REVIEW

Effects of Resistance and Combined training on Vascular Function in Type 2 Diabetes: A Systematic Review of Randomized Controlled Trials

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■ Abstract

BACKGROUND: Cardiovascular disease (CVD) is the main cause of mortality in type 2 diabetes (T2D). Exercise can reduce the risk factors associated with CVD in T2D patients. However, research evaluating its beneficial effects in these patients has used different measurement protocols and types of exercise, complicating comparison. **AIM**: To assess the effects of resistance training (RT) and combined training (CT) on the vascular function of T2D patients. **METHODS**: A database search (MEDLINE, Scopus, and Web of Science) was performed to identify relevant articles that were published up to August 2017. Only original studies evaluating the effects of RT or CT interventions on vascular function in T2D patients were included. The articles were reviewed independently by at least three reviewers. The Cochrane guidelines were used to assess the methodological quality of the studies. Fourteen studies were finally included. Two studies only used RT and twelve studies used CT as intervention strategy. **RESULTS** and **CONCLUSIONS**: The results show that resistance training is a useful means for primary treatment of vascular diseases and maintenance of vascular function in T2D patients. However, more studies are necessary to gain full knowledge of the beneficial effects and to identify tailored exercise plans to optimize these benefits. The information provided in this review may help to improve current treatment of vascular diseases in T2D patients and to design future studies.

Keywords: type 2 diabetes · resistance training · vascular disease · endothelial function · non-aerobic exercise · glucose intolerance · flow-mediated dilation

1. Introduction

According to the International Diabetes Federation (IDF), 382 million people were diagnosed with diabetes in 2015. It is expected that by 2035 more than 592 million people will be affected [1]. This development results in approximately 5 million deaths per year in individuals between 20 and 79 years old, representing 8.2% of world mortality, and placing a major burden on global health expenditure. It is estimated that health systems spent at least 673 billion dollars in 2015, representing 12% of total spend [2]. The larger part of this amount was related to the prevention and treatment of T2D.

Individuals with T2D have a greater risk of cardiovascular disease (CVD) because of chronic hyperinsulinemia and hyperglycemia, along with increased proinflammatory cytokines, oxidative stress, obesity, dyslipidemia, and physical inactivity, all of which contribute to vascular dysfunction [3-5]. These abnormal effects on vascular tissue may result in fibrosis, arterial stiffness [6, 7], and endothelial dysfunction [5, 8].

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A pharmacological approach is the first line of treatment for restoring optimal glycemic control, despite its side effects. Exercise can help to prevent or even reduce CVD-related risk factors, such as dyslipidemia [9], hyperglycemia [10], and insulin resistance [10, 11]. Exercise also appears to exert beneficial effects on vascular function, resulting in increased blood flow, which places repetitive shear stress on endothelial cells [12]. This contributes to increased production and release of nitric oxide (NO), mediated by the endothelium, which acts as an important regulator of vascular tonus, improving arterial compliance and reducing arterial stiffness [13]. Beside complementing conventional cardiovascular drug therapy for restoring vascular function, exercise may also be considered as a substitute therapy, which replaces drugs, as it is able to improve vascular function in T2D patients in a safer way than drug treatment [14, 15].

The beneficial effects of aerobic exercise on the cardiovascular system have been described in detail [15]. Non-aerobic exercise such as resistance training (RT) is also considered essential for maintaining several aspects of health, and is associated with a number of important benefits, including increased functional capacity [16], increased muscle mass [17], strength [18], and improved body composition [19]. However, the impact of RT on vascular function is controversial. Some studies have shown that high-intensity RT increased arterial stiffness [20] and reduced arterial compliance [21, 22]. On the other hand, when resistance training is associated with aerobic training (AT), some studies have reported a substantial positive effect on vascular function in healthy individuals, including reduction in arterial stiffness, pulse wave velocity, and blood flow [23].

Most studies on RT have focused on healthy subjects. However, the beneficial effects may be more or less distinct in diabetic patients. To define these effects, it is important to examine RT effects in individuals with T2D, either alone or in combination with aerobic exercise [24, 25]. The aim of this systematic review is to evaluate the importance of resistance and combined training for the maintenance of vascular function in T2D patients.

2. Methods

2.1. Search strategy

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. The search strategies were re-

Abbreviations:	
1RM	1 maximum repetition
Ach	acetylcholine
AT	aerobic training
Aix	aortic augmentation index
BA	brachial artery
CVD	cardiovascular disease
CA	Carotid artery
cIMT	carotid intima-media thickness
CT	combined training
CO	control
D	diabetic
ECG	electrocardiogram
EID	endothelium independent vasodilation
ET	exercise training
FBF	forearm blood flow
FMD	flow-mediated dilation
GTN	glyceryl trinitrate
HR	heart rate
HRR	percentage of heart rate reserve
HRmax	percentage of maximal heart rate
LNMMA	blocker NG-monomethyl-L-arginine
NO	nitric oxide
MVC	maximal voluntary contractions
ND	non-diabetic
NR	not reported
PA	popliteal artery
PCVR	peak calf vasodilatory reserve
PPW	peripheral pressure waveforms
PRT	progressive resistance training
PWA	pulse wave analysis
PWV	pulse wave velocity
RA	radial artery
RT	resistance training
SFA	superficial femoral artery
SNP	sodium nitroprusside
T2D	type 2 diabetes
US	ultrasonography
VO_2max	percentage of maximal rate of oxygen consumption

ported to ensure the integrity of the results and to enable the same methods to be used for any new emerging evidence. Boolean and proximity operators were used, and the search strategy was correctly adapted for each database using different combinations of the following keywords using MeSH and DeCS terms:

- Diabetes mellitus type II
- Glucose intolerance
- Insulin resistance
- Resistance training
- Strength training
- Weight training
- Progressive training
- Progressive resistance
- Weight lifting
- Vascular endothelium

- Blood vessels
- Vascular smooth muscle
- Vascular diseases
- Vascular resistance
- Vascular stiffness
- Vascular remodeling

The studies retrieved were identified by searching the following electronic databases: PubMed/MEDLINE (via the National Library of Medicine) and Scopus (Elsevier). The search was not limited by date, but the oldest study identified dated from 2001. The last search was conducted in August 2017.

In the next step, the abstracts of the articles were reviewed, and complete versions of the papers that met the inclusion criteria were obtained. In addition, the references of the papers were checked for any additional studies that met the inclusion criteria. Duplicate studies and those with irrelevant content were excluded after title, abstract, and full-text had been inspected.
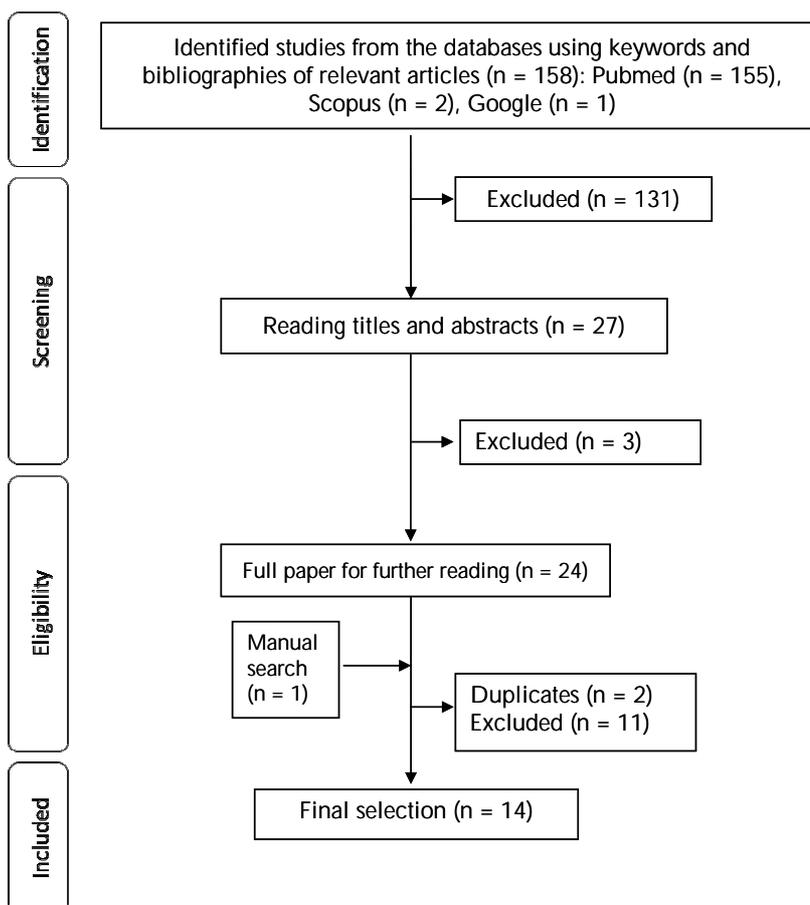

Figure 1. Flowchart of articles included.

2.2. Selection criteria

All selected titles, abstracts, and full-text articles were independently reviewed by at least three reviewers (J.E.S.A., A.S.B, and J.S.S.Q.). Disagreement on inclusion or exclusion of a study was resolved by consensus. The following inclusion criteria were applied:

- Population consisting of adult individuals with type 2 diabetes.
- Exercise intervention of four weeks or more.
- Trials where participants were either randomized to or placed in an intervention involving resistance training (RT) or resistance training with aerobic exercise.

The following types of articles were excluded:

- Articles on animal studies
- Articles on type 1 diabetes mellitus
- Articles on aerobic exercise only

- Review articles
- Meta-analyses
- Abstracts
- Conference proceedings
- Editorials and letters
- Case reports
- Monographs (**Figure 1**)

2.3. Outcome measures

The outcome measures assessed for the chronic effects of resistance and combined exercise on vascular function in subjects with T2D were:

- Flow-mediated dilation (FMD)
- Endothelium-independent vasodilation (EID)
- Pulse wave velocity (PWV)
- Pulse wave analysis (PWA)
- Carotid intima-media thickness (cIMT)

- Arterial stiffness
- Arterial compliance
- Forearm resistance vessel function
- Conduit vessel function
- Analysis of conduit artery diameter
- Wall thickness

2.4. Quality assessment

We assessed the risk of bias according to the Cochrane guidelines. The following criteria were used for evaluation:

1. Sequence generation and allocation concealment (selection bias)
2. Blinding of participants and personnel (performance bias)
3. Blinding of outcome assessment (detection bias)
4. Incomplete outcome data (attrition bias)
5. Selective outcome reporting (reporting bias)
6. Other potential sources of bias (**Figure 2**)

We rated the risk of bias as low, unclear, or high according to established criteria [27]. Disagreements between authors were settled by consensus.

3. Results

3.1. Research strategy

A total of 158 articles was identified from electronic and manual searches for preliminary review: 155 from PUBMED, 2 from SCOPUS, and 1 from manual search. After removal of duplicates and screening for relevant titles and abstracts, a total of 27 articles was considered for a full-text review. Thirteen articles met the inclusion criteria established. A flow chart illustrating the study selection process and the number of articles at each stage is given in **Figure 1**.

After applying the inclusion and exclusion criteria, thirteen articles were selected for the review;
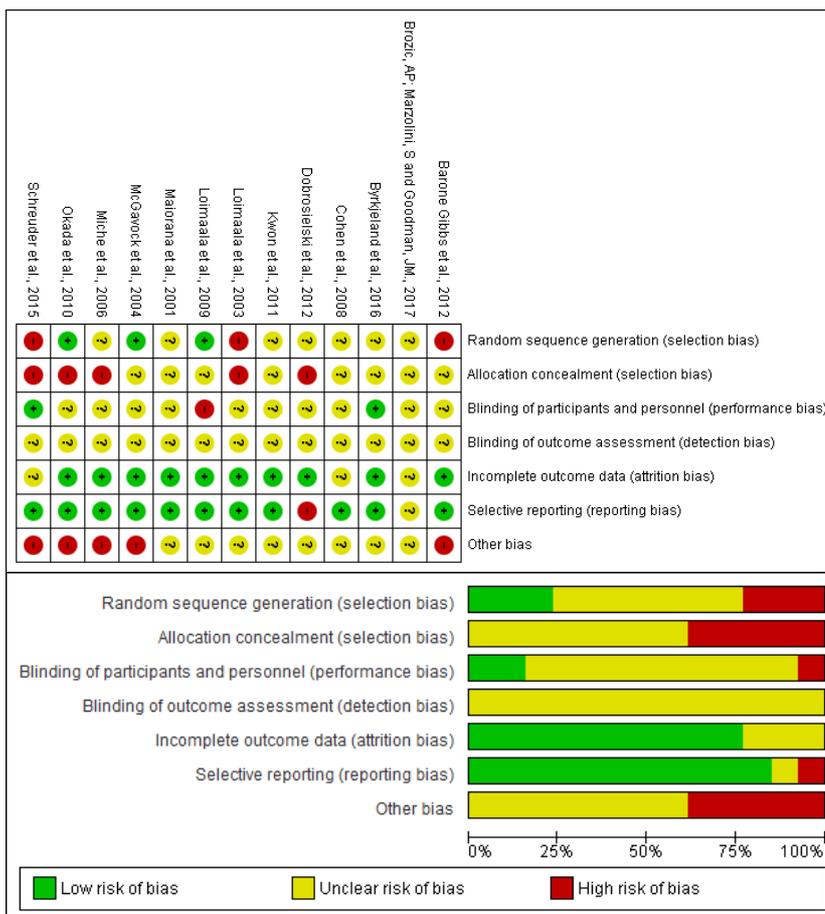
Figure 2. Risk of bias assessment. Notation: (+) low risk of bias; (-) high risk of bias; (?) unclear risk of bias.

two studies using RT and eleven using RT combined with AT (**Table 1**). The selected articles were all studies with humans, aged between 40 and 63 years. The results were presented by the type of exercise, its intensity, its duration, and the effects observed in the subjects.

3.2. Methodological quality assessment

All studies included were assessed for bias risk using the risk of bias tool [27]. As shown in **Figure 2**, only 3 (23%) of the 13 studies used a method of randomization, and none reported any information on allocation concealment. It is not possible to use the blinding method given the nature of the intervention, thereby increasing the risk of detection bias. Only two studies masked their outcome assessors. Of the 13 studies, 10 (77%) presented a low risk of bias of incomplete

Table 1. Characteristics of studies included

Study	Age (yr)	Gender, disease	Exercise				Parameter settings and vessels	Results after training
			Fitness level	Type	Body segment	Protocol		
Maiorana et al. (2001)	52±2	Both T2D	Sedentary	Aerobic + resistance (machine)	Lower + upper limb w/o forearm; bilateral	20 min (70-85% HRpeak)/3x10-12 (55-65% MVC), 8 wk	FMD (%), EID (%), forearm resistance vessel function, conduit vessel function, brachial artery	Increase in FMD, forearm resistance and conduit vessel function. Responses to EID were unchanged.
Loimaala et al. (2003)	53.3±5.1	Men T2D	Sedentary	Aerobic + resistance (machine)	Lower and upper limb; bilateral	30 min (65-75% VO₂max)/ 3x10-12 (70-80% MVC), 12 mo	PWV (m/s); between aortic arch and popliteal artery	No changes in arterial stiffness
McGavock et al. (2004), CAN	59±7	Women T2D	Sedentary	Aerobic + resistance (machine)	Lower and upper limb; bilateral	30-55 min (65-75% HRR) 3 x 10-15 (50-65% 1RM) 10 wk	PWA (ml/mmHg); radial artery	Decrease in arterial stiffness. Exercise training improves large artery compliance.
Miche et al. (2006), GER	D: 67±6/ ND: 68±10	Both T2D	Sedentary	Aerobic + resistance (elastic bands)	Lower limb; bilateral	(60-80% VO₂max) (resistance dependent on band length) 4 wk	FMD (%) and EID (%); brachial artery	No changes in FMD and EID in the D and ND groups
Cohen et al. (2008), AUS	60.5±7.6	Both T2D	Sedentary	Resistance (machine)	Lower + upper limb; bilateral	3x8 (75-85% 1RM), 14 mo	Laser Doppler flow; skin microcirculation of the forearm	Increase in vascular response endothelium-dependent and -independent vasodilator
Loimaala et al. (2009), FIN	52.3±5.6	Men T2D	Sedentary	Aerobic + resistance (machine)	Lower + upper limb; bilateral	20 min (65-75% VO₂máx)/ 3x10-12 (60-80% 1RM), 24 mo	PWV (m/s); between aortic arch and popliteal artery	Decrease in arterial stiffness. Exercise training did not improve an arterial elasticity.
Okada et al. (2010), JPN	ET:61.9± 8.6/CO: 64.5±5.9	Both T2D	Sedentary	Aerobic + resistance (NR)	NR	40 min/ 20 min, 3 mo	FMD (%); brachial artery	Increase in FMD in ET group; no change in the CO group.
Kwon et al. (2011)	57.0±6.8	Women T2D	Sedentary	Resistance (elastic bands)	Lower + upper limb; bilateral	3x10-15 (Resistance-dependent on band length), 12 wk	FMD (%) and EID (%); brachial artery	No changes in FMD and EID
Dobrosielski et al. (2012), USA	56.0±6.0	Both T2D	Sedentary	Aerobic + resistance (machine)	NR	30 min (65-75% HRmax)/3x10-15 (50% 1RM) 26 wk	PWV (m/s); carotid-femoral	No changes in arterial stiffness
Barone Gibbs et al. (2012), USA	ET:58±5 CO:56±6	Both T2D	Sedentary	Aerobic + resistance (machine)	Lower + upper limb; bilateral	45 min (60-90% HRmax)/2x10-15 (50% 1RM) 26 wk	FMD (%); brachial artery	No changes in FMD
Schreuder et al. (2015), NLD	ET:59±6 CO:58±7	Men T2D	Sedentary	Aerobic + resistance (machine)	Lower + upper limb; bilateral	60 min (70-75% HRR)/3x12, 8 wk	Conduit artery diameter + wall thickness; brachial, carotid + superficial femoral artery	No changes in SFA or CA diameter in T2D or CO. BA diameter increased in T2D, no change in the CO group.
Byrkjeland et al.(2016), NOR	63.1±7.9	Both T2D	Sedentary	Aerobic + resistance (free wght)	Upper limb; bilateral	150 min (10-15) Borg's scale 12 mo	cIMT; carotid artery	Decrease in cIMT
Brozic et al. (2017), CAN	56.1±10	Both DM2	Sedentary	Aerobic + resistance (free wght)	Lower + upper limb; bilateral	60 min (70-75% VO₂peak)/70% 1RM), 12 wk	PWV (m/s) and AIx; radial and Aorta artery	Decrease in arterial stiffness

Legend: 1RM - 1 maximum repetition; Aix - aortic augmentation index; BA - brachial artery; CA - carotid artery; cIMT - carotid intima-media thickness; CO - control; D - diabetic; EID - endothelium-independent vasodilation; ET - exercise training; FMD - flow-mediated dilation; HR - heart rate; HRmax - percentage of maximal heart rate; HRR - percentage of heart rate reserve; MVC - maximal voluntary contractions; ND - non-diabetic; NR - not reported; PRT - progressive resistance training; PWA - pulse wave analysis; PWV - pulse wave velocity; SFA - superficial femoral artery; T2D – Type 2 Diabetes; VO₂max - maximal oxygen uptake; VO₂peak - peak oxygen uptake.

outcome data, while the results for the remaining 3 (23%) were not clear. Twelve studies showed a low risk of bias for selective outcome. However, 5 (38%) studies showed a high risk of bias for other criteria, whereas in 8 (62%) studies it was unclear whether there was an additional bias.

3.3. Characteristics of the studies and summary of outcome measures

All studies were conducted in sedentary individuals. Eight studies recruited both male and female participants [28-35], three studies exclusively recruited male participants [36-38], and two studies recruited females exclusively [39, 40]. Only 3 studies had a control group [28, 35, 38].

Exercise intervention characteristics are shown in **Table 1**. RT on weight machines was used in one study with high intensity [31] and elastic resistance bands with low intensity were used in another study [39]; frequency of training was 3 days a week for 14 months and 5 days a week for 12 weeks, respectively. The usage of resources for combined training among the 11 studies was as follows:

- 7 studies used weight machines [28, 32, 33, 36-38, 40]
- 2 free weights [29, 30]
- 1 elastic resistance bands [34]
- 1 did not include information on the kind of exercise [35]

The frequency of CT was most commonly 2 or 3 days per week and duration was between 4 weeks and 12 months.

The intensity of RT, quantified as a percentage of one-repetition maximum (1RM) in six studies [28, 29, 31, 32, 37, 40], ranged between 50-85% 1RM. Two studies used a percentage of maximal voluntary contraction (MVC) [33, 36], with a range between 55-80% MVC. Kilogram equivalents for resistance bands were used in two studies to prescribe intensity [34, 39], one study used Borg's scale [30] and two studies did not report the intensity progression during the intervention period [35, 38]. AT intensity was expressed as:

- Percentage of maximal heart rate (HRmax) [28, 32, 35]
- Percentage of heart rate reserve (HRR) [38, 40]
- Percentage of maximal rate of oxygen consumption (VO$_2$max) [34, 36, 37] or
- Percentage of peak rate of oxygen consumption (VO$_2$peak) [29, 33]

The intensity ranged from 60-90%. The most commonly reported intensity was 65-75% of heart rate reserve or VO$_2$max, which is classified as moderate intensity.

Outcome measures for the studies are displayed in **Table 1**. Of the two studies that used RT, one evaluated vascular function through laser Doppler flow responses [31] and the other used flow-mediated dilation (FMD) and endothelium-independent vasodilation (EID) [39]. Of the studies that used combined RT and AT:

- 5 used a common technique for assessment of vascular stiffness (PWV) [29, 32, 36, 37] or PWA [40]
- 5 used FMD [28, 33-35, 41]
- 2 used EID [33, 34]
- 1 used conduit artery diameter and wall thickness [38]
- 1 used Doppler flow responses [41]
- 1 used carotid intima-media thickness (cIMT) [30]

Contradictory results were observed in relation to changes in vascular function following resistance exercise programs. One study observed an improvement in vascular function after 14 weeks of RT in type 2 diabetes patients using Doppler flow responses [31]. Another study observed no differences after RT in flow-mediated dilation (FMD) and endothelium-independent vasodilation (EID) [39] (**Table 1**).

In combined training studies, the following positive effects were observed:

- Improved endothelial function and reduced arterial stiffness [29, 30, 38].
- Increased arterial elasticity and compliance [33, 35, 40].
- Remodeling of peripheral arteries [38], promoting improved vasodilatory function in type 2 diabetes patients.

In contrast, some combined training studies did not observe any changes in vascular parameters [28, 32, 34, 36, 37] (**Table 1**).

4. Discussion

One of the most common causes of mortality in patients with T2D is (cardio-) vascular dysfunction [42, 43]. Older age, longer duration of diabetes, and treatment with insulin are associated with vascular dysfunction [43]. Many factors contribute to the appearance of cardiovascular complications,

including structural and functional alterations caused by insulin resistance and/or disturbances in insulin excretion, hyperinsulinemia, oxidative stress, and inflammation, which compromise vascular health and cause endothelial dysfunction [4, 44, 45]. Therefore, the use of long-term RT and/or combined exercise programs to reverse or attenuate damage to vascular function in T2D individuals may be an important strategy.

The studies included in this review consider vascular function in individuals with T2D. Of the two studies that used RT, only one showed beneficial effects on endothelial function [31]. In this study, the researchers observed an improvement in endothelial function after 14 weeks of supervised or non-supervised high-intensity (75-85% 1RM) RT in a group of elderly individuals with T2D [31]. In another study, a small improvement in endothelial function was observed after 12 weeks of RT with an intensity of 40-50% 1RM, but with no statistically significant difference in relation to the T2D group without exercise [39]. The RT duration may have been too short to induce an improvement in endothelial function. This outcome is in line with the above-mentioned study by Cohen *et al.* [31], where no significant change in endothelial cell function was observed after 2 months either. Significant change was observed only after 14 months.

In contrast to the outcome of studies with RT, most studies that used combined training found beneficial effects on vascular function [29, 30, 33, 35, 38, 40]. These results are in line with other studies that have observed that combined training is capable of restoring endothelial function [14, 46]. However, some studies using combined training found no significant effect of exercise on vascular function [28, 32, 34, 36, 37]. This disagreement in results may be related to the degree of endothelial dysfunction in the study populations, since individuals with a longer duration of T2D may suffer from greater damage to the arterial wall. According to Naka et al. (2012), the duration of diabetes may be a major contributor to endothelial dysfunction compared to short-term glycemia indices and other risk factors that involve complete endothelium exposure to diabetes and hyperglycemia as well as other comorbidities related to diabetes, hypertension, dyslipidemia, and obesity [43].

It is important that the extent of exercise is tailored correctly to the individual patient, which may promote positive effects on vascular function [39]. Future studies may focus on combined training protocols that have beneficial, or at least non-detrimental, effects on vascular function. The

studies in this review used different methodologies such as pulse wave velocity (PWV), flow-mediated dilation (EID), endothelium-independent vasodilation (EID), and carotid intima-media thickness (cIMT) to evaluate vascular function in people with T2D. The vascular changes observed in T2D individuals are related to an increase in oxidative stress and inflammation, which leads to a blockade of endothelial nitric oxide synthase (eNOS), an enzyme that reduces the bioavailability of nitric oxide, and also to an increase in vasoconstriction, caused by an increase in endothelin, angiotensin, and prostaglandin actions [3, 4, 47]. These changes harm the resistance arteries and capillary vessels, and result in the fragmentation of elastin and the deterioration of collagen deposits, contributing to arterial stiffness in T2D patients [48-50].

This review observed that RT [31] and CT [29, 30, 33, 35, 38, 40] can contribute to an improvement in vascular function in T2D individuals and a reduction in arterial stiffness. These changes in vascular function caused by RT are due to the suppression of vascular sympathetic activity, promoting a chronic restriction on the vascular wall, and consequently reducing arterial distensibility [24]. The hypoxic and acidic intramuscular environment may also contribute to increased arterial distensibility because of NO production stimulated by muscular hypoxia attenuating arterial stiffness. Moreover, arterial extension seems to be related to reduced vascular smooth muscle tone or structural remodeling, and may help to decrease arterial stiffness [24].

The same effects on vascular function are well documented in the literature in healthy individuals. This beneficial response seems to be linked to the shear stress in endothelial cells, which is the site of the conversion of mechanical stimulus to chemical signaling. Exercise training promotes a rise in blood flow velocity because of an increased O_2 demand in activated muscles, thus producing increased shear stress during exercise. This leads to a rise in NO bioavailability, mediated by elevated eNOS and antioxidant enzyme expression, which in turn reduces free radical generation and NO degradation [12, 50-52]. Furthermore, regular exercise can reduce the expression of pro-inflammatory molecules, such as adhesion molecules, interleukins, selectins, and C-reactive protein, causing a rise in anti-inflammatory effects by increasing the quantity of endothelial progenitor cells (EPCs). This contributes to vascular regeneration and angiogenesis, which is important in enhancing vascular function in T2D individuals [51].

The information available in the present review shows that RT can promote substantial benefits in vascular function, but this was only possible by prolonged duration of RT [31]. When resistance exercise was performed combined with AT, improvements in vascular function were observed in most studies even at a shorter duration [29, 30, 33, 35, 38, 40]. This response was also seen in meta-analysis where high-intensity RT increased arterial stiffness, while the combination of RT and AT was able to prevent this increase [20]. Furthermore, in another meta-analysis, FMD brought about a greater increase via AT than RT or a combination of RT and AT, but the latter two groups also significantly increased FMD [51].

In our review, it is not possible to assert what type of training was responsible for these improvements in vascular function, because most studies used both AT and RT simultaneously. Although there are a few studies that investigate the effects of RT and AT alone on vascular function in T2D patients, the literature has shown that AT is more likely to be beneficial than RT [15, 51]. However, RT should be included in the training protocol since both scientific studies and organizations providing exercise prescriptions for this T2D population recommend the inclusion of this training modality [31, 53, 54].

Our study has a few limitations which must be taken into account. Only fourteen studies met the inclusion criteria. RT and CT yielded distinct results. However, most of the studies showed an improvement in vascular function. There is clearly a need for more studies examining the efficacy of exercise interventions on vascular health in T2D individuals. Also, training protocols should be standardized, as most of the studies used different exercise intensities, durations, frequencies, and intervention periods. Finally, the studies in this review used different vascular points:

- 6 studies collected data from the brachial artery [28, 29, 33-35, 39]
- 3 studies collected data from the aorta [32, 36, 37]
- 1 study collected data from the femoral, brachial, and carotid arteries [38]
- 1 study collected data from the carotid artery [30]
- 1 study collected data from the radial artery [40]
- 1 study collected data from cutaneous microcirculation [31]

This heterogeneity in vascular function evaluation may have affected the responses assessed after exercise training.

5. Conclusions

Despite the limitations, this systematic review provides important information in relation to the types of exercise used in individuals with T2D and their effects. The results show that both RT and CT can enhance vascular function as an important strategy to reverse cardiovascular complications in these patients. However, more studies are necessary to determine the optimum intensity, duration, and frequency of training in specific patient groups in order to maximize the benefits of exercise training on vascular function in T2D.

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