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Effect of physical activity on tissue perfusion in patients with diabetes mellitus: Systematic review and meta-analysis

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ABSTRACT

Aims: The objective of this systematic review and meta-analysis is to identify and assess the literature exploring the impact of physical activity on enhancing tissue perfusion in the feet of patients with diabetes mellitus (DM).

Materials and methods: All the selected studies were evaluated using the Cochrane risk of bias tool, to assess the risk of bias for randomized controlled trials. A thorough search was conducted in April 2024 through PubMed and Web of Science to identify randomized clinical trials (RCTs) and comparative studies that assessed the effect of physical activity enhancing tissue perfusion. Data analysis was performed using RevMan v5.4., employing the Mantel-Haenszel method for dichotomous outcomes.

Results: A total of nine studies compared changes in microcirculation before and after physical exercise in patients with DM. A meta-analysis of the data collected from seven studies estimated a mean difference of 4.87 (95 % CI 2.37–7.38) favouring the improvement of microvascular parameters post-exercise, with a minor level of heterogeneity ($x^2 = 10.54$, df = 6, p = 0.1, $I^2 = 43$ %) and a statistically significant difference between the two groups ($p \leq 0.001$). However, a second evaluation, which included four studies involving patients with and without DM, indicated high heterogeneity ($x^2 = 661.32$, df = 3, $p \leq 0.00001$, $I^2 = 100$ %) with no observable statistically significant differences between the two groups (p = 0.62).

Conclusion: Physical activity in patients with DM may be effective in improving blood microcirculation in the lower limbs.

1. Introduction

Diabetes mellitus (DM)-related foot disease is defined by the International Working Group on the Diabetic Foot (IWGDF) as the presence of one or more of the following foot disorders: peripheral neuropathy, peripheral arterial disease (PAD), infection, ulcer(s), neuro-osteoarthropathy, gangrene or amputation, in a person diagnosed with DM [1]. These complications mainly occur due to sustained hyperglycemia [2]. Neuropathy and PAD are considered risk factors for developing diabetic foot ulcers (DFU), indicative of micro- and macrovascular impairment [3].

The microcirculation is the terminal vascular network of the systemic circulation consisting of microvessels with diameters <20 μm. It is responsible for the transport of all nutrients to the tissue cells. It is probably the most important compartment of the cardiovascular system, as it is in direct contact with parenchymal cells [4]. Previous research has predominantly focused on the role of macrovascular status and neuropathy in the development of DFU. However, it has also been observed that microcirculation is not only essential for proper skin nutrition and thermoregulation but also vital as it facilitates tissue repair and regeneration after dermal injury. Therefore, a disturbance in microcirculation can negatively impact the skin [3]. There is evidence that cutaneous microangiopathy precedes the development of other complications such as neuropathy or retinopathy [5].

Nerves in the feet can respond to thermal, mechanical, and chemical stimuli, although the protective mechanism may be absent due to neuropathy in individuals with DM [6,7]. Meanwhile, microcirculation plays a crucial role in tissue lesion responses to stimuli like local heat or

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pressure [8]. An accurate diagnosis of the neurovascular status is necessary to detect and prevent complications. It is been demonstrated that there are certain protective microcirculatory hyperemia responses, known as reactive hyperemia, in response to such stimuli, controlled by neuronal, metabolic, hormonal, and chemical mechanisms [7]. Reactive hyperemia indicates an organ or tissue's intrinsic capability to autoregulate its local blood supply, a function that is impaired in individuals with DM [8,9]. There are two ways to evaluate the microvascular response: the local application of a stimulus that generates pressure and/or thermal changes. In individuals with DM, the cutaneous blood flow observed in response to locally applied pressure and heating is altered due to microangiopathy [10].

Patients with DM experience increased blood pressure in the lower extremity capillaries. This increase is linked with sympathetic denervation and a rise in flow through arteriovenous anastomoses. Elevated capillary pressure amplifies fluid leakage and triggers inflammatory responses in the microvascular endothelium, contributing to the thickening of the capillary basement membrane. Arteriolar sclerosis and the diminution in the diameter of small blood vessels restrict vasodilation, consequently reducing skin nutrition [11]. Hyperglycemic conditions suppress nitric oxide (NO) synthesis, impacting insulin resistance and limiting the vasodilatory response in microvessels [12,13]. It also stimulates the glycolytic and polyol pathways in peripheral nerves. The modification of proteins with advanced glycation end products (AGEs) and the accumulation of AGEs result in both structural and functional damage, such as the loss or demyelination of nerve fibres and thickening of the endothelial basement membrane in small vessels [14]. Glycation-related alterations in the microvasculature, including basement membrane thickening and changed permeability, lead to nerve fibre hypoxia, culminating in functional loss [14,15].

Endothelial cell damage and malfunction contribute to the progressive loss of microvascular repair mechanisms [16]. Patients with DM are more likely to suffer from a decreased neurovascular response associated with microangiopathy. Symptoms include reduced capillary perfusion, increased thrombosis, heightened vascular permeability, arteriovenous shunting, and hypoxia. These conditions can be caused by infection-induced endothelial cell injury, stasis from vascular resistance, or oedema [17].

A sedentary lifestyle is a modifiable risk factor that leads to the development of micro- and macrovascular complications [18]. A clinical trial [19] emphasized the importance of maintaining adequate glycemic control as it could be associated with a lower rate of microvascular complications. A meta-analysis by Qiu et al. [20] suggests that exercise can cause increased blood flow, which in turn leads to increased NO synthesis and decreased oxidative stress in individuals with type 2 diabetes.

Recent studies suggest that physical activity can enhance plantar pressure distribution, nerve conduction, and joint mobility. This could also extend maximal walking time, potentially reducing the incidence of foot injuries and bolstering the quality of life in patients with DM [21,22].

However, to the best of our knowledge, there is currently no systematic review examining the impact of exercise on the microvascular health of patients with DM. Thus, this systematic review and meta-analysis aim to identify and assess studies exploring the effect of physical activity on the enhancement of tissue perfusion in the feet of patients with DM.

2. Material and methods

A systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [23].

2.1. Selection of studies

The inclusion criteria were as follows: clinical trials and observational studies, published in English, Spanish, French, or German, involving patients of any age diagnosed with Type 1 or 2 DM, or having DM-associated foot disease. The exclusion criteria included: in vitro, animal or pre-clinical studies; non-original articles such as reviews, case reports, letters, or commentaries; and studies with no available data for analysis.

Articles were examined if they incorporated at least one physical exercise or training modality. Chosen studies had to ascertain tissue perfusion in patients with DM or DM-foot related dissease before and after the exercise program. Experimental or quasi-experimental studies were required to compare physical activity with standard care, such as suggesting that the patient undertake daily physical activity, but without a specific guideline, or abstain from exercise entirely.

2.2. Search strategy

The PubMed (Medline) database was utilized to ascertain studies related to the effect of physical exercise on microvascular fitness in patients with DM.

A first search was performed using the Medical Subject Headings (MesH) terms "diabetes", "exercise", "walking", "transcutaneous" and "microcirculation". In addition, further searches were performed with the keywords "diabetic", "skin blood flow" and "physical activity". References of all retrieved studies were checked for additional articles.

All articles published up to April 2024 were evaluated. Full-text articles that met the inclusion criteria for the present study were assessed after pre-screening their titles and abstracts.

All articles considered for inclusion were independently reviewed by two investigators (LPA and ATG), with consensus as the goal. If consensus could not be achieved, they sought the opinion of a third author (JLLM).

2.3. Outcome assessment

Primary outcomes included measurements of tissue perfusion using transcutaneous oxygen pressure ($TcPO_2$), transcutaneous carbon dioxide pressure ($TcPCO_2$), skin perfusion pressure (SPP), or perfusion units (PUs) values, irrespective of the chosen microcirculation assessment tool.

2.4. Data extraction

Data were extracted using a standardized Microsoft Excel spreadsheet. The extracted data included the following: first author and year of publication, type of study, total number of participants included, comparison group, type of DM, characteristics of the intervention group (history of DFU or active DFU), outcome, presence of neuropathy, microcirculation assessment tool, quantitative values of microvascular status, type of exercise, physical activity, or training performed, follow-up time, and improvement in the intervention group.

2.5. Statistical analysis

All studies were analysed descriptively, incorporating the mean, median, and standard deviation (SD). Frequency and descriptive analyses were carried out using SPSS® software (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 27.0. Armonk, NY, USA: IBM Corp).

The patient served as the unit of analysis for all studies. When the studies compared similar interventions and reported identical outcome measures, their data were amalgamated for a meta-analysis. To analyse the data, Review Manager statistical software (RevMan, Version 5.4. The Cochrane Collaboration, London, UK, 2020) was used, employing the

Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes using either fixed or random effects model. Estimates of intervention effects are expressed as the standardized mean difference (SMD) (95 % CI) for continuous outcomes.

The clinical and methodological heterogeneity was estimated. When it exceeded 50 %, we used a random effects model. To assess the significance of any discrepancies in estimates of treatment effects from various trials, we used the Cochrane test for heterogeneity and the I2 statistic.

2.6. Risk of bias assessment

Following the guidelines of the "Cochrane Risk of Bias Tool" [24] scales for experimental studies, two investigators (LPA and ATG) independently assessed the methodological quality and potential bias of the included studies. If consensus was not reached, a third independent assessor was consulted (JLLM) to achieve a consensus on the risk of bias.

A risk of bias assessment table (Quality assessment using the Cochrane risk of bias tool) was created for the included studies [25]. For quasi-experimental studies, we adhered to the guidelines of the Effective Practice and Organization of Care (EPOC) [26], a supplement to the Cochrane Handbook for Systematic Reviews. Each category was classified as either low, unclear, or high risk.

Finally, for pre-post studies without a control group, we utilized the National Institutes of Health (NIH) Risk of Bias Assessment Guidelines [27]. We classified each category as either good, fair, or poor.

All studies were deemed low risk owing to the impossibility of blinding the assessors and patients during the exercise.

3. Results

3.1. Search results and study characteristics

An initial search of the PubMed database using the search strategy "Diabetes AND exercise OR walking AND microcirculation OR transcutaneous oximetry" generated a total of 3311 results. A subsequent search using the terms "Diabetic foot AND skin blood flow AND physical activity" produced 15 results. Applying selection criteria to focus on full-text clinical trials, observational, and comparative studies in both searches yielded 795 references. After title and abstract screenings, 22 articles that met the selection criteria were chosen.

After reviewing the full-text articles, nine were ultimately chosen for analysis. The selection process is illustrated in greater detail within the flowchart presented in Fig. 1, following the criteria outlined by the

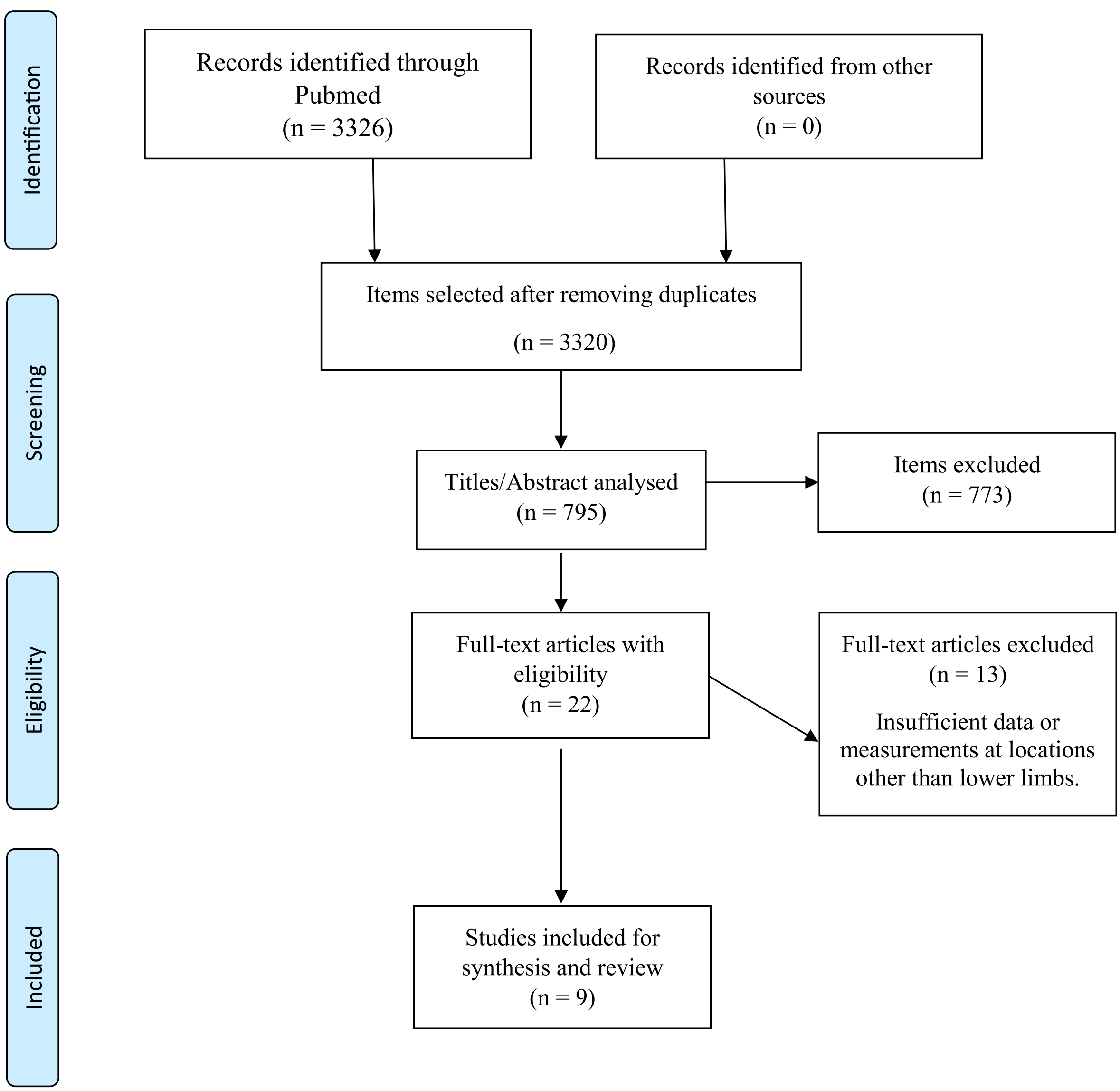

Fig. 1. Flow chart.

PRISMA [23] guide. The articles analysed were dated between 2003 [28] and 2022 [29], with the year 2021 [29,30] being the most repeated date with two articles analysed.

Of the nine articles included, four were comparative studies [28, 30–32], four were quasi-experimental studies [29,33–35] – one of which was a controlled clinical trial [28], and one was a randomized controlled clinical trial [27].

The analysis of the articles incorporated a total of 338 participants. The study with the most subjects reported a sample size of 86 participants [28], while the smallest sample was eight participants [34].

Finally, concerning the intrinsic characteristics of the patient group with DM, we observed that eight analysed articles used patients with type 2 DM as inclusion criteria. Only one article [33] did not specify the type of DM afflicting the subjects studied. Additionally, we found that only one study [33] included patients with active UPD. Conversely, we noted that four of the nine selected articles [28,30,32] listed severe neuropathy as an exclusion criterion, while one article [34] made no specification.

3.2. Description of the study variables analysed

The primary variable examined in all the articles reviewed was the measurement of distal blood flow, before and up to a maximum of 72 h post-exercise. Notably, in the article by Krcma et al. [34], an additional measurement was taken 8 weeks after the intervention.

Laser Doppler flowmetry was the method of choice for most investigators in measuring the primary endpoint [28,29,31–33], followed by transcutaneous oximetry [36,34,35] and laser speckle contrast imaging [29]. Colberg et al. [28,31,32] and Reynès et al. [29] performed a local thermal reactive hyperemia test by heating the skin under the laser Doppler sensor to 42–44 °C, a methodology distinct from other analysed studies. Krcma et al. [34] also opted to perform a post-occlusion hyperemia test.

In most of the studies included in the review [26,28–30,36], PUs were most commonly used to quantitatively express the measurement of tissue perfusion in lower limbs. This was followed by transcutaneous oxygen pressure (TcPO2), expressed in millimetres of mercury (mmHg) [36,34,35], SPP, also expressed in mmHg [33], and microvascular reactivity [34]. In their study, Reynès et al. [29] used PUs but expressed the results as the percentage of perfusion at rest.

In two of the analysed studies [31,32], no statistically significant differences were found in the improvement of tissue perfusion following the intervention. However, positive differences were reported after the chosen physical activity in the remaining seven articles. The data retrieved from the selected studies are summarized in Table 1.

3.3. Control groups

All but three of the analysed articles [33–35] included a comparative group in their methodological design. In the randomized clinical trial conducted by Rodríguez-Reyes et al. [36], the control group received an intervention consisting of education and empowerment techniques. These techniques included recommendations for comprehensive foot care and taking at least 10,000 steps per day, which were following the guidelines of the CAIPaDi protocol. Conversely, the controlled clinical trial by Duan et al. [30] included young, healthy subjects as the control group, but did not perform any comparative intervention.

In the comparative studies, the control group was distinguished from the study group by the absence of DM [30], the lack of DM in subjects with a body mass index (BMI) exceeding 30.0 [30,32], and the absence of DM in either athletic or sedentary individuals [28,32].

3.4. Development of the interventions

The physical activities incorporated in the chosen studies exhibited variability in methodology, with different numbers of interventions executed and tracked. Out of the ten studies reviewed, three chose walking as the physical activity for microcirculation assessments [29,30, 34]. Rodríguez-Reyes et al. [36,35] selected strength training on a vibrating platform for their studies. Other training programs included moderate aerobic exercise [31], moderate resistance exercise [32], Buerger's exercise [33], and maximal cycloergometry on an exercise bike [28].

Regarding the duration of the interventions, there was significant variability among the selected articles. In the study conducted by Chang et al., participants were required to perform the Buerger exercise thrice daily for 3 months [33]. A moderate aerobic activity program comprised aerobic exercise three times weekly for 10 weeks. The duration of continuous exercise escalated as the weeks proceeded, peaking at 45 min per session. Each participant had the option to choose from treadmills, exercise bikes, or rowing machines [31]. The moderate resistance exercise program involved three sets of 8–12 repetitions for 8 weeks. At the 4-week mark, the weight was reassessed and augmented if the subject could surpass 12 repetitions in the third set. Some of the integrated exercises were the seated leg press and extension, biceps curl or triceps extension [32]. In both of the said training programs, the subjects were observed by a qualified professional.

The exercise on the vibrating platform involved strengthening, stretching, massage, and relaxation exercises, executed three times a week for 12 weeks. The duration and intensity progressively increased throughout the study period, with an oscillation frequency of 30 Hz [36, 35].

Regarding the analysed studies that included walking as physical activity, Reynès et al. [29] evaluated the cutaneous microcirculation of the lower limbs after implementing a 6-min walking test (6MWT). Krcma et al. [34] evaluated the effect of escalating moderate physical activity on tissue perfusion by incrementing the daily steps count by 10–15 % after a 4-week phase of regular activity. Lastly, Duan et al. [30] conducted two types of interventions, implementing a randomization method between two groups: the 'low cumulative pressure-time integral (APTI)' protocol, tantamount to walking for 15 min at a pace of 54 steps per minute for a pressure-time integral of 90 kPa-s; and the 'high APTI' protocol which augmented the low APTI protocol by 1.5 times.

Lastly, we discovered that for evaluating microcirculation post-maximum-intensity exercise [28], each participant performed a stress test on a cycloergometer maintaining a cadence of 50 rpm. The power was incrementally elevated until the participant voluntarily finished the test.

3.5. Risk of bias of the included studies

Out of the nine articles analysed, five were categorized as 'high risk' of bias and two as 'some risk' of bias. The most frequent high-risk biases were identified in the categories of staff and participant blinding as well as data analysis blinding. None of the examined articles exhibited a risk of bias in the category encompassing other types of bias. Thus, the bias included in the risk of bias analysis was confined to the remaining categories under examination.

The full risk of bias analysis of the articles included in this review can be seen in Fig. 2. This includes the Quality Assessment (Cochrane risk of bias tool) for randomized trials that can be seen in Fig. 3, the RoB-EPOC tool for studies with a separate control group seen in Fig. 4, and the NIH Quality Assessment Tool for pre-post studies without a control group.

4. Meta-analysis

4.1. Assessment of blood perfusion before and after exercise in DM patients

A total of seven studies [28,36,30–33,35], involving 244 patients, compared the changes in microcirculation before and after physical exercise in patients with DM. A meta-analysis of these data estimated a

Table 1
Table data.

First author/Year	Type of study	No. participants	Outcome	Comparative group	Evaluation tool/ Assessment unit	Measuring features	Tissue perfusion			p-value	Intervention	Number of interventions	Follow up	Improved tissue perfusion after exercise
							Pre *Mean ±SD*	Post *Mean ±SD*	Improvement *Mean±SD*					
Chang 2016	Quasi-experimental	30	Pre and post exercise perfusion assessment	No	Laser Doppler/SPP	Baseline and after exercise program	58.3 ± 23.3	70.0 ± 23.3	11.7 ± 2.1	<0.001	Buerger's Exercise	3 times/day	3 months	Yes
Colberg 2006	Comparative	19	Pre and post exercise perfusion assessment	Sedentary without DM	Laser Doppler/PU	Baseline and 72h after exercise. Local heat 44 °C	*DM* 91.6 ± 14.9 *CS* 119.7 ± 12.0	*DM* 102.9 ± 16.9 *CS* 149.8 ± 20.0	*DM* 11.3 ± 1.86 CS 30.1 ± 2.49	≥0.05	Moderate resistance exercise	3 sets of 8–12 reps	8 weeks	No
Colberg 2005	Comparative	19	Pre and post exercise perfusion assessment	Obese without DM	Laser Doppler/PU	Baseline and 48–72h after exercise	*DM* 68.59 ± 12.8 *Control* 107.1 ± 12.2	*DM* 76.09 ± 12.35 *Control* 110.3 ± 12.3	*DM* 7.5 ± 1.8 *Control* 3.2 ± 1.7	≥0.05	Moderate aerobic exercise	3 times/week	10 weeks	No
Reynès 2021	Comparative	86	Pre and 10 min post exercise perfusion assessment	Obese without DM and healthy	Laser Doppler/% tissue perfusion at rest	Baseline and after exercise program	–	–	*Healthy* 17.7 ± 6.2 *Obese* 24.2 ± 5.3 *No DPN* 22.0 ± 14.8 *DPN* 18.1 ± 11.5	<0.05	6-min walking test	1	No	Yes, but no differences between groups
Colberg 2003	Comparative	58	Pre and post exercise perfusion assessment	Exerciser with and without DM and sedentary with and without DM	Laser Doppler/PU	Baseline and after exercise. Local heat 44 °C	*CE* 108.5 ± 17.6 *CS* 91.2 ± 9.0 *DME* 75.20 ± 6.3 *DMS* 74.9 ± 6.4	*CE* 114.2 ± 13.3 *CS* 89.9 ± 9.0 *DME* 88.3 ± 16.7 *DMS* 70.9 ± 9.7	*CE* 5.7 ± 0.7 *CS* −1.3 ± 0.4 *DME* 13.1 ± 0.6† *DMS* −4.0 ± 0.4	<0.05	Maximum cycloergometry	1	No	Yes, in DM exerciser group
Rodríguez Reyes 2017	Quasi-experimental	38	Pre and post exercise perfusion assessment	No	Transcutaneous Oximetry/$TcPO_2$	Baseline and 72h after exercise	28.7 ± 12.1	35.7 ± 9.9	7.0 ± 0.7	<0.001	Exercise on a 30Hz vibrating platform	3 times/day	12 weeks	Yes
Krcma 2009	Quasi-experimental	8	Pre and post exercise perfusion assessment and after back to baseline	No	Laser Doppler/ Microvascular reactivity/TcPO2	Baseline, after 4 weeks (V2) and after 8 weeks (V4)	4.8 [4.2–5.5]* $TcPO_2 > 30$	*V2* 6.1 [5.7–6.8]* $TcPO_2 > 30$ *V4***	1.3 [0.2]*	<0.01	Walking	Increase number of steps after 4 weeks	12 weeks	Yes
Rodríguez Reyes 2022	RCT	41	Pre and post exercise perfusion assessment	Educational intervention in DM	Transcutaneous Oximetry/$TcPO_2$	Baseline and 72h after exercise	*Intervention* 46.31 ± 6.65 *Control* 45.17 ± 8.24	*Intervention* 47.76 ± 6.08 *Control* 44.37 ± 7.51	*Intervention* 1.4 ± 0.4 *Control* −0.8 ± 0.5	0.028	Exercise on a 30Hz vibrating platform	3 times/week	12 weeks	Yes
Duan 2021	Comparative	30	Pre and post exercise perfusion assessment	Healthy	Laser Doppler/PU	Baseline and 6 min after exercise	*Low APTI healthy* 46.8 ± 42.9	*Low APTI healthy* 71.4 ± 53.3	*Low APTI healthy* 24.6 ± 5.0	<0.05	Walking	Low APTI and High APTI stimuli protocol	No	Yes, in low APTI stimuli.

(*continued on next page*)

Table 1 (*continued*)

First author/Year	Type of study	No. participants	Outcome	Comparative group	Evaluation tool/ Assessment unit	Measuring features	Tissue perfusion Pre *Mean ±SD*	Post *Mean ±SD*	Improvement *Mean±SD*	p-value	Intervention	Number of interventions	Follow up	Improved tissue perfusion after exercise
							High APTI healthy 42.8 ± 40.1	*High APTI healthy* 101.3 ± 64.5	*High APTI healthy* 58.5 ± 4.95	<0.05				
							Low APTI DM 83.5 ± 49.8	*Low APTI DM* 103.5 ± 50.1	*Low APTI DM* 20.0 ± 4.6	<0.05				
							High APTI DM 77.02 ± 52.08	*High APTI DM***	–	≥0.05				

RCT: randomized control trial; SPP: Skin Perfusion Pressure (expressed in mmHg); PU: perfusion unit; $TcPO_2$: transcutaneous oxygen pressure (expressed in mmHg); DM: *Diabetes mellitus*; DPN: diabetic peripheral neuropathy CE: exerciser control patients; CS: sedentary control patients; DMS: sedentary DM patients; DME: exerciser DM patients; †<0.05 vs. healthy exerciser and sedentary patients; *Expressed as mean and interquartile range; APTI: accumulated pressure-time integral; ** There was no statistically significant difference with the baseline measurement, so not shown.

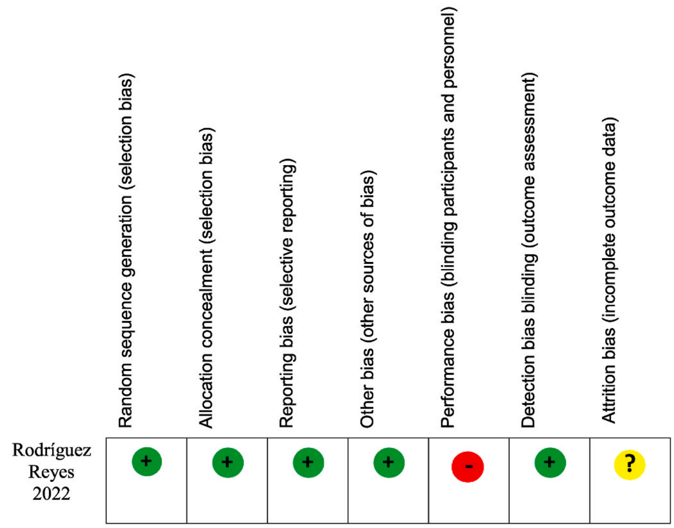

Fig. 2. Quality assessment (Cochrane risk of bias tool) for randomized trials.

mean difference of 4.87 (95 % CI 2.37–7.38) in favour of improved microvascular parameters after exercise, with low heterogeneity (x^2 = 10.54, df = 6, p = 0.1, I^2 = 43 %). Also, there was a statistically significant difference between the two groups (p ≤ 0.001) (see Fig. 5 for a comparison of blood perfusion before and after exercise in DM patients).

4.2. *Assessment of blood perfusion before and after exercise in patients with and without DM*

A total of four studies [28,30,32], involving 126 patients both with and without DM, provided data on changes in microcirculation, comparing results after exercise between the two patient groups. This subsequent analysis exhibited high heterogeneity (χ^2 = 661.32, df = 3, p = <0.00001, I^2 = 100 %). However, no statistically significant differences were observed between the two groups (p = 0.62). Refer to Fig. 6 for the comparison of blood perfusion before and after exercise in patients with and without DM.

5. Discussion

Upon analysing the chosen articles, it is firstly notable that all but two of the studies [31,32] reported an improvement in vascular parameters following certain physical activities. This suggests that exercise may positively affect the enhancement of blood microcirculation in patients with DM. Previous research [37] strongly supports physical exercise not only for better glycaemic control, but also for the improvement of macrovascular parameters in people with type 2 DM. These authors highlight the importance of aerobic exercise in combination with resistance training for further improvement of these values. However, they conclude that the evidence regarding the association between exercise and peripheral neuropathy and DFU risks in people with type 2 DM remains insufficient. Therefore, our research is relevant because of the positive relationship between improved microcirculation and exercise, as we know that there is a close relationship between microangiopathy and the development of complications such as neuropathy, as mentioned above. Essentially, exercise appears as an additional tool in preventing complications associated with impaired microcirculation and reduced tissue perfusion. Such issues, like diabetic neuropathy, can lead to the development of UPD, subsequently decreasing patient life quality and increasing healthcare system costs [38,39].

Regarding the methods of microcirculation assessment, two main systems exist laser Doppler flowmetry and transcutaneous oxygen pressure. Transcutaneous oximetry has previously been proven to serve

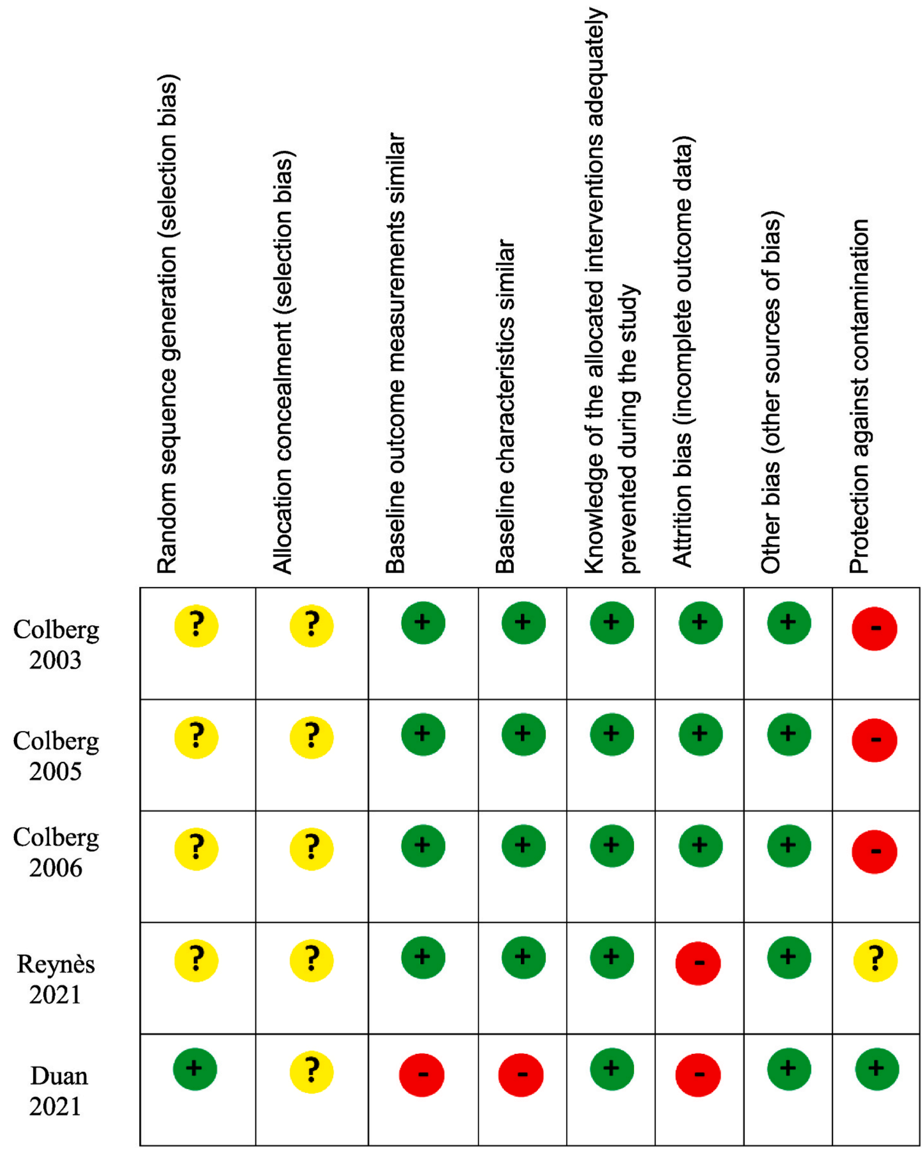

Fig. 3. RoB-EPOC (Cochrane risk of bias tool) for studies with a separate control group.

Author	Year	Quality Rating
Krcma[33]	2009	Moderate
Chang[32]	2016	Good
Rodríguez-Reyes[34]	2017	Good

Fig. 4. NIH Quality assessment tool for pre-post studies with no control group.

as a reliable tool in assessing tissue perfusion in patients with DM during exercise. Its non-invasive and user-friendly nature makes it particularly useful in patients with PAD. This is because the measurement results are not influenced by the increased stiffness of the arterial walls and abnormalities in vasodilatation present in these patients [40]. Furthermore, laser Doppler flowmetry, particularly when combined with provocation testing as seen in the studies by Colberg et al. [28,31,32], Reynès et al. [29], and Krcma et al. [34], is an operator-independent technique allowing for quick assessment of endothelial function [41].

Concerning the selection of physical activities, we discovered significant variation in the utilized procedures. Even among articles evaluating identical activities, such as walking, we noted that the chosen methodology differs from one author to another.

The results gleaned from the studies by Rodríguez-Reyes et al. [36, 35], initially in the quasi-experimental study and later validated in the RCT, indicate that performing strength and stretching exercises on a vibrating platform enhances microcirculation. This proves to be a safe, cost-efficient, and accessible option, particularly for patients with limited mobility. This discovery has been linked to an activation of muscle spindle receptors that stimulate muscle activity and the release of nitric oxide, which evokes vasodilation.

In the study by Duan et al. [30], they suggested weight-bearing physical exercises such as walking for patients with DM. They observed an altered vascular response in these patients during

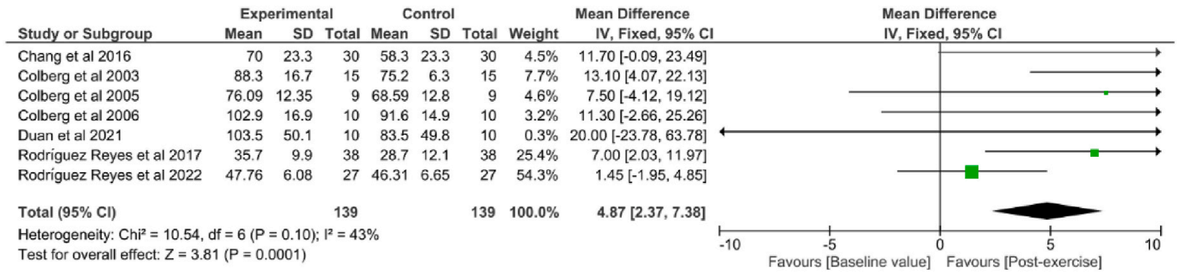

Fig. 5. Forest plot of blood perfusion before and after exercise
Comparison of blood perfusion before and after exercise in DM patients.

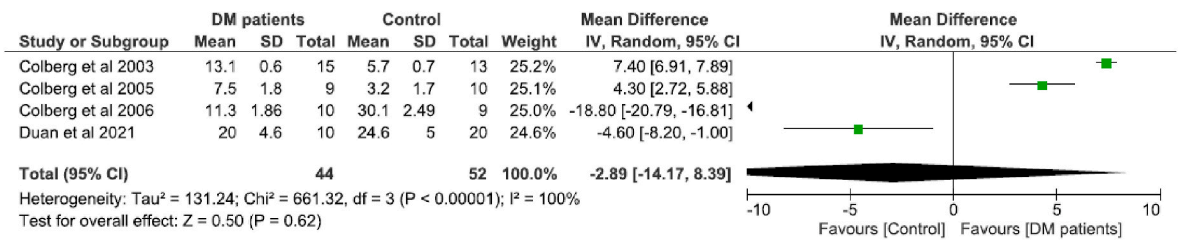

Fig. 6. Forest plot of blood perfusion before and after exercise
Comparison of blood perfusion before and after exercise in patients with and without DM.

high-intensity physical activity, implying the need to determine a safety range for sports activities to prevent excessive plantar pressures that could potentially cause UPD. Post weight-bearing exercise, it was also noted that a rest of at least 2 min is necessary to allow complete vasodilation of blood flow in the lower limbs.

Conversely, the 6MWT (Six Minute Walk Test) successfully induced cutaneous vasodilation in all groups analysed in the study conducted by Reynès et al. [29] Despite the enhancement of cutaneous perfusion, a reduced vasodilator response was observed in patients with severe diabetic neuropathy. This outcome could potentially be explained by the presence of arteriovenous shunts, which result in decreased blood flow during a vasodilator stimulus.

Similarly, increased habitual physical activity, such as augmenting daily step count and distance [34], resulted in an enhancement in tissue perfusion, as well as a decrease in time to perfusion in laser Doppler measurements compared to baseline. However, the transcutaneous oximetry measurement did not exhibit any change, suggesting this might be due to the exclusion of patients in the sample who were already diagnosed with microangiopathy at baseline.

Regarding the performance of Buerger's exercise [33], it was found that, even in patients with UPD, it can enhance skin perfusion and serve as an adjunct treatment to expedite the healing process. This positive outcome may be associated with increased vasodilation due to the effect of gravity following a period of ischemia caused by the elevation of the lower limbs. The subsequent contraction of the posterior leg muscles may further amplify vasodilation. Additionally, this exercise may enhance ankle joint mobility. However, the absence of a control group in this study might limit the quality of the evidence.

Following the medium-term aerobic and resistance exercise programs of Colberg et al.'s studies [31,32], it was observed that the results before and after the intervention were similar in the group of patients both without and with DM. This finding might be due to the exclusion of DM patients with impaired microcirculation as suggested by Krcma et al. [34]. Consequently, we could hypothesize that, in patients with more severe microvascular impairment coupled with poor DM control, a medium-term moderate physical activity intervention might enhance microcirculation. However, studies are needed to confirm this. On the other hand, it is been noted that short-term high-intensity exercise does improve microcirculation in patients with DM, especially those who exercise regularly [28,42]. This outcome could be attributed to a vasodilator response triggered by the increase in tissue temperature during exercise, resulting in increased skin perfusion that can persist even during rest periods [42].

After conducting the initial meta-analysis, we found that physical activity significantly improves microvascular perfusion in patients with DM, as indicated by the results' low heterogeneity among different studies. Nevertheless, the subsequent meta-analysis that compared groups of patients both with and without DM found no statistically significant differences. This lack of significant findings can be attributed to the small sample size and high heterogeneity of the studies reviewed. These results support the notion that perfusion is controlled by small C-fibre nociceptors, which may be impaired in subjects with DM due to the loss of neural control over arteriovenous shunts [11,17,39]. Consequently, a higher improvement in perfusion is observed in patients without DM, as shown in Fig. 6, which compares blood perfusion before and after exercise in patients with and without DM.

Two of the articles included in the systematic review could not be incorporated into the meta-analysis due to different units of measurement for tissue perfusion [34] and insufficient data for analysis in patient groups with and without DM [29]. Thus, we can emphasize the role that physical activity may play in reducing the complications related to microangiopathy.

5.1. Limitations

The main limitation we encountered while conducting this review was the limited availability of published literature in this area, in addition to the high degree of heterogeneity in the data provided by the selected studies, which complicated their analysis. Therefore, while we know that incorporating physical activity can be beneficial to patients with DM, specifically improving microcirculation, we cannot highlight the role of any specific sport due to the lack of consistency in the included studies. On the other hand, we understand that walking – due to its ease of incorporation for most patients – may be a safe and feasible option for improving circulation in patients with DM. This conclusion was reached by Lyu et al. [43] in their systematic review that included patients with PAD. Other authors [37,44] suggest that the intensity of physical exercise, especially resistance exercise, is closely related to the variety of results obtained in cardiorespiratory parameters such as maximal oxygen consumption (VO2max) or even HbA1c. These results are associated with the fact that the increase in intensity involves a series of circulatory adjustments in response to an increase in cardiac demand, which contributes to a greater transport of O2 and an improvement in its utilisation by skeletal muscle, as well as better glucose consumption. However, further research is necessary in this field due to the inconsistent establishment of criteria, protocols, and implementation of these interventions.

We also emphasize the notable absence of patients with a history of UPD in the reviewed studies. We firmly believe that the inclusion of patients embodying such characteristics is essential for evaluating the impact of these interventions on microcirculation as a preventative strategy against re-ulceration. This is in line with previous reviews such as Crews et al. [45], which confirm the importance of supporting patients at risk of ulceration to undertake controlled and gradual physical exercise after wound healing, as it has been shown that patients who do not exercise are more likely to develop reulcerations, although it is vital to customize the interventions in this vulnerable population.

While assessing the risk of bias, we discovered that the most prevalent biases in the reviewed articles were related to the randomization and blinding of patients, assessors, and data analysis. These issues limit the level of evidence in this review. However, given the impossibility of blinding in the three previously mentioned areas due to the nature of the intervention performed, we believe they should be considered as having "some risk".

The sample size in several studies was small, and most did not describe the statistical methods used to calculate the necessary sample size. This could potentially lead to inaccurate estimations of the effect.

Therefore, we propose future research directions that could potentially enlarge the sample size and improve the study methodology. These improvements could include standardizing the use of the same units of measurement for tissue perfusion, whenever possible. Secondly, we believe it is crucial to continue conducting RCTs to credibly demonstrate the relationship between the incorporation of a physical exercise routine and the improvement of microvascular status in patients with DM. This will involve comparing the performance of a specific physical activity with standard care in two groups of patients - those devoid of a DFU history and those at risk of developing reulcerations.

5.2. Strengths

A primary strength of the review we would like to highlight is the selection of articles describing patients' baseline tissue perfusion before initiating the chosen physical exercise. This approach allows for a clear demonstration of the positive relationship between exercise and microcirculation improvement.

Furthermore, we note that different investigators independently developed the procedures for data extraction, interpretation, and subsequent analysis.

6. Conclusions

Physical activity in patients with DM may be effective in improving blood microcirculation within the lower extremities. These results can potentially guide healthcare professionals in prescribing adapted physical exercise programs for individuals with DM. Unfortunately, the different interventions reviewed demonstrate the wide variety of exercises and durations available for the improvement of tissue microcirculation. Simple physical activities such as walking or performing strength and stretching exercises on a vibrating platform are effective and safe options for patients with DM. Future research is needed to determine the frequency, intensity and duration of exercise to establish an effective protocol for individuals with DM.

Declaration of competing interest

The authors declare no conflicts of interest.

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