor 1 (IGF-1) signaling. The levels of both ERK1/2 and CREB appear to increase following physical exercise [30, 31].

Discussion

Diabetes is a serious health condition that affects a large proportion of people worldwide and its prevalence is expected to continue to increase over the next decade [2]. Physical aerobic activity is beneficial in diabetes management and has been associated with a decrease in HbA1c levels in diabetic patients [32]. Both moderate and high intensity aerobic exercises have been shown to improve insulin sensitivity and directly reduce blood glucose levels [33]. The mechanism of this is thought to be related to increased GLUT-4 mediated glucose uptake, increased nitric oxide production, and sympathetic nervous system activation [21]. By understanding the relationship and mechanisms between physical aerobic exercise and HbA1c levels, we will be able to explore the potential of using physical activity as a strategy for reducing HbA1c levels and the non-pharmacologic management of diabetes.

One way in which the effect of aerobic exercise on HbA1c was studied was in juxtaposition with resistance training. A prior meta-analysis of 12 trials in adults with T2DM examined the change in HbA1c following aerobic training compared with resistance training and showed some heterogeneity in the results [34]. One study demonstrated a 0.40% reduction in HbA1c after aerobic exercise and a 0.35% reduction in HbA1c after resistance training [35], and Kadoglou et al. saw a 0.6% and 0.2% reduction after aerobic and resistance training, respectively [36]. Aerobic exercise increases insulin sensitivity and vascular function, which ultimately augments exercise-induced blood glucose uptake by skeletal muscle, a key regulator in glycemic control [37]. Resistance exercise works via a similar mechanism, where targeting increased muscle mass can increase glucose uptake by skeletal muscle and improve glycemic control [38]. Another meta-analysis of 14 trials compared reductions in HbA1c across aerobic and resistance training, as well as concurrent training. The overall result of this meta-analysis suggested that aerobic exercise saw a further decrease in HbA1c when compared to resistance training alone, but ultimately a combination of the two yielded the largest improvement in HbA1c with a change of -0.17% [39]. One study included in the meta-analysis by Yavari et al. in 2012 yielded a 1.33%, 0.55%, and 1.74% statistically significant decrease in HbA1c for aerobic, resistance, and concurrent training, respectively, whereas the control group saw a 0.2% elevation in HbA1c [40]. Other studies did not find a statistically significant difference in the mean changes in HbA1c in resistance training or aerobic training alone, however, they did find that a combination of the two modalities resulted in improved HbA1c levels [41]. This data supports the notion that concurrent training may be the ideal training modality for glucose control compared not only to the control group but also to each training method performed individually [39].

The relationship between high-intensity interval training (HIIT), moderate-intensity continuous training (MICT), and HbA1c reduction was also explored. A meta-analysis of 19 studies compared these variables and found that the HIIT group saw a 0.34% decrease in HbA1c compared to the no exercise control group, while MICT demonstrated a similar but milder improvement in HbA1c when compared to HIIT with a mean difference of 0.07% [42]. The mechanisms by which HIIT and MICT both aid in HbA1c reduction are thought to be related to a combination of improved pancreatic beta cell function and hepatic and peripheral insulin resistance [43]. Like aerobic and resistance training, improved insulin sensitivity augments GLUT 4 receptor expression and thus increases glucose uptake [44]. Despite the increased improvement of HbA1c following HIIT compared to MICT, there appears to be no statistically significant difference between HIIT and MICT's effects on insulin resistance or sensitivity, as evidenced by a previous meta-analysis in 2018 [45]. Overall, these findings suggest a positive relationship between aerobic exercise, resistance training, HIIT, MICT, and concurrent training and HbA1c level reduction, which demonstrates the potential benefit of incorporating these training modalities in the non-pharmacologic management of diabetes. However, the quantification of effectiveness has varied, and thus the long-term implications of these exercise methods among patients with diabetes warrant further exploration.

Conclusion

Various forms of aerobic exercises can be incorporated into a plan involving running, swimming, HIIT, and MICT. There is a substantial need for further research to understand differences among different aerobic exercise models and their effect on HbA1c. However, choosing a particular type of exercise should be personalized based on factors such as type of diabetes, patient's comorbidities, and access to resources in terms of equipment and safe spaces for outdoor exercise. It is also important to consider that people with T2DM can have certain barriers to exercise such as decreased cardiovascular fitness, old age, and obesity that need to be considered and overcome. Overall, existing research shows physical aerobic exercise is an effective tool that improves blood glucose levels through a multitude of biochemical mechanisms. Numerous studies have shown over time,

exercise can effectively reduce an individual's HbA1c. In addition to improving HbA1c, exercise decreases stress and anxiety, which can help reduce the burden of chronic conditions like T2DM. Exercise also helps in lowering the percentage of body fat and the risk of cardiovascular diseases. Hence, exercise should be considered an effective strategy in the non-pharmacological management of T2DM and should be discussed with patients more often in the outpatient treatment setting. Future studies should be aimed at describing and quantifying the specific type of exercise regimens that can be implemented and provided to patients with T2DM, thus strengthening and diversifying treatment strategies for reducing HbA1c.

Abbreviations

T2DM	Type II Diabetes Mellitus
DM	Diabetes Mellitus
HbA1c	Hemoglobin A1c
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
PA	Physical activity
ATP	Adenosine triphosphate
GLUT-4	Glucose transporter 4
AMPK	Adenosine monophosphate-activated protein kinase
AS-160	Akt substrate of 160 kDa
cGMP	Cyclic guanosine monophosphate
SNS	Sympathetic nervous system
PDX1	Pancreatic and duodenal homeobox 1
CREB	CAMP responsive element binding protein
ERK1/2	Extracellular signal-regulated kinase ½
IGF-1	Insulin-like growth factor 1
HIIT	High-intensity interval training
MICT	Moderate-intensity continuous training

Acknowledgements
Not applicable.

Authors' contributions
BS wrote the pathophysiology and abstract, YCK wrote the introduction, HZ and SGK worked on discussion, IM wrote the conclusion, AS edited the manuscript and RJ supervised the research and manuscript preparation All authors have reviewed and agree with the content of this article. None of the article contents are under consideration for publication in any other journal or have been published in any journal. No portion of the text has been copied from other material in the literature (unless in citation).

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 5 July 2023 Accepted: 9 August 2023
Published online: 17 August 2023

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