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Systematic Review

The Impact of Moderate-to-High-Intensity Exercise Protocols on Glycated Hemoglobin Levels in Type 2 Diabetes Patients

Ana Pedrosa [1,2,*], Guilherme Furtado [1,3,*], Marcelo Paes de Barros [4], André Luís Lacerda Bachi [5], José Pedro Ferreira [1], Vilma A. Sardão [2,6], Luís Rama [1] and Ana Teixeira [1]

1 Faculty of Sport Sciences and Physical Education (FCDEF-UC), University of Coimbra-Research Unit for Sport and Physical Activity (CIDAF, UID/PTD/04213/2020), 3040-256 Coimbra, Portugal
2 CNC-Center for Neuroscience and Cell Biology, CIBB-Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, 3004-504 Coimbra, Portugal
3 Polytechnic Institute of Coimbra, Applied Research Institute, Rua da Misericórdia, Lagar dos Cortiços–S. Martinho do Bispo, 3045-093 Coimbra, Portugal
4 Institute of Physical Activity Sciences and Sports (ICAFE), MSc/PhD Interdisciplinary Program in Health Sciences, Cruzeiro do Sul University, São Paulo 01506-000, Brazil
5 Post-Graduation Program in Health Sciences, Santo Amaro University (UNISA), São Paulo 04829-300, Brazil
6 Multidisciplinary Institute of Aging (MIA Portugal), University of Coimbra, 3004-504 Coimbra, Portugal
* Correspondence: anapedrosa90@gmail.com (A.P.); guilhermefurtado@ipc.pt (G.F.)

Abstract: Type 2 diabetes mellitus (T2DM) is a growing global health issue that is closely linked to the epidemic of obesity. In addition to genetic factors, environmental and health-risk behaviours (i.e., high-carbohydrate diet and physical inactivity) contribute to a variety of pathophysiological disorders. Advanced exercise protocols, such as Moderate-to-intensity (MIT) and High Intensity Interval Training (HIIT), revealed a strategy for mitigating and/or attenuating the DTMII's harmful effects by controlling glycated haemoglobin (HbA1c) levels. The goals of this review were to summarize the most recent evidence on the impact of HIIT on HbA1c levels. A mini-review protocol was performed through the PubMed/Medline database. The search comprised experimental and randomized controlled trial studies published in English between 2016 and 2021. The terms HbA1c, T2DM, MIT and HIIT, and their analogues were used. A total of seven studies were finally included. Our findings showed that the HIIT protocol is an effective strategy to induce HbA1c balance and improve glycaemic control than moderate training. The HIIT conducted in the laboratory and involving aerobic exercise on a cycle ergometer appears to be more efficient that MIT. Additional findings include improved beta-cell function, decreased low-grade inflammation, and the induction of cardiovascular benefits. More research is required to investigate the feasibility and safety of HIIT protocols in T2DM patients.

Keywords: type 2 diabetes; exercise; glycated haemoglobin; blood glucose; nutrition

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1. Introduction

The increase in type 2 diabetes mellitus (T2DM is an expanding global health problem closely linked to the epidemic of obesity [1]. This problem is considered a severe public health problem in terms of human life and average life expectancy [2]. In recent years, there has been an incidence increase, affecting individuals of all ages. The global burden of T2DM on people 20–79 years old is projected to increase to 629 million in 2045 compared to 425 million in 2017 [3]. T2DM is a metabolic disturbance characterized by a high level of sugar (glucose) in the blood, and it can cause symptoms such as excessive thirst, increase urination, and tiredness [4]. The body cannot use energy intake from food properly. The pancreas produces insulin, but it produces less over time, and cells resist insulin, resulting in insulin resistance metabolic syndrome [5]. Furthermore, individuals with this illness are at high risk for both micro- and macrovascular complications, such as retinopathy, nephropathy, and neuropathy [1]. Insulin deficiency also invariably leads to chronic hyperglycaemia, causing disturbances in carbohydrate, fat, and protein metabolism [6].

Insulin is a hormone produced by the pancreas, responsible for transporting the glucose in the bloodstream into the cells to be converted into energy [7]. A lack of insulin or the inability of cells to respond to its transport leads to hyperglycemia and the absence of glucose within the cell to perform its functions in the body [6,8]. The pancreatic β-cells are responsible for insulin production, synthesized as pre-proinsulin [9]. β-cell dysfunction is initially characterized by an impairment of insulin secretion during glucose stimulation and may occur before the inception of glucose intolerance in T2DM [10]. This dysfunction is characterized by a complex network of interactions between environmental factors such as obesity, an unhealthy diet, physical inactivity, and genetic factors that lead to multiple pathophysiological disturbances responsible for impaired glucose homeostasis in T2DM [2].

Both genetic and environmental factors significantly contribute to the multiple pathophysiological disturbances that cause impaired glucose homeostasis in type 2 diabetes. A high carbohydrate diet and sedentary lifestyle are the major factors for the rapidly increasing incidence of DM in developing countries [11]. Excessive fast sugar consumption and sedentary habits frequently result in hyperglycemia and hyperlipidemia, which can promote insulin resistance and chronic inflammation [12]. T2DM elevated glycated hemoglobin (HbA1c) level has recently been considered one the major risk factors for developing microvascular and macrovascular complications [1]. HbA1c is widely regarded as the gold standard for monitoring glycemic control and as a predictor of diabetes-related illnesses [13]. A decreased HbA1c level can be achieved through diet management [11], with recent research demonstrating the health benefits of regular exercise combined (or not) with a healthy diet in the balance of HbA1c [14]. A recent study observed that people who were inactive for more than 5–8 h a day had an average of 28% increased risk of T2DM [15].

Several studies indicated that regular exercise training has a positive impact on glucose homeostasis [16]. This impact is associated with a release of counter-regulatory hormones, training condition, and whether exercise was performed in the postabsorptive or the postprandial state. Nonetheless, the energy equivalent on exercise seems to represent the major determinant on changes in glucose homeostasis [17]. So, a single exercise training can increase the insulin sensibility by more than 48 h until recuperation, but this impact is relative to the intensity, duration, and type of exercise [18]. Traditional exercise guidelines have emphasized increasing moderate-to-intensity exercise training (MIT), with a minimum of 150 min week or 5 days/week of 30 min (i.e., with walking, jogging, cycling, muscle strength) in sedentary people [19], including the subgroups of T2DM patients [18]. Unlike LMPA, which requires staying in intervals of 40–60% of maximal aerobic capacity [19]. HIIT involves alternating between periods of vigorous exercise (defined as 70% maximum aerobic capacity) and periods of rest or recovery [18]. HIIT protocol positively impacts insulin resistance markers. This effect occurs from a metabolic adaptation resulting in a reduction of body fat and perhaps higher membrane-bound Glut-4 translocation [16].

In general, both MIT and HIIT protocols were linked to an increase in the insulin receptor phosphorylation at threonine G12, AKT phosphorylation at serin 473, and oxidative capacity in skeletal muscle increase [20]. Additionally, the increase in protein activities associated with glucose uptake, AMPK, CaMKII, and PGC1-α, improving insulin sensitivity, and glycemic marker of HbA1c were observed [20]. In fact, exercise has been shown to have clinical benefits such as improved insulin sensitivity, reduced HbA1c, and increased peak oxygen consumption, which are preventative of diabetes [21]. Furthermore, a growing body of literature has examined HIIT protocols but has not specifically focused on this marker. The present study aimed to review the impact of different types of exercise on HbA1c in patients with T2DM.

2. Materials and Methods

This mini systematic review (MSR) was guided by using the adapted version of Preferred Reporting Items for Systematic Review guidelines [22], and the previous published

MSR statement [23]. The search strategies were developed by three authors (A.P., G.E.F., and J.P.F.). For the final study selection, the following criteria were used: (i) randomized control trials carried out on T2DM patients of both sexes over 18 years old; (ii) studies with reported quantitative or calculable HbA1c before and after the exercise intervention. We excluded studies that did not report pre-DM and type 1 DM conditions, did not present an exercise intervention, and did not measure HbA1c before and after the exercise protocol. The searches were conducted between December 2021 and February 2022. Only papers in the English language were included. The study search strategies were centered on three indexed Medical Subject Heading (MeSH) concepts and their similarities. These concepts were used to restrict the obtained results to those related to humans due to our group desire to conduct future research on this population Table 1. The PICO (participants, intervention, comparison, and outcomes) framework was used to characterize each study of this MSR [24].

Table 1. Strategy of meta-search using MeSH terms and PICO guidelines.

Acronym	Information	Concepts	MeSH Terms
P	T2DM patients	People diagnosed with type II diabetes, which causes insulin resistance, among other symptoms	"Diabetes Mellitus, Type 2" OR/AND "Type 2 Diabetes"
I	HIIT	A type of exercise proocol that involves moderate continuos and/or alternating between periods of vigorous exercise and rest or recovery	"exercise" OR/AND "exercise therapy" OR/AND "moderate exercise" OR/AND "High Intensity Interval training"
C	T2DM patients	Without a specific treatment and/or involving isolated or combined physical exercise.	-
O	Hb1C	Reflects erythrocytes' cumulative glucose exposure over a time period proportional to erythrocyte survival.	"Glycated hemoglobin" AND Glycated human hemoglobin"

Notes: MIT = Moderate-to-intensity training; HIIT = High intensity interval training; T2DM = type 2 diabetes mellitus; Hb1C = glycated hemoglobin; PICO = participants, intervention, comparison, and outcomes.

3. Results

3.1. Identifying Eligible Studies

During the article search, 73 articles were found in the PubMed database and imported into the Endnote reference manager, which found no duplication. Following the title selection, 41 articles were eliminated for the following reasons: (i) other diseases than diabetes type 2, (ii) supplementation; (iii) under 18 years of age. Following a review of the abstracts, 14 articles were eliminated for the following reasons: (i) there was no control group; (ii) there was no exercise program; (iii) reviews; and (iv) an animal model was used. Finally, seven articles were chosen for this MSR.

3.2. General Characteristics of Studies

The studies chosen included interventions in women and men over 50 years old with T2DM, with a sample size ranging from 11 to 265 participants [25–31]. The body mass index of participants ranged from 23 to 40 kg/m^2, and they were diagnosed with T2DM within 4 years. All included articles measured HbA1c, before and after the exercise intervention. High-intensity interval training (HIIT, 3 studies) [25,29,31], high-intensity progressive resistance training (PRT, 1 study) [26], endurance training (END, 2 studies) [30,31], high-intensity interval training combined with resistance training (HIIT+RT, 1 study) [28], moderate-intensity training combined with resistance training (MCT+RT, 1 study) [28], and endurance training combined with resistance training (END+RT, 1 study) [27] were the different types of training protocols found, as shown in Table 2. The intervention time varies between two weeks and twelve months. Of all the selected studies, three studies include a control group without exercise [25–27], two studies compare two different protocols of exercise [28,31], and two studies compare the impact of exercise pre- and post-meals [29,30]. The study participants' ages are quite similar, indicating that the studies focus was on middle-to-older-aged adults. In general, all types of exercise positively impact HbA1c, but the studies involving a HIIT protocol presented more promising results [25,26,28,29,31].

Table 2. Summary of included studies according PICO guidelines.

Author	Participants (Mean Age)	Description of Interventions	Comparison (Controls)	Outcome (HbA1c/mmol/mol)
Cassidy, S. et al. 2019 [25]	n = 22 60 years old	12 weeks, HIIT group: 36 cycle sessions (3 sessions/week). 1 week was 2 min, increasing 10 s each week.	No Exercise	Decreased on HIIT Group on HbA1c 54.4 ± 3.3 vs. 51.6 ± 3.2 compared no exercise group 55.0 ± 1.8 57.0 ± 2.3.
Hangping, Z. et al. 2019 [26]	n = 265 66 years old	1 training session/week, 5–10 min weekly, 4 exercises.	No Exercise	PRT protocol was more efficient 6.83 ± 1.31vs 6.75 ± 0.93, than no exercise group 6.92 ± 1. Vs. 6.85 ± 1.17.
Johansen, M. et al. 2020 [27]	n = 95 56 years old	12 months 5 or 6 aerobic exercise sessions/week, 2 or 3 sessions/week, combined with resistance exercise.	No Exercise	BG reduced in the END + RT, 48.7 (9.0) vs −3.3 (−5.0, −1.7) compared with the standard care group, 50.2 (9.6). vs. −0.5 (−2.7, 1.8).
Magalhães, J. et al. 2018 [28]	n = 80 59 years old	12 months, MCT–continuous cycling at 40 to 60% HRR, HIIT group, both groups complete RT 10–12 repetitions.	HIIT RT MCT RT	No interaction between the intervention groups, HIIT + RT Group 52.1 ± 9.6 vs. 52.8 ± 7.1, MCT + RCT Group 53.0 ± 17.4. vs. 54.0 ± 14.8, and control group 51.7 ± 11.7 vs. 54.8 ± 11.1, in glycemic variables.
Savikj, M. et al. 2019 [29]	n = 11 60 years old	Cycle ergometer: 7 min warm-up, 6 pulses of 1 min (220 W, range 180–350 W) 75 rpm. 2 weeks, 3 sessions/week.	Post-morning Post-afternoon	Afternoon HIIT 48.3 ± 3.9 vs. 46.1 ± 2.7, was better at improving BG, but post-Morning 48.3 ± 3.9 vs. 45.1 ± 2.1, was better on HbA1c reduction in post-morning intervention.
Verboven, K. et al. 2020 [30]	n = 25 61 years old	12-week endurance training (3 exercise sessions/week), 25 min—walking, 20 min cycling, 65% of baseline VO2peak.	Fasted state Fed state	HbA1c better improved with exercise performed in the postprandial period 6.6 [6.3–7.5] vs. 6.3 [6.0–6.9], than 7.4 [6.8–8.2] vs. 7.7 [6.7–8.3].
Winding, K. et al. 2018 [31]	n = 29 56 years old	11-week, on bicycle, 3 days/week. END—40 min/session at 50% of Wpeak, group. HIIT—20 min/session of 95% Wpeak.	END HIIT	HIIT Intervention 7.4 [6.8–8.2] vs 7.7 [6.7–8.3] a statistically significant difference was observed in the reduction of HbA1c, when compare bout group, END group 52.2 ± 10.1. vs 51.4 ± 8.8 and, no exercise group 53.2 ± 12.6 vs 51.8 ± 11.3

Notes: HIIT = high-intensity interval training; MCT = moderate-intensity training; HRR= heart rate reserve; RT = resistance training; END = endurance training; Con = control; MICT = moderate-intensity continuous training; eWLmax= estimated maximum workload; PRT = high-intensity progressive resistance training; ILG = intensive lifestyle group; BG = blood glucose.

3.3. Main Findings of the Studies

Comparing the different protocols applied, HIIT protocol showed a reduction in HbA1c. Low-volume HIIT exercise, typically involving less than 15 min of high-intensity exercise per session, can be safely implemented as a time-efficient exercise option for reducing blood glucose levels in individuals with, or at risk for, T2DM [18]. In the HIIT group, when compared to the control group (no exercise), the glycaemic control was improved, with a reduction in HbA1c [25]. Two studies presented the role of nutritional status during exercise, when comparing the moment of application of the HIIT protocol, in the afternoon (3 h later) or in the morning (1 h later). The HIIT exercise practice in the afternoon was more efficacious at improving blood glucose, but the HbA1c levels had increased reductions in the post-morning intervention [29]. These results indicated that the glucose intolerance, insulin sensitivity, and skeletal muscle oxidative capacity can fluctuate with circadian oscillations. The END exercise seemed to better improve HbA1c levels when performed in the postprandial period [30]. One study compared HIIT with MCT with RT with both groups presenting no differences in glycaemic control, but the MCT with RT improved the body composition and cardiorespiratory fitness [28]. Another study compared HIIT with END: the HIIT group reduced fasting glucose, HbA1c levels, and glycaemic variability, while the END group showed a reduction in gynoid fat mass and a tendency towards a reduction in whole body mass and visceral fat mass [31]. A PRT protocol showed a reduction in HbA1c at 6 months, improving glycaemic indices in elderly patients' adjunct to diet and medication [26]. Aerobic exercise combined with RT improved beta cell function, decreased low-grade inflammation and body weight, and reduced the HbA1c levels [27].

4. Discussion

Different exercise strategies demonstrate benefits for patients with T2DM, in terms of glycemic control, beta cell function, cardiovascular health and/or body weight. After our search through the recent literature, we observed that HIIT showed better results in reducing HbA1c than other (MCT, RT, END, MICT) exercise programs. In a study by Karstoft et al. [32], the impact of postprandial glycemic control and free-living glycemic control showed that HIIT had a greater impact in both variables than MICT. Our review confirms the results in the study of Savikj M. et al. 2019 [29], which showed that HIIT performed in the afternoon was better at improving blood glucose and HbA1c when compared to a post-morning intervention. Additionally, in the study by Verboven, K. et al. 2020 [30], HbA1c seems to be improved more with exercise performed in the postprandial period. In another study, Elsisi et al. 2015 [33] determined the impact of high-intensity interval training (HIIT) on glycated hemoglobin (HbA1c) in T2DM on a short-term basis (after 12 weeks of training), the results showing that HIIT was more effective and an alternative to aerobic training in improving HbA1c in T2DM. This confirms the results presented by Winding, K. et al. 2018 [31] in which, with the HIIT intervention, a statistically significant difference was observed in the reduction in HbA1c.

The main finding of this MSR was that HIIT improves glucose control centers' ability to recruit more muscle fibers and rapidly deplete muscle glycogen levels, thereby promoting a greater increase in post-exercise muscle insulin sensitivity [18]. With an increase in post-exercise muscle insulin sensitivity between 24 and 48 h after a single exercise, HIIT may be an effective strategy to improve glucose control acutely and in the long term. A HIIT protocol for 12–16 weeks may show a positive impact on reducing abdominal fat and increasing lean muscle mass. This type of exercise recently assumed a prominent role in physical activity and health, showing cardiovascular and metabolic benefits in patients with chronic diseases, including T2DM [34–36]. However, the HIIT protocol may induce increases in VO_{2max} in patients with metabolic disorders and healthy individuals. This protocol also improves the change in the systolic volume of the heart, induced by increased cardiac contractility and the oxidative capacity of skeletal muscle, in addition to changes in glucose transport, which improve the mitochondrial function to generate more adenosine triphosphate, as well as increasing the aerobic capacity [37].

This MSR presented some limitations as the search was performed in one database and only included articles published within the last 5 years. This review focused on HbA1c as the ultimate measure of glycemic control due to the lack of studies regarding the impact of exercise on dietary sugars. Considering that physical exercise has a positive impact on T2DM patients, it would be interesting in the future to analyze the independent and combined effect of exercise on these variables in T2DM patients. A systematic review with meta-analysis can be future performed, controlling for the type of exercise, which represents the main publication bias in this type of work.

5. Conclusions

The exercise protocol of HIIT seems to be a more effective exercise strategy to improve HbA1c compared to other training protocols in middle-aged patients with T2DM. This type of exercise seems to be safe in these patients, but a pre-exercise clinical evaluation is necessary for its safe performance.

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