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SYSTEMATIC REVIEW

Effect of Exercise Intervention on Cardiac Function in Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

Background The effect of exercise on cardiac function/structure in type 2 diabetes mellitus (T2DM) with or without diabetic cardiomyopathy (DCM) is not yet completely understood. To date, results of studies have been controversial with variable outcomes due to the variety of exercise modalities.

Objectives The aim of the present review was to examine the impact of exercise intervention, and different types of exercise, on cardiac function and structure in T2DM through a systematic literature review, combining both pre-clinical and clinical studies.

Methods A systematic literature search was performed on PubMed, Web of Science, and PEDro to identify studies up to 2 April 2018. Articles were included when well-defined exercise protocols were provided, and cardiac function in T2DM patients or validated animal models was examined.

Results In diabetic animals, improvements in both diastolic and systolic function through exercise therapy were mainly attributed to reduced collagen deposition. In T2DM patients, improvements were observed in diastolic function, but not consistently in systolic function, after endurance (and combined resistance) exercise training. Different exercise intervention modalities and exercise types seemed equally effective in improving cardiac structure and function.

Conclusion Exercise training elicits significant improvements in diastolic function and beneficial remodeling in T2DM and DCM animal models, but not necessarily improvements in systolic function and left ventricular structure, regardless of exercise type. Therefore, exercise intervention should be a cornerstone in the treatment of T2DM patients not only to improve glycemic control but also to specifically enhance cardiac function.

Key Points

In this systematic literature review, exercise intervention is shown to improve diastolic function and counteract adverse remodeling leading to cardiac dysfunction in animals and humans with type 2 diabetes mellitus (T2DM) or diabetic cardiomyopathy.

Given the therapeutic effects of exercise intervention on cardiac function and structure, it should be a cornerstone in the treatment of T2DM patients not only to improve glycemic control but also to specifically enhance cardiac function.

Maxim Verboven, Lisa Van Ryckeghem, Dominique Hansen, and Virginie Bito have shared authorship.

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1 Introduction

Diabetes is a major global health problem, affecting > 400 million individuals worldwide, where the majority have type 2 diabetes mellitus (T2DM) [1]. In T2DM patients, cardiovascular diseases are the major cause of mortality and morbidity. The risk of developing heart failure in T2DM is closely related to an increase in blood hemoglobin A_{1c} (HbA_{1C}) levels, and is closely associated with insulin resistance and/or hyperglycemia [2]. In addition, diastolic dysfunction and left ventricular (LV) hypertrophy, early markers of cardiac failure, occur in T2DM patients, respectively, in 19.6–54.4% and 21% of the cases [3, 4]. Diabetic cardiomyopathy (DCM) is defined as diabetes-associated structural and functional changes in the myocardium, not directly attributable to other confounding factors such as coronary artery disease (CAD), valve disease, or hypertension [5, 6]. The prevalence of DCM is not yet clear due to the lack of large cohort studies on different diabetic populations and the discrepancy in outcomes [7]. DCM is characterized by extracellular and cardiomyocyte remodeling, both contributing to the observed impaired cardiac output [8] and resulting in impaired diastolic and/or systolic function. These molecular changes are also known to be partially driven by inflammation, hyperglycemia, hyperinsulinemia, and lipotoxicity [9]. Patients diagnosed with T2DM and DCM generally receive medication that is aimed at better glucose control and/or lipid-lowering therapies, but for these patients, specific cardiac remodeling is often neglected.

Exercise intervention is an effective, low-cost, and safe strategy for the prevention and treatment of cardiovascular diseases (CVD) [10]. Indeed, repeated bouts of endurance exercise lead to advantageous LV remodeling, improvements in cardiac performance, and greater tolerance for ischemia and reperfusion injury [11, 12], resulting in a slower myocardial disease progression and greater survival and/or lower hospital admission rates [13–15]. In addition, exercise is known to exert anti-inflammatory effects, reduce blood HbA_{1c} concentrations, oxidative stress and hyperglycemia, and improve insulin action and lipid profile in T2DM [16–21]. In this context, supplementing current approaches with exercise interventions could substantially improve cardiac outcome for T2DM with DCM, which would be of great advantage for the patient and society.

However, it remains unclear which type of exercise intervention (with regard to intensity, type, duration, etc.) can improve cardiac function and reverse adverse remodeling. In this review, we therefore systematically evaluated the impact of different exercise-training modalities on cardiac function and structure in T2DM with or without DCM. Because underlying mechanisms can only be unraveled in animal models, it was deliberately decided to examine and combine outcomes from pre-clinical and clinical studies in the present systematic review, which represents a further novelty of our approach.

2 Methods

2.1 Literature Search and Selection Criteria

The primary objective of this systematic review was to assess the impact of exercise intervention on cardiac function in animals and patients with T2DM [PICO: P = patients (with T2DM), I = intervention (exercise), C = comparison (of different exercise types), O = outcome (cardiac function)]. The secondary objective was to assess the impact of different types of exercise on cardiac function. In this systematic review, databases were searched for articles published from inception until 2 April 2018, for both animal and patient studies. For animal studies, the electronic databases PubMed and Web of Science were used with the following Mesh Terms: 'diabetic cardiomyopathy,' 'exercise,' and 'training'. For human studies, the electronic databases PubMed and PEDro were used. In PubMed, the following keywords were used: (training OR exercise) AND (type 2 diabetes OR diabetic cardiomyopathy OR diabetic*) AND (diastolic OR systolic OR cardiac OR heart). In PEDro, the search strategy was adjusted to Diabet*, exercis*, and train* to find all relevant articles. Literature searches for animal and patient studies were independently performed by two reviewers (LVR and MV). In case of disagreement, a consensus-based decision was made by the two reviewers (LVR and MV) and the last authors (DH and VB) to include/exclude an article. Results of the search are shown in Fig. 1 for the patient studies and in Fig. 2 for the animal studies. A detailed overview of the inclusion and exclusion criteria is shown in Electronic Supplementary Material Appendix S1.

Quality assessment was based on the table of Kilkenny et al. for animal studies [22], examining 20 criteria. For the patient studies, methodological quality was evaluated via manually calculated PEDro scores including 11 criteria, and PEDro scores ≥ 6 were considered as "good quality" [23].

As mentioned in the Electronic Supplementary Material Appendix S1, outcome parameters (relating to cardiac function and structure) for animal and patient studies were based on echocardiographic assessments, hemodynamic measurements, or measurements of myocardial fibrosis.

3 Results

3.1 Quality Control of Included Studies

All patient studies consisted of clinical trials, of which nine were randomized (RCT) and four were non-randomized

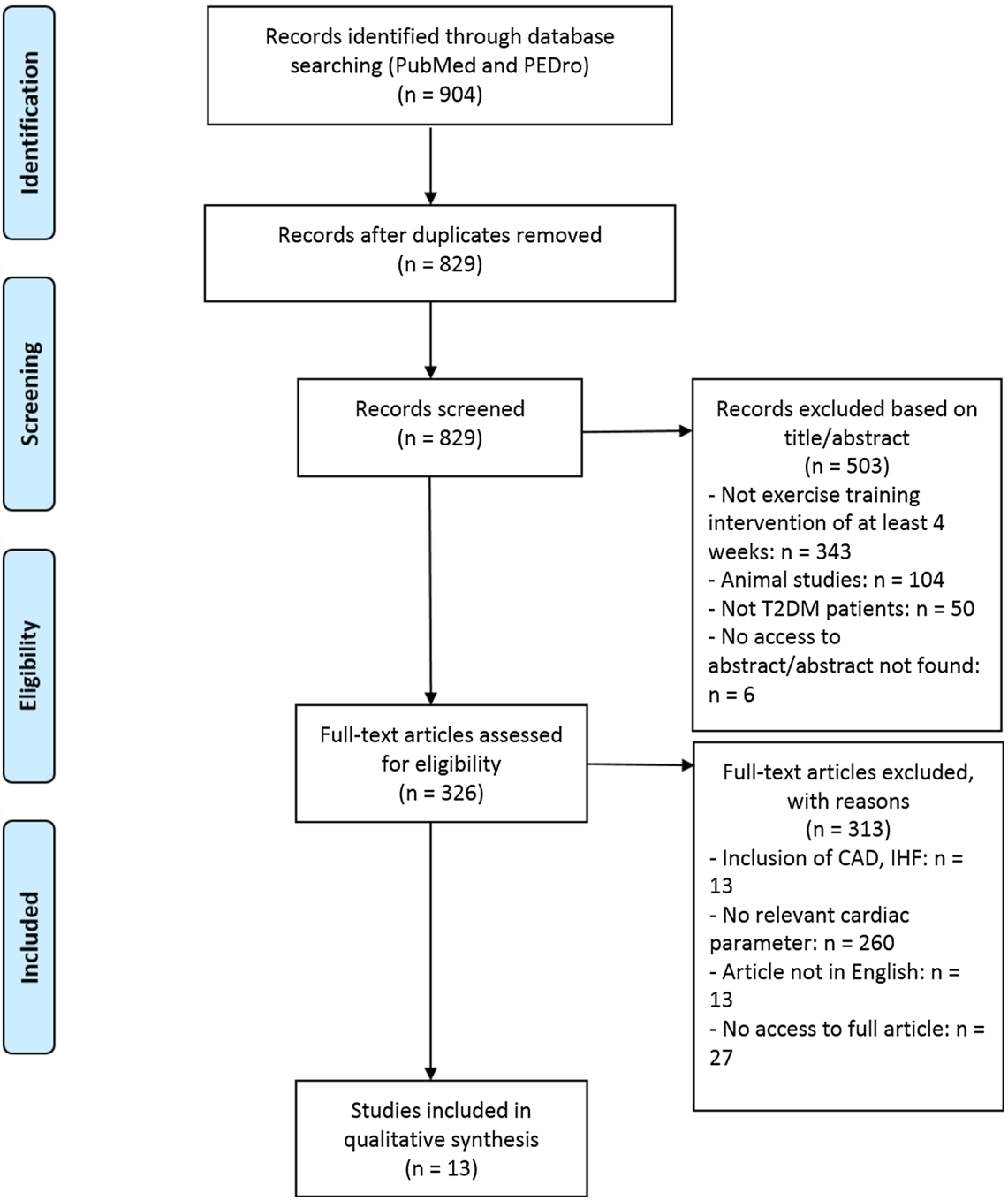

Fig. 1 Flowchart summary of the search for and selection of the human studies. *IHF* ischemic heart failure, *T2DM* type diabetes mellitus, *CAD* coronary artery disease

(non-RCT). In all of them exercise therapy was used as an intervention for T2DM patients. Five out of nine RCTs displayed a score of ≥ 6 for PEDro and were therefore considered as "good quality." The lack of blinding of subjects and therapists were the main limitations. The use of control groups was only applied in the RCTs. Details regarding sample sizes, use of control groups, intervention period, etc. can be found in Electronic Supplementary Tables S1 and S2.

In all animal studies, exercise therapy was used to treat DCM in rats or mice models of T2DM. According to the Kilkenny et al. table, all animal studies were considered to be "good quality" [22].

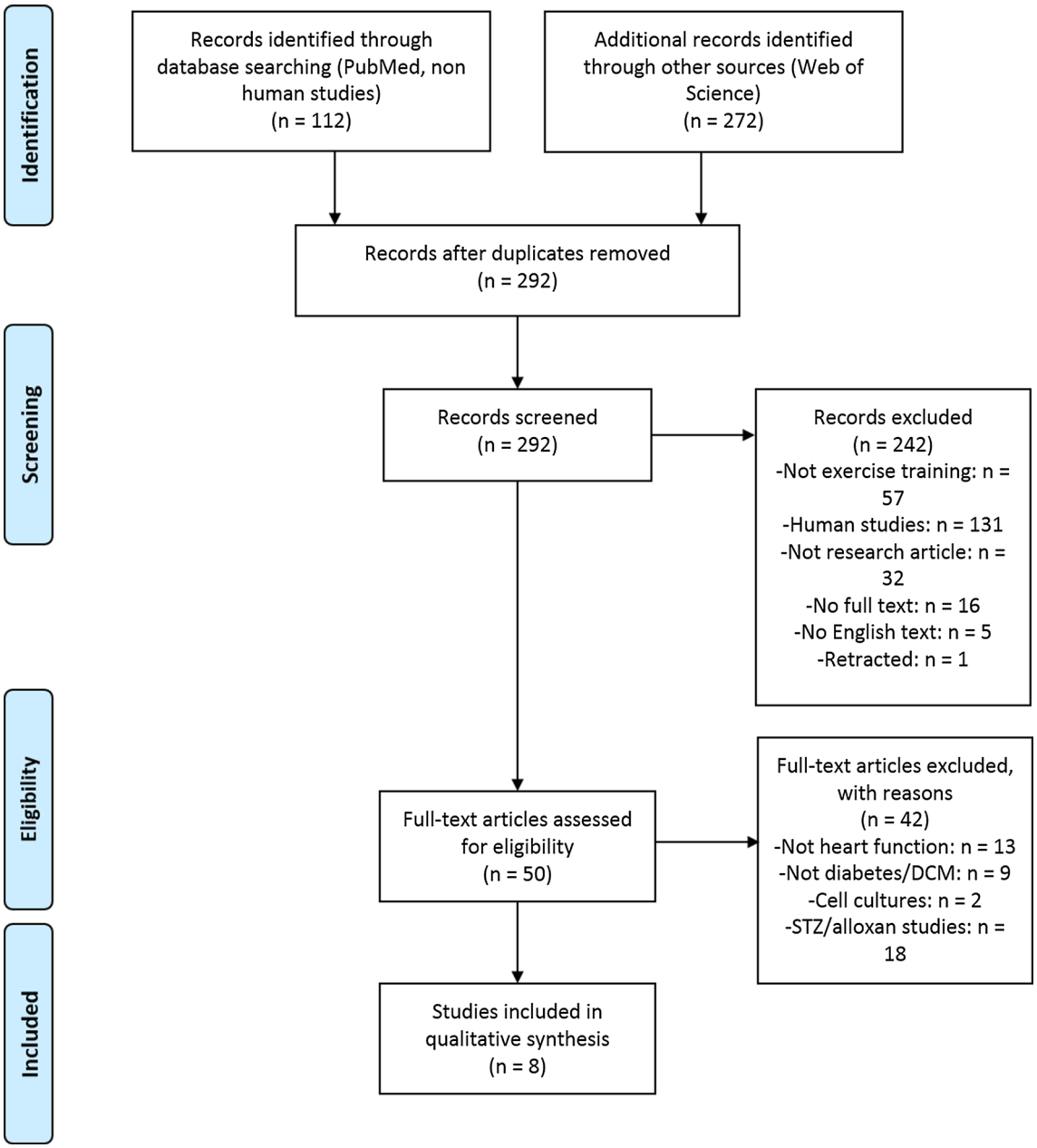

Fig. 2 Flowchart summary of the search for and selection of the animal studies. *DCM* diabetic cardiomyopathy, *STZ* streptozotocin

3.2 Human studies

3.2.1 Diastolic Function

As shown in Table 1, primary read-out parameters and manner of comparison (within- or between-group analyses) differed substantially between studies. In order to specifically investigate the isolated effect of exercise training, only studies reporting between-group analyses are discussed; other comparisons can be found in Table 1 and Electronic Supplementary Material Tables S1 and S2. Between-group analyses were reported for the following diastolic parameters: early diastolic filling E ($n=3$ out of four studies), atrial filling (A) ($n=1$ out of two studies), LV filling pressure (E/e') ($n=3$ out of five studies), E/A ($n=3$ out of five studies), early diastolic tissue velocity (e') ($n=3$ out of four studies), and deceleration time (Dt) ($n=2$ out of three studies). Exercise training was not able to exert superior effects on E or A compared with the control group or alternative exercise training (e.g., high-intensity interval training (HIIT) compared with moderate intensity training (MIT)) [24–26]. However, it should be noted that one study reported an increase in E after HIIT

Table 1 Summary of studies in humans included in the review, showing training type and intensity, and effects on diastolic and systolic function and left ventricle morphology

Study	Training			Method	Effect on cardiac function		
	Type of training	Intensity	Duration and frequency	Outcome	Diastolic function	Systolic function	LV structure and other measurements
Brassard et al. [57]	Endurance exercise training Cycling	60–70% VO_{2max}	12 weeks (3/week)	TTE	Normalization of LVDD ↗ *E*/*A* ↘ *A* wave ↔ Dt, *E* wave	↔ LVEF	↔ LV dimensions, LV mass, LA volume, posterior wall thickness ↗ IVRT (control group)
Cassidy et al. [10]	HIIT Cycling	Borg rating of perceived exertion (16–17)	12 weeks (3/week)	Cardiac MRI	↗ Early filling rate, early diastolic filling rate ↔ Late diastolic filling rate Significant between-group comparisons of changes ↗ Early filling rate (control group < exercise group)	↗ SV and LVEF ↔ Cardiac output and longitudinal shortening Significant between-group comparisons of changes ↗ SV and LVEF (control group < exercise group)	↗ LV wall mass, EDV ↔ ESV ↗ Wall thickness during systole and diastole (control group) Significant between-group comparisons of changes ↗ LV wall mass, EDV (control group < exercise group)
Cugusi et al. [58]	Endurance exercise training Aquatic exercises	50–75% VO_{2max}	12 weeks (3/week)	TTE	↘ *E*/*e*′	↔ LVEF, S wave, strain rate	↔ EDV and ESV
Hollekim-Strand et al. [28]	HIIT vs. MIT HIIT: walking/running MIT: home-based exercise	HIIT: 90–95% HRmax MIT: guidelines of the The Norwegian Diabetes Association [61]	12 weeks (3/week)	TTE			↘ Time to peak basal UTR, time to peak apical UTR and time to peak UTR (both groups) ↘ Apical UTR (MIT group) ↔ Peak apical and basal rotation, basal twist and untwist rate (TR and UTR), apical TR, peak twist, peak TR and UTR Significant between-group comparisons of changes See Electronic Supplementary Material, Table 2

Table 1 (continued)

Study	Training			Method	Effect on cardiac function		
	Type of training	Intensity	Duration and frequency	Outcome	Diastolic function	Systolic function	LV structure and other measurements
Hollekim-Strand et al. [24]	HIIT vs. MIT Home-based exercise	HIIT: 90–95% HRmax MIT: unknown	12 weeks (3/week)	TTE	↗ *e′* (both groups) ↗ *E*, *E/A* ↔ *E/e′* Significant between-group comparisons of changes ↗ *e′* (HIIT group > MIT group)	↗ S wave ↘ Global strain rate Significant between-group comparisons of changes ↗ S wave (HIIT group > MIT group) ↘ Global strain rate (HIIT group > MIT group)	
Hordern et al. [14]	Endurance exercise training Gym sessions and home-based exercise	Moderate (Borg scale 12–13)	1 year (3/week)	TTE	↗ *e′* (both groups)	↗ S wave, myocardial strain[a] (both groups) ↔ LVEF and myocardial strain rate	↔ LV mass, LV mass index, LV dimensions
Howorka et al. [39]	Endurance exercise training Cycling	60–70% HRmax	12 weeks (2/week)	TTE	Improvements in relaxation disturbances		↔ Intraventricular wall thickness and LVEDD
Jonker et al. [59]	Endurance/resistance exercise training Individualized training program	Moderate intensity	24 weeks (4/week)	MRI, magnetic resonance spectroscopy	↔ *E/A* and *E/e′*	↔ LVEF, SV, and cardiac index	↔ LV mass, LV mass index, and LV dimensions (EDV and ESV) ↔ Epicardial fat and myocardial triglycerides content ↘ Pericardial fat
Loimaala et al. [25]	Endurance/resistance exercise training Running/walking	Running/walking: 65–75% VO_{2max} Resistance exercise: 70–80% MVC	12 months (2/week)	TTE	↔ *E*, *A*, mean peak mitral annular early diastolic velocity and mean peak mitral annular late diastolic velocity	↔ Mean peak mitral annular systolic velocity	
Sacre et al. [26]	Endurance/resistance training Gym sessions and home-based exercise	Moderate-vigorous	24 weeks (2/week)	TTE	↗ *E/A* (control group) ↗ *e′* (both groups) ↔ Dt ↗ *E/e′* Significant between-group comparisons of changes ↗ *E/A* (control group > exercise group)	↗ Strain[a] and strain rate[a] (both groups) ↔ S wave and LVEF	↔ LV mass index

Table 1 (continued)

Study	Training			Method	Effect on cardiac function		
	Type of training	Intensity	Duration and frequency	Outcome	Diastolic function	Systolic function	LV structure and other measurements
Schmidt et al. [27]	Endurance exercise training Soccer training	Unknown	24 weeks (2/week)	TTE	↗ *E/A*, *E′* and *e′* ↘ Dt, *E/e′* ↔ *A′* Significant between-group comparisons of changes: ↗ *E/A*, *E′* and *e′* (control group < exercise group) ↘ *E/e′* (control group < exercise group)	↗ TAPSE ↗ Global strain and LV displacement (both groups) ↔ LVEF, S wave Significant between-group comparisons of changes ↗ TAPSE (control group < exercise group) ↘ Global strain and LV displacement (control group > exercise group)	↗ LVEDD, EDV and LV mass index Significant between-group comparisons of changes ↗ LVEDD, EDV and LV mass index (control group < exercise group)
Schrauwen-Hinderling et al. [60]	Endurance/resistance exercise training Unknown	55% of predetermined maximal workload (aerobic exercise) 55–75% of MVC (resistance exercise)	12 weeks (3/week)	MRI, magnetic resonance spectroscopy		↗ LVEF, cardiac index, cardiac output	↘ ESV ↔ EDV and cardiac lipid content
Schultz et al. [46]	Endurance/resistance exercise training Gym sessions and home-based exercise	Moderate intensity (Borg scale 12–13)	12 months (4 weeks: 2/week, thereafter: home-based)	TTE			↔ LV mass index, LV RWT ratio

Changes refer to exercise group, unless stated otherwise

A atrial mitral inflow velocity, *A′* peak late diastolic velocity measured at the annulus, *Dt* deceleration time, *E* early mitral inflow velocity, *E′* peak early diastolic velocity measured at the mitral annulus, *e′* peak early diastolic tissue Doppler velocity, *E/e′* left ventricle filling pressure, *E/A* ratio of early (*E*) and atrial (*A*) inflow velocity, *EDV* end-diastolic volume, *ESV* end-systolic volume, *HIIT* High-intensity interval training, *HRmax* maximal heart rate, *LV* left ventricle, *LVDD* left-ventricular diastolic dysfunction, *LVEDD* LV end-diastolic diameter, *LVEF* left ventricular ejection fraction, *IVRT* isovolumic relaxation time, *MIT* moderate-intensity training, *MR* magnetic resonance, *MRI* magnetic resonance imaging, *MVC* maximum voluntary contraction, *RWT* relative wall thickness, *S wave* systolic tissue velocity, *SV* stroke volume, *TAPSE* tricuspid annular plane systolic excursion, *TR* twist rate, *TTE* transthoracic echocardiography, *UTR* untwist rate, VO_{2max} maximal oxygen uptake, ↗ increase, ↘ decrease, ↔ no changes

[a]Strain rate analyses positively expressed

training, which did not occur in the MIT group [24]. Results for *E*/*A* are inconsistent. Two studies reported a between-group interaction; however, one of these studies reported an increase in *E*/*A* in the exercise group [27], whereas the other study reported an increase in the control group [26]. Comparable to the effect on *E*, Hollekim-Strand et al. [24] reported an increase for *E*/*A* after HIIT training, which was not the case for MIT training. Further, two studies reported superior effects of exercise training in terms of increases in e' [24, 27], although another study failed to confirm this [14]. Again, HIIT seemed to be superior compared to MIT [24]. Lastly, one study reported superior effects of exercise training with respect to reductions in *E*/*e*′ and Dt [27], although other studies failed to confirm these effects [24, 26]. Again, Hollekim-Strand et al. [24] reported reductions in *E*/*e*′ in the HIIT group and not in the MIT group.

Overall, these studies indicate that endurance (and/or resistance) exercise training can to a certain extent ameliorate or at least positively influence different aspects (*E*/*A*, *E*/*e*′, *e*′, Dt) of diastolic function. The influence of type and modality of exercise intervention remains unclear. Although the study by Hollekim-Strand et al. [24] justifies the current interest in HIIT training.

3.2.2 Systolic Function

Between-group analyses were reported for the following parameters: left ventricular ejection fraction (LVEF) ($n=3$ out of seven studies), strain rate ($n=4$ out of five studies), stroke volume ($n=1$ out of one study), cardiac output ($n=1$ out of one study), systolic tissue velocity ($n=5$ out of six studies), and tricuspid annular plane systolic excursion (TAPSE) ($n=1$ out of one study). HIIT training was able to improve LVEF and SV compared to the control group [10], although endurance exercise-training studies failed to exert these effects on LVEF [26, 27]. Regarding strain rate and systolic velocity, only one study reported improvements with HIIT training compared to MIT training [24], whereas these effects were not confirmed in the study by Cassidy et al. [10]. The same applies to endurance exercise-training studies, as only the study by Schmidt et al. [27] reported improvements in strain rate compared to the control group, whereas this could not be confirmed in other studies [14, 25, 26]. Schmidt et al. [27] also reported superior effects on TAPSE compared to the control group [27]. However, it is worth noting that LVEF was normal at baseline in the majority of the studies, which may suggest that LVEF was not suitable as a surrogate for impaired systolic cardiac function. Lastly, one study reporting twist (systolic function) and untwist (diastolic function) rates found contradictory results, as different results were observed in regional domains [28]. Overall, only three studies indicated a superior effect on one of the systolic parameters. Given these heterogeneous results, it is objectively impossible to draw unambiguous conclusions regarding the effect and the type of exercise training on systolic function, even if the general perception of exercise training and systolic function is different.

3.2.3 LV Dimensions and Structure

Between-group analyses were reported for the following parameters: LV mass ($n=2$ out of four studies), LV mass index ($n=3$ out of four studies), LV dimensions ($n=1$ out of three studies), end-diastolic volume (EDV) ($n=2$ out of five studies), end-systolic volume (ESV) ($n=1$ out of four studies), LV end-diastolic diameter (LVEDD) ($n=1$ out of one study). HIIT training superiorly increased LV mass [10] whereas MIT was not able to exert this effect [14]. For LV mass index, only one study reported a superior effect of exercise training [27]. Regarding EDV, both endurance training and HIIT training were able to increase this parameter [10, 27]. However, exercise training was not able to exert superior effects on ESV or LV dimensions [10, 14].

3.3 Animal Studies

As shown in Table 2, the majority of animal studies were performed in genetically modified mice or rats mimicking T2DM (6/8), and only one study used female mice.

3.3.1 Diastolic Function

Despite the fact that T2DM is characterized by important changes in cardiac diastolic function, only 3/8 studies specifically examined the effect of exercise intervention on cardiac diastolic parameters (Table 2).

In these studies, exercise intervention was able to improve cardiac diastolic function, as assessed by hemodynamic parameters (e.g., $-\mathrm{d}P/\mathrm{d}t$) [29, 30] and time to 50% relengthening [31]. In the articles included, only the studies of Hafstad et al. and Boardman et al. compared the effect of exercise type on diastolic function [29, 30]. In their studies, MIT and HIIT were equally effective in improving diastolic function.

3.3.2 Systolic Function

Changes in systolic function as a result of exercise intervention were assessed in 7/8 studies. All studies reported improved systolic function, by examining either LVEF, fractional shortening (FS), or arterial pressure after exercise training [29–35]. Both MIT and HIIT training appeared to be equally effective in improving systolic function.

Table 2 Summary of studies in animals included in the review, showing training type and intensity, and effects on diastolic and systolic function and left ventricle morphology

Study	Animal model	Training			Outcome assessment method	Effect on cardiac function		
		Type	Intensity	Duration (weeks)		Diastolic function	Systolic function	Cardiac remodeling
Ko et al. [35]	Male OLETF rats (28 weeks)	Resistance exercise (ladder climbing)	Moderate	12	Echocardiography	–	↗ Systolic function	–
Boardman et al. [30]	Male C57BL/6J mice + high-fat diet	Running	High and moderate	10 or 3	Hemodynamic measurements	↗ Diastolic function	↗ Systolic function	↗ Hypertrophy in HIIT
Veeranki et al. [33]	Male db/db mice	Running	Low to moderate	5	Echocardiographic analyses, blood pressure recording, Sirius Red staining	–	↗ FS ↗ EF ↗ SV ↗ Mean arterial pressure	↘ Fibrosis
Wang et al. [34]	Male db/db mice	Running	Moderate	15	Echocardiographic analyses, Masson's trichrome staining	–	↗ EF ↗ FS	↘ Fibrosis
Kesherwani et al. [32]	Female C57BL/6J + high-fat diet	Swimming	Low	8	Echocardiographic analyses, Masson's trichrome staining	–	↗ %EF ↗ %FS	↘ Fibrosis
Hafstad et al. [29]	DIO mice, high-fat diet initially, after 9 weeks Western diet	Running	High and moderate	8–10	Hemodynamic measurements, Sirius Red staining	↗ Early and late diastolic function	↗ Systolic function	↘ Fibrosis in MIT ↗ Hypertrophy in HIIT
Van Hoose et al. [36]	Male Zucker Diabetic Fatty rats	Running	Low to moderate	7	Electrocardiogram	–	–	↘ Hypertrophy
Stolen et al. [31]	Male db/db mice	Interval running	High	13	Echocardiographic analyses	↘ Time to 50% relengthening	↗ SV ↗ FS	–

OLETF Otsuka Long-Evans Tokushima Fatty, *db* diabetes, *DIO* diet-induced obesity, *FS* fractional shortening, *EF* ejection fraction, *SV* stroke volume, *HIIT* high-intensity interval training, *MIT* moderate intensity training, / not applicable, ↗ increased, ↘ decreased

3.3.3 Cardiac Remodeling

Interstitial fibrosis is also a common feature observed in the diabetic heart and is partially responsible for the impaired diastolic function. In all studies examining collagen content (4/8 studies), exercise intervention was able to reduce myocardial fibrosis [29, 32–34]. However, only MIT, but not HIIT, was able to exert such an effect in the study by Hafstad et al. [29].

Regarding LV hypertrophy, one study reported a less pronounced hypertrophy after exercise training [36] and another decreased cell volume after exercise intervention [31], while in the studies by Hafstad et al. [29] and Boardman et al. [30] only HIIT was able to induce physiological hypertrophy.

4 Discussion

According to this systematic literature review, exercise training elicits significant improvements in diastolic function in T2DM with or without DCM and a reduction in myocardial fibrosis, but not necessarily improvements in systolic function. The impact of different exercise modalities on these outcomes remains uncertain.

4.1 Exercise Improves Cardiac Function

In both T2DM patients and animal models for T2DM with or without DCM, cardiac function improves significantly following exercise intervention. Effective improvements were observed in diastolic function after only 12 (human studies) and 3 (animal studies) weeks of exercise training (mainly endurance). These data thus indicate that significant improvements in diastolic function can be achieved by exercise training in a relatively short timeframe of 12 weeks in T2DM patients. However, it should be noted that studies examining the effects of shorter-term exercise interventions (< 12 weeks) in the T2DM population have not thus far been performed. Targeting diastolic function with exercise intervention is important as impaired diastolic function is an early marker of DCM, and can eventually lead to heart failure.

Systolic function in animal models shows substantial improvements after just 3 weeks of exercise training associated with a decrease in myocardial collagen deposition (after 5 weeks). Conversely, effects of exercise on systolic function in T2DM patients remain controversial. An explanation for this apparent discrepancy could possibly rely on the fact that LVEF was preserved in the T2DM patient groups included in this review. It is therefore likely that the potential positive effects of exercise intervention on systolic function were underestimated and/or could not be detected in the patient studies due to non-impaired LVEF at baseline. The impact of exercise intervention thus remains to be studied in T2DM patients with impaired systolic function.

Currently, it is recommended that diabetes patients perform exercise at least 150 min/week at moderate to vigorous intensity and for at least 3 days/week [37, 38]. Regarding HIIT, the American Diabetes Association (ADA) states that vigorous-intensity or interval training for at least 75 min/week may be sufficient for younger adults and more physically fit individuals. For four out of the 13 studies, it was doubtful whether the prescribed exercise training volume was sufficient to comply with current guidelines [10, 25, 27, 39]. However, the outcomes from these studies seemed comparable with those of the other studies. Nevertheless, these are guidelines aiming to specifically improve glycemic control, rather than cardiac function. For a patient with diabetes and impaired cardiac function, the European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool could be useful [40]. To improve cardiac function and glycemic control, the EXPERT tool recommends daily activity of at least 30 min/session at moderate intensity for at least 8 weeks. Therefore, it appears to be appropriate to use the ADA recommendations.

4.2 Type of Exercise Does not Seem to Affect Outcome

Surprisingly, the variance in applied training modalities was small and different parameters were used to describe cardiac function/structure, thus impeding the detection of a clear relation between exercise modalities and changes in cardiac function/structure.

Recently, the impact of HIIT has attracted greater interest in cardiovascular rehabilitation. Epidemiological and experimental data suggest that HIIT might provide additional benefits and be more potent than the classical MIT modality [41]. In healthy subjects, sparse data suggest that the potential of HIIT in comparison to MIT to improve cardiac function is most likely attributable to a higher mitochondrial fatty acid oxidation and metabolism [42]. HIIT, but not MIT, also lowers systolic blood pressure (SBP), and reduces HbA_{1C}, high-density lipoprotein cholesterol (HDL-C), malondialdehyde (MDA) levels, nitric oxide (NO), and von Willebrand factor (vWF) in T2DM patients [43]. Overall, HIIT seems superior in improving vascular functions compared with MIT. In animal studies, three studies focused on HIIT, while all others examined MIT. We observed no difference between diastolic and systolic improvements after both exercise modalities. However, only MIT and not HIIT was able to reduce cardiac fibrosis, while only HIIT induced physiological hypertrophy. Physiological hypertrophy is a result of developmental growth and exercise with normal cardiac structure without dilated cardiomyopathy, while in diabetes pathological hypertrophy can occur through pathological stimuli (pressure or volume overload) creating a compensating response [44, 45].

For clinical studies, three studies investigated the effect of HIIT in diabetic patients. Two of these studies investigated mitral inflow pattern as a marker of diastolic function and reported beneficial results. However, only one study used echocardiography, whereas the other used magnetic resonance imaging (MRI), further complicating the comparison with the MIT studies and making it unable to draw firm conclusions. In addition to exercise mode, exercise frequency (from two up to four sessions/week) and applied continuous

intensity [50–75% of maximal oxygen uptake (VO_{2max})] were comparable between studies and did not display different beneficial patterns. Finally, it is important to mention that beneficial changes in cardiac function (mainly diastolic) were already noticed after a relatively short exercise intervention (12 weeks) in most studies (Table 1). These data may thus contradict the widely held belief that prolonged exercise interventions are mandatory to enhance cardiac function.

4.3 Differential Underlying Mechanisms of Exercise Training Modalities in T2DM with DCM Remain Unclear

Underlying mechanisms involved in T2DM and DCM from animal studies and the potential beneficial effects of exercise intervention are shown in Fig. 3. Altered contractile and electrophysiological cardiomyocyte function combined with an increased fibrosis are known to contribute to impaired cardiac function in T2DM, especially in the presence of inflammation, hyperglycemia, hyperinsulinemia, and elevated blood free fatty acid (FFA) concentrations [8]. Although HbA_{1C} decreased significantly (up to 0.7%) after exercise intervention in most human studies, this was not always accompanied by decreased fasting blood glucose concentrations. In addition, exercise training intervention did not consistently modulate blood insulin concentrations or indicators of insulin resistance [14, 25, 46]. However, diastolic function was enhanced. As a result, it appears that improvements in blood glucose and insulin concentrations are not prerequisites to enhancement of cardiac function in T2DM patients, but probably other blood parameters may be (such as FFAs or inflammatory factors). This is further suggested in animal studies where blood glucose concentrations do not consistently improve after exercise intervention, despite improvements in cardiac function [29, 31–33]. Indeed, as shown in the studies by Stolen et al. [31], Ko et al. [35], and Hafstad et al. [29], exercise did reduce FFAs and triglycerides in the plasma of diabetic animals [30]. In addition, the balance between inflammation markers, i.e., interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF-α), was positively affected after exercise in heart tissue itself [32]. Taken together, data indicate that changes in lipids rather than changes in glucose levels play a role in the improved cardiac function. However, the importance of improved inflammation parameters in enhancing cardiac

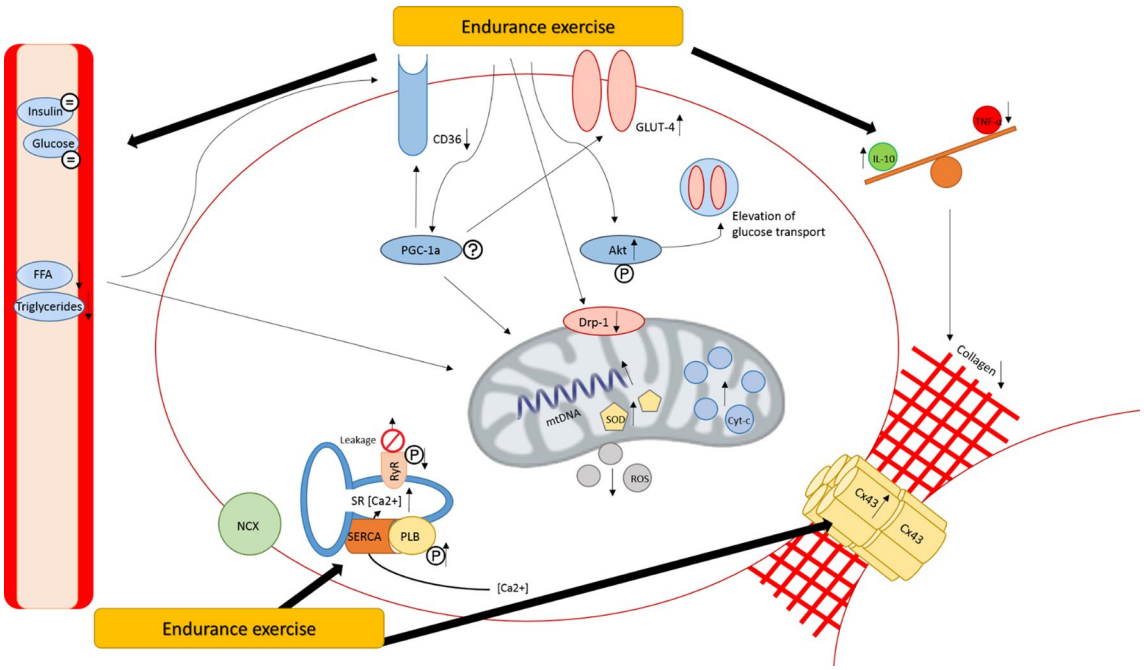

Fig. 3 Exercise affects both cardiomyocyte function itself and circulating factors in DCM. The circulatory concentrations in pro-inflammatory cytokines, as well as FFAs, decrease during exercise intervention, which relates to less fibrotic tissue in the heart. Balance in substrate metabolism between FFA and glucose oxidation is restored after exercise intervention. Mitochondrial function is improved, with less mitochondrial fission and less oxidative stress. Calcium handling in the cardiomyocyte is improved and communication between cells through increased gap junctions is significantly altered after exercise intervention. *DCM* diabetic cardiomyopathy, *FFAs* free fatty acids, *TNF-α* tumor necrosis factor alpha, *PLB* phospholamban, *SERCA* sarcoplasmic/endoplasmic reticulum Ca ($^{2+}$) ATPase 2a, *SR* sarcoplasmic reticulum, *NCX* sodium-calcium exchanger, *GLUT-4* glucose transporter type 4, *PGC-α* peroxisome proliferator-activated receptor gamma coactivator 1-α, *Drp-1* dynamin-related protein 1, *mtDNA* mitochondrial DNA, *SOD* superoxide dismutase, *Cyt-c* cytochrome-*c*, *ROS* reactive oxygen species, *IL-10* interleukin-10, *P* phosphorylated, *?* no disclosure about effect between groups

function in T2DM with or without DCM and the underlying mechanisms involved remain to be determined. It is well described that an excess of lipid accumulation in cardiac tissue results in cardiac lipotoxicity, leading to myocyte apoptosis and contractile dysfunction [47, 48]. Alterations in the lipid metabolism at the cardiac level contribute to the pathogenesis of diabetic cardiomyopathy by increasing myocardial triacylglycerol (TAG) and ceramide content [49, 50].

Extracellular remodeling and reduced fibrosis are known to be associated with improved cardiac function [51, 52]. All studies that were included showed a reduction of fibrotic tissue in the heart, together with less apoptosis after exercise intervention. However, whether exercise modality and duration play differential roles in the beneficial remodeling remains unclear.

In addition, adequate mitochondrial function to ensure proper metabolism is mandatory to induce improved cardiac function, given the high energetic demand of the heart. In that context, it is well known that mitochondrial function is decreased in DCM [53]. Energy availability and demand in the diabetic heart are imbalanced, resulting in a heart with reduced working capacity. In the studies included, exercise training was able to restore impairments in mitochondrial DNA (mtDNA) transcription and replication and increase mtDNA. Dynamin-related protein 1 (Drp-1) levels were normalized after exercise, balancing the excessive mitochondrial fission in DCM and repairing contractile defects in the myocytes. In addition, mitochondrial transmembrane depolarization improved mitochondrial cytochrome *c* levels contributing to improved myocyte function, and exercise increased mitochondria levels and restored their appearance. Effects of exercise also reduced myocardial reactive oxygen species (ROS) content and increased mitochondrial superoxide dismutase (SOD), further emphasizing the beneficial effect of exercise on mitochondrial function [29, 35]. After exercise intervention, mitochondrial respiratory capacity and efficiency will be improved, resulting in enhanced cardiac function due to improved ATP synthesis and energy handling [54].

Peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) plays a key role in the regulation of myocardial energy metabolism and is important in mitochondrial biogenesis. After diabetic animals were subjected to exercise, messenger RNA (mRNA) and protein levels of PGC-1α and other components of the pathway were upregulated, while inhibition of Akt phosphorylation in the heart was reversed [34, 35]. However, another study showed no difference between diabetic animals and wildtype animals in PGC-1α [31]. Finally, Hafstad et al. showed an increased myocardial glucose oxidation metabolism and lower fatty acid oxidation rates, resulting in a mild change in substrate utilization after exercise [29]. The altered substrate metabolism was confirmed by Ko et al., where exercise upregulated protein expression levels of glucose transporter type 4 (GLUT4), while peroxisome proliferator-activated receptor alpha (PPARα) levels were lowered [35].

Changes in $[Ca^{2+}]$ homeostasis are disrupted in DCM animals and were reversed after exercise [54]. Indeed, diastolic and systolic Ca^{2+} levels were normalized with HIIT training [31]. These changes were associated with improved SR Ca^{2+} load, sarcoplasmic reticulum (SR) Ca^{2+} leak, phospholamban (PLB) phosphorylation, sarcoplasmic/endoplasmic reticulum $Ca(^{2+})$ ATPase 2a (SERCA2a), and sodium-calcium exchanger (NCX) protein expression and function, all contributing to improved cardiomyocyte function with exercise [31]. However, changes in SERCA2a or Ryr2 mRNA expression were not confirmed by others [29].

4.4 Limitations

The main limitation of our review was that conducting a meta-analysis was very difficult, mostly due to the substantial heterogeneity of outcome parameters, the different techniques/methods used (e.g., some researchers included both septal and lateral early diastolic velocity to calculate *E*/*e*′, whereas others used only one of these) and the lack of explanation in the methodology sections; these considerations impeded appropriate comparisons and the performance of a meta-analysis. This emphasizes the need for the standardized use of echocardiographic parameters as per official guidelines (e.g., guidelines for the evaluation of diastolic dysfunction [55] or speckle tracking echocardiography for deformation imaging [56]) and detailed explanations of methodologies, which would enable appropriate comparisons to be made.

In addition, as very few human studies have explored the molecular pathways leading to improvements in cardiac function/structure, conclusions on underlying mechanisms involved are solely based on results obtained from animal studies. Therefore, translation of the observed mechanisms in the clinical context remains speculative.

Finally, in patient studies, an accurate PEDro score could only be assessed in 9/13 studies due to study design. Quality scores were lower than expected (due to lack of blinding subjects, therapist administering the exercise therapy, and assessors who evaluated the tests). Indeed, 4/9 studies had a score < 6 and were considered "poor quality" studies. However, the outcomes for low- and high-quality studies were similar.

5 Conclusion

Our systematic literature review shows that exercise intervention in patients with T2DM results not only in improved metabolic parameters but also in molecular adaptations

(e.g., extracellular remodeling and reductions in fibrosis) that enhance cardiac function in most cases. More specifically, exercise training ameliorates (or at least positively influences) different aspects (*E*/*A*, *E*/*e′*, *e′*, Dt) of diastolic function and leads to beneficial remodeling in T2DM and DCM animal models. However, exercise training is not necessarily accompanied by improvements in systolic function and LV structure, and more extensive studies are therefore required to elucidate these issues, particularly in terms of unravelling the roles of specific types of exercise. Nevertheless, our review strongly suggests that exercise training should be a cornerstone in the treatment of T2DM, not only to improve glycemic control but also to specifically enhance cardiac function.

Compliance with Ethical Standards

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Conflict of interest Maxim Verboven, Lisa Van Ryckeghem, Jamal Belkhouribchia, Paul Dendale, Bert O. Eijnde, Dominique Hansen, and Virginie Bito declare that they have no conflicts of interest relevant to the content of this review.

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