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ORIGINAL ARTICLE

Effects of Physical Exercise on Left Ventricular Function in Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

Background: The incidence of diabetes mellitus in younger adults is rising over the years. The diabetic population has an increased risk of developing heart failure, and diabetic individuals with heart failure have four times greater mortality rate. Studies results about exercise effect on left ventricular function in type 2 diabetes mellitus are heterogenous.

Objective: This review aimed to analyze the effects of physical exercise on left ventricular dysfunction in type 2 diabetes mellitus (T2DM).

Methods: Only randomized clinical trials with humans published in English were included. Inclusion criteria were studies with type 2 diabetes patients, physical exercise, control group and left ventricular function. Exclusion criteria were studies with animals, children, teenagers, elderly individuals and athletes, presence of diet intervention, and patients with type 1 diabetes, cancer, cardiac, pulmonary, or neurological diseases. Electronic databases PubMed, Web of Science, Cochrane, and Scopus were last searched in September 2021. Risk of bias was assessed by the Physiotherapy Evidence Database (PEDro) scale.

Results: Five studies were included, representing 314 diabetic individuals submitted to resistance and aerobic exercise training. Of the variables analyzed, physical exercise improved peak torsion (PTo), global longitudinal strain, global strain rate (GSR), time to peak untwist rate (PUTR), early diastolic filling rate (EDFR) and peak early diastolic strain rate (PEDSR).

Conclusion: To our knowledge, this is the first systematic review on the effects of exercise on left ventricular function in T2DM including only randomized clinical trials with humans. Physical exercise seems to improve systolic and diastolic strain, twist, and torsion. High intensity exercise was reported to be superior to moderate intensity exercise in one study. This review was limited by the small number of studies and their heterogeneity regarding exercise protocols, follow-up period, exercise supervision and left ventricular function variables analyzed. This review was registered in PROSPERO (CRD42021234964).

Keywords: Diabetes Mellitus; Ventricular Function, Left; Exercise; Echocardiography.

Introduction

Diabetes mellitus has a high prevalence worldwide, and the incidence of type 2 diabetes mellitus (T2DM) in younger adults has increased over the years. About 90% of diabetic population have T2DM. When compared to the non-diabetic population, T2DM individuals have two times greater risk of developing cardiovascular diseases such as heart failure (HF). Diabetic individuals with HF have four times greater mortality rate when compared to diabetics without HF.[1]

Reduced left ventricular ejection fraction (LVEF) has been shown in T2DM regardless of the presence and extent coronary artery disease (CAD) and may partially explain worse cardiac survival rates in this population.[2] Individuals with impaired fasting glucose (IFG) and increased glycated hemoglobin (HbA1c) show lower absolute values of myocardial longitudinal strain of the left ventricle – i.e., global longitudinal systolic strain (GLS) - and global strain rate (GSR), and early and late diastolic strain rates) when compared to individuals with

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IFG and normal HbA1c.[3] Estimates of the prevalence of left ventricular diastolic dysfunction (LVDD) in T2DM range from 23% to 54%.[4] Moreover, diabetes duration longer than four years was independently associated with LVDD – left ventricular diastolic filling pressure (E/e´ ratio) greater than 15 (normal value <8) – even after adjustment for age, gender, body mass index (BMI), prior CAD, prior systemic hypertension and LVEF.[5]

Physical exercise has been considered an important non-pharmacological treatment strategy for diabetes and its complications.[6–8] T2DM pre-clinical and clinical studies have shown beneficial effects of exercise including weight loss, glycemic control, insulin signaling, cardiac and vascular function improvement,[8–10] improvement of cardiorespiratory fitness,[11,12] risk reduction of cardiovascular diseases and delayed onset of diabetic cardiomyopathy.[9]

Aerobic and resistance exercises have known benefits to cardiovascular function such as improvement in the early preload measure of diastolic function (e') and GLS.[10] T2DM individuals should ideally perform both types of exercise training for optimal health outcomes.[7] Guidelines recommend at least 150 minutes of moderate-to-vigorous aerobic exercise a week and 2-3 sessions per week of moderate-to-vigorous intensity resistance exercise.[7,13,14]

While studies have shown many beneficial effects of physical training on several organic systems,[7,10–14] review studies of randomized clinical trials focusing the effect of physical exercise on left ventricular function in T2DM are lacking. So, this systematic review aimed to provide an overview of the effects of physical exercise interventions on left ventricular systolic and diastolic function in T2DM individuals.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] and was registered in PROSPERO (CRD42021234964).

Eligibility criteria

The eligibility criteria were based on the PICO strategy (P=population, T2DM; I=intervention, physical exercise training; C=comparison, control group; O=outcome, left ventricular function).[16] Only randomized clinical trials with a control group published in English were included.

Exclusion criteria were studies with animals, children, teenagers, elderly individuals and athletes, presence of diet intervention, patients with cardiac diseases (myocardial ischemia, valve stenosis or insufficiency, or rhythm disorders), pulmonary and/or neurological diseases, type 1 diabetes, and cancer.

Information sources and search strategy

The electronic databases PubMed, Web of Science, Cochrane, and Scopus were searched for articles published between 2010 and February 2021, using Mesh Terms: (exercise OR training) AND ("left ventricular function" OR diastolic OR systolic) AND (type 2 diabetes). In PubMed, the search strategy was restricted to "randomized clinical trials", "clinical trials" and "humans".

Selection and data collection process

The electronic search was independently performed by two authors between February and May 2021, and another search was conducted in September 2021 by the same authors. In case of disagreement, a third investigator was consulted. Data were independently collected from all included reports by the same two authors.

Data systematization and extraction were conducted using the StArt software[17] for systematic reviews.

No left ventricular function variable was chosen for analysis due to the reduced number of randomized clinical trials found. The variables analyzed in the included studies were LVEF,[18–21] peak systolic tissue Doppler velocity (S´),[20,22] GLS,[19,21,22] peak endocardial circumferential strain (PECS),[22] peak whole wall circumferential strain (PWWCS),[18] GSR,[21,22] peak twist (PT),[22] peak twist rate (PTR),[26] peak torsion (PTo),[22] peak early diastolic tissue Doppler velocity (e´ wave),[20–22] transmitral peak early diastolic velocity (E wave),[20,22] diastolic filling pressure (E/e´ ratio),[18,20,22] transmitral peak late diastolic velocity (A wave),[20] E/A ratio,[18,20,22] early filling percentage (EFP),[18] early diastolic filling rate (EDFR),[18] late diastolic filling rate (LDFR),[18] peak untwist rate (PUTR),[22] time to peak untwist rate (TPUTR)[22] and peak early diastolic strain rate (PEDSR).[18] For detailed information see supplementary Table 1.

One letter[23] was used as complementary material to one of the included studies.[22]

Risk of bias assessment

The methodological quality and risk of bias of selected studies was individually assessed by two independent researchers using the Physiotherapy Evidence Database (PEDro) scale which consists of a 10-point rating checklist, developed to assess the quality of clinical trials. Studies with a score > 6 were considered to have "good quality"; between 4 to 6 "fair quality", and ≤3 "poor quality".[23,24] There was full agreement between the researchers concerning the classification of the studies and their risk of bias.

Results

Study selection

Flowchart of the study selection is illustrated in Figure 1.

Risk of bias in the studies

Based on PEDro scale, four studies were classified as having a good methodological quality and one as fair quality (see supplemental Table 2). The lack of blinding of subjects and therapists was a common limitation in all studies, that can be explained by the nature of intervention type. The primary outcome (echocardiographic variable) was statistically different between intervention and control group at baseline in three studies.[18,21,22] Two studies[20,21] had less than 85% of the outcome data available for analysis. One study[20] did not specify either randomization blinding or the number of subjects in the intervention group.

Study characteristics

The five included studies were the studies by Hare et al.,[21] Hollekim-Strand et al.,[22] Cassidy et

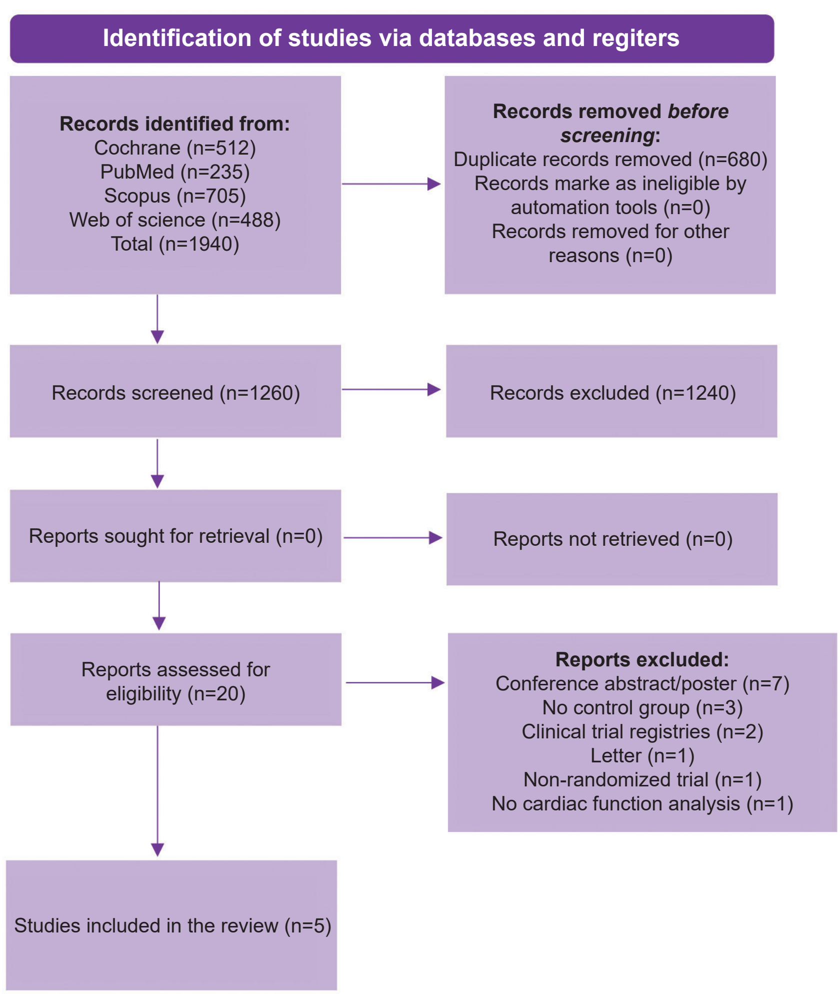

Figure 1 – Identification of studies via databases using PRISMA[15]

al.,[18] Wilson et al.,[20] and Gulsin et al.,[19] All these studies were randomized clinical trials on exercise intervention in T2DM patients published in English.

Participants were randomized to usual care or exercise intervention. The usual care group was instructed to maintain their usual lifestyle during the intervention period, with no change in medication, physical activity, or diet. Physical activity monitoring was carried out by exercise diary, questionnaires and total active time calculation.

Baseline characteristics of the population

A total of 474 individuals were evaluated – 401 diabetic individuals (24 of which were included in an energy-restricted diet intervention)[19] and 73 healthy individuals (control group).[19,22] There was a 33% dropout rate (133 individuals). Therefore, 314 diabetic individuals were included in this review and randomized to usual care (n=138) or exercise intervention (n=176).

Fifty-eight percent of the studied population were male, with an average age of 54.85 years old and a mean BMI of 32.47 Kg/m^2. The mean duration of diabetes was 5.33 years with an average HbA1c of 7.4%. All exercise intervention groups had higher blood pressure compared to the usual care group. Mean peak oxygen consumption (VO_2 peak) at baseline was higher in the exercise intervention groups. One study[22] did not describe all baseline data of the healthy control group. These data are summarized in Table 1.

Characteristics of the exercise intervention

The studies differ in the exercise intervention protocols and one of them[20] did not specify the type of exercise protocol used. The protocols consisted of combined aerobic and resistance exercise,[21] or aerobic exercise alone.[18,19,22] The intensity of aerobic exercise varied from moderate-intensity exercise (MIE),[19,21] high-intensity intermittent training (HIIT),[18,20] and one study[22] compared MIE and HIIT. Exercise session's duration varied from 20 to 60 minutes, two to three times per week. The follow-up period was 12 weeks in four studies,[18-20,22] reaching three years in one of them.[21] The protocols also differ on follow-up period of exercise supervision. These data are summarized in Table 2.

Left ventricular function measurements and outcomes

All studies assessed both systolic and diastolic left ventricular function by analysis of different variables. Regarding the method to assess left ventricular function, the studies used echocardiography,[20–22] magnetic resonance imaging (MRI),[18] or both methods.[19]

Left ventricular systolic function

The systolic function variables analyzed were LVEF,[18-21] S′,[20,22] GLS,[19,21,22] PECS,[18] PWWCS,[18] GSR,[21,22] PT,[22] PTR,[22] and PTo.[18] Between-group analysis was reported in all studies and within-group analysis was reported in four[18-20,22] of the five studies. In some studies, variables shown at baseline were not analyzed after exercise intervention.

In all studies, both usual care and intervention group had normal baseline LVEF. In one study, S′ values were significantly different between MIE and HIIT groups, and significantly lower in the intervention groups than in controls.

In all studies that analyzed LVEF, patients had normal baseline values, and all studies that analyzed systolic strain had compromised strain at baseline, *i.e.*, systolic strain>-20.[21] PECS was normal, with no difference between intervention and control groups, and PWWCS was compromised, with no difference in between-group analysis. GSR was statistically different in between-group (MIE vs. HIIT) analysis in one study.[22] Baseline PTo, PT and PTR were not different between usual care and exercise intervention group. These baseline characteristics are summarized in Table 3.

Only one study[18] reported within-group improvement in LVEF after intervention, with HIIT being superior to usual care in between-group analysis. There was no change in LVEF in within-group or between-group analysis in the other studies.

One study[22] reported improvement of S′ with HIIT in within-group analysis. Between-group analysis showed a superiority of HIIT to MIE, although it is worth remembering that the HIIT group had a more compromised S′ at baseline. Another study[20] evaluating HIIT did not report any improvement in S′ with the intervention. HIIT improved both GLS and GSR in within-group analysis in only one study[26] but there was no superiority of HIIT when compared to MIE in between-group analysis. There were no changes in PECS,[18] PWWCS,[18] or PTR.[22] HIIT improved PTo[18] when compared to usual care. These data are summarized in Table 4.

Table 1 – Demographic characteristics of the studied populations at baseline

	Hare, 2011		Cassidy, 2015		Hollekim-Strand, 2016		Wilson, 2018		Gulsin, 2020	
	UC	EI	UC	EI	EI		UC	EI	UC	EI
					MIE	HIIT				
	n=92	n=94	n=11	n=12	n=17	n=20	n=5	n=11	n=30	n=31
Age, y	55.00±8.00	56.00±11.00	59.00±9.00	61.00±9.00	54.70±5.30**	58.60±5.00	51.00±5.00	52.00±2.00	50.70±6.40	50.50±7.20
Male sex	54.00(59%)	49.00(52%)	8.00(72%)	10.00(83%)	64.70%	60.00%	3.00(60%)	7.00(64%)	18.00(60%)	18.00(58%)
T2DM duration, y	6.30±6.60	6.30±6.50	4.00±2.00	5.00±3.00	3.00±2.60	4.20±2.30	6.00±1.80	7.80±1.30		
BMI, Kg/m^2	31.60±5.90	31.90±5.30	32.00±6.00	31.00±5.00	29.70±3.70	30.20±2.80	32.10±3.30	33.50±1.70	36.70±4.80	36.00±5.80
SBP, mmHg	129.00±15.00	136.00±17.00*	126.00±3.00	123.00±4.00	135.40±11.90	142.10±18.30			138.00±13.00	138.00±18.00
DBP, mmHg	80.00±9.00	83.00±10.00*	84.00±2.00	81.00±2.00	80.90±7.10*	81.70±6.90*			85.00±7.00	88.00±10.00
VO_2, mL/Kg/min	23.80±7.10	21.50±6.00*	20.30±6.10	21.80±5.40	33.20±7.40	31.50±6.10	20.10±2.20	24.10±2.00	16.70‡	17.20‡
HbA1c, %	7.60±1.40	7.50±1.50	7.20±0.50	7.10±1.00	6.70±0.70	7.00±1.20	7.90±0.90	8.00±1.10	7.30±0.90	7.60±1.30
Cholesterol, mmoL/L	4.80±0.99	4.84±0.93	4.50±0.90	4.00±1.00						
LDL, mmoL/L	2.66±0.87	2.69±0.87								
HDL, mmoL/L	1.39±0.43	1.35±0.35								
Triglycerides, mmoL/L	1.78±1.29	1.85±1.08	1.10±0.45	1.10±0.30						

*UC: usual care; EI: exercise intervention; MIE: moderate-intensity exercise; HIIT: high-intensity intermittent exercise; T2DM: type 2 diabetes mellitus; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_2: oxygen consumption; HbA1c: glycated hemoglobin; LDL: low density lipoprotein; HDL: high density lipoprotein. *: difference between routine care and intervention group ($p<0.05$); **: difference between MIE and HIIT intervention group ($p<0.05$), ‡: mean value.*

Table 2 – Intervention characteristics by clinical trial

	Hare, 2011		Cassidy, 2015	Hollekim-Strand, 2016		Wilson, 2018	Gulsin, 2020
Exercise type	Gym-based Aerobic+Resistance	Home-based Aerobic+Resistance	Gym-based Aerobic	Home-based Aerobic	Gym-based Aerobic	Not described	Gym-based Aerobic
Exercise intensity	Moderate	Moderate	HIIT	Moderate	HIIT	HIIT	Moderate
Session's frequency	2x/wk.		3x/wk.	bouts≥10 min	3x/wk.	3x/wk.	3x/wk.
Session's duration	1h	30min	40min	210min/wk.	40min	20min	50min
Follow-up period	4wk.	3years	12wk.	12wk.	12wk.	12wk.	12wk.
Supervision	Yes	No	1st session	No	Yes	Yes	Yes
Adherence	Total activity time calculation	Total activity time calculation	Exercise diary	Exercise diary	Exercise diary	Heart rate monitor	Assessed by a therapist

wk.: week; h: hour; min: minute; HIIT: high intensity intermittent exercise.

Table 3 – Variables of left ventricular systolic function at baseline

	Hare, 2011		Cassidy, 2015#		Hollekim-Strand, 2016			Wilson, 2018		Gulsin, 2020#	
	UC	EI	UC	EI	HC	EI		UC	EI	UC	EI
		MIE		HIIT		MIE	HIIT		HIIT		MIE
	n=92	n=94	n=11	n=12	n=37	n=17	n=20	n=5	n=11	n=30	n=22
EF, %	66.0±8.0	66.0±6.0	64.00±11.0	65.0±8.0				62.0±2.0	59.0±2.0	65.0±5.0	68.0±7.0#*
S′, cm/s					(+1.4)‡*	7.70±1.20	6.80±0.80**	7.00±0.00	8.00±0.00		
Strain, %	20.40±4.00	20.30±4.00				16.70±2.20	17.20±1.90			17.60±1.50	16.90±2.60#
Strain Rate, s^{-1}	1.36±0.33	1.34±0.34				1.00±0.15	0.87±0.11**				
PECS, %			23.10±4.10	25.20±4.60							
PWWCS, %			16.50±3.10	16.50±3.10							
PTo, °			7.10±2.20	8.10±1.80							
PT					13.10±3.60	12.50±5.70	12.20±4.70				
Peak TR, deg/s					65.40±20.90	72.00±33.80	73.30±30.90				

*UC: usual care; EI: exercise intervention; HC: healthy control; EF: ejection fraction; S´: peak systolic tissue doppler velocity; PECS: peak endocardial circumferential strain; PWWCS: peak whole wall circumferential strain; TR: twist rate; MIE: moderate intensity exercise; HIIT: high intensity intermittent exercise; PT: peak twist; PTo: peak torsion; ‡: estimated mean difference; *: statistical difference between routine care and intervention group (p<0.05); **: statistical difference between MIE and HIIT intervention group (p<0.05); #: data from magnetic resonance image.*

Table 4 – Left ventricular systolic function after exercise intervention

	Exercise Intensity	EF	S´	PECS	PWWCS	PTo	PTR	GLS	GSR
Hare, 2011	MIE	↔							
Cassidy, 2015	HIIT	↑		↔	↔	↑			
Hollekim-Strand, 2016	MIE		↔				↔	↔	↔
	HIIT		↑				↔	↑	↑
Wilsom, 2018	HIIT	↔	↔						
Gulsin, 2020	MIE	↔						↔	

EF: ejection fraction; S´: peak systolic tissue doppler velocity; PECS: peak endocardial circumferential strain; PWWCS: peak whole wall circumferential strain; PTo: peak torsion; PTR: peak twist rate; GLS: global longitudinal systolic strain; GSR: global strain rate; MIE: moderate intensity exercise; HIIT: high intensity intermittent exercise. ↔: no significative change; ↑: improvement; ↓: deterioration.

Left ventricular diastolic function

The diastolic variables analyzed were e´ wave,[20–22] E wave,[20,22] E/e´ ratio,[19,20,22] A wave,[20] E/A ratio,[19,20,22] EFP,[18] EDFR,[18] LDFR,[18] PUTR,[22] TPUTR[22] and PEDSR.[19] Between-group analysis was reported in all studies and within-group analysis was reported in four studies.[18,20,22]

In all studies, baseline left ventricular diastolic function variables were normal, with no difference between the usual care and the intervention groups. Although within the normal range, one study[19] reported statistically significant differences in the E/e´ ratio, E/A ratio and PEDSR between the usual care and the intervention groups. These data are summarized in Table 5.

There was no within-group or between-group changes in A wave, EFP, LDFR and PUTR after exercise intervention.[18,20,22]

E/A ratio, EDFR, TPUTR and PEDSR improved after exercise intervention.[18,20,22] Both MIE and HIIT were able to improve TPUTR with no significant difference in between-group analysis.[22] PEDSR improved in the intervention group and deteriorated in the usual care group, with a significant difference in between-group analysis.[19]

Results of E wave, e´ wave and E/e´ ratio were not homogenous between the studies. Only one study[22] reported E wave improvement with HIIT, with no clear superiority of HIIT over MIE. The same study reported e´ wave improvement with both HIIT and MIE, with a superiority of HIIT over MIE. One study[21] reported e´ wave deterioration in the intervention group, with no significant change in between-group analysis after this variable was normalized by its baseline difference. There was no e´ wave changes after intervention in the remaining studies.[20] Only one study[22] reported an improvement in the E/e´ ratio with HIIT, with no clear superiority of HIIT to MIE. There was no change in the E/e´ ratio in the other studies.[20,21] These data are summarized in Table 6.

Metabolic profile after exercise intervention

There were no significant changes in body weight, BMI and HbA1c after exercise intervention compared to usual care in most studies.[19–22] Only one study reported reductions in body weight, fat liver and HbA1c after exercise intervention.[18]

Discussion

This systematic review provided an overview of the main findings related to different exercise interventions and their effects on left ventricular systolic and diastolic functions in T2DM patients. Physical exercise seems to improve variables related to left ventricular systolic function, such as EF, PTo, S′ and GSR,[18,22] and variables related to diastolic function such as EDFR, TPUTR, e´ wave and PEDSR.[18,20,22] These findings will be discussed below.

Physical exercise: a non-pharmacological strategy for diabetes

Physical exercise is a known non-pharmacological treatment strategy for diabetes and its complications.[8,25-27] Physical exercise, in conjunction with diet and behavior

Table 5 – Variables of left ventricular diastolic function at baseline

	Hare, 2011		Cassidy, 2015#		Hollekim-Strand, 2016			Wilson, 2018		Gulsin, 2020#	
	UC	EI	UC	EI	HC	EI		UC	EI	UC	EI
		MIE		HIIT		MIE	HIIT		HIIT		MIE
	n=92	n=91	n=11	n=12	n=37	n=17	n=20	n=5	n=11	n=30	n=22
E, cm/s					(+11.7)‡ °	63.4±9.5	64.8±10.7	64.0±6.0	63.0±4.0		
e´, cm/s	6.2±1.6	6.7±1.6			(+4.0)‡ °	7.1±0.7	7.0±0.7	6.0±0.0	8.0±1.0		
E/e´					(-2.6)‡ °	9.1±1.8	9.3±1.7	9.6±0.5	8.5±0.6	6.2‡	8.1‡*
A, cm/s					(-0.1)‡ °			70.0±7.0	70.0±4.0		
E/A					(+0.40)‡ °	0.92±0.18	0.93±0.21	0.98±0.16	0.93±0.08	1.21±0.25	0.95±0.21*
LAVI, mL/m²	30.2±6.2	29.6±7.8									
EFP, %			58.0±11.0	57.0±9.0							
EDFR, mL/s			250.0±44.0	241.0±84.0							
LDFR, mL/s			310.0±143.0	278.0±67.0							
PUTR, deg/s					92.8±23.4	86.5±34.9	80.2±32.6				
TPUTR (% diastole)					10.5±7.4	16.1±9.0	16.5±9.0				
PEDSR, s^{-1}										1.10±0.16	1.01±0.19#*

*UC: usual care; EI: exercise intervention; HC: healthy control; E: transmitral peak early diastolic velocity; e´: peak early diastolic tissue doppler velocity; E/e´: diastolic filling pressure; A: transmitral late diastolic velocity; E/A: E/A ratio; LAVI: left atrium volume index; EFP: early filling percentage; EDFR: early diastolic filling rate; LDFR: late diastolic filling rate; PUTR: peak untwist rate; TPUTR: time to peak untwist rate; PEDSR: peak early diastolic strain rate; MIE: moderate intensity exercise; HIIT: high intensity intermittent exercise. ‡: estimated mean difference; °: statistical difference between healthy controls and T2DM (p<0.05); *: statistical difference between routine care and intervention group (p<0.05); **: statistical difference between MIE and HIIT intervention group (p<0.05); #: data from magnetic resonance image.*

Table 6 – Left ventricular diastolic function after exercise intervention

	Exercise Intensity	LAVI	E	e´	E/e´	A	E/A	EFP	EDFR	LDFR	PUTR	TPUTR	PEDSR
Hare, 2011	MIE	↔		↓									
Cassidy, 2015	HIIT							↔	↑	↔			
Hollekim-Strand, 2016	MIE		↔	↑	↔		↔				↔	↑	
	HIIT		↑	↑	↑		↑				↔	↑	
Wilsom, 2018	HIIT		↔	↔	↔	↔	↔						
Gulsin, 2020	MIE				↔		↔						↑

LAVI: left atrium volume index; E: transmitral peak early diastolic velocity; e´: peak early diastolic tissue doppler velocity; E/e´: diastolic filling pressure; A: transmitral late diastolic velocity; E/A: E/A ratio; EFP: early filling percentage; EDFR: early diastolic filling rate; LDFR: late diastolic filling rate; PUTR: peak untwist rate; TPUTR: time to peak untwist rate; PEDSR: peak early diastolic strain rate; MIE: moderate intensity exercise; HIIT: high intensity intermittent exercise. ↔: no significative change; ↑: improvement; ↓: deterioration.

modification, has been recommended for controlling diabetes by prevention programs.[8] T2DM pre-clinical and clinical studies have shown beneficial effects of exercise such as weight loss, glycemic control, insulin signaling, improvement of cardiac and vascular functions,[8,9,10] risk reduction of cardiovascular diseases and delayed onset of diabetic cardiomyopathy.[9]

In T2DM aerobic training improves glycemic control, insulin sensitivity, oxidative capacity, oxidative enzymes, blood vessel compliance, lung function and cardiac output,[11,12] while resistance training improves muscle strength, blood pressure, lipid profile, bone mineral density, cardiovascular health, insulin sensitivity, and muscle mass.[7] In older adults, resistance training is recommended to prevent sarcopenia and decrease the prevalence of T2DM with aging.[7]

HIIT increases skeletal muscle oxidative capacity, glycemic control, and insulin sensitivity in T2DM adults.[28,29] A recent meta-analysis reported superior effects of HIIT compared to MIE training on glucose regulation and insulin resistance, showing a 0.19% decrease in HbA1c and a 1.3kg decrease in body weight for interventions lasting at least two weeks.[28]

Several exercise modalities have demonstrated benefits to cardiovascular health. Current guidelines[7,14,15] recommend combined aerobic and resistance training for T2DM aiming optimal health outcomes. These guidelines recommend at least 150 minutes of moderate-to-vigorous intensity aerobic activity per week, and 2-3 sessions/ week of moderate-to-vigorous intensity resistance exercise. For older adults, it is recommended associating flexibility and balance training.[7,8,14,15]

A head-to-head meta-analysis of 27 controlled trials including a total of 1003 T2DM individuals showed that aerobic training, resistance training, and combined training provide favorable effects on HbA1c, fasting and postprandial glucose levels, fasting insulin levels and insulin sensitivity, with little difference between modalities.[29] A network meta-analysis reported that combined aerobic and resistance exercises showed greater improvement magnitude in HbA1c levels, and a less marked improvement in cardiovascular risk factors when compared to aerobic or resistance exercise alone.[30-32] Therefore, these three training modalities have been recommended mainly for metabolic control in T2DM, and thee combined training modality appears to be the one that brings more benefits. However, studies focusing on left ventricular function are lacking.

Left ventricular systolic function

Assessment of LV systolic function can be performed using different indices/measurements and methods. In the present review, improvement of some of these indices after physical training was observed in T2DM.

Cassidy et al.[18] reported LVEF improvement after intervention, with HIIT being superior to the usual care. This result is in agreement with those reported by Gusso et al.,[31] who observed improvement of left ventricular function in type 1 DM adolescents submitted to regular vigorous aerobic and resistance exercise combined. There was no change in LVEF in the other studies included in this review.

Hollekim-Strand et al.[22] reported S′ improvement with HIIT, and HIIT was superior to MIE, although there was a more compromised baseline S′ in the HIIT group. There was no S′ improvement with HIIT in the study by Wilson et al.[20]

Although Wilson et al.[20] were unable to report any significant effect of exercise on LVEF and S′, the intervention group showed a 15% improvement in VO_2 and improvement of LV output during exercise by increased LV end diastolic volume.

HIIT improved both GLS and GSR in only one study,[22] although there was no superiority of HIIT over MIE. This result is consistent with a study in athletes that showed significantly higher values of GLS and GSR compared to controls.[33] Cassidy et al.[18] showed that HIIT improved PTo when compared to routine care.

While HIIT seems to improve systolic variables (PTo, GLS and GSR); the same is not true for MIE. These data are consistent with those by Anand et al.,[10] who reported improvement of GLS with physical exercise.

Left ventricular diastolic function

Hollekim-Strand et al.[22] reported improvement in e′ wave, and HIIT was superior to MIE. There was no improvement in e′ wave with the exercise intervention in the study by Hare et al.,[21] but e′ wave was statistically different between the groups at baseline.

The T2DM intervention group in the study by Gulsin et al.[19] had higher E/e′ ratio at baseline, which tended to improve after exercise intervention (although there was no statistical significance). Hollekim-Strand et al.[22] showed an improvement in the E/e′ ratio, E wave, e′ wave and E/A ratio after the HIIT intervention.

Hollekim-Strand et al.[22] reported a significant improvement in TPUTR with both MIE and HIIT, with no significant difference between exercise intensity. Cassidy et al.[18] showed that HIIT improved EDFR. Gulsin et al.[19] showed a greater improvement of PEDSR after exercise when compared to usual care.

HIIT seems to improve the diastolic variables E wave, e´ wave, E/e´ ratio, E/A ratio, EDFR and TPUTR; MIE seems to improve diastolic variables TPUTR and PEDSR. These data are consistent to Verboven et al.[34] that reported improvement only in the left ventricular diastolic function with exercise.

Could HIIT have any additional benefit compared to mie?

For an adequate exercise prescription, guidelines recommend considering exercise type, intensity, duration, frequency, and progression,[7,14] with exercise intensity as one of the main determinants of physical training.[12] Moderate-intensity aerobic exercise (e.g. continuous exercise at 70-85% of maximal heart rate) and HIIT (ex. four bouts of four minutes each at 90-95% of maximal heart rate alternating with two-minute active recovery at a reduced intensity or rest), if applied with similar volume (40-minute sessions three times a week), brings similar benefits in T2DM. If the applied volume is different, the adaptive responses will also be different.[7,12,14]

Metabolic responses to moderate-intensity aerobic physical training have been observed in T2DM individuals, with reductions in HbA1c, triglycerides, blood pressure, and insulin resistance.[7] For regular HIIT training, it is observed enhancement of skeletal muscle oxidative capacity, insulin sensitivity, and glycemic control.[7]

Exercise intensity is an essential factor in improving cardiac function in early stages of T2DM cardiomyopathy.[23] Nonetheless, in HIIT, it is important to consider cardiovascular safety when compared to MIE. Giallauria et al.[35] reported that HIIT did not reveal major cardiovascular safety issues even in patients with chronic HF, although these patients should be clinically stable, have appropriate supervision and monitoring during exercise sessions, and have had recent exposure to regular MIE.

Ness at al.[36] studied the effects of acute cardiac stress after a HIIT session in T2DM versus healthy controls. Even though there were significant differences in cardiorespiratory fitness between the groups, cardiac response in the recovery phase of the HIIT session was similar in both groups, with changes in the e′ wave, E/A ratio, and left atrial end-systolic volume. These findings indicated that even a single session of exhaustive HIIT can cause at least a transient impairment of left ventricular diastolic function. Extreme amounts of HIIT must be carefully considered due to the risks for developing myocardial fibrosis, especially in patients predisposed to cardiac dysfunction.[37]

Thus, the impact of HIIT on cardiac function remains uncertain. HIIT should not replace, but rather, complement other training modalities in T2DM patients with diastolic dysfunction. The benefits depend on the volume of applied training.

Mechanism of ventricular dysfunction and improvement of cardiac function by physical exercise in T2DM

A literature review by Okoshi et al.[38] describes the main mechanisms involved in hypertrophy and LVDD in T2DM. Insulin resistance increases insulin production leading to hyperinsulinemia, which contributes to the production of growth factors, activation of the renin-angiotensin-aldosterone and the sympathetic nervous systems and increase of aortic stiffness. Consequently, there is an increased systolic stress on the left ventricular wall leading to cardiac myocyte hypertrophy. In long term, left ventricular hypertrophy can lead to altered relaxation and reduced ventricular compliance, which is one of the contributing factors of LVDD.[39]

It is believed that dyslipidemia and increased essential fatty acid levels may contribute to increased consumption of lipids as a source of energy to cardiac cells,[40] and cardiac steatosis with consequent myocardial growth and rigidity.[46] In long term, fatty acid oxidation can negatively influence myocardial contractility by shortening the action potential, altering intracellular calcium handling and by direct myocyte lipotoxicity resulting in apoptosis and reduced ventricular function.[40,41]

Mechanisms involved in the improvement of cardiac function by regular exercise are not totally clear. Some of these mechanisms may be related to decreased afterload,[10] cardiac remodeling,[42,43] changes in cardiac lipid deposition[47], improved cardiac sympathovagal balance,[44] improved endothelial function[9,45] reduction of oxidative stress damage,[46] improvement of cardiomyocyte metabolism,[9] attenuation of myocardial fibrosis and inhibition of cardiomyocyte apoptosis,[9,46] and improvement of cardiac mitochondrial function, and calcium sensitivity and regulation.[46] For Cassidy et al.[18] improvement in PTo may be explained by reductions in the endocardial damage and perfusion deficits with exercise. These findings suggest that HIIT may influence both systolic and diastolic LV functions, by improving myocardial contractility and relaxation in less severe cases of T2DM.[18]

This review shows that exercise training seems to improve variables related to subclinical systolic dysfunction such as GLS, GSR and PTo, and early diastolic dysfunction such as EDFR, TPUTR and PEDSR. These findings are consistent with other systematic reviews.[10,40]

Conclusion

To our knowledge, this is the first systematic review of the effects of exercise on left ventricular systolic and diastolic functions in T2DM individuals including only randomized clinical trials with humans. Physical exercise seems to improve different variables of systolic and diastolic function in diabetes mellitus. However, this review was limited by the low number of studies included, the lack of adherence to exercise by the intervention group in some studies, and the heterogeneity of studies regarding exercise protocol, follow-up period, supervision, and left ventricular function variables analyzed. The lack of adherence to exercise in some studies by the intervention group could be a considerable bias in the final findings. Thus, more homogeneous studies are necessary for more consistent conclusions.

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Conception and design of the research and critical revision of the manuscript for intellectual content: Petronilho A, Gois MO, Frade MCM, Sakaguchi CA, Roscani MG, Catai AM; acquisition of data: Petronilho A, Gois MO, Frade MCM, Sakaguchi CA; analysis and interpretation of the data and Writing of the manuscript: Petronilho A, Gois MO, Roscani MG, Catai AM; obtaining financing: Catai AM.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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