REVIEW ARTICLE

High-Intensity Interval Training as A Game-Changer in Type 2 Diabetes Mellitus Management: A Narrative Review

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ABSTRACT

Diabetes mellitus (DM) is a chronic health condition that affects millions of people worldwide. Diabetes mellitus is characterized by high blood sugar or glucose levels due to the body's inability to produce or use insulin, a hormone that regulates blood sugar levels. Type 2 diabetes mellitus (Type 2 DM) is the most common form of diabetes, accounting for up to 90% of all cases, and is often linked to lifestyle factors such as poor diet, lack of exercise, and obesity. Physical activity is a highly effective intervention for managing and preventing Type 2 DM. Exercise helps to lower blood sugar levels, improve insulin sensitivity, and promote weight loss. High-intensity interval training (HIIT) is a specific type of exercise that involves short bursts of intense activity followed by periods of rest or low-intensity exercise. HIIT has been found to be particularly effective for patients with Type 2 DM, as it can improve glucose control and cardiovascular health in a relatively short amount of time. This review delves into the role of HIIT in managing Type 2 DM, highlighting its ability to increase insulin sensitivity through processes such as GLUT 4 translocation, mitochondrial activity, and vasodilator function, as well as improving glycaemic control by increasing aerobic capacity and the activity of mitochondria. By synthesizing recent research, we aimed to provide insights in a narrative review of the benefits and mechanisms of HIIT for managing Type 2 DM.

Keywords
exercise, high-intensity interval training, musculoskeletal physiological phenomena, noninsulin-dependent diabetes mellitus, physical conditioning

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition that causes blood sugar levels to rise above normal values. There are two types of DM: type 1 diabetes (DM), which results from damage to pancreatic cells, and Type 2 DM, caused by diminished insulin sensitivity in the peripheral system. Other types of diabetes include monogenic and gestational diabetes.[1] Type 2 DM is a significant global health issue because it can lead to microvascular and macrovascular complications, which can increase morbidity rates, reduce quality of life, and raise mortality rates. Additionally, complications due to DM also escalate the cost of managing the condition, making it a substantial health concern that requires significant financial resources.[2]

Research suggests that DM will has a significant impact on the world's adult population, with an estimated 537 million affected between the ages of 20 and 79 years in 2021. This number is predicted to rise to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045.[3] In Indonesia, the 2018 Riskesdas report found that around 2% of the population aged 15 years and above suffer from DM, an increase from the 2013 report. Type 2 DM accounts for 90-95% of all DM cases, and a leading risk factor is the lack of physical exercise.[4]

The implementation of holistic care programs and spiritual care programs, can be beneficial for diabetic patients, improving their well-being and quality of life.[5] Particularly, individuals diagnosed with Type 2 DM can greatly benefit from engaging in physical activity, as it can lead to improved glycaemic control and insulin levels.[6] However, adhering to recommended exercise routines can be challenging due to limited available time for diabetic persons.[2]

High-intensity interval training (HIIT) is a popular exercise method that involves short bursts of intense activity followed by brief rest periods, performed multiple times.[2,6] Compared to continuous moderate-intensity exercise (MICT), HIIT requires less time and is thus a preferred option by many.[2] Research has suggested that HIIT can enhance glycaemic control (measured by glycated haemoglobin or HbA1C), insulin sensitivity, and cardiorespiratory fitness in individuals with Type 2 DM. This means that HIIT could be a practical alternative for those with Type 2 DM who have limited time for longer exercise regimens. The purpose of this review is to delve into the molecular mechanisms underlying the benefits of HIIT for individuals with Type 2 DM.

METHODOLOGY

This study employs a narrative literature review approach to examine the effects of HIIT on the management of Type 2 DM. Literature searches were conducted using scientific databases such as PubMed and Google Scholar, utilizing keywords including "High-Intensity Interval Training," "HIIT," "Type 2 Diabetes Mellitus," "exercise intervention," and "metabolic control." The articles selected for this review used specific inclusion criteria: they were published within the last 10 years, written in English, and addressed the relationship between HIIT and Type 2 DM, with a particular focus on physiological mechanisms, clinical outcomes, and metabolic benefits. Studies that utilized different methodologies were excluded from consideration. The selection process involved the screening of titles, abstracts, and full texts. Key findings were organized into themes such as glycaemic control and enhanced insulin sensitivity. A thorough critical analysis of all relevant articles was conducted to underscore the potential impact of HIIT as a viable intervention for the management of Type 2 DM.

TYPE 2 DIABETES MELLITUS

Type 2 DM, also referred to as non-insulin-dependent diabetes mellitus (NIDDM), is a condition that impacts the body's physiological processes. It arises from a combination of genetic, metabolic, and environmental factors.[7–9] Of these factors, modifiable risks such as obesity, low physical activity, and unhealthy dietary habits are believed to heighten the possibility of developing type 2 DM. Therefore, taking steps to modify these risks could potentially prevent the onset of type 2 DM.[9]

Type 2 DM stems from an interruption in the feedback loop between insulin action and secretion. This disruption is brought about by malfunctioning pancreatic β cells, which results in inadequate insulin secretion. Consequently, the body fails to regulate glucose levels in the bloodstream effectively. Moreover, this condition is correlated with insulin resistance, which diminishes insulin sensitivity in peripheral tissues like muscle, liver, and adipose tissue.[7,8]

At the onset of Type 2 DM, insulin sensitivity declines, prompting the pancreas to augment insulin production. However, over time, the produced insulin becomes insufficient to regulate glucose levels effectively, resulting in pancreatic β cell dysfunction and insulin resistance.[7] This, in turn, leads to hyperglycaemia, ultimately culminating in the development of Type 2 DM.[9]

HIGH-INTENSITY INTERVAL TRAINING (HIIT)

High-intensity interval training (HIIT) is a form of physical exercise that involves alternating between short bursts of intense exercise and periods of rest or low-intensity exercise. The intensity of the workout is based on factors such as maximal oxygen uptake (VO2max), maximal heart rate (HRmax), maximal run velocity, peak power output (PPO), or ratings of perceived exertion (RPE). High intensity is typically defined as exercising at close to maximum capacity, usually around 80-85% of HRmax. HIIT can take various forms, including running, cycling, rowing, swimming, or full-body workouts.[10]

To incorporate a HIIT workout into a routine, one should begin with a 4–5-minute warm-up at the same level of intensity as the cool-down period. Then, proceed to the main activity, consisting of 4-8 challenging physical exercises performed at a high intensity in a brief timeframe. Finally, cool down for a total of less than 30 minutes. Depending on the length of the workout, HIIT can be classified into three types - high-volume HIIT (HV -HIIT), moderate-volume HIIT (MV-HIIT), and low-volume HIIT (LV-HIIT). HV-HIIT is utilized for HIIT protocols requiring 15 minutes of work, MV-HIIT is used for protocols with 5-15 minutes of work, and LV-HIIT is used for protocols with only 5 minutes of work.[10]

Extensive meta-analysis studies have revealed HIIT produces more positive results compared to Moderate-Intensity Continuous Training (MICT). These benefits encompass enhancements in cardiorespiratory fitness, physical performance, body composition, and lower risk factors for cardiometabolic disease.[11,12] Additionally, scientific evidence suggests that HIIT significantly amplifies insulin sensitivity and glycaemic control in both healthy individuals and those with Type 2 DM, surpassing the effects of MICT.[11]

THE ROLE OF HIIT IN IMPROVING INSULIN SENSITIVITY AMONG TYPE 2 DM PATIENTS

Insulin is a hormone that is naturally produced by the pancreas in response to an increase in glucose levels in the bloodstream after eating. Its main function is to help increase glucose uptake in peripheral tissues such as skeletal muscle, adipose tissue, and the liver while also regulating glucose production in the liver. If there is a significant disruption in insulin activity within the body, it can lead to a decrease in insulin sensitivity.[10] To determine insulin sensitivity, there are several methods available, such as measuring fasting insulin concentration, conducting oral glucose tolerance testing (OGTT), performing hyperinsulinaemic-euglycaemic clamp or hyperglycaemic clamp tests, using the homeostatic model assessment of insulin resistance (HOMA-IR) or HOMA-β, or utilizing the quantitative insulin sensitivity check index (QUICKI).[13]

Multiple research studies have indicated that HIIT can have a positive impact on individuals with Type 2 DM. Compared to MICT or a sedentary lifestyle, HIIT has been shown to increase insulin sensitivity and decrease fasting insulin concentrations. In addition, HIIT has the potential to improve HOMA-IR and HOMA-β% values, especially in individuals with Type 2 DM who also have obesity.[10] For example, a previous study discovered a significant decrease in HOMA-IR values in Type 2 DM patients who engaged in HIIT for eight weeks, as opposed to individuals who did MICT.[14] A systematic review also demonstrated a reduction in HOMA-IR values for Type 2 DM patients who participated in Low-Volume HIIT (LV-HIIT). However, there were no significant differences in fasting insulin concentrations between Type 2 DM patients who performed LV-HIIT and the control group.[15]

Research has found that Type 2 DM patients who engage HIIT experience a boost in insulin sensitivity. This improvement can be attributed to a range of molecular mechanisms that are activated in response to HIIT, such as heightened translocation of glucose transporter 4 (GLUT 4), enhanced mitochondrial activity, and increased vasodilator function and blood flow to the muscles. These discoveries are highly noteworthy and indicate that HIIT could potentially serve as a valuable means of enhancing insulin sensitivity in individuals with Type 2 DM.[10]

Increased Translocation of Glucose Transporter 4 (GLUT 4)

Glucose enters peripheral tissues through two pathways: insulin-dependent and insulin-independent. The insulin-dependent pathway involves insulin binding to its receptor, while the insulin-independent pathway uses AMP-activated protein kinase (AMPK) and calcium/calmodulin-dependent protein kinase (CaMKK). Understanding the insulin-independent pathway helps us appreciate the benefits of physical exercise in controlling glucose balance and preventing diabetes. The uptake of glucose in skeletal muscle heavily depends on the presence of GLUT-4 in the cell membrane.[13,16] Typically, during periods of rest, most of the GLUT-4 molecules remain stored within vesicles situated inside the cell. However, upon receiving a signal, these vesicles will release GLUT-4 into the cell membrane, thus enabling glucose uptake. Hence, insulin availability plays a crucial part in glucose uptake while the body is at rest.[16]

GLUT-4 presence in muscle cells depends on transport efficiency. Insulin surge stimulates membrane transport, while muscle contraction increases and reduces transport to and from vesicles. This increases GLUT-4 availability in the membrane and T-tubules of skeletal muscle cells. During physical activity, increased blood flow to muscles causes vasodilation and expands the surface area for glucose absorption. Muscle contractions activate specific proteins that prompt GLUT-4 translocation, leading to an increase in glucose uptake and metabolism.[16]

HIIT requires a significant amount of energy, leading to an increase in the ADP/ATP and AMP/ATP ratio. This, in turn, causes the phosphorylation of liver kinase B1 (LKB1), activating AMPK.[16,17] Numerous research studies have shown that the intensity and duration of physical exercise positively correlate with AMPK phosphorylation.[17] Once activated, AMPK phosphorylates several enzymes involved in lipid regulation, protein metabolism, and glucose transport, including TBC1D1. Phosphorylation of TBC1D1 renders it inactive, allowing GTP to react with the Rab protein present in GLUT-4 vesicles, thereby increasing GLUT-4 translocation and availability in cell membranes. This process enhances glucose uptake and insulin sensitivity.[13,16–18]

Increased Mitochondrial Activity

Type 2 DM can be caused by mitochondrial dysfunction, which is linked to insulin resistance. Reactive oxygen species (ROS) accumulation triggers this dysfunction, which can interfere with the insulin signalling pathway. The body activates mitophagy to eliminate damaged mitochondria or cause cellular stress, leading to apoptosis.[9] Cells contain organelles called mitochondria that are commonly referred to as energy stores or powerhouses. This is because mitochondria facilitate the oxidative phosphorylation process that generates ATP, an essential energy source for various cellular functions. Mitochondrial biogenesis is regulated by proliferator-activated receptor gamma coactivator 1a (PGC-1a), which activates transcription factors such as mitochondrial transcription factor A (TFAM) and nuclear respiratory factors (NRFs) by binding to them.[19,20]

Previous research indicated that physical exercise is capable of activating PCG-1a. After just one HIIT session, an increase in PGC-1a mRNA expression and other proteins associated with mitochondrial biogenesis was observed in human skeletal muscle. Similar studies have also demonstrated increased PGC-1a mRNA expression in human skeletal muscle three hours after one HIIT session.[20] These findings suggest that HIIT can promote mitochondrial biogenesis by enhancing PGC-1a expression, which may contribute to improved insulin sensitivity.

During HIIT, the skeletal muscles require a significant amount of energy for contraction. This energy demand leads to an increased need for Adenosine Triphosphate (ATP), resulting in elevated levels of Adenosine Monophosphate (AMP). This increase in AMP triggers the activation of AMP-activated protein kinase (AMPK), which is associated with improved mitochondrial number and function.[17,19,20] HIIT also promotes the release of Calcium ($Ca2+$) from the sarcoplasmic reticulum and the formation of Reactive Oxygen Species (ROS). The rise in ROS levels due to physical activity augments the activity of mitogen-activated protein kinase 38 (p38MAPK).[17,19] This, in turn, activates Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 (PGC-1), either directly or indirectly. PGC-1 activation occurs through phosphorylation, deacetylation, and/or regulation of PGC -1 expression, ultimately resulting in improved mitochondrial number and function.[17,19,20]

Increased Vasodilator Function of Blood Flow to Muscles

Insulin and its receptor, IRS-1, activate two signalling pathways. The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway promotes anti-atherogenic and vasodilator signalling, while the Ras/MAPK/Edothelin-1 (ET-1) pathway stimulates pro-atherogenic and vasoconstrictor signalling. When insulin resistance occurs, it diminishes the signalling along the PI3K/Protein Kinase B (Akt)/Nitric Oxide (NO). pathway and increases the signalling along the MAPK/ET-1 pathway, or maintains the signalling pathway unchanged. This sets off an atherogenic and vasoconstrictor process, which subsequently leads to decreased blood flow to the skeletal muscles.[21]

Studies have shown that engaging in physical exercise can enhance blood flow to the muscles that are being worked.[10,21] The degree of this blood flow increase is directly linked to the intensity of the physical activity. As the physical exercise becomes more intense, the blood flow to the muscles being worked also increases. The distribution of this blood flow is determined by the specific muscles that are being contracted during the exercise. When maximum physical activity is reached, blood flow to the muscles can increase by as much as ten times compared to when the body is at rest. This is because muscle fibres that are subjected to increased activity during exercise undergo an elevation in vascular shear stress, which is the frictional force that occurs between the blood and the walls of blood vessels.[21]

The act of contracting our skeletal muscles initiates a response in the endothelial cells that line our blood vessels. This response then prompts the activation of a signalling pathway known as the PI3K/Akt/NO pathway, which is sensitive to mechanical changes. As a result of this activation, there is an increase in the vasodilator function of blood vessels, thereby facilitating an improved flow of glucose to muscle cells.[21] This increase in glucose flow is thought to enhance insulin sensitivity and improve HOMA-IR values, ultimately leading to better health outcomes.[10]

THE ROLE OF HIIT IN MARKERS OF GLYCEMIC CONTROL IN TYPE 2 DM PATIENTS

The term glycaemic control pertains to maintaining a healthy glucose level in the bloodstream of individuals with diabetes. This can be gauged using three factors: HbA1C, fasting blood glucose concentration, and postprandial glucose concentration. Among these, HbA1C is considered the most reliable indicator of glycaemic control. When glycaemic control is inadequate, it heightens the likelihood of complications associated with Type 2 DM, which can adversely affect a patient's well-being and reduce their lifespan.[22]

The values of HbA1C can be utilized to evaluate glycaemic control over a long period. For individuals with Type 2 DM, higher levels of HbA1C are associated with decreased mitochondrial and skeletal muscle activity. One effective method of decreasing HbA1C levels in Type 2 DM patients is through HIIT. Research conducted by Elsisi et al. in 2020 found that patients with Type 2 DM who participated in HIIT for 12 weeks experienced significantly lower HbA1C levels compared to those who engaged in MICT.[10] Additionally, a systematic review by Peng et al. in 2023 demonstrated a reduction in HbA1C levels among Type 2 DM patients who performed LV-HIIT when compared to the control group.

According to recent research, there exists a positive connection between a rise in aerobic capacity, like VO2 max, and shifts in HbA1C levels post-HIIT. During physical activity, an upsurge in aerobic capacity is linked to heightened oxidative capacity and the quantity of mitochondria in skeletal muscle. HIIT triggers specific proteins that aid mitochondrial biogenesis, thus stimulating PCG-1α and amplifying the process of mitochondrial biogenesis and activity.[17,19,20] As a result, individuals with Type 2 DM who participate in HIIT can experience an increase in the number, function, and activity of mitochondria, which can lead to an improvement in both aerobic capacity and HbA1C levels.[10]

METABOLIC BENEFITS OF HIIT IN T2DM

High-intensity interval training (HIIT) is recognized for its benefits in glycaemic control and positively affects various metabolic features in individuals with Type 2 DM. Previous studies demonstrated that HIIT provides more effective improvements in anthropometric measures and cardiorespiratory health in Type 2 DM patients compared to control groups, MICT, and low-intensity training (LIT) groups.[12] It also improved lipid profiles by lowering triglyceride levels and increasing high-density lipoprotein (HDL) cholesterol, crucial for cardiovascular health.[23]

Additionally, HIIT is linked to reduced blood pressure, enhancing several aspects of metabolic syndrome in Type 2 DM patients.[24] Regular HIIT not only potentially lowers blood pressure but also improves endothelial function and vascular health, essential for reducing cardiovascular risk. Overall, these findings suggest that HIIT is an effective intervention for improving multiple dimensions of metabolic health in individuals with Type 2 DM.

CONCLUSION

In the treatment of Type 2 DM patients, regular physical exercise can be a highly effective intervention. Among the various forms of physical activity, High-Intensity Interval Training (HIIT) has emerged as a particularly beneficial option, earning its status as "the game-changer" in Type 2 DM management. This designation is warranted due to its exceptional capability to deliver substantial health benefits in a shorter time frame compared to conventional exercise regimens. Studies shown that High-Intensity Interval Training (HIIT) significantly enhances insulin sensitivity by facilitating the translocation of GLUT-4 proteins to muscle cell membranes, which allows for effective glucose uptake. Additionally, HIIT activates PGC-1α and AMPK, improving mitochondrial function and addressing insulin resistance. Moreover, HIIT enhances vascular function and boosts blood flow to active muscles, optimizing glucose delivery during exercise. Studies have shown that HIIT yields greater improvements in glycaemic markers, such as HbA1c and fasting glucose levels, compared to Moderate-Intensity Continuous Training (MICT). This emphasizes HIIT's effectiveness in regulating glucose levels and mitigating the risk of related complications. By utilizing HIIT, healthcare providers can offer an innovative and effective strategy that addresses both metabolic health and patient adherence, ultimately transforming the landscape of Type 2 DM management - being the "game changer".

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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