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

Christos Kourek, Eleftherios Karatzanos, Vasiliki Raidou, Ourania Papazachou, Anastassios Philippou, Serafim Nanas, Stavros Dimopoulos

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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 VO<sub>2</sub> 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 VO<sub>2</sub> 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 VO<sub>2</sub>; 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 VO<sub>2</sub> 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.

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## MATERIALS AND METHODS

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### 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  $\geq 18$  years, v. exercise training programs using HIIT with duration of  $\geq 2$  wk compared to either MICT or controls and; and (5) outcome measures focused on either cardiorespiratory fitness assessed by peak oxygen uptake (peak  $\text{VO}_2$ ) and/or endothelial function through FMD or other indices of microcirculation (leg blood flow during knee-extensions, muscle fractional  $\text{O}_2$  extraction through near-infrared spectroscopy, *etc.*). HIIT was defined as exercise sessions performing intervals of exercise at a high intensity (according to the initial  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{HbA}_{1c}$  ranged from 6.4 to 7.5% while BMI was from 26.5 to 33.9  $\text{kg}/\text{m}^2$ . 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  $\text{VO}_2$ . Peak  $\text{VO}_2$  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 <sup>a</sup>	√	√	√	√		√	√			√	√	√
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

<sup>a</sup>Eligibility 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 VO<sub>2</sub>.

Specifically, Balducci *et al*[20] found an increase in peak VO<sub>2</sub> 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 VO<sub>2</sub> 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 <sup>2</sup> )	HbA <sub>1c</sub> (%)
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	6.0 ± 2 <sup>a</sup> ; 6.1 ± 2 <sup>a</sup> ; 6.2 ± 2 <sup>a</sup>
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 <sup>a</sup> ; 55.5 ± 6.0 <sup>a</sup>
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

<sup>a</sup>Expressed 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.

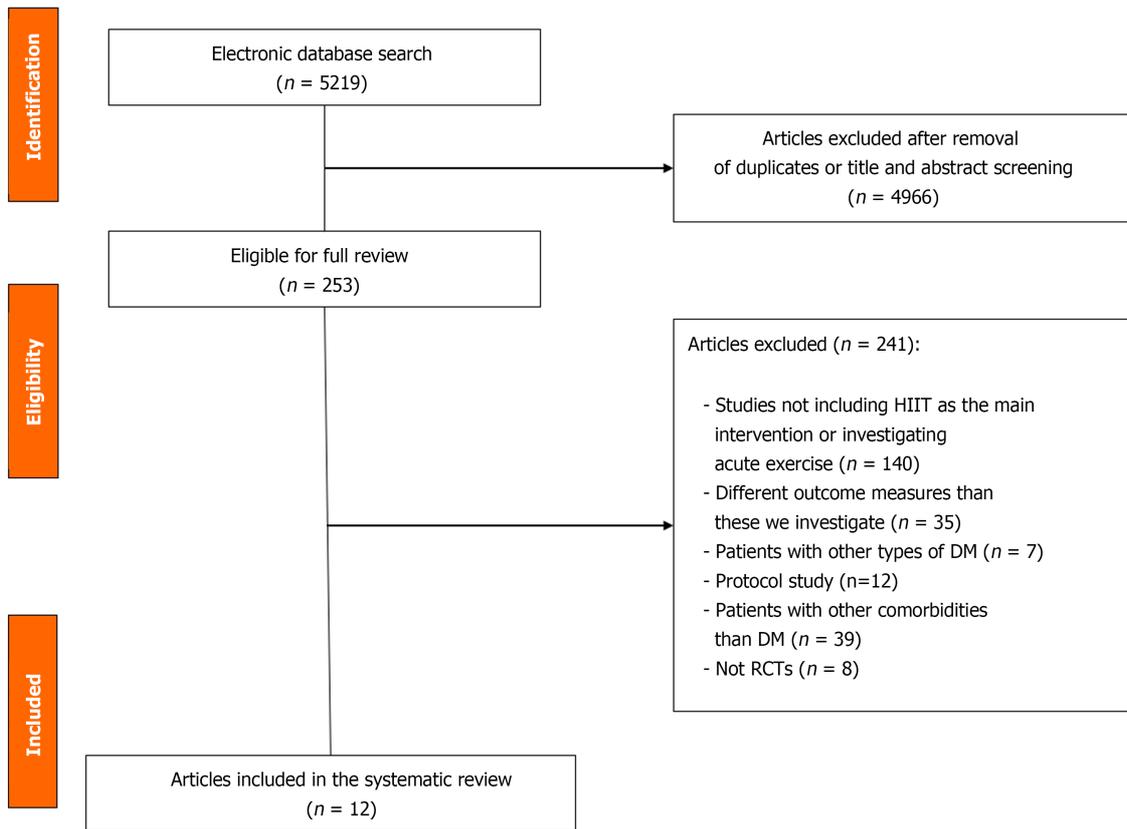
25.2 ± 2.0 mL/min/kg,  $P > 0.05$ ). In addition, increase in peak VO<sub>2</sub> was higher in the HIIT compared to the MICT and the control group ( $P < 0.05$ ). In another study by Mitranun *et al*[23], HIIT group increased peak VO<sub>2</sub> from 24.2 ± 1.6 to 30.3 ± 1.2 mL/min/kg ( $P < 0.05$ ), 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 VO<sub>2</sub> 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> ]. <b>HI:</b> Aerobic training at 70% of predicted VO <sub>2</sub> max and resistance training at 60% of predicted 1-RM. <b>LI:</b> Aerobic training at 55% of predicted VO <sub>2</sub> 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 <sub>2</sub>	↑ peak VO <sub>2</sub> 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 <sub>2</sub> 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	<b>HIIT:</b> Treadmill training or cycling intervals 1' (100% VO <sub>2</sub> max). And 3' (20% VO <sub>2</sub> max). <b>MICT:</b> continuous treadmill training or cycling (40% VO <sub>2</sub> max)	5 times/wk	30-60 min	12 wk	Peak VO <sub>2</sub>	No difference in peak VO <sub>2</sub> 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 <sub>2</sub> between HIIT and MICT groups ( <i>P</i> > 0.05)
Karstoft <i>et al</i> [22], 2013	<b>HIIT:</b> Interval walking training with 3-min repetitions at low (< 70% peak energy-expenditure rate) and high (> 70%) intensity. <b>MICT:</b> Continuous - walking training (< 55%). <b>CON:</b> No intervention	5 times/wk	60 min	16 wk	Peak VO <sub>2</sub>	↑ peak VO <sub>2</sub> 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 <sub>2</sub> 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	<b>HIIT:</b> 4-6 intervals (85% VO <sub>2</sub> max) during 1 min following 4 min of active rest (50% VO <sub>2</sub> max.). <b>MICT:</b> 50%-65% VO <sub>2</sub> max. <b>CON:</b> No intervention	3 times/wk	30-40 min	12 wk	Peak VO <sub>2</sub> , FMD	<b>Peak VO<sub>2</sub>:</b> ↑ 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). <b>FMD:</b> ↑ 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	<b>HIIT:</b> 4 × 4' (90%-95% HR max). <b>MICT:</b> according to guidelines	<b>HIIT:</b> 3 times/wk. <b>MICT:</b> 210 min/wk	<b>HIIT:</b> 40 min. <b>MICT</b> : ≥ 10 min	12 wk	Peak VO <sub>2</sub> , FMD	<b>Peak VO<sub>2</sub>:</b> ↑ 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). <b>FMD:</b> ↑ 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	<b>HIIT:</b> 10 × 1 min intervals cycling at 95% of peak workload interspersed by 1 min active recovery. <b>END:</b> 40 min cycling at 50% of peak workload. <b>CON:</b> No intervention	3 times/wk	<b>HIIT:</b> 20 min. <b>END:</b> 40 min	11 wk	Peak VO <sub>2</sub>	↑ 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>	<b>HIIT:</b> 10-min warm-up and a 5-min cooldown at 70% of HR	4 times/wk	<b>HIIT:</b> 40 min. <b>MICT</b>	8 wk	Peak VO <sub>2</sub>	↑ 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. <b>MICT</b> : 10-min warm-up and a 5-min cooldown at 70% of HR peak, 32 min at 70% HR peak. <b>CON</b> : 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	<b>HIIT</b> : 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. <b>CON</b> : No intervention	3 times/wk	40-60 min	12 wk	Peak VO <sub>2</sub>	No difference in peak VO <sub>2</sub> 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 <sub>2</sub> between HIIT and the control group ( <i>P</i> = 0.71)
Mortensen <i>et al</i> [28], 2019	<b>HIIT</b> : 20 min of cycling consisting of 10 times 1 min at 95% Wpeak and 1 min of active recovery 20% Wpeak). <b>END</b> : 40 minutes of cycling at 50% of Wpeak	3 times/wk	<b>HIIT</b> : 20 min. <b>END</b> : 40 min	11 wk	Peak VO <sub>2</sub> , Leg blood flow	<b>Peak VO<sub>2</sub></b> : ↑ 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). <b>Leg blood flow</b> : 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	<b>10-20-30</b> : 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. <b>MICT</b> : 50 minutes of moderate-intensity continuous cycling at an intensity of 60%-75% of HR reserve	3 times/wk	<b>10-20-30</b> : 31 min. <b>MICT</b> : 50 min	10 wk	Peak VO <sub>2</sub>	Peak VO <sub>2</sub> 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 <sub>2</sub> 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. <b>HIIT</b> : 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. <b>MICT</b> : 50 min of cycling at a power output equivalent to 80%-90% of ventilatory threshold. <b>CON</b> : No intervention	3 times/wk	<b>HIIT</b> : 30 min. <b>MICT</b> : 60 min	12 wk	Peak VO <sub>2</sub> , Muscle fractional O <sub>2</sub> extraction [% Δ (HHb+Mb)] versus %PO slope of the first linear segment (slope1)]	<b>Peak VO<sub>2</sub></b> : ↑ 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). <b>Muscle fractional O<sub>2</sub> extraction</b> : 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. <b>HIIT</b> : 1 min power cycling (80%-95% maximal oxygen uptake (VO <sub>2</sub> max), 1 min passive or active rest (25%-30% VO <sub>2</sub> max), and 2 min rounds of eight groups. <b>MICT</b> : Power bike for 30 min of continuous training (50%-70% VO <sub>2</sub> max). <b>CON</b> : Relevant medicine, exercise, and nutrition knowledge	5 times/wk	<b>HIIT</b> : 25 min. <b>MICT</b> : 40 min	12 wk	Peak VO <sub>2</sub> (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 <i>vs</i> 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:  $4.1 \pm 2.9$  vs  $1.2 \pm 2.2$  mL/min/kg, respectively;  $P = 0.002$ ). In the second study[31], HIIT group increased peak  $VO_2$  from  $3.4 \pm 0.4$  to  $3.9 \pm 0.4$  L/min ( $P = 0.001$ ) and MICT group from  $3.5 \pm 0.4$  to  $3.7 \pm 0.5$  L/min ( $P = 0.001$ ) while it remained unchanged in the control group (from  $3.5 \pm 0.4$  to  $3.5 \pm 0.5$  L/min,  $P > 0.05$ ). Increase was higher in the HIIT group compared to the MICT group (difference:  $0.52 \pm 0.06$  vs  $0.31 \pm 0.13$ ,  $P < 0.001$ ).

On the other hand, Terada *et al*[21] did not observe any differences either within (HIIT: From  $22.8 \pm 5.4$  to  $24.3 \pm 7.4$  mL/min/kg,  $P > 0.05$ ; MICT: From  $18.1 \pm 2.7$  to  $18.9 \pm 4.1$  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  $15.4 \pm 2.9$  to  $15.2 \pm 2.2$  mL/min/kg,  $P = 0.52$ ; control: From  $15.5 \pm 3.1$  to  $15.0 \pm 2.4$  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 O<sub>2</sub> 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  $5.4 \pm 1.1$  to  $7.4 \pm 0.9\%$  ( $P < 0.05$ ) in HIIT and from  $4.8 \pm 1.6$  to  $6.1 \pm 1.8\%$  ( $P < 0.05$ ) in MICT group. Control group did not show any difference (from  $5.1 \pm 1.3$  to  $5.6 \pm 1.8\%$ ,  $P > 0.05$ ). Similarly, in the study of Hollekim-Strand *et al*[24] FMD increased from  $9.2 \pm 9.6$  to  $18.5 \pm 9.6\%$  ( $P = 0.004$ ) in the HIIT group, but it remained unchanged in the MICT group (from  $13.0 \pm 9.8$  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  $1.56 \pm 0.09$  to  $1.44 \pm 0.09$  L/min,  $P > 0.05$ ) and END group (from  $1.42 \pm 0.13$  to  $1.26 \pm 0.18$  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  $1.89 \pm 0.63$  to  $1.31 \pm 0.12$ ,  $P < 0.05$ ) and MICT groups (from  $1.96 \pm 0.60$  to  $1.37 \pm 0.22$ ,  $P < 0.05$ ), but no difference was found in the control group (from  $1.80 \pm 0.49$  to  $1.85 \pm 0.25$ ,  $P > 0.05$ ). 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  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$ , 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  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{VO}_2$  (mean difference: 3.37 mL/kg/min, 95%CI: 1.88 to 4.87,  $P < 0.0001$ ) and absolute peak  $\text{VO}_2$  (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  $\text{VO}_2$  (mean difference 1.76 mL/kg/min, 95%CI: 1.06 to 2.46 mL/kg/min,  $P < 0.001$ ) and  $\text{VO}_2$  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  $\text{VO}_2$  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 VO<sub>2</sub>, 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 VO<sub>2</sub> 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 VO<sub>2</sub> 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.

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## 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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## REFERENCES

- 1 Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health* 2020; **10**: 107-111 [PMID: 32175717 DOI: 10.2991/jegh.k.191028.001]

- 2 **Tönnies T**, Brinks R, Isom S, Dabelea D, Divers J, Mayer-Davis EJ, Lawrence JM, Pihoker C, Dolan L, Liese AD, Saydah SH, D'Agostino RB, Hoyer A, Imperatore G. Projections of Type 1 and Type 2 Diabetes Burden in the U.S. Population Aged <20 Years Through 2060: The SEARCH for Diabetes in Youth Study. *Diabetes Care* 2022; dc220945 [DOI: [10.2337/figshare.21514014](https://doi.org/10.2337/figshare.21514014)]
- 3 **Szmitko PE**, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S. New markers of inflammation and endothelial cell activation: Part I. *Circulation* 2003; **108**: 1917-1923 [PMID: [14568885](https://pubmed.ncbi.nlm.nih.gov/14568885/) DOI: [10.1161/01.cir.0000089190.95415.9f](https://doi.org/10.1161/01.cir.0000089190.95415.9f)]
- 4 **Dhananjayan R**, Koundinya KS, Malati T, Kutala VK. Endothelial Dysfunction in Type 2 Diabetes Mellitus. *Indian J Clin Biochem* 2016; **31**: 372-379 [PMID: [27605734](https://pubmed.ncbi.nlm.nih.gov/27605734/) DOI: [10.1007/s12291-015-0516-y](https://doi.org/10.1007/s12291-015-0516-y)]
- 5 **Maejima K**, Nakano S, Himeno M, Tsuda S, Makiishi H, Ito T, Nakagawa A, Kigoshi T, Ishibashi T, Nishio M, Uchida K. Increased basal levels of plasma nitric oxide in Type 2 diabetic subjects. Relationship to microvascular complications. *J Diabetes Complications* 2001; **15**: 135-143 [PMID: [11358682](https://pubmed.ncbi.nlm.nih.gov/11358682/) DOI: [10.1016/s1056-8727\(01\)00144-1](https://doi.org/10.1016/s1056-8727(01)00144-1)]
- 6 **O'Connor E**, Green S, Kiely C, O'Shea D, Egaña M. Differential effects of age and type 2 diabetes on dynamic vs. peak response of pulmonary oxygen uptake during exercise. *J Appl Physiol (1985)* 2015; **118**: 1031-1039 [PMID: [25701005](https://pubmed.ncbi.nlm.nih.gov/25701005/) DOI: [10.1152/jappphysiol.01040.2014](https://doi.org/10.1152/jappphysiol.01040.2014)]
- 7 **Kiely C**, O'Connor E, O'Shea D, Green S, Egaña M. Hemodynamic responses during graded and constant-load plantar flexion exercise in middle-aged men and women with type 2 diabetes. *J Appl Physiol (1985)* 2014; **117**: 755-764 [PMID: [25123197](https://pubmed.ncbi.nlm.nih.gov/25123197/) DOI: [10.1152/jappphysiol.00555.2014](https://doi.org/10.1152/jappphysiol.00555.2014)]
- 8 **Regensteiner JG**, Bauer TA, Reusch JE, Brandenburg SL, Sippel JM, Vogelsong AM, Smith S, Wolfel EE, Eckel RH, Hiatt WR. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. *J Appl Physiol (1985)* 1998; **85**: 310-317 [PMID: [9655791](https://pubmed.ncbi.nlm.nih.gov/9655791/) DOI: [10.1152/jappl.1998.85.1.310](https://doi.org/10.1152/jappl.1998.85.1.310)]
- 9 **Poitras VJ**, Hudson RW, Tschakovsky ME. Exercise intolerance in Type 2 diabetes: is there a cardiovascular contribution? *J Appl Physiol (1985)* 2018; **124**: 1117-1139 [PMID: [29420147](https://pubmed.ncbi.nlm.nih.gov/29420147/) DOI: [10.1152/jappphysiol.00070.2017](https://doi.org/10.1152/jappphysiol.00070.2017)]
- 10 **Pagan LU**, Gomes MJ, Okoshi MP. Endothelial Function and Physical Exercise. *Arq Bras Cardiol* 2018; **111**: 540-541 [PMID: [30365677](https://pubmed.ncbi.nlm.nih.gov/30365677/) DOI: [10.5935/abc.20180211](https://doi.org/10.5935/abc.20180211)]
- 11 **Higashi Y**. Exercise is a double-edged sword for endothelial function. *Hypertens Res* 2016; **39**: 61-63 [PMID: [26559608](https://pubmed.ncbi.nlm.nih.gov/26559608/) DOI: [10.1038/hr.2015.127](https://doi.org/10.1038/hr.2015.127)]
- 12 **Kourek C**, Alshamari M, Mitsiou G, Psarra K, Delis D, Linardatou V, Pittaras T, Ntalianis A, Papadopoulos C, Panagopoulou N, Vasileiadis I, Nanas S, Karatzanos E. The acute and long-term effects of a cardiac rehabilitation program on endothelial progenitor cells in chronic heart failure patients: Comparing two different exercise training protocols. *Int J Cardiol Heart Vasc* 2021; **32**: 100702 [PMID: [33392386](https://pubmed.ncbi.nlm.nih.gov/33392386/) DOI: [10.1016/j.ijcha.2020.100702](https://doi.org/10.1016/j.ijcha.2020.100702)]
- 13 **Kourek C**, Dimopoulos S, Alshamari M, Zouganeli V, Psarra K, Mitsiou G, Ntalianis A, Pittaras T, Nanas S, Karatzanos E. A Cardiac Rehabilitation Program Increases the Acute Response of Endothelial Progenitor Cells to Maximal Exercise in Heart Failure Patients. *Acta Cardiol Sin* 2022; **38**: 516-520 [PMID: [35873120](https://pubmed.ncbi.nlm.nih.gov/35873120/) DOI: [10.6515/ACS.202207\\_38\(4\).20220221B](https://doi.org/10.6515/ACS.202207_38(4).20220221B)]
- 14 **Hambrecht R**, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, Yu J, Adams V, Niebauer J, Schuler G. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation* 1998; **98**: 2709-2715 [PMID: [9851957](https://pubmed.ncbi.nlm.nih.gov/9851957/) DOI: [10.1161/01.cir.98.24.2709](https://doi.org/10.1161/01.cir.98.24.2709)]
- 15 **Sawyer BJ**, Tucker WJ, Bhammar DM, Ryder JR, Sweazea KL, Gaesser GA. Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults. *J Appl Physiol (1985)* 2016; **121**: 279-288 [PMID: [27255523](https://pubmed.ncbi.nlm.nih.gov/27255523/) DOI: [10.1152/jappphysiol.00024.2016](https://doi.org/10.1152/jappphysiol.00024.2016)]
- 16 **Khalafi M**, Sakhaei MH, Kazeminasab F, Symonds ME, Rosenkranz SK. The impact of high-intensity interval training on vascular function in adults: A systematic review and meta-analysis. *Front Cardiovasc Med* 2022; **9**: 1046560 [PMID: [36465439](https://pubmed.ncbi.nlm.nih.gov/36465439/) DOI: [10.3389/fcvm.2022.1046560](https://doi.org/10.3389/fcvm.2022.1046560)]
- 17 **Taylor JL**, Bonikowske AR, Olson TP. Optimizing Outcomes in Cardiac Rehabilitation: The Importance of Exercise Intensity. *Front Cardiovasc Med* 2021; **8**: 734278 [PMID: [34540924](https://pubmed.ncbi.nlm.nih.gov/34540924/) DOI: [10.3389/fcvm.2021.734278](https://doi.org/10.3389/fcvm.2021.734278)]
- 18 **Yue T**, Wang Y, Liu H, Kong Z, Qi F. Effects of High-Intensity Interval vs. Moderate-Intensity Continuous Training on Cardiac Rehabilitation in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2022; **9**: 845225 [PMID: [35282360](https://pubmed.ncbi.nlm.nih.gov/35282360/) DOI: [10.3389/fcvm.2022.845225](https://doi.org/10.3389/fcvm.2022.845225)]
- 19 **Rahmati M**, Malakoutinia F. Aerobic, resistance and combined exercise training for patients with amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Physiotherapy* 2021; **113**: 12-28 [PMID: [34555670](https://pubmed.ncbi.nlm.nih.gov/34555670/) DOI: [10.1016/j.physio.2021.04.005](https://doi.org/10.1016/j.physio.2021.04.005)]
- 20 **Balducci S**, Zanuso S, Cardelli P, Salvi L, Bazuro A, Pugliese L, Maccora C, Iacobini C, Conti FG, Nicolucci A, Pugliese G; Italian Diabetes Exercise Study (IDES) Investigators. Effect of high- versus low-intensity supervised aerobic and resistance training on modifiable cardiovascular risk factors in type 2 diabetes; the Italian Diabetes and Exercise Study (IDES). *PLoS One* 2012; **7**: e49297 [PMID: [23185314](https://pubmed.ncbi.nlm.nih.gov/23185314/) DOI: [10.1371/journal.pone.0049297](https://doi.org/10.1371/journal.pone.0049297)]
- 21 **Terada T**, Friesen A, Chahal BS, Bell GJ, McCargar LJ, Boulé NG. Feasibility and preliminary efficacy of high intensity interval training in type 2 diabetes. *Diabetes Res Clin Pract* 2013; **99**: 120-129 [PMID: [23183390](https://pubmed.ncbi.nlm.nih.gov/23183390/) DOI: [10.1016/j.diabres.2012.10.019](https://doi.org/10.1016/j.diabres.2012.10.019)]
- 22 **Karstoft K**, Winding K, Knudsen SH, Nielsen JS, Thomsen C, Pedersen BK, Solomon TP. The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2013; **36**: 228-236 [PMID: [23002086](https://pubmed.ncbi.nlm.nih.gov/23002086/) DOI: [10.2337/dc12-0658](https://doi.org/10.2337/dc12-0658)]
- 23 **Mitranun W**, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scand J Med Sci Sports* 2014; **24**: e69-e76 [PMID: [24102912](https://pubmed.ncbi.nlm.nih.gov/24102912/) DOI: [10.1111/sms.12112](https://doi.org/10.1111/sms.12112)]
- 24 **Hollekim-Strand SM**, Bjørgaas MR, Albrektsen G, Tjønnå AE, Wisløff U, Ingul CB. High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. *J Am Coll Cardiol* 2014; **64**: 1758-1760 [PMID: [25323267](https://pubmed.ncbi.nlm.nih.gov/25323267/) DOI: [10.1016/j.jacc.2014.07.971](https://doi.org/10.1016/j.jacc.2014.07.971)]
- 25 **Winding KM**, Munch GW, Iepsen UW, Van Hall G, Pedersen BK, Mortensen SP. The effect on glycaemic control of

- low-volume high-intensity interval training versus endurance training in individuals with type 2 diabetes. *Diabetes Obes Metab* 2018; **20**: 1131-1139 [PMID: 29272072 DOI: 10.1111/dom.13198]
- 26 **Hwang CL**, Lim J, Yoo JK, Kim HK, Hwang MH, Handberg EM, Petersen JW, Holmer BJ, Leey Casella JA, Cusi K, Christou DD. Effect of all-extremity high-intensity interval training vs. moderate-intensity continuous training on aerobic fitness in middle-aged and older adults with type 2 diabetes: A randomized controlled trial. *Exp Gerontol* 2019; **116**: 46-53 [PMID: 30576716 DOI: 10.1016/j.exger.2018.12.013]
  - 27 **Suryanegara J**, Cassidy S, Ninkovic V, Popovic D, Grbovic M, Okwose N, Trenell MI, MacGowan GG, Jakovljevic DG. High intensity interval training protects the heart during increased metabolic demand in patients with type 2 diabetes: a randomised controlled trial. *Acta Diabetol* 2019; **56**: 321-329 [PMID: 30387015 DOI: 10.1007/s00592-018-1245-5]
  - 28 **Mortensen SP**, Winding KM, Iepsen UW, Munch GW, Marcussen N, Hellsten Y, Pedersen BK, Baum O. The effect of two exercise modalities on skeletal muscle capillary ultrastructure in individuals with type 2 diabetes. *Scand J Med Sci Sports* 2019; **29**: 360-368 [PMID: 30480353 DOI: 10.1111/sms.13348]
  - 29 **Baasch-Skytte T**, Lemgart CT, Oehlenschläger MH, Petersen PE, Hostrup M, Bangsbo J, Gunnarsson TP. Efficacy of 10-20-30 training versus moderate-intensity continuous training on HbA1c, body composition and maximum oxygen uptake in male patients with type 2 diabetes: A randomized controlled trial. *Diabetes Obes Metab* 2020; **22**: 767-778 [PMID: 31903682 DOI: 10.1111/dom.13953]
  - 30 **Gildea N**, McDermott A, Rocha J, O'Shea D, Green S, Egaña M. Time-course of Vo(2) kinetics responses during moderate-intensity exercise subsequent to HIIT versus moderate-intensity continuous training in type 2 diabetes. *J Appl Physiol (1985)* 2021; **130**: 1646-1659 [PMID: 33792400 DOI: 10.1152/jappphysiol.00952.2020]
  - 31 **Li J**, Cheng W, Ma H. A Comparative Study of Health Efficacy Indicators in Subjects with T2DM Applying Power Cycling to 12 Weeks of Low-Volume High-Intensity Interval Training and Moderate-Intensity Continuous Training. *J Diabetes Res* 2022; **2022**: 9273830 [PMID: 35071605 DOI: 10.1155/2022/9273830]
  - 32 **Ahmadian HR**, Sclafani JJ, Emmons EE, Morris MJ, Leclerc KM, Slim AM. Comparison of Predicted Exercise Capacity Equations and the Effect of Actual versus Ideal Body Weight among Subjects Undergoing Cardiopulmonary Exercise Testing. *Cardiol Res Pract* 2013; **2013**: 940170 [PMID: 23653881 DOI: 10.1155/2013/940170]
  - 33 **ERS Task Force**, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, O'Donnell DE, Puente-Maestu L, Schols AM, Singh S, Whipp BJ. Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; **29**: 185-209 [PMID: 17197484 DOI: 10.1183/09031936.00046906]
  - 34 **Ferrazza AM**, Martolini D, Valli G, Palange P. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. *Respiration* 2009; **77**: 3-17 [PMID: 19145106 DOI: 10.1159/000186694]
  - 35 **Pichurko BM**. Exercising your patient: which test(s) and when? *Respir Care* 2012; **57**: 100-10; discussion 110 [PMID: 2222129 DOI: 10.4187/respcare.01428]
  - 36 **Blair SN**, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989; **262**: 2395-2401 [PMID: 2795824 DOI: 10.1001/jama.262.17.2395]
  - 37 **Nauman J**, Nes BM, Lavie CJ, Jackson AS, Sui X, Coombes JS, Blair SN, Wisløff U. Prediction of Cardiovascular Mortality by Estimated Cardiorespiratory Fitness Independent of Traditional Risk Factors: The HUNT Study. *Mayo Clin Proc* 2017; **92**: 218-227 [PMID: 27866655 DOI: 10.1016/j.mayocp.2016.10.007]
  - 38 **Mirza KK**, Szymanski MK, Schmidt T, de Jonge N, Brahmabhatt DH, Billia F, Hsu S, MacGowan GA, Jakovljevic DG, Agostoni P, Trombara F, Jorde U, Rochlani Y, Vandersmissen K, Reiss N, Russell SD, Meyns B, Gustafsson F; PRO-VAD Investigators. Prognostic Value of Peak Oxygen Uptake in Patients Supported With Left Ventricular Assist Devices (PRO-VAD). *JACC Heart Fail* 2021; **9**: 758-767 [PMID: 34391745 DOI: 10.1016/j.jchf.2021.05.021]
  - 39 **Coeckelberghs E**, Buys R, Goetschalckx K, Cornelissen VA, Vanhees L. Prognostic value of the oxygen uptake efficiency slope and other exercise variables in patients with coronary artery disease. *Eur J Prev Cardiol* 2016; **23**: 237-244 [PMID: 25633586 DOI: 10.1177/2047487315569410]
  - 40 **Church TS**, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med* 2005; **165**: 2114-2120 [PMID: 16217001 DOI: 10.1001/archinte.165.18.2114]
  - 41 **Look AHEAD Research Group**, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145-154 [PMID: 23796131 DOI: 10.1056/NEJMoa1212914]
  - 42 **Francisco CO**, Catai AM, Moura-Tonello SC, Lopes SL, Benze BG, Del Vale AM, Leal AM. Cardiorespiratory fitness, pulmonary function and C-reactive protein levels in nonsmoking individuals with diabetes. *Braz J Med Biol Res* 2014; **47**: 426-431 [PMID: 24760118 DOI: 10.1590/1414-431x20143370]
  - 43 **Baldi JC**, Aoina JL, Oxenham HC, Bagg W, Doughty RN. Reduced exercise arteriovenous O<sub>2</sub> difference in Type 2 diabetes. *J Appl Physiol (1985)* 2003; **94**: 1033-1038 [PMID: 12571134 DOI: 10.1152/jappphysiol.00879.2002]
  - 44 **Guazzi M**, Belletti S, Bianco E, Lenatti L, Guazzi MD. Endothelial dysfunction and exercise performance in lone atrial fibrillation or associated with hypertension or diabetes: different results with cardioversion. *Am J Physiol Heart Circ Physiol* 2006; **291**: H921-H928 [PMID: 16461374 DOI: 10.1152/ajpheart.00986.2005]
  - 45 **Kiely C**, Rocha J, O'Connor E, O'Shea D, Green S, Egaña M. Influence of menopause and Type 2 diabetes on pulmonary oxygen uptake kinetics and peak exercise performance during cycling. *Am J Physiol Regul Integr Comp Physiol* 2015; **309**: R875-R883 [PMID: 26269520 DOI: 10.1152/ajpregu.00258.2015]
  - 46 **Mac Ananey O**, Malone J, Warmington S, O'Shea D, Green S, Egaña M. Cardiac output is not related to the slowed O<sub>2</sub> uptake kinetics in type 2 diabetes. *Med Sci Sports Exerc* 2011; **43**: 935-942 [PMID: 21131874 DOI: 10.1249/MSS.0b013e3182061cdb]

- 47 **Gürdal A**, Kasikcioglu E, Yakal S, Bugra Z. Impact of diabetes and diastolic dysfunction on exercise capacity in normotensive patients without coronary artery disease. *Diab Vasc Dis Res* 2015; **12**: 181-188 [PMID: 25670849 DOI: 10.1177/1479164114565631]
- 48 **Segerström ÅB**, Elgzyri T, Eriksson KF, Groop L, Thorsson O, Wollmer P. Exercise capacity in relation to body fat distribution and muscle fibre distribution in elderly male subjects with impaired glucose tolerance, type 2 diabetes and matched controls. *Diabetes Res Clin Pract* 2011; **94**: 57-63 [PMID: 21636160 DOI: 10.1016/j.diabres.2011.05.022]
- 49 **Bjornstad P**, Truong U, Dorosz JL, Cree-Green M, Baumgartner A, Coe G, Pyle L, Regensteiner JG, Reusch JE, Nadeau KJ. Cardiopulmonary Dysfunction and Adiponectin in Adolescents With Type 2 Diabetes. *J Am Heart Assoc* 2016; **5**: e002804 [PMID: 26994128 DOI: 10.1161/JAHA.115.002804]
- 50 **Estacio RO**, Regensteiner JG, Wolfel EE, Jeffers B, Dickenson M, Schrier RW. The association between diabetic complications and exercise capacity in NIDDM patients. *Diabetes Care* 1998; **21**: 291-295 [PMID: 9539998 DOI: 10.2337/diacare.21.2.291]
- 51 **Moxley EW**, Smith D, Quinn L, Park C. Relationships Between Glycemic Control and Cardiovascular Fitness. *Biol Res Nurs* 2018; **20**: 422-428 [PMID: 29609470 DOI: 10.1177/1099800418767572]
- 52 **Nojima H**, Yoneda M, Watanabe H, Yamane K, Kitahara Y, Sekikawa K, Yamamoto H, Yokoyama A, Hattori N, Kohno N; Hiroshima University Health Promotion Study group. Association between aerobic capacity and the improvement in glycemic control after the exercise training in type 2 diabetes. *Diabetol Metab Syndr* 2017; **9**: 63 [PMID: 28828040 DOI: 10.1186/s13098-017-0262-9]
- 53 **Grace A**, Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2017; **16**: 37 [PMID: 28292300 DOI: 10.1186/s12933-017-0518-6]
- 54 **Liu JX**, Zhu L, Li PJ, Li N, Xu YB. Effectiveness of high-intensity interval training on glycemic control and cardiorespiratory fitness in patients with type 2 diabetes: a systematic review and meta-analysis. *Aging Clin Exp Res* 2019; **31**: 575-593 [PMID: 30097811 DOI: 10.1007/s40520-018-1012-z]
- 55 **Xie B**, Yan X, Cai X, Li J. Effects of High-Intensity Interval Training on Aerobic Capacity in Cardiac Patients: A Systematic Review with Meta-Analysis. *Biomed Res Int* 2017; **2017**: 5420840 [PMID: 28386556 DOI: 10.1155/2017/5420840]
- 56 **Gomes-Neto M**, Durães AR, Reis HFCD, Neves VR, Martinez BP, Carvalho VO. High-intensity interval training versus moderate-intensity continuous training on exercise capacity and quality of life in patients with coronary artery disease: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2017; **24**: 1696-1707 [PMID: 28825321 DOI: 10.1177/2047487317728370]
- 57 **Qiu S**, Cai X, Yin H, Sun Z, Zügel M, Steinacker JM, Schumann U. Exercise training and endothelial function in patients with type 2 diabetes: a meta-analysis. *Cardiovasc Diabetol* 2018; **17**: 64 [PMID: 29720185 DOI: 10.1186/s12933-018-0711-2]
- 58 **van Sloten TT**, Henry RM, Dekker JM, Nijpels G, Unger T, Schram MT, Stehouwer CD. Endothelial dysfunction plays a key role in increasing cardiovascular risk in type 2 diabetes: the Hoorn study. *Hypertension* 2014; **64**: 1299-1305 [PMID: 25225211 DOI: 10.1161/HYPERTENSIONAHA.114.04221]
- 59 **Zhang L**, Gong D, Li S, Zhou X. Meta-analysis of the effects of statin therapy on endothelial function in patients with diabetes mellitus. *Atherosclerosis* 2012; **223**: 78-85 [PMID: 22326029 DOI: 10.1016/j.atherosclerosis.2012.01.031]
- 60 **Santi D**, Giannetta E, Isidori AM, Vitale C, Aversa A, Simoni M. Therapy of endocrine disease. Effects of chronic use of phosphodiesterase inhibitors on endothelial markers in type 2 diabetes mellitus: a meta-analysis. *Eur J Endocrinol* 2015; **172**: R103-R114 [PMID: 25277671 DOI: 10.1530/EJE-14-0700]
- 61 **Di Francescomarino S**, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. *Sports Med* 2009; **39**: 797-812 [PMID: 19757859 DOI: 10.2165/11317750-000000000-00000]
- 62 **Teixeira-Lemos E**, Nunes S, Teixeira F, Reis F. Regular physical exercise training assists in preventing type 2 diabetes development: focus on its antioxidant and anti-inflammatory properties. *Cardiovasc Diabetol* 2011; **10**: 12 [PMID: 21276212 DOI: 10.1186/1475-2840-10-12]
- 63 **Koutroumpi M**, Dimopoulos S, Psarra K, Kyprianou T, Nanas S. Circulating endothelial and progenitor cells: Evidence from acute and long-term exercise effects. *World J Cardiol* 2012; **4**: 312-326 [PMID: 23272272 DOI: 10.4330/wjcv.v4.i12.312]
- 64 **Kourek C**, Briasoulis A, Zouganeli V, Karatzanos E, Nanas S, Dimopoulos S. Exercise Training Effects on Circulating Endothelial and Progenitor Cells in Heart Failure. *J Cardiovasc Dev Dis* 2022; **9** [PMID: 35877584 DOI: 10.3390/jcdd9070222]
- 65 **Yamashina A**, Tomiyama H, Arai T, Koji Y, Yambe M, Motobe H, Glunizia Z, Yamamoto Y, Hori S. Nomogram of the relation of brachial-ankle pulse wave velocity with blood pressure. *Hypertens Res* 2003; **26**: 801-806 [PMID: 14621183 DOI: 10.1291/hypres.26.801]
- 66 **Ashor AW**, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2014; **9**: e110034 [PMID: 25333969 DOI: 10.1371/journal.pone.0110034]
- 67 **Huang C**, Wang J, Deng S, She Q, Wu L. The effects of aerobic endurance exercise on pulse wave velocity and intima media thickness in adults: A systematic review and meta-analysis. *Scand J Med Sci Sports* 2016; **26**: 478-487 [PMID: 26059748 DOI: 10.1111/sms.12495]
- 68 **MacInnis MJ**, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *J Physiol* 2017; **595**: 2915-2930 [PMID: 27748956 DOI: 10.1113/JP273196]
- 69 **Way KL**, Sultana RN, Sabag A, Baker MK, Johnson NA. The effect of high Intensity interval training versus moderate intensity continuous training on arterial stiffness and 24h blood pressure responses: A systematic review and meta-analysis. *J Sci Med Sport* 2019; **22**: 385-391 [PMID: 30803498 DOI: 10.1016/j.jsams.2018.09.228]
- 70 **da Silva MR**, Waclawovsky G, Perin L, Camboim I, Eibel B, Lehnen AM. Effects of high-intensity interval training on endothelial function, lipid profile, body composition and physical fitness in normal-weight and overweight-obese

- adolescents: A clinical trial. *Physiol Behav* 2020; **213**: 112728 [PMID: 31676260 DOI: 10.1016/j.physbeh.2019.112728]
- 71 **Hu J**, Liu M, Yang R, Wang L, Liang L, Yang Y, Jia S, Chen R, Liu Q, Ren Y, Zhu L, Cai M. Effects of high-intensity interval training on improving arterial stiffness in Chinese female university students with normal weight obese: a pilot randomized controlled trial. *J Transl Med* 2022; **20**: 60 [DOI: 10.21203/rs.3.rs-920357/v1]



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