

Effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in type 2 diabetes: A systematic review

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Abstract

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by insulin resistance and hyperglycemia that may lead to endothelial dysfunction, reduced functional capacity and exercise intolerance. Regular aerobic exercise has been promoted as the most beneficial non-pharmacological treatment of cardiovascular diseases. High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving brachial artery flow-mediated dilation (FMD) and cardiorespiratory fitness to a greater extent. However, the beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

AIM

To evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with T2DM.

METHODS

We performed a search on PubMed, PEDro and CINAHL databases, selecting papers published between December 2012 and December 2022 and identified published randomized controlled trials (RCTs) in the English language that included community or outpatient exercise training programs in patients with T2DM. RCTs were assessed for methodological rigor and risk of bias *via* the Physiotherapy Evidence Database (PEDro). The primary outcome was peak VO₂ and the secondary outcome was endothelial function assessed either by FMD or other indices of microcirculation.

RESULTS

Twelve studies were included in our systematic review. The 12 RCTs resulted in 661 participants in total. HIIT was performed in 310 patients (46.8%), MICT to 271 and the rest 80 belonged to the control group. Peak VO₂ increased in 10 out of 12 studies after HIIT. Ten studies compared HIIT with other exercise regimens (MICT or strength endurance) and 4 of them demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens. Moreover, 4 studies explored the effects of HIIT on endothelial function and FMD in T2DM patients. In 2 of them, HIIT further improved endothelial function compared to MICT and/or the control group while in the rest 2 studies no differences between HIIT and MICT were observed.

CONCLUSION

Regular aerobic exercise training has beneficial effects on cardiorespiratory fitness and endothelial function in T2DM patients. HIIT may be superior by improving these parameters to a greater extent than MICT.

Key Words: Type 2 diabetes mellitus; Exercise; High intensity interval training; Cardiorespiratory fitness; Peak VO₂; Endothelial function

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Core Tip: Beneficial effects of high intensity interval training (HIIT) in patients with type 2 diabetes mellitus (T2DM) still remain under investigation and number of studies is limited. We investigated the effectiveness of HIIT on cardiorespiratory fitness and endothelial function in patients with T2DM. We observed that regular aerobic exercise training has beneficial effects on peak VO₂ and flow-mediated dilation in type 2 diabetic patients. Moreover, HIIT may be superior by improving these parameters to a greater extent than moderate-intensity continuous training.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by persistent hyperglycemia due to low production from the pancreas or/and abnormal response of cells to insulin that may lead to disorders of the circulatory, nervous and immune system. T2DM is a usual comorbidity worldwide, corresponding to 462 million people or to 6.28% of the world's population affecting not only the elderly, but also younger adults[1]. Especially in developed countries, prevalence is even higher compared to the global prevalence. Unhealthy lifestyle, junk food consumption, obesity and lack of exercise are major factors, responsible for developing T2DM. In Europe, there are 8529 patients per 100000 cases while in the US the number is 8911 per 100000 cases[1]. Based on mathematical models, scientists predicted the future prevalence of T2DM among youth aged < 20 years in the United States population and the potential trends in incidence. Specifically, number of youths aged < 20 with T2DM will increase from 28000 in 2017 to 48000 in 2060 under the condition that incidence will remain constant

as observed in 2017[2]. Moreover, corresponding relative increases may raise to 673% (95%CI: 362%; 1341%) for T2DM[2].

Endothelium is a significant modulator of the vascular tone and structure, endothelial progenitor cells proliferation and migration, fibrinolysis and coagulation, inflammation, platelet and leukocyte adherence resulting, thus, in vascular homeostasis[3]. T2DM, and specifically insulin resistance and hyperglycemia, may lead to endothelial dysfunction throughout a number of mechanisms, including disturbances of sub cellular signaling pathways common to both insulin action and nitric oxide (NO) production, oxidative stress, endothelin, imbalance of the renin angiotensin system, as well as the secretion of hormones and cytokines by the adipose tissue[4]. Decreased endothelium-dependent vasodilation in diabetic patients is associated with the impaired action of NO secondary to its inactivation resulting from increased oxidative stress[5]. As a result, T2DM patients usually present endothelial dysfunction causing impaired vasodilation, exercise intolerance and significantly reduced aerobic capacity[6-9].

Regular aerobic exercise has been promoted as the most beneficial non-pharmacological treatment of cardiovascular diseases resulting in improvements in body composition, physical capacity, arterial hypertension, insulin resistance, vascular tone, antioxidant status, quality of life, and, most important, endothelial function and exercise tolerance[10-13]. As far as endothelial function is concerned, exercise training has been shown to improve both basal endothelial NO formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with cardiovascular diseases[14]. The improvement of endothelium dysfunction is associated with a significant increase in exercise capacity[14]. High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving brachial artery flow-mediated dilation (FMD)[15,16] and cardiorespiratory fitness[17,18] to a greater extent. However, most studies focus on the effectiveness of HIIT in patients with cardiovascular diseases and metabolic syndrome. The beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present the most updated knowledge in literature.

MATERIALS AND METHODS

Search strategy

The search was conducted within 1-month time period, from December 20, 2022 until January 20, 2023 in 3 Large databases; PubMed, PEDro and CINAHL. The aim of the investigators was to identify published studies that included community or outpatient exercise training programs in patients with T2DM. Specific terms were used for the search including ("type 2 diabetes mellitus" OR "diabetes" OR "T2DM" OR "DM") AND ("rehabilitation" OR "exercise" OR "exercise training" OR "aerobic exercise" OR "high intensity interval exercise" OR "HIIT" OR "sprint interval training" OR "high intensity intermittent training"). Studies that occurred from this search were selected according to the PRISMA and the PRISMA checklist. Duplicates were removed from the initial number of studies and the rest were evaluated twice. Firstly, they were screened using only the title and the abstract and then, the full text of the articles was reviewed for eligibility by 2 independent reviewers of different Institutions. Moreover, we performed manual searching of references of all eligible studies, so that to include all potential randomized trials that may not have been identified in the original search. The final evaluation of the process was performed by a university professor.

Study selection criteria

Studies were included in the systematic review only if the necessary eligible criteria were met. Inclusion criteria were: (1) Studies available as full texts in English; (2) published randomized controlled trials (RCTs) in peer-reviewed journals; (3) study groups including patients with diagnosed T2DM under stable medication during the last 3 mo or in the initial stages without medication; (4) aged ≥ 18 years, v. exercise training programs using HIIT with duration of ≥ 2 wk compared to either MICT or controls and; and (5) outcome measures focused on either cardiorespiratory fitness assessed by peak oxygen uptake (peak VO_2) and/or endothelial function through FMD or other indices of microcirculation (leg blood flow during knee-extensions, muscle fractional O_2 extraction through near-infrared spectroscopy, *etc.*). HIIT was defined as exercise sessions performing intervals of exercise at a high intensity (according to the initial VO_2 max or HR max) mixed with brief intervals at a lower intensity or even breaks.

Exclusion criteria were: (1) Non RCTs, reviews, guidelines, commentaries, case reports, editorials or conference abstracts; (2) additional interventions in study groups except for exercise training; (3) studies including patients with other comorbidities except for DM (cardiovascular diseases, obesity, metabolic syndrome); (4) studies including patients with other types of DM such as type 1 DM and prediabetes, v. studies including patients aged < 18 years; (5) exercise training including acute exercise bouts or programs with duration < 2 wk and; and (6) studies including HIIT and other exercise modalities that

were unable to be quantified.

All patients were considered to have controlled type 2 diabetes under medication and normal eating habits that did not cause severe hypoglycemic events.

Quality assessment

All RCTs that were included in the systematic review were assessed for methodological rigor and risk of bias by 2 independent reviewers, using similar methods with a recently published study[19], via the Physiotherapy Evidence Database (PEDro). PEDro is an 11-point scale for assessing RCTs for internal validity and control of bias. Maximum score is 10 as the first question does not contribute to total score. A study with a score of 6-10 is considered of excellent quality, a study with 4-5 of fair quality, and a score of 3 or less gives a poor-quality study. If the 2 reviewers did not agree for their quality score, then an independent third reviewer made the final decision.

Outcome measures

The primary outcome measure assessing cardiorespiratory fitness was peak VO₂ index after cardiopulmonary exercise testing. The secondary outcome measure of our systematic review was endothelial function assessed either by FMD or other indices of microcirculation. FMD was calculated as the percent change in diameter following reactive hyperemia compared with the baseline diameters at rest. Both outcomes were evaluated at baseline and post-intervention.

RESULTS

Search results

Search and screening results are demonstrated in the PRISMA flowchart (Figure 1). The initial search strategy identified 5219 articles from PubMed, PEDro and CINAHL databases. The removal of duplicate publications, and title and abstract screening excluded 4966 articles. After a full-text review by the investigators, 241 articles were further excluded. Specifically, 140 articles either did not present HIIT as the main intervention or included acute exercise regimens, 35 articles measured different outcomes than those we defined, 7 articles included patients with other types of DM such as type 1 DM and prediabetes, 12 articles were RCT protocols without results, 39 articles included patients with other comorbidities than T2DM, and 8 articles were not RCTs. After the evaluation, 12 studies were finally included in our systematic review[20-31].

Assessment of the methodological quality of the studies

We assessed methodological quality of the included RCTs using PEDro scale. PEDro scores ranged from 4 to 7. None of the studies scored 3 points or less. Eight out of 12 studies scored 4-5 points, being assessed as fair-quality studies while 4 out of 12 scores 6 points or more being assessed as high-quality studies (Table 1). The weakest field of scoring was blindness of therapists and participants.

Characteristics of participants

The 12 RCTs resulted in 661 participants in total with the majority of them being males (406 vs 255 females). HIIT was performed in 310 patients (46.8%), MICT to 271 and the rest 80 belonged to the control group. The mean age of the participants ranged from 38 to 65 years, while the mean time since the diagnosis of DM ranged from 1.79 to 21.1 years. Mean HbA_{1c} ranged from 6.4 to 7.5% while BMI was from 26.5 to 33.9 kg/m². Studies were mainly conducted in Italy[20], Canada[21], Denmark[22,25,28,29], Thailand[23], Norway[24], the United States[26], the United Kingdom[27], Ireland[30] and China[31]. The main baseline characteristics of patients from the included studies are described in Table 2.

Exercise training protocols

Populations, intervention, comparison, outcomes and study design of the included RCTs are reported in detail in Table 3. Exercise training protocols of the intervention group included HIIT in all studies with small differences in intensity, sets and sessions duration among studies. Eleven out of 12 studies included a second group of T2DM patients with MICT as an exercise regimen[20-26,28-31] while a control group including patients with usual care only was included in 7 studies[22,23,25-27,30,31]. The main HIIT program ranged in duration from 8 wk to 12 mo (12 mo in 1 study, 16 wk in 1 study, 12 wk in 6 studies, 11 wk in 2 studies, 10 wk in 1 study, and 8 wk in 1 study) and sessions were performed from 2 to 5 times weekly. A comprehensive analysis of the characteristics of exercise training programs is demonstrated in Table 3.

Effect of exercise training on cardiorespiratory fitness

The effectiveness of high intensity interval training on cardiorespiratory fitness was assessed by peak VO₂. Peak VO₂ increased in 10 out of 12 studies[20,22-26,28-31] whereas in 2 studies no difference was observed[21,27]. Moreover, 10 studies[20-26,29-31] compared HIIT with other exercise regimens (MICT

Table 1 Quality assessment of the included studies using the physiotherapy evidence database

	Balducci <i>et al</i> [20], 2012	Terada <i>et al</i> [21], 2013	Karstoft <i>et al</i> [22], 2013	Mitranun <i>et al</i> [23], 2014	Hollekim-Strand <i>et al</i> [24], 2014	Winding <i>et al</i> [25], 2018	Hwang <i>et al</i> [26], 2019	Suryanegara <i>et al</i> [27], 2019	Mortensen <i>et al</i> [28], 2019	Baasch-Skytte <i>et al</i> [29], 2020	Gildea <i>et al</i> [30], 2021	Li <i>et al</i> [31], 2022
Eligibility criteria ^a	√	√	√	√		√	√			√	√	√
Random allocation	√	√	√	√	√	√	√	√	√	√	√	√
Concealed allocation									√		√	
Baseline comparability	√	√	√	√	√	√	√	√	√	√	√	√
Blinded subjects												
Blinded therapists												
Blinded assessors		√	√									√
Adequate follow-up	√	√	√	√			√			√		√
Intention-to-treat analysis		√					√					
Between-group comparisons	√	√	√	√	√	√	√	√	√	√	√	√
Point estimates and variability	√	√	√	√	√	√	√	√	√	√	√	√
Total score	5/10	7/10	6/10	5/10	4/10	4/10	6/10	4/10	5/10	5/10	5/10	6/10

^aEligibility criteria item does not contribute to total score.

and/or strength endurance) while 6 studies compared HIIT with patients of the control group who received usual care[22,23,25,27,30,31]. Four studies[22,23,24,31] demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens, while 6 studies[20,21,25,26,29,30] did not observe statistically significant difference between HIIT and MICT. One single study[27] that compared HIIT to usual care only, failed to show superiority of HIIT in peak VO₂.

Specifically, Balducci *et al*[20] found an increase in peak VO₂ from 26.5 ± 5.3 to 31.1 ± 5.9 mL/min/kg (*P* < 0.001) in the high intensity (HI) group, an increase from 25.1 ± 5.4 to 29.6 ± 5.6 mL/min/kg (*P* < 0.001) in the low intensity (LI) group while no difference was observed between HI and LI groups [mean dif (95% CI): 0.14 (20.65,0.92) *P* = 0.866]. In Karstoft *et al* study[22] patients of the HIIT group increased peak VO₂ from 27.1 ± 1.5 to 31.5 ± 2.2 mL/min/kg (*P* < 0.001), but there was no difference within MICT (from 26.1 ± 1.4 to 26.8 ± 1.9 mL/min/kg, *P* > 0.05) and CON groups (from 24.8 ± 1.8 to

Table 2 Main baseline characteristics among patients with type 2 diabetes mellitus of each study included in the systematic review

Ref.	Groups	Males/Females (n)	Year after diagnosis	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m ²)	HbA _{1c} (%)
Balducci <i>et al</i> [20], 2012	HI (n = 152); LI (n = 136)	91/61; 83/53	7.8 ± 6.2; 5.9 ± 4.0	59.5 ± 8.3; 58.4 ± 8.9	NA	NA	31.2 ± 4.6; 31.9 ± 4.7	7.24 ± 1.39; 6.99 ± 1.39
Terada <i>et al</i> [21], 2013	HIIT (n = 7); MICT (n = 8)	4/4; 4/3	6 ± 4; 8 ± 4	62 ± 3; 63 ± 5	80.5 ± 9.9; 93.9 ± 18.3	NA	28.4 ± 4.1; 33.1 ± 4.5	6.6 ± 0.6; 6.7 ± 0.6
Karstoft <i>et al</i> [22], 2013	HIIT (n = 12); MICT (n = 12); CON (n = 8)	7/5; 8/4; 5/3	3.5 ± 0.7; 6.2 ± 1.5; 4.5 ± 1.5	57.5 ± 2.4; 60.8 ± 2.2; 57.1 ± 3	84.9 ± 4.9; 88.2 ± 4.7; 88.5 ± 4.7	NA	29.0 ± 1.3; 29.9 ± 1.6; 29.7 ± 1.9	6.9 ± 0.2; 6.6 ± 0.2; 6.4 ± 0.2
Mitranun <i>et al</i> [23], 2014	HIIT (n = 14); MICT (n = 14); CON (n = 15)	5/9; 5/9; 5/10	19.5 ± 0.4; 20.5 ± 0.4; 21.1 ± 0.6	61.2 ± 2.8; 61.7 ± 2.7; 60.9 ± 2.4	66.5 ± 3.7; 65.8 ± 3.1; 67.7 ± 3.2	149 ± 4; 149 ± 5; 152 ± 5	29.6 ± 0.5; 29.4 ± 0.7; 29.7 ± 0.4	60 ± 2 ^a ; 61 ± 2 ^a ; 62 ± 2 ^a
Hollekim-Strand <i>et al</i> [24], 2014	HIIT (n = 20); MICT (n = 17)	12/8; 11/6	4.2 ± 2.3; 3 ± 2.6	58.6 ± 5; 54.7 ± 5.3	NA	NA	30.2 ± 2.8; 29.7 ± 3.7	7.0 ± 1.2; 6.7 ± 0.7
Winding <i>et al</i> [25], 2018	HIIT (n = 13); END (n = 12); CON (n = 7)	7/6; 7/5; 5/2	8 ± 4; 6 ± 4; 7 ± 5	54 ± 6; 58 ± 8; 57 ± 7	84.2 ± 11.1; 82.1 ± 13.7; 87.7 ± 11.3	NA	28.1 ± 3.5; 27.4 ± 3.1; 28.0 ± 3.5	6.8 ± 0.8; 6.9 ± 0.9; 7.0 ± 1.2
Hwang <i>et al</i> [26], 2019	HIIT (n = 23); MICT (n = 19); CON (n = 16)	11/12; 11/8; 8/8	7.8 ± 1.3; 8.3 ± 1.5; 8.2 ± 1.5	65 ± 2; 62 ± 2; 61 ± 2	92.0 ± 4.7; 92.6 ± 4.5; 91.5 ± 3.9	170 ± 3; 170 ± 3; 164 ± 2	31.7 ± 1.3; 31.8 ± 1.4; 33.9 ± 1.4	7.1 ± 0.3; 7.2 ± 0.3; 7.4 ± 0.4
Suryanegara <i>et al</i> [27], 2019	HIIT (n = 13); CON (n = 13)	3/10; 3/10	4.8 ± 1.2; 4.3 ± 1.4	61.1 ± 8.6; 59.8 ± 8.6	90.5 ± 15.0; 91.0 ± 9.8	170.4 ± 7.6; 169.8 ± 8.6	31.3 ± 5.4; 31.9 ± 5.3	53.6 ± 10.5 ^a ; 55.5 ± 6.0 ^a
Mortensen <i>et al</i> [28], 2019	HIIT (n = 11); END (n = 10)	6/5; 7/3	7 ± 4; 5 ± 4	53 ± 7; 57 ± 9	85 ± 12; 86 ± 11	NA	NA	6.8 ± 0.9; 6.9 ± 0.9
Baasch-Skytte <i>et al</i> [29], 2020	10-20-30 (n = 23); MICT (n = 21)	23/0; 21/0	8.0 ± 5.9; 7.0 ± 5.7	61.0 ± 6.2; 61.2 ± 7.1	101.9 ± 22.8; 100.3 ± 13.8	181.5 ± 6.5; 180.4 ± 7.2	30.6 ± 5.4; 30.7 ± 4.4	7.5 ± 1.6; 7.3 ± 1.1
Gildea <i>et al</i> [30], 2021	HIIT (n = 9); MICT (n = 10); CON (n = 9)	6/3; 7/3; 4/5	6.6 ± 3.5; 6.4 ± 3.8; 6.6 ± 3.3	52 ± 10; 53 ± 10; 54 ± 9	92.0 ± 4.7; 92.6 ± 4.5; 91.5 ± 3.9	NA	28.7 ± 3.0; 30.0 ± 5.7; 30.5 ± 3.6	7.3 ± 0.5; 6.9 ± 0.5; 6.8 ± 1.0
Li <i>et al</i> [31], 2022	HIIT (n = 13); MICT (n = 12); CON (n = 12)	13/0; 12/0; 12/0	1.95 ± 0.55; 1.79 ± 0.52; 1.84 ± 0.49	38 ± 6; 39 ± 5; 40 ± 7	75 ± 9.98; 73.1 ± 7.8; 71.76 ± 9.7	166.9 ± 6.25; 165.8 ± 5.56; 166.7 ± 6.86	27.4 ± 5.5; 26.8 ± 4.2; 26.5 ± 5.0	7.2 ± 0.5; 7.02 ± 0.44; 7.06 ± 0.38

^aExpressed in mmol/moL. CON: Control group; NA: Not available; HIIT: High-intensity interval training; HI: Moderate-to-high intensity; MICT: Moderate intensity continuous training; END: Endurance training; LI: Low-to-moderate intensity.

25.2 ± 2.0 mL/min/kg, $P > 0.05$). In addition, increase in peak VO₂ was higher in the HIIT compared to the MICT and the control group ($P < 0.05$). In another study by Mitranun *et al*[23], HIIT group increased peak VO₂ from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg ($P < 0.05$), MICT group from 23.8 ± 1.0 to 27.1 ± 1.2 mL/min/kg ($P < 0.05$) while no difference was observed in CON group (from 24.4 ± 1.3 to 23.9 ± 1.0 mL/min/kg, $P > 0.05$). Increase was greater in the HIIT group compared to the MICT and the control group ($P < 0.05$). Similar results were demonstrated in 2 other RCTs, the first performed by Hollekim-Strand *et al*[24] in 2014 and the other more recent by Li *et al*[31] in 2022. In the first study[24], HIIT group increased peak VO₂ from 31.5 ± 6.1 to 35.6 ± 6.3 mL/min/kg ($P < 0.001$) and MICT from 33.2 ± 7.4 to 34.4 ± 7.7 mL/min/kg ($P = 0.04$), while HIIT group showed better improvement compared to MICT

Table 3 Population, Intervention, Comparison, Outcomes and Study (PICOS) design of each study included in the systematic review

Ref.	Interventions by group	Frequency	Session duration	Intervention duration	Outcomes	Main results
Balducci <i>et al</i> [20], 2012	Both groups performed mixed aerobic (<i>treadmill, step, elliptical, arm or cycle-ergometer</i>) and resistance exercise [4 resistance exercises, <i>i.e. thrust movement on the transverse plane (chest press or equivalent), traction movement on the frontal plane (lateral pull down or equivalent), squat movement (leg press or equivalent), and trunk flexion for the abdominals, plus three stretching positions</i>]. HI : Aerobic training at 70% of predicted VO ₂ max and resistance training at 60% of predicted 1-RM. LI : Aerobic training at 55% of predicted VO ₂ max and resistance training at 60% of predicted 1-RM	2 times/wk	Varied to obtain the same caloric expenditure per kg body weight in the two groups, independent of intensity	12 mo	Peak VO ₂	↑ peak VO ₂ within HI (from 26.5 ± 5.3 to 31.1 ± 5.9 mL/min/kg, <i>P</i> < 0.001) and LI group (from 25.1 ± 5.4 to 29.6 ± 5.6 mL/min/kg, <i>P</i> < 0.001). No difference in peak VO ₂ between HI and LI groups [mean dif (95%CI): 0.14 (20.65, 0.92) <i>P</i> = 0.866]
Terada <i>et al</i> [21], 2013	HIIT : Treadmill training or cycling intervals 1' (100% VO ₂ max). And 3' (20% VO ₂ max). MICT : continuous treadmill training or cycling (40% VO ₂ max)	5 times/wk	30-60 min	12 wk	Peak VO ₂	No difference in peak VO ₂ within HIIT (from 22.8 ± 5.4 to 24.3 ± 7.4 mL/min/kg, <i>P</i> > 0.05) and MICT (from 18.1 ± 2.7 to 18.9 ± 4.1 mL/min/kg, <i>P</i> > 0.05) groups. No difference in peak VO ₂ between HIIT and MICT groups (<i>P</i> > 0.05)
Karstoft <i>et al</i> [22], 2013	HIIT : Interval walking training with 3-min repetitions at low (< 70% peak energy-expenditure rate) and high (> 70%) intensity. MICT : Continuous - walking training (< 55%). CON : No intervention	5 times/wk	60 min	16 wk	Peak VO ₂	↑ peak VO ₂ in HIIT group (from 27.1 ± 1.5 to 31.5 ± 2.2 mL/min/kg, <i>P</i> < 0.001). No difference in peak VO ₂ in MICT (from 26.1 ± 1.4 to 26.8 ± 1.9 mL/min/kg, <i>P</i> > 0.05) and CON groups (from 24.8 ± 1.8 to 25.2 ± 2.0 mL/min/kg, <i>P</i> > 0.05). Increase was higher in the HIIT compared to the MICT group (<i>P</i> < 0.05)
Mitranun <i>et al</i> [23], 2014	HIIT : 4-6 intervals (85% VO ₂ max) during 1 min following 4 min of active rest (50% VO ₂ max.). MICT : 50%-65% VO ₂ max. CON : No intervention	3 times/wk	30-40 min	12 wk	Peak VO ₂ , FMD	Peak VO₂ : ↑ in HIIT (from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg, <i>P</i> < 0.05) and MICT groups (from 23.8 ± 1.0 to 27.1 ± 1.2 mL/min/kg, <i>P</i> < 0.05), no difference in CON group (from 24.4 ± 1.3 to 23.9 ± 1.0 mL/min/kg, <i>P</i> > 0.05). Increase was greater in the HIIT group compared to the MICT and the control group (<i>P</i> < 0.05). FMD : ↑ in HIIT (from 5.4 ± 1.1 to 7.4 ± 0.9%, <i>P</i> < 0.05) and MICT groups (from 4.8 ± 1.6 to 6.1 ± 1.8%, <i>P</i> < 0.05), no difference in CON group (from 5.1 ± 1.3 to 5.6 ± 1.8%, <i>P</i> > 0.05). Increase was higher in the MICT group compared to the control group (<i>P</i> < 0.05). Increase was higher in the HIIT group compared to the MICT and the control group (<i>P</i> < 0.05)
Hollekim-Strand <i>et al</i> [24], 2014	HIIT : 4 × 4' (90%-95% HR max). MICT : according to guidelines	HIIT : 3 times/wk. MICT : 210 min/wk	HIIT : 40 min. MICT : ≥ 10 min	12 wk	Peak VO ₂ , FMD	Peak VO₂ : ↑ in HIIT (from 31.5 ± 6.1 to 35.6 ± 6.3 mL/min/kg, <i>P</i> < 0.001) and MICT groups (from 33.2 ± 7.4 to 34.4 ± 7.7 mL/min/kg, <i>P</i> = 0.04). Increase was greater in the HIIT group compared to the MICT group (difference: 4.1 ± 2.9 vs 1.2 ± 2.2 mL/min/kg, respectively; <i>P</i> = 0.002). FMD : ↑ in HIIT group (from 9.2 ± 9.6 to 18.5 ± 9.6%, <i>P</i> = 0.004), no difference in MICT group (from 13.0 ± 9.8 to 13.0 ± 9.9%, <i>P</i> = 0.99). Increase was higher in the HIIT group compared to the MICT group (difference: 9.2 ± 11.2 vs 0.0 ± 6.2%, respectively; <i>P</i> = 0.03)
Winding <i>et al</i> [25], 2018	HIIT : 10 × 1 min intervals cycling at 95% of peak workload interspersed by 1 min active recovery. END : 40 min cycling at 50% of peak workload. CON : No intervention	3 times/wk	HIIT : 20 min. END : 40 min	11 wk	Peak VO ₂	↑ in HIIT (from 28.4 ± 6.1 to 34.2 ± 6.3 mL/min/kg, <i>P</i> < 0.05) and END groups (from 27.8 ± 5.5 to 30.3 ± 7.5 mL/min/kg, <i>P</i> < 0.05), no difference in CON group (from 27.2 ± 9.1 to 26.3 ± 6.8 mL/min/kg, <i>P</i> > 0.05). Increase was greater in the HIIT group compared to the control group (<i>P</i> < 0.05), but no significant difference between HIIT and END groups (<i>P</i> > 0.05)
Hwang <i>et al</i>	HIIT : 10-min warm-up and a 5-min cooldown at 70% of HR	4 times/wk	HIIT : 40 min. MICT	8 wk	Peak VO ₂	↑ in HIIT group (from 22.3 ± 1.0 to 24.6 ± 1.3 mL/min/kg, <i>P</i> < 0.0001) and

[26], 2019	peak, 4 × 4-min intervals at 90% of HR peak interspersed by 3 × 3-min active recovery at 70% of HR peak. MICT : 10-min warm-up and a 5-min cooldown at 70% of HR peak, 32 min at 70% HR peak. CON : No intervention		: 47 min			MICT group (from 21.6 ± 1.2 to 23.3 ± 1.2 mL/min/kg, <i>P</i> < 0.005), no difference in CON group (from 21.4 ± 1.3 to 20.9 ± 1.2 mL/min/kg, <i>P</i> = 0.4). No difference between HIIT and MICT groups (increase by 10% in HIIT and 8% in MICT, <i>P</i> > 0.99)
Suryanegara <i>et al</i> [27], 2019	HIIT : Cycle ergometry sessions, exercise intensity with scale ranging from 6 to 20 (5 min of warm up of increasing intensity from 9 to 13, then intensity 16-17 with pedal rate > 80 rev/min for five intervals of 2 min for the first week. It inclined 10s for every week until it reached 3 min and 50s of interval after 12 weeks of training. Each interval was followed with 3 min recovery cycle including 90s of passive recovery. CON : No intervention	3 times/wk	40-60 min	12 wk	Peak VO ₂	No difference in peak VO ₂ within HIIT (from 15.4 ± 2.9 to 15.2 ± 2.2 mL/min/kg, <i>P</i> = 0.52) and within CON group (from 15.5 ± 3.1 to 15.0 ± 2.4 mL/min/kg, <i>P</i> = 0.37). No difference in peak VO ₂ between HIIT and the control group (<i>P</i> = 0.71)
Mortensen <i>et al</i> [28], 2019	HIIT : 20 min of cycling consisting of 10 times 1 min at 95% Wpeak and 1 min of active recovery 20% Wpeak). END : 40 minutes of cycling at 50% of Wpeak	3 times/wk	HIIT : 20 min. END : 40 min	11 wk	Peak VO ₂ , Leg blood flow	Peak VO₂ : ↑ in HIIT (from 29 ± 6 to 35 ± 7 mL/min/kg, <i>P</i> < 0.01) and END groups (from 28 ± 6 to 31 ± 8 mL/min/kg, <i>P</i> < 0.05). Leg blood flow : No difference within HIIT (from 1.56 ± 0.09 to 1.44 ± 0.09 L/min, <i>P</i> > 0.05) and END group (from 1.42 ± 0.13 to 1.26 ± 0.18 L/min, <i>P</i> > 0.01)
Baasch-Skytte <i>et al</i> [29], 2020	10-20-30 : 10-min low-intensity warmup before completing three 5-min sessions of 10-20-30 training interspersed by 2 min of passive recovery. 5 consecutive 1-min exercise periods divided into 30, 20 and 10 s at low (approximately 30-100 W), moderate (approximately 60-180 W) and maximal (≥ 400 W) intensity. MICT : 50 minutes of moderate-intensity continuous cycling at an intensity of 60%-75% of HR reserve	3 times/wk	10-20-30 : 31 min. MICT : 50 min	10 wk	Peak VO ₂	Peak VO ₂ increased within 10-20-30 and MICT groups after exercise training by 1.8 ± 2.9 and 2.2 ± 3.2 mL/min/kg, respectively (<i>P</i> < 0.01). No difference in peak VO ₂ between 10-20-30 and MICT groups (<i>P</i> = 0.86)
Gildea <i>et al</i> [30], 2021	5 min warm up and 5 min cool down before and after each session on an aerobic machine (elliptical, treadmill, rowing, or cycle ergometer) in both groups. HIIT : 10 × 60-s bouts of high-intensity cycling interspersed with 60 sec of light cycling at a power output equivalent to 70% of the difference between participant's peak power output (PO peak) and the power output at ventilatory threshold (VT). Target heart rate of 90% HR max. MICT : 50 min of cycling at a power output equivalent to 80%-90% of ventilatory threshold. CON : No intervention	3 times/wk	HIIT : 30 min. MICT : 60 min	12 wk	Peak VO ₂ , Muscle fractional O ₂ extraction [% Δ (HHb+Mb)] versus %PO slope of the first linear segment (slope1]	Peak VO₂ : ↑ in HIIT (from 26.4 ± 4.0 to 30.0 ± 4.0 mL/min/kg, <i>P</i> < 0.05) and MICT groups (from 22.1 ± 4.4 to 27.6 ± 5.1 mL/min/kg, <i>P</i> < 0.05). It remained unchanged in the control group (from 21.5 ± 3.6 to 22.0 ± 3.4 mL/min/kg, <i>P</i> > 0.05). Increase was greater in the HIIT group compared to the control group (<i>P</i> < 0.05), but no significant difference between HIIT and MICT groups (<i>P</i> > 0.05). Muscle fractional O₂ extraction : Improvement within HIIT (from 1.89 ± 0.63 to 1.31 ± 0.12, <i>P</i> < 0.05) and MICT groups (from 1.96 ± 0.60 to 1.37 ± 0.22, <i>P</i> < 0.05). No difference in the control group (from 1.80 ± 0.49 to 1.85 ± 0.25, <i>P</i> > 0.05). Improvement was higher in the HIIT and MICT groups compared to the control group (<i>P</i> < 0.05), but no significant difference between HIIT and MICT groups (<i>P</i> > 0.05)
Li <i>et al</i> [31], 2022	5 min warm-up and 5 min to complete the relaxation and finishing process in both groups. HIIT : 1 min power cycling (80%-95% maximal oxygen uptake (VO ₂ max), 1 min passive or active rest (25%-30% VO ₂ max), and 2 min rounds of eight groups. MICT : Power bike for 30 min of continuous training (50%-70% VO ₂ max). CON : Relevant medicine, exercise, and nutrition knowledge	5 times/wk	HIIT : 25 min. MICT : 40 min	12 wk	Peak VO ₂ (L/min)	HIIT (from 3.4 ± 0.4 to 3.9 ± 0.4 L/min, <i>P</i> = 0.001) and MICT groups (from 3.5 ± 0.4 to 3.7 ± 0.5 L/min, <i>P</i> = 0.001). It remained unchanged in the control group (from 3.5 ± 0.4 to 3.5 ± 0.5 L/min, <i>P</i> > 0.05). Increase was higher in the HIIT group compared to the MICT group (difference: 0.52 ± 0.06 vs 0.31 ± 0.13, <i>P</i> < 0.001)

CON: Control group; END: Endurance training; HI: Moderate-to-high intensity; HIIT: High-intensity interval training; HR: Heart rate; HHb: Hemoglobin; MICT: Moderate intensity continuous training; Mb: Myoglobin; LI: low-to-moderate intensity; PO: Power output; NA: Not available.

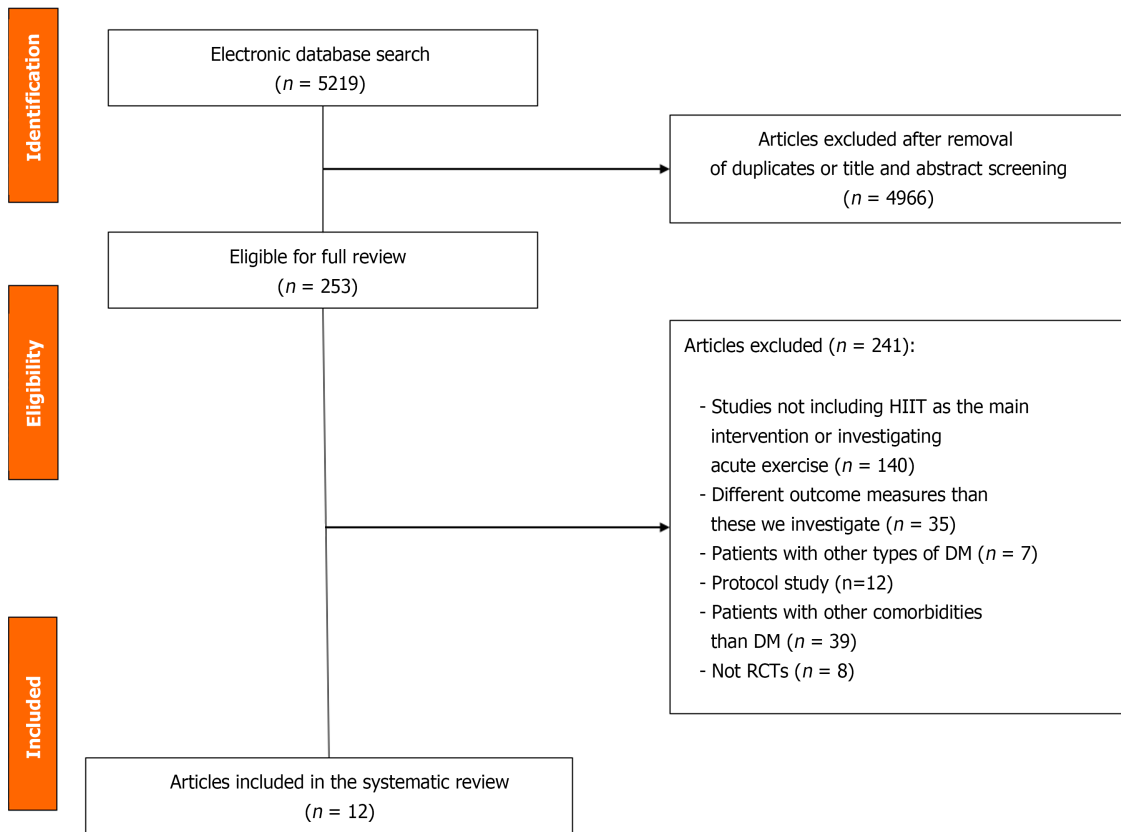


Figure 1 PRISMA flowchart regarding the screening results of the systematic review. DM: Diabetes mellitus; HIIT: High-intensity interval training; RCTs: Randomized controlled trials.

(difference: 4.1 ± 2.9 vs 1.2 ± 2.2 mL/min/kg, respectively; $P = 0.002$). In the second study[31], HIIT group increased peak VO_2 from 3.4 ± 0.4 to 3.9 ± 0.4 L/min ($P = 0.001$) and MICT group from 3.5 ± 0.4 to 3.7 ± 0.5 L/min ($P = 0.001$) while it remained unchanged in the control group (from 3.5 ± 0.4 to 3.5 ± 0.5 L/min, $P > 0.05$). Increase was higher in the HIIT group compared to the MICT group (difference: 0.52 ± 0.06 vs 0.31 ± 0.13 , $P < 0.001$).

On the other hand, Terada *et al*[21] did not observe any differences either within (HIIT: From 22.8 ± 5.4 to 24.3 ± 7.4 mL/min/kg, $P > 0.05$; MICT: From 18.1 ± 2.7 to 18.9 ± 4.1 mL/min/kg, $P > 0.05$) or between the 2 groups ($P > 0.05$). More recent studies performed the last 5 years[25,26,29,30], did not manage to show additional benefits of HIIT over MICT, although peak VO_2 improved after exercise training within each group. Finally, a single study[27] which compared HIIT to usual care did not manage to show differences in peak VO_2 within (HIIT: from 15.4 ± 2.9 to 15.2 ± 2.2 mL/min/kg, $P = 0.52$; control: From 15.5 ± 3.1 to 15.0 ± 2.4 mL/min/kg, $P = 0.37$) or between the 2 groups ($P = 0.71$).

Effect of exercise training on endothelial function

Four studies[23,24,28,30] explored the effects of HIIT on endothelial function in type 2 diabetes patients. Two of them assessed the influence of HIIT in FMD[23,24], 1 study assessed leg blood flow during knee-extensions[28] and the last one assessed muscle fractional O₂ extraction[30]. In both studies assessing FMD[23,24], FMD further improved in HIIT compared to MICT and/or the control group ($P < 0.05$). In the study of Mitranun *et al*[23], FMD increased from 5.4 ± 1.1 to $7.4 \pm 0.9\%$ ($P < 0.05$) in HIIT and from 4.8 ± 1.6 to $6.1 \pm 1.8\%$ ($P < 0.05$) in MICT group. Control group did not show any difference (from 5.1 ± 1.3 to $5.6 \pm 1.8\%$, $P > 0.05$). Similarly, in the study of Hollekim-Strand *et al*[24] FMD increased from 9.2 ± 9.6 to $18.5 \pm 9.6\%$ ($P = 0.004$) in the HIIT group, but it remained unchanged in the MICT group (from 13.0 ± 9.8 to $13.0 \pm 9.9\%$, $P = 0.99$).

A more recent study by Mortensen *et al*[28] that investigated leg blood flow during knee-extension did not observe any differences within HIIT (from 1.56 ± 0.09 to 1.44 ± 0.09 L/min, $P > 0.05$) and END group (from 1.42 ± 0.13 to 1.26 ± 0.18 L/min, $P > 0.01$) after exercise training. Finally, Gildea *et al*[30] investigated muscle deoxygenation [deoxygenated hemoglobin and myoglobin, (HHb + Mb)] by near-infrared spectroscopy at the vastus lateralis muscle in adults with T2DM after HIIT, MICT and usual care. They observed that there was improvement within HIIT (from 1.89 ± 0.63 to 1.31 ± 0.12 , $P < 0.05$) and MICT groups (from 1.96 ± 0.60 to 1.37 ± 0.22 , $P < 0.05$), but no difference was found in the control group (from 1.80 ± 0.49 to 1.85 ± 0.25 , $P > 0.05$). Beneficial effects of HIIT and MICT were superior compared to usual care ($P < 0.05$), but there was no significant difference between HIIT and MICT

groups ($P > 0.05$).

DISCUSSION

The present systematic review investigated the effectiveness of HIIT on cardiorespiratory fitness and endothelial function in type 2 diabetic patients and compared HIIT with other exercise training regimens including MICT, as well as usual care. Through our systematic review, we demonstrated a significant improvement in peak VO_2 and FMD after HIIT in T2DM. By the findings of the present systematic review we also emerged that HIIT may be superior to MICT in functional capacity indices and endothelial function.

Peak VO_2 is considered the best available index for assessment of exercise capacity[32] and is also a strong predictor of outcomes in many cardiopulmonary diseases[33-35]. Reduced peak VO_2 bears a solid negative prognostic value both in the general population[36] and in high risk patients with cardiovascular diseases[37-39]. Moreover, in T2DM subjects, reduced exercise capacity appears to be a predictor of all-cause mortality[40]. Asymptomatic T2DM patients, with no clinically evident cardiovascular disease or overt diabetic complications, usually present reduced exercise tolerance and reduced maximal aerobic capacity, measured by peak VO_2 , compared to normal subjects as shown through a big number of studies the last years[41-46]. This reduction corresponds to 20%-30% in peak VO_2 in both adults and adolescents[47-49]. Sustained hyperglycemia leading to poor metabolic control and microvascular complications, could clearly indicate a potential pathophysiological mechanism and a relationship between reduced peak VO_2 and diabetes[47,50,51]. Vice versa, low cardiorespiratory fitness seems to be associated with an increased risk for impaired glycemic control[52]. Therefore, improvement on functional capacity may also improve HbA1c in T2DM.

Aerobic exercise intensity seems to be the primary stimulus for improved peak VO_2 in patients with T2DM[53]. In our study, we showed that HIIT is probably superior to other exercise training regimens, and especially MICT, on peak VO_2 and endothelial function in these patients. These findings are in agreement with the findings of previous meta-analyses not only in T2DM, but also in cardiovascular diseases. A recent meta-analysis by Liu *et al*[54] showed that HIIT presents a great improvement in relative peak VO_2 (mean difference: 3.37 mL/kg/min, 95%CI: 1.88 to 4.87, $P < 0.0001$) and absolute peak VO_2 (mean difference: 0.37 L/min, 95%CI: 0.28 to 0.45, $P < 0.00001$) compared to MICT. Another meta-analysis by Xie *et al*[55], included 21 studies involving 736 participants with cardiac diseases and showed that HIIT was associated with greater improvement in peak VO_2 (mean difference 1.76 mL/kg/min, 95%CI: 1.06 to 2.46 mL/kg/min, $P < 0.001$) and VO_2 at anaerobic threshold (mean difference 0.90 mL/kg/min, 95%CI: 0.0 to 1.72 mL/kg/min, $P = 0.03$). Finally, another recent meta-analysis by Gomes-Neto *et al*[56] investigated the effects of HIIT *vs* MICT in coronary artery disease patients. Authors included 12 studies with 609 patients and showed that HIIT resulted in improvement in peak VO_2 weighted mean difference (1.3 mL/kg/min, 95%CI: 0.6-1.9, $n = 594$) compared with MICT.

As far as endothelial function is concerned, our study showed that HIIT results in greater improvement in FMD and other indices of microcirculation compared to MICT and usual care in T2DM. A recent meta-analyses by Qiu *et al*[57] investigated different types of exercise on endothelial function in T2DM. Authors included 16 datasets and, although they found that exercise training resulted in an overall improvement in FMD by 1.77% (95%CI: 0.94%-2.59%), however, HIIT did not significantly improve FMD over MICT. The relationship between FMD and endothelial function is quite significant, as it has been shown that every 1% increase in FMD is correlated with an estimated 13% risk reduction of cardiovascular events[58]. Moreover, this increase in FMD from a non-pharmacological therapy is even larger than those from pharmacological interventions like statins[59] or phosphodiesterase inhibitors[60], which result in an improvement in FMD by 0.94% (95%CI: 0.38%-1.5%) and 2.19% (95%CI: 0.48%-3.90%), respectively.

Potential pathophysiological mechanisms regarding the beneficial effects of exercise training on endothelial function have been proposed over the years. Three of them seem to be the most prevailing. The first one supports that the increase in blood flow caused by exercise training augments shear stresses on the endothelium, leading to increased nitric oxide synthesis and bioavailability[61]. The second one describes reduction in oxidative stress and the expression of pro-inflammatory molecules after exercise training, which are considered as initiating factors for endothelial dysfunction[62]. Finally, the last one suggests the promotion of endothelial repair and the facilitation of vascular angiogenesis, as a result of the restoration of the function of endothelial progenitor cells after exercise training[63,64].

Arterial stiffness in another characteristic dysfunction in T2DM patients, being recognized as an important predictor for hypertension. Pulse wave velocity (PWV) and augmentation index (Aix) are both criteria for clinical assessment of arterial stiffness[65]. Previous studies have shown that aerobic exercise significantly reduces both PWV[66,67] and Aix[66], increases systemic arterial compliance and, indeed, there is an inverse relationship between exercise intensity and reductions in arterial stiffness, which may suggest that HIIT could be a more effective modality than MICT[66,67]. HIIT is thought to induce a greater amount of shear stress on arterial/vascular walls, particularly in exercising muscles, through utilizing small periods of higher intensity activity, which may explain the larger benefits seen

in vascular function outcomes[68,69]. The well-established beneficial effects of HIIT on endothelial indices in T2DM patients result in improvement in arterial stiffness, as arterial stiffness is mainly influenced by vascular endothelial function[70]. HIIT has been reported to increase endothelial eNOS protein content and NO availability and cause significant improvements in brachial artery endothelial-dependent dilatation and aortic stiffness in patients with elevated CVD risk[15]. Finally, arterial stiffness-associated indices such as arterial velocity pulse index and arterial pressure volume index seem to significantly improve after HIIT, lowering close to the normal ranges[71].

Clinical perspectives

Patients with T2DM may present endothelial dysfunction, impaired functional capacity, exercise intolerance and poor prognosis after a few years since the diagnosis due to complications. The present systematic review aims to evaluate the additional beneficial effects of HIIT programs on prognostic cardiorespiratory fitness indices such as peak VO₂, as well as endothelial function in type 2 diabetic patients in comparison to other aerobic exercise regimens. Moreover, it tries to present all the potential pathophysiological mechanisms of diabetes on endothelial dysfunction and, thus, exercise intolerance. Exercise has been proven to be safe and efficient. Initial screening assessment and appropriate exercise training protocols based on HIIT should be implemented in outpatient settings under supervision in patients with T2DM. A multidisciplinary team approach is necessary prior to participation at these programs. The importance of HIIT does not limit only to cardiorespiratory or endothelial indices, but there are also practical benefits in T2DM patients' performance by improving their duration and strength in daily activities and reducing their fatigue and dyspnea, indicating thus, improvement in their quality of life. Other additional benefits of aerobic exercise are better glycemic control, improvement in arterial stiffness, as well as improvement in their lipidemic and inflammatory profile.

Limitations

Randomized controlled studies regarding the effectiveness of HIIT in patients with T2DM are limited in literature and, therefore, this field still remains under investigation. A potential limitation of the systematic review is that the included studies may present heterogeneity of the study samples, due to different mean age, different duration since diagnosis, and different functional capacity at baseline. As a result, the effects of HIIT on cardiorespiratory fitness indices in patients of different age (for instance between 18y and 70y) may be different due to different arterial stiffness levels.

Our hypothesis of heterogeneity is based on observed differences among means of age, duration since diagnosis, *etc.* among samples of the included RCTs and cannot be confirmed by statistical methods. The reason that we did not perform a meta-analysis was that we did not have access to data of all the included RCTs. Another limitation is that there were studies without adjustment for multiple comparisons and potential confounders in their results. However, the results were consistent and clear in all studies supporting final conclusions. Finally, patients who undertook an exercise intervention may have been more motivated with better functional status than those who did not participate in training programs and, thus, we could not exclude a potential inclusion bias.

CONCLUSION

Regular aerobic exercise training has been shown to have beneficial effects on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes mellitus. HIIT seems to be superior by improving these parameters to a greater extent than MICT. This type of exercise training regimen should be established as significant part of the non-pharmacological therapeutic strategy of this metabolic syndrome. Larger multicenter RCTs are required in order to better understand the potential mechanisms of exercise in T2DM and its therapeutic targets, and define its main characteristics including type, duration, frequency and intensity.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes mellitus (T2DM) is a chronic metabolic syndrome characterized by insulin resistance and hyperglycemia that may lead to endothelial dysfunction, reduced functional capacity and exercise intolerance. The improvement of endothelial dysfunction is associated with a significant increase in exercise capacity.

Research motivation

High intensity interval training (HIIT) seems to be superior than moderate-intensity continuous training (MICT) in cardiovascular diseases by improving endothelial indices and cardiorespiratory fitness to a

greater extent. However, the beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited.

Research objectives

The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present updated knowledge in literature.

Research methods

A search on three large databases was performed, selecting randomized controlled trials (RCTs) published between 2012 and 2022 regarding exercise training programs in patients with T2DM. The primary outcome was peak VO₂ and the secondary outcome was endothelial function assessed either by FMD or other indices of microcirculation.

Research results

Twelve RCTs resulted in 661 participants in total. Peak VO₂ increased in 10 out of 12 studies after HIIT. Four out of 10 studies demonstrated additional beneficial effects of HIIT over MICT or other exercise regimens. In 2 out of 4 studies, HIIT further improved endothelial function compared to MICT and/or the control group.

Research conclusions

Regular aerobic exercise has been proven to be safe and efficient and presents beneficial effects on cardiorespiratory fitness and endothelial function in T2DM patients. HIIT may be superior by improving these parameters to a greater extent than MICT.

Research perspectives

Initial screening assessment and appropriate exercise training protocols based on HIIT should be implemented in outpatient settings under supervision in patients with T2DM. A multidisciplinary team approach is necessary prior to participation at these programs.

FOOTNOTES

Author contributions: Dimopoulos S designed the research; Kourek C performed the research; Kourek C, and Dimopoulos S analysed the data; Kourek C wrote the paper; All authors revised the paper.

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