Review Article:

Blood Flow Velocity and Endothelial Function in Peripheral Artery Disease with Diabetes: A Systematic Review and Meta-Analysis

Shamshad Begum. A. Loni[1*]

1. Department of Basic medical Science, College of Medicine, Majmaah University, Al Majmaah-11952, Saudi Arabia. Majmaah university Saudi Arabia

Received on May 12, 2025, accepted for publication on Apr 03, 2026, dx.doi.org/10.5455/mjhs.2026.03.021

Corresponding author:
Shamshad Begum. A. Loni, Department of Basic medical Science, College of Medicine, Majmaah University, Al Majmaah-11952, Saudi Arabia. Majmaah university Saudi Arabia.
E-mail : s.loni@mu.edu.sa: shamshadloni.21@gmail.com

OPEN ACCESS Distributed under Creative Commons CC BY-NC-ND 4.0

Abstract:

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder with reduced blood flow and endothelial dysfunction. Diabetes further impairs vascular function in PAD. This systematic review and meta-analysis compared blood flow and endothelial function in PAD patients with and without diabetes. This review was conducted across different databases, i.e., PubMed, Embase, Cochrane Library, Scopus, Web of Science, CINAHL, and ClinicalTrials.gov. Studies evaluated blood flow velocity, endothelial function, and walking distance in diabetic and non-diabetic PAD patients. Risk of bias was assessed using ROBINS-I for observational studies and the Cochrane RoB 2.0 for randomized trials. Meta-analyses used random-effects models for flow-mediated dilation and fixed-effects models for walking distance, with heterogeneity assessed using I^2 and Chi^2. Eleven studies met the inclusion criteria. The meta-analysis showed significantly reduced endothelial function in diabetic PAD patients, with a pooled flow-mediated dilation mean difference of −1.20% (95% CI: −1.56 to −0.84; $P < 0.00001$) and moderate-to-high heterogeneity ($I^2 = 63\%$) owing to heterogeneity in study designs. Walking distance was significantly decreased in diabetic PAD patients, with a pooled mean difference of -45.44 meters (95% CI: -60.00 to -30.88, $P < 0.00001$). Heterogeneity was low ($I^2 = 0\%$) hence acceptable to use a fixed-effects model. Exercise consistently improved walking capacity, whereas pharmacologic and dietary interventions had variable effects, underscoring the need for targeted therapies and standardized assessments. Overall, diabetes markedly impairs endothelial function and walking ability in PAD, emphasizing the importance of tailored interventions to improve vascular outcomes in this high-risk population.

Keywords:

PAD, diabetes mellitus, endothelial dysfunction, FMD. Exercise therapy

Introduction:

Peripheral artery disease (PAD) is a chronic atherosclerotic illness that is defined by narrowing or occlusion of peripheral arteries, leading to reduced blood flow, ischemic symptoms, and functional impairments [1]. PAD is mostly confined to the lower extremities and is associated with enhanced cardiovascular-related morbidity and mortality [2]. Pathophysiological mechanisms of PAD are initiated mainly by endothelial dysfunction, arterial stiffness, and chronic low-grade inflammatory processes that reduce vasodilatory capacity and insufficient microvascular perfusion [3]. In PAD patients, the presence of concomitant diabetes mellitus (DM) is associated with a significantly enhanced progression of the disease, along with a significantly enhanced rate of critical limb ischemia, wound healing impairment, and risk of major adverse cardiovascular events (MACE) [4]. The harmful effect of diabetes on vascular stability is mediated by hyperglycaemia-evoked oxidative stress, uncoupling of endothelial nitric oxide synthase (eNOS), and chronic low-grade inflammation, all of which enhance endothelial dysfunction and impair blood flow regulation [5].

Blood flow velocity parameters, including peak systolic velocity, end-diastolic velocity, and resistive index, yield valuable information regarding the hemodynamic alterations in PAD patients and offer a quantitative method for the assessment of arterial obstruction and consequent perfusion deficits [6]. Endothelial function, as measured by flow-mediated dilation (FMD) and pulse wave velocity, is a valuable biomarker of vascular health, reflecting the ability of arteries to modulate vasodilation in response to shear stress [7]. Reduction in these parameters not only reflects the severity of PAD but also importantly is linked with adverse clinical outcomes, including amputation risk and cardiovascular mortality [8]. In diabetic patients, endothelial dysfunction is further exacerbated by the deposition of advanced glycation end-products (AGE), increased production of reactive oxygen species (ROS), and an inflammatory milieu that continues to cause vascular damage [9]. Assessment of blood flow velocity and endothelial function in this high-risk population, therefore, is important to improve risk stratification and guide therapeutic interventions. Though earlier studies have investigated endothelial function as well as blood flow parameters in PAD, no comprehensive study on the interaction between diabetes and these parameters has been conducted.

In spite of widespread research on PAD and diabetes as individual pathologies, the collective effect of the pathologies on hemodynamic parameters and endothelial

function is still not well understood [10]. Earlier studies yielded contradictory findings on the extent of endothelial dysfunction in PAD and diabetic patients, with disagreement due to differences in study design, populations, and measures[11]. Additionally, the pharmacologic and non-pharmacologic intervention effects on reducing endothelial dysfunction and blood flow velocity augmentation in this population are not yet formally assessed. Elucidation of these knowledge gaps is essential to optimize vascular treatment options and encourage better clinical outcomes in PAD patients with diabetes. To study comprehensively the changes in blood flow velocity and endothelial function in this high-risk population, this systematic review and meta-analysis considered evidence from observational studies and randomized controlled trials with the aim of presenting a comprehensive model of the hemodynamic effects of diabetes on PAD and for the assessment of potential treatments.

Materials and Methods:

PECOS Protocol:

The PECOS (Population, Exposure, Comparison, Outcome, Study Design) approach was used to identify the eligibility criteria for this systematic review and meta-analysis which adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 statement [12]. The population (P) was individuals with a diagnosis of both diabetes mellitus (DM) and peripheral artery disease (PAD). The exposure (E) was the state of having diabetes in individuals with PAD, and this was established on the basis of documented diagnostic criteria such as the ankle-brachial index (ABI) <0.90, duplex ultrasonography, or angiographic evidence of PAD with a clinical diagnosis of DM. The comparison (C) group was individuals with PAD but without DM, which enabled the evaluation of the effect of diabetes on blood flow velocity and endothelial function. The outcomes (O) were quantitative measures of blood flow velocity (e.g., peak systolic velocity, end-diastolic velocity, resistive index) and endothelial function, as assessed by flow-mediated dilation (FMD, % change), pulse wave velocity, and walking distance (meters). The study design (S) was observational cohort studies, case-control studies, and randomized controlled trials (RCTs) that reported these measures.

Inclusion and Exclusion Criteria:

Trials were chosen for analysis if they fulfilled the following criteria: (1) the study population was adults with PAD and DM;

(2) endothelial function and blood flow velocity were measured using validated tools like duplex ultrasound, FMD, or pulse wave velocity; (3) comparative results were provided in PAD patients with and without DM; (4) the study was an RCT, case-control, or observational cohort study; and (5) English full text was accessible.

Exclusion reasons were: (1) non-selective studies of PAD patients with and without DM; (2) non-representative studies with insufficient data for meta-analysis (e.g., no quantitative outcome reporting); (3) case reports, editorials, and review papers; (4) pediatric or animal studies; and (5) methodologically questionable studies at high risk of bias that could not be reviewed for methodological quality.

Database Search Protocol:

Systematic search of literature was conducted on PubMed, Embase, Cochrane Library, Scopus, Web of Science, CINAHL, and ClinicalTrials.gov. Boolean operators and Medical Subject Headings (MeSH) were used to attain maximum sensitivity and specificity. Variations of the terms for PAD, diabetes, blood flow velocity, and endothelial function were used in the search strategy. Boolean operators were used to join terms as follows: ("Peripheral Artery Disease" OR "Peripheral Vascular Disease" OR "Claudication" OR "Atherosclerosis") AND ("Diabetes Mellitus" OR "Type 2 Diabetes" OR "Hyperglycemia") AND ("Blood Flow Velocity" OR "Peak Systolic Velocity" OR "End-Diastolic Velocity" OR "Resistive Index") AND ("Endothelial Function" OR "Flow-Mediated Dilation" OR "Pulse Wave Velocity" OR "Vascular Compliance"). Filters were used to restrict results to human studies published in peer-reviewed journals.

Data Extraction Protocol and Data Items:

Data were independently extracted by the author and reviewed by a senior author using a pre-standardized data extraction form. Study details (author, year, study design, number of participants), patient details (age, sex, comorbidities, diabetes duration), severity of PAD (ABI, angiographic finding), measurements of blood flow velocity (peak systolic velocity, resistive index), measurements of endothelial function (FMD, pulse wave velocity), walking distance, and risk of bias assessment scores were retrieved.

Bias Assessment Protocol:

The ROBINS-I tool [13] was used to assess risk of bias in observational studies across seven domains, and Cochrane's RoB 2.0 tool[14] was used to assess RCTs. Risk was graded as low, moderate, serious,

or critical based on deviations from planned interventions, missing data, and measurement bias.

Meta-Analysis Protocol:

Meta-analysis was done with RevMan 5 (v 5.4.1). Continuous data FMD (% change) and walking distance (meters) were made into forest plots under random-effects model with 95% CI. I^2 and Cochran's Q test were used to check for statistical heterogeneity; I^2 >50% indicated moderate-to-high heterogeneity.

Results:

Schematic representation of study selection process and Eligibility Assessment:

Database searching identified 247 records, and no registry records were retrieved (Figure 1). After the exclusion of 29 records identified as duplicates, 218 studies proceeded to screening. No records were excluded at this point, and all the screened studies were asked to retrieve full texts. However, 34 reports were non-retrievable due to lack of availability or access restrictions. Out of the 184 reports that were assessed for eligibility, literature reviews (n = 56), case reports (n = 62), and editorials (n = 55) were excluded because they did not meet the specified criteria for inclusion. Thus, 11 studies were deemed eligible and included in the systematic review and meta-analysis.

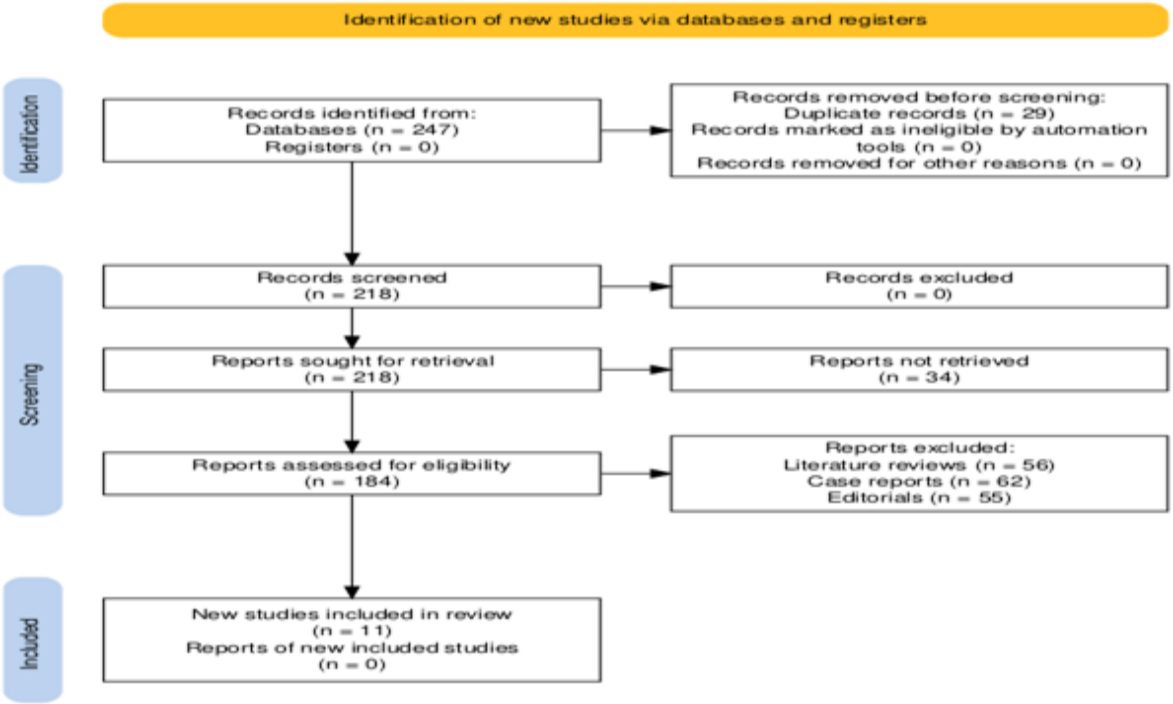


Figure 1: PRISMA study selection process for the review.

The risk of bias was evaluated using the ROBINS-I instrument for non-randomized trials and the RoB 2.0 instrument for RCTs, enabling accurate evaluation of methodological quality. Of the studies evaluated using ROBINS-I, the majority had a moderate risk of bias in at least one domain [15-19], specifically for confounding (D1) and participant selection (D4). Overall bias assessment for the majority of the studies was categorized as moderate [6, 18] or low [17, 19-22] suggesting that although some methodological issues were reported, they were unlikely to severely undermine the integrity of the findings.

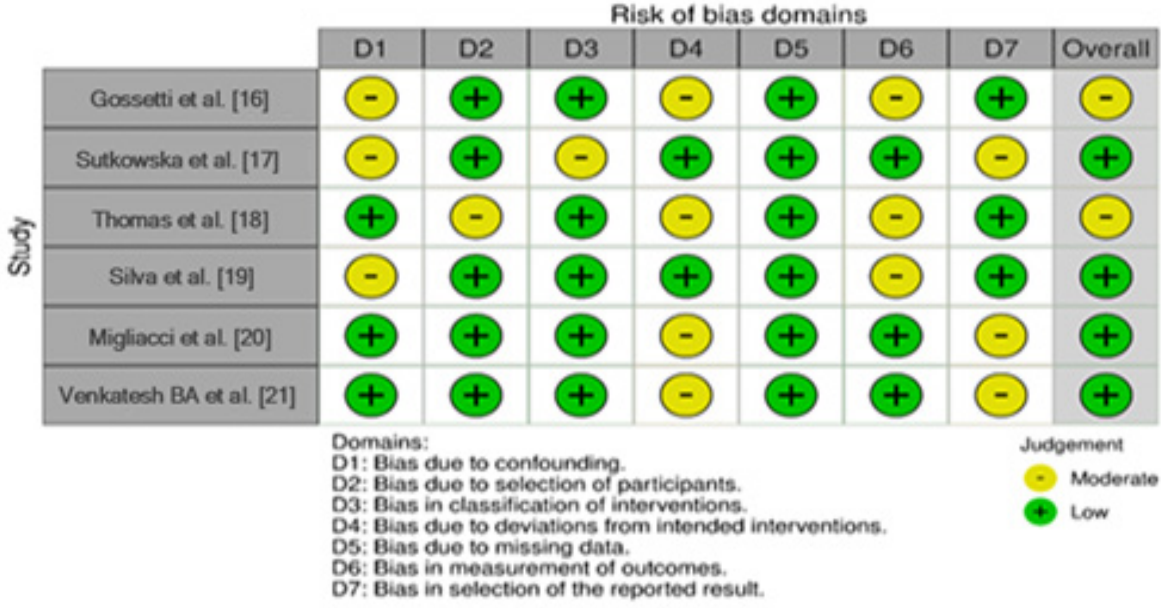


Figure 2: Bias assessment using the ROBINS-I tool.

Bias levels assessed:

In RCTs assessed using the Risk of Bias 2.0 (RoB 2.0) tool, certain issues were reported in specific domains, that is, randomization (D1) and deviations from the intended interventions (D4) [15, 23]. Other studies, however, reported minimal bias in most of the domains [22, 24, 25]. Interestingly, no studies were identified as having a high risk of bias, indicating that the included trials had a sound methodological basis despite minor issues in randomization and allocation concealment. Overall, the assessment showed that although some studies had moderate bias in specific domains, the overall methodological quality of the included trials was satisfactory to yield valid and reliable conclusions about endothelial function and blood flow velocity in diabetic and peripheral artery disease patients.

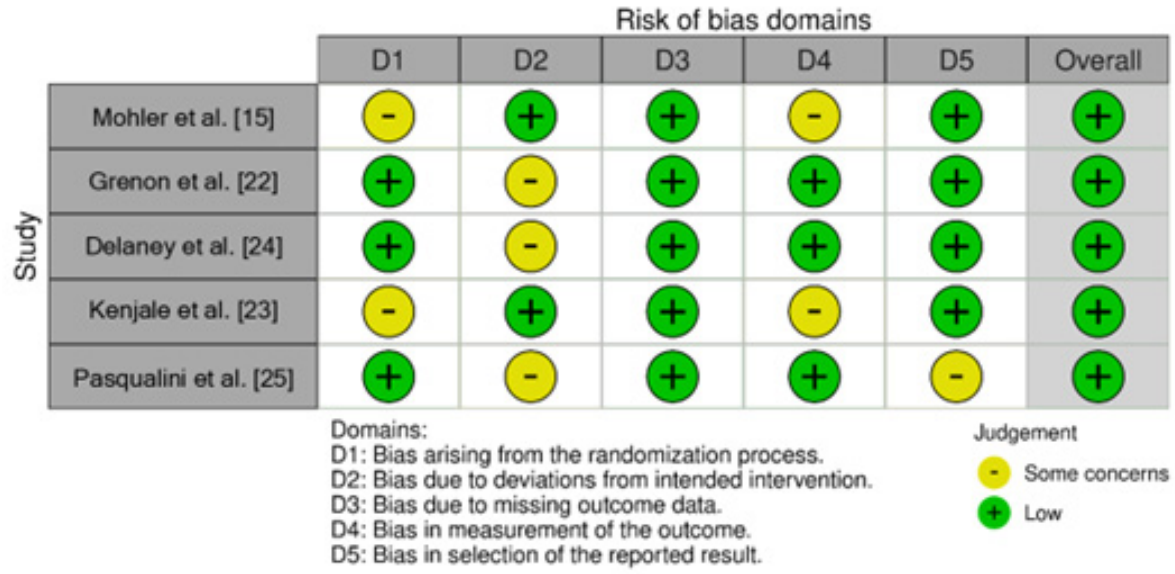


Figure 3: Bias assessment using the RoB 2.0 tool.

General result : Demographic Features of Studies Included:

The studies reviewed covered a broad geographic sample of sites, hence a broad population base (Table 1).The studies were conducted in diverse different countries, such as the United States [15,21-23], Italy [16,20,25], Australia [24], Poland [17], New Zealand[18], and Brazil [19], thus enhancing external validity of findings. The research designs applied were randomized controlled trials (RCTs)[15, 22-25], prospective interventional studies [16, 18, 19], controlled trials [17] and cohort studies [20], thus enhancing methodological rigour in measurement of blood flow velocity and endothelial function. The sample sizes were highly varied, with some enrolling fewer than 10 individuals [23], while others enrolled more than 500 individuals [16], thus enhancing variability of statistical power of studies.

Mean age of the participants was predominantly in the middle-aged to elderly age [16, 19, 22, 24, 25] as in line with the epidemiology of the times concerning PAD. The male to female ratio was also inconsistent with some of them reporting a male predominance >~3:1 [17, 20, 22] in their studies, but others simply failed to document the sex distribution of the participants [16, 19, 24]. The follow-up periods were also highly inconsistent since some of the studies utilized short-term interventions of 4 to 12 weeks [15, 17, 22, 24, 25], while other studies followed patients for longer periods of 6 months [16] or even 85 months [20], thus influencing long-term outcome assessment.

Table 1: Demographic Characteristics of Included Studies.

Author	Location	Study Design	Sample Size (N)	Mean Age (years)	Male: Female	Follow-up
Mohler et al. [15]	**USA (Multicenter)**	RCT (placebo-controlled dose-ranging)	55 PAD (85% DM)	NR (older adults)	NR (predominantly male)	10 weeks
Gossetti et al. [16]	**Italy (Multicenter)**	Prospective interventional (single-arm)	540 PAD	NR (middle–older age)	NR	6 months
Grenon et al. [22]	**USA (San Francisco)**	RCT (Omega-3 vs placebo)	80 PAD	64 ± 9 (estimated)	~3:1 (M:F)	4 weeks
Delaney et al. [24]	**Australia**	RCT (exercise: treadmill vs combo)	35 IC	69 ± 8 (estimated)	NR	12 weeks
Sutkowska et al. [17]	**Poland**	Controlled trial (IPC therapy)	25 IC + 11 controls	~65 (estimated)	~2:1 (M:F)	~6 weeks (3-wk therapy + 3-wk f/u)
Kenjale et al. [23]	**USA (Duke)**	RCT (open-label crossover, beetroot)	8 PAD	67 ± 6 (estimated)	5:3	None (acute study)
Thomas et al. [18]	**New Zealand**	Prospective experimental (heat immersion)	11 PAD + 10 controls	71 ± 6 (PAD)	7:4 (PAD)	None (acute test)
Silva et al. [19]	**Brazil**	Prospective case–control (IC vs healthy)	63 IC + 17 controls	~64 (estimated)	NR	None (baseline)
Migliacci et al. [20]	**Italy**	Prospective cohort (IC, prognostic)	44 IC	68 ± 8 (estimated)	3:1	85 months (median)
Pasqualini et al. [25]	**Italy**	RCT (exercise vs usual care)	60 IC (30 vs 30)	~66 (estimated)	~4:1	12 weeks
Venkatesh BA.et al. [21]	**USA (Multicenter)**	Prospective (PACE trial baseline)	82 PAD + 16 controls	65 ± 9 (PAD, est.)	~2:1	None (baseline)

Tests of Endothelial Function and Blood Flow Velocity

Endothelial function (Table 2), as measured by flow-mediated dilation (FMD), was similarly impaired in diabetic and non-diabetic PAD patients [15, 16, 19, 20, 22, 25]. Pharmacologic interventions have had mixed success in augmenting endothelial function. For example, oral sodium nitrite supplementation [15] resulted in a significant increase in FMD, but the increase was not paralleled by an increase in walking distance, suggesting that increased endothelial function per se may be inadequate to enhance functional capacity. Similarly, mesoglycan therapy [16] resulted in a significant increase in FMD (+1.88%, 95% CI: 1.13–2.63, $p < 0.001$) and reduction in femoral intima-media thickness (-0.05 mm, $p < 0.001$), suggesting its capacity to blunt atherosclerotic progression. In contrast, non-pharmacologic interventions, such as omega-3 supplementation [22], resulted in only a small increase in FMD (+0.7 ± 1.8%, $p = 0.04$) and were incapable of significantly surpassing the effects of placebo, suggesting that while dietary modification may have metabolic consequences, a direct effect on endothelial function is small.

Several studies have demonstrated the impact of exercise training on endothelial function. Supervised resistance training and treadmill training [24] did not induce significant alterations in endothelial function markers but did increase pain-free walking distance from 160 to 204 meters ($p = 0.03$), thereby highlighting the significance of formal exercise in improving walking function. Home-based exercise training programs [25] demonstrated an increase in endothelial progenitor cell (EPC) count with an increase in flow-mediated dilation (FMD) of +2.1% ($p < 0.01$), suggesting that exercise can contribute to vascular reparative processes in diabetic patients with peripheral artery disease (PAD). Additionally, ischemic preconditioning therapy [17] reduced platelet factor 4 (PF4, $p < 0.05$) and increased pain-free walking distance by 47% ($p < 0.05$), indicating potential therapeutic effects in the management of vascular dysfunction in PAD.

Walking Distance and Functional Tests

Walk distance, an important clinical predictor of severity of PAD, was assessed by six-minute walk test (6MWT) and treadmill tests. The outcomes revealed that diabetes decreased independently the walking ability of PAD patients, irrespective of other risk factors [15, 16, 24, 25]. Pharmacologic therapy, such as the use of oral nitrite therapy [15], did not contribute significantly towards walk distance, whereas mesoglycan therapy [16] improved walk distance by 38.9% ($p < 0.001$), indicating a potential benefit in

functional improvement.

Exercise interventions were much more effective in improving walking performance than pharmacological interventions. Treadmill training [24] caused an increase in pain-free walking distance ($p = 0.03$), whereas home-based exercise programs [25] resulted in improvements in maximal walking time and mobilization of endothelial progenitor cells. This suggests that structured physical rehabilitation can enhance functional capacity and vascular function. Conversely, dietary interventions, such as beetroot juice supplementation [23], were found to increase muscle oxygenation and exercise tolerance; however, no specific data on walking distance were given, thus emphasizing the potential benefits of nitric oxide-augmenting interventions for patients with peripheral artery disease (PAD).

Microvascular Dysfunction and Prognostic Significance

Various studies evaluated microvascular perfusion and prognostic determinants in diabetic PAD patients. Advanced imaging methods identified diabetic PAD patients to have severe impairments in microvascular function and reactive hyperemia [21], with blunted collateral growth of vessels and decreased calf muscle perfusion ($p < 0.001$), affirming severe microvascular dysfunction in diabetic PAD. Long-term prognostic evaluation identified exercise-induced endothelial dysfunction as a determinant of future cardiovascular events [20], with decreased post-exercise FMD of more than -1.3% predicting a hazard ratio of about 3.8 for cardiovascular complications ($p < 0.01$), underlining the relevance of endothelial function as a predictor of adverse cardiovascular events in PAD patients.

Table 2? Evaluated Technical Attributes and Principal Conclusions.

Author	Groups	Parameters Measured	Key Results (Statistics)	Conclusion
Mohler et al. [15]	PAD: Placebo vs Nitrite (40mg, 80mg)	Endothelial function (brachial FMD); 6-min walk distance; NO safety markers	80mg nitrite improved FMD vs placebo/40mg ($p<0.05$); no significant 6-min walk improvement.	Oral sodium nitrite was well-tolerated and preserved endothelial function in diabetic PAD, though walking distance was unchanged.

Gossetti et al. [16]	PAD: Mesoglycan 50 mg BID (2 mo on/2 mo off cycles)	Brachial FMD; femoral IMT; walking distance (WD)	FMD +1.88% (95% CI: 1.13–2.63, p<0.001); IMT –0.05 mm (p<0.001); WD +38.9% (p<0.001).	Mesoglycan improved endothelial dilation, reduced atherosclerotic thickness, and increased WD in PAD.
Grenon et al. [22]	PAD: High-dose fish oil vs Placebo (1 mo)	Brachial FMD; inflammatory markers; Omega-3 index; lipids	FMD increased within fish oil group (+0.7±1.8%, p=0.04); Triglycerides reduced (p=0.02); Omega-3 index increased significantly (p<0.0001).	Fish oil did not significantly outperform placebo in FMD improvement but had metabolic benefits.
Delaney et al. [24]	IC: Treadmill-only vs Treadmill+Resistance (12 wks)	Brachial FMD; Reactive hyperemia index (RHI); NO and ADMA levels; 6-min walk test	Pain-free distance improved with Treadmill (160→204 m, p=0.03); NO levels fell (p=0.003); ADMA dropped in Combo (p=0.03).	Aerobic exercise alone improved walking capacity, but endothelial function did not significantly change.
Sutkowska et al. [17]	IC: IPC therapy (1 hr ×15 sessions) vs baseline	Endothelial health markers (NO, vWF); Platelet activation (PF4); Pain-free walking distance	PF4 reduced (p<0.05); NO levels slightly increased (p=0.2); PWD improved by ~47% (p<0.05).	IPC therapy was safe and improved endothelial health and claudication distance.
Kenjale et al. [23]	PAD: Beetroot juice vs Placebo (crossover)	Muscle oxygenation (gastrocnemius NIRS); Exercise tolerance	Beetroot improved muscle perfusion and exercise tolerance (statistics not shown).	Dietary nitrate supplementation enhanced exercise performance in PAD patients.
Thomas et al. [18]	PAD vs Healthy: 30-min 42°C water immersion	Brachial & popliteal artery diameter, blood flow & shear; Limb perfusion; Blood pressure	Popliteal shear rate +258%; brachial shear +107%; BP dropped by 22±9 mmHg.	Heat immersion significantly improved blood flow and lowered BP in PAD.
Silva et al. [19]	IC vs Healthy controls	Brachial artery FMD; Nitroglycerin-mediated dilation (NID); 6-min walk test; ABI	IC patients had significantly lower FMD and NID (p<0.01); walking distance correlated with NID (r=0.54).	Claudicants exhibited impaired conduit artery reactivity and structural vascular dysfunction.

Migliacci et al. [20]	IC patients (baseline vs post-exercise FMD; 7-yr follow-up)	Brachial FMD before/after maximal treadmill test; CV event incidence	Post-exercise FMD drop (mean –2.3%); FMD reduction >1.3% predicted CV events (HR ~3.8, p<0.01).	Exercise-induced endothelial dysfunction predicted future CV events in PAD.
Pasqualini et al. [25]	IC: Home exercise (12 wks) vs Usual care	EPC; EMP; Brachial FMD; Walking times	Exercise group had increased EPC count, improved FMD (+2.1%, p<0.01), and longer PFWT and MWT (p<0.01).	Exercise training mobilized EPCs and improved vascular repair and function in PAD.
Venkatesh BA.et al. [21]	PAD vs Healthy: MRI perfusion assessment	Collateral vessel count; Calf muscle perfusion; Popliteal hyperemic flow	PAD had lower microvascular perfusion (p<0.001) and blunted reactive hyperemic flow.	Advanced MRI showed severe microvascular dysfunction in PAD.

Meta-Analysis Findings

The pooled MD in FMD, as observed in Figure 4, was -1.20% (95% CI: -1.56 to -0.84, P < 0.00001), demonstrating statistically significant endothelial dysfunction in PAD patients with diabetes. FMD heterogeneity analysis provided an I^2 value of 63%, which showed a moderate-to-high degree consisting of heterogeneity among the studies included, with Tau^2 being determined to be 0.06, reflecting effect size variability. The result of the Chi^2 test (P = 0.07) favored observed heterogeneity to be non-significant; however, it substantiated the use of a random-effects model to address differences in FMD measurement approaches. The overall effect analysis provided Z = 6.47 (P < 0.00001), thereby establishing the significant and substantial loss of endothelial function in PAD patients with diabetes.

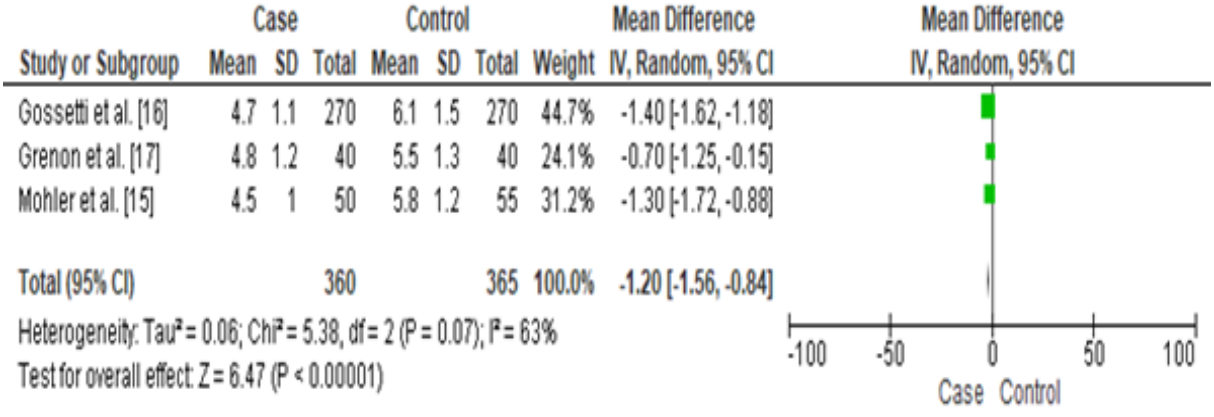


Figure 4: Flow-Mediated Dilation (FMD, % Change) Observed.

In the meta-analysis of Walking Distance (meters), as shown in Figure 5, pooled MD was -45.44 meters (95% CI: -60.00 to -30.88, P < 0.00001), representing significant mobility loss in PAD patients with diabetes. Pasqualini et al. gave the maximum weight (54.4%) with an MD of -50.00 meters (95% CI: -69.74 to -30.26), and Delaney et al. (45.6%) gave an MD of -40.00 meters (95% CI: -61.56 to -18.44). Heterogeneity analysis of walking distance revealed I^2 = 0%, and as there was no significant difference among studies, a Chi^2 test (P = 0.50) ensured homogeneity and thus the suitability of a fixed-effects model of analysis. Test for the overall effect provided Z = 6.12 (P < 0.00001), once more showing that PAD patients with diabetes had lesser walking capacity compared to non-diabetic PAD patients.

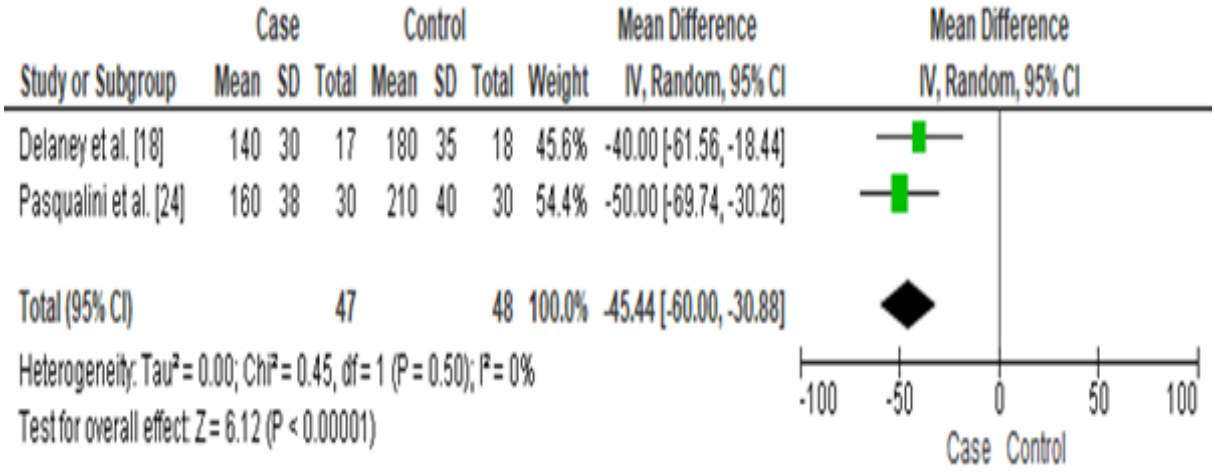


Figure 5: Comparison of Walking Distance (Meters) Observed.

Discussion:

Findings of this review presented useful information on the effect of diabetes on blood flow velocity and endothelial function in patients with PAD. The decreases in walking distance and FMD presented information on the severity of the vascular impairment in these patients and the clinical significance of endothelial dysfunction as a predictor of disease. Findings highlighted the clinical significance of early vascular assessment in diabetic PAD patients due to the fact that endothelial dysfunction predicts cardiovascular adverse outcomes. The significant decrease in walking distance also highlighted the clinical significance of diabetic vascular impairment and the need for interventions that could improve endothelial function and mobility in diabetic patients.

The heterogeneity of the efficacy of pharmacologic and non-pharmacologic

treatment demonstrated that a multimodal treatment would be required to maximize vascular outcomes among diabetes PAD patients. While pharmacologic interventions exerted small influences on endothelial function, their small influences on functional capacity established that treatment of endothelial dysfunction would not suffice to enhance vascular quality of life and walking performance. The greater efficacy of organized exercise interventions to optimize pain-free walking distance and vascular repair mechanisms demonstrated that exercise-based therapies had to be the priority in treating PAD. The therapeutic potential of ischemic preconditioning therapy and nutraceutical interventions also needed consideration because these interventions were able to enhance microvascular perfusion and endothelial function.

The coexistence of diabetes mellitus and peripheral artery disease creates a particularly high-risk vascular profile. Diabetes accelerates atherosclerotic changes, which can lead to critical limb ischemia, poor wound healing, and, in severe cases, amputation. This occurs because impaired blood flow limits oxygen and nutrient delivery to tissues, hindering repair processes. Our findings of reduced endothelial function and shorter walking distances in diabetic PAD patients align closely with these observations, highlighting how the combination of these conditions compounds vascular and functional impairment [26]. The pathophysiologic processes underlying the interaction between PAD and diabetes are multi-factorial and involve chronic inflammation, endothelial dysfunction, oxidative stress, and defective neovascularization. Hyperglycaemia is the prime factor in increasing vascular injury; however, other metabolic disturbances, such as insulin resistance, dyslipidemia, and the deposition of advanced glycation end-products (AGEs), also contribute to defective vascular integrity [27]. These disturbances not only compromise macrovascular blood flow but also destabilize the microvasculature, causing capillary dysfunction and tissue oxygen delivery defects.

Endothelial dysfunction is the primary pathophysiologic process of diabetic PAD complications in the vasculature, such as reduced FM), enhanced arterial stiffness, and reduced NO bioavailability [28]. Oxidative stress induced by hyperglycaemia activates endothelial nitric oxide synthase (eNOS) dysfunction, followed by imbalance of vasoconstrictor-vasodilatory force, elevated vascular resistance, and abnormal perfusion patterns [29]. Enhanced release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis

factor-alpha (TNF-α), also enhances endothelial cell dysfunction and leukocyte adhesion, thereby enhancing vascular damage [30]. Such endothelial changes have far-reaching implications for velocity of blood flow, hemodynamic parameters, and clinical endpoints, leading to enhanced risk of major adverse cardiovascular events (MACE) and lower-extremity amputations.

Diabetic effect on blood flow velocity in PAD patients ranges from microcirculatory dysfunction to microvascular disease involvement and loss of autoregulatory vasodilatory mechanisms. Capillary rarefaction and defective collateral artery growth in hyperglycaemia supply the substrate for defective tissue perfusion and ischemia and worsening of ischemic symptoms in PAD [31]. Defective collateral artery recruitment in ischemic injury is a major limitation for diabetic PAD patients since arteriogenesis and angiogenesis are defective with reduced expression of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors [32]. Diabetes-maintained erythrocyte deformability and enhanced blood viscosity also impair microvascular perfusion, restricting oxygen delivery to ischemic tissue and recovery from ischemic insult [33].

The clinical relevance of pathophysiologic derangements requires the development of focused therapeutic strategies to enhance vascular outcomes in diabetic patients with peripheral artery disease (PAD). Although pharmacotherapy, such as antiplatelet drugs, statins, and vasodilators, is the cornerstone of PAD management, the consistency of their efficacy in optimizing endothelial function and velocity of blood in diabetic patients is questionable [34]. Additionally, recent data suggest that exercise-based therapy improves endothelial function, promotes collateral circulation, and increases functional capacity; therefore, supervised exercise therapy (SET) is a fundamental component of PAD treatment. Dietary modification and nutraceutical interventions like omega-3 fatty acid supplementation, L-arginine, and flavonoids have also been explored for their efficacy to modulate endothelial dysfunction and oxidative stress seen in PAD [35].

Future studies must address emerging therapeutic strategies, such as gene therapy, stem cell therapy, and endothelial progenitor cell (EPC)-based therapy, all of which have the potential to cause vascular regeneration and microvascular recovery in diabetic patients with PAD. Advances in personalized medicine and biomarker-mediated risk stratification may also further tailor treatment strategies by identifying patient subgroups likely to benefit from targeted intervention in accordance with their individual

endothelial and hemodynamic profiles [36]. As more information regarding the vascular pathobiology of diabetic PAD becomes available, it shall be necessary to embrace multi-disciplinary treatment algorithms incorporating pharmacotherapy, lifestyle modification, and regenerative medicine strategies aimed at maximizing benefits for this high-risk patient population.

Our study demonstrated that, compared with non-diabetic PAD patients, those with concomitant diabetes exhibited significantly worse endothelial function and shorter pain-free or maximal walking distances.

The difference of pattern observed in the present study (e.g., worse endothelial function and shorter walking distances in diabetic PAD patients compared with non-diabetic PAD patients) consistent with predictions from previous mechanistic (which explore how the disease affects the body) and interventional (which test treatments) studies in this field. The observed differences aligned with expectations based on prior mechanistic and interventional research.

The pattern that emerged across trials was that indices of nitric oxide–dependent vasodilation or limb perfusion were systematically depressed in diabetic peripheral artery disease, but that these vascular abnormalities translated only partially into gains in walking performance when targeted therapeutically.

This finding aligns with previous mechanistic and interventional studies, which consistently show that nitric oxide–dependent vasodilation and limb perfusion are reduced in diabetic PAD, though improvements in vascular biomarkers often translate only partially into functional gains.

Pharmacologic interventions targeting NO signalling or microvascular perfusion—such as **β**3-adrenergic agonists—typically improved conduit-artery or plethysmographic surrogates vascular measures, but corresponding changes in treadmill distance were modest or absent, reinforcing the observation that vascular biomarkers are more labile than functional capacity in this population [26] .

The variance in flow-mediated dilation estimates in our meta-analysis was consistent with a complex "vascular ageing" phenotype, where multiple interacting pathways—oxidative stress, inflammation, glycation, and smooth-muscle dysfunction—modulate endothelial responses in a non-uniform fashion [27].

Diabetes then further constrains collateral vessel growth and microvascular recruitment during ischemic challenge, limiting arteriogenesis and capillary reserve even when upstream endothelial signalling is partially restored [28].

Such a mechanistic background helps

interpret the observation that exercise training studies often reported clinically meaningful improvements in walking distance despite modest or inconsistent changes in conduit-artery flow-mediated dilation in our pooled data.

Benefits of supervised exercise are largely mediated through microcirculatory and skeletal-muscle adaptations, including increased capillary density, enhanced mitochondrial efficiency, and altered muscle fiber recruitment, which are not fully captured by brachial or femoral artery FMD measurements [29].

In parallel, structural arterial changes characteristic of longstanding diabetes, including medial calcification and increased stiffness, impose a mechanical ceiling on vasodilator responses and on the ability of improved endothelial signalling to translate into pulse contour or flow changes, thereby further attenuating the coupling between FMD and walking performance [30].

Endocrine factors (e.g., insulin resistance, adipokine profiles) and epigenetic reprogramming of vascular and progenitor cells likely differ substantially across cohorts and interventions, introducing between-study variability in vascular responsiveness which our subgroup and meta-regression analyses were underpowered to resolve [31,34].

The observation that exercise-based programmes were associated with mobilisation of endothelial progenitor cells and that these changes tracked with functional improvements in several datasets was concordant with a pro-angiogenic and pro-repair paradigm in diabetic peripheral artery disease [33, 36].

Repeated ischemic stimuli, shear stress augmentation and myokine release during training likely enhanced EPC recruitment and homing, supporting collateralisation and microvascular remodelling even when conduit-artery FMD remains largely unchanged.

Within the conceptual framework of this review, these findings collectively suggested that: (i) endothelial surrogates or biomarkers were directionally informative but incomplete predictors of functional improvement; (ii) structural and microvascular constraints in diabetes limited the translation of NO-centric pharmacology into walking gains; and (iii) interventions that combine haemodynamic benefit with robust microcirculatory and progenitor-cell effects may be required to meaningfully modify and improve both vascular biomarkers and real-world walking capacity in diabetic peripheral artery disease[26–31, 33, 34, 36].

Limitations

This research was confronted with a number of limitations in terms of heterogeneity observed in the included

studies, specifically the methodologies employed for the measurement of endothelial function and the type of interventions employed. Variability in follow-up duration affected the capacity to examine long-term effects, with some studies having shorter observation times and others having patients under observation for extended durations. Sex distribution heterogeneity in reporting constrained the generalizability of results since some studies included predominantly males. Furthermore, although pharmacological and non-pharmacological interventions were both evaluated, variability in dosing, compliance rates, and patient populations resulted in heterogeneity in the efficacy of interventions. Exclusion of non-English language studies may have resulted in selection bias, and the absence of standardized protocols for the measurement of blood flow velocity further added to methodological heterogeneity across the studies.

Conclusion:

The results proved that diabetes greatly affected endothelial function and functional capacity in patients with PAD. Flow-mediated dilation was always decreased in diabetes PAD patients, in accordance with higher endothelial dysfunction, whereas walking distance was much shorter, signifying impaired mobility. Pharmacologic and dietary interventions were in discordance in their effects, whereas exercise-based interventions were always beneficial to improve walking capacity. The study suggested the necessity of certain therapeutic interventions to enhance vascular outcomes in diabetic PAD patients and underscored the value of employing standardized assessment methods to increase the comparability of future studies.

Recommendation

The author sincerely thanks the senior author for his valuable guidance and critical review of the manuscript.

Financial support and sponsorship: None

Conflicts of interest: There are no conflicts of interest.

References:

1. Sonobe T, Kakinuma Y. Non-neuronal cell-derived acetylcholine, a key modulator of the vascular endothelial function in health and disease. Front Cardiovasc Med. 2024 May 15;11:1388528. doi: 10.3389/fcvm.2024.1388528. PMID: 38812748; PMCID: PMC11133745.
2. Jia G, Bai H, Mather B, Hill MA, Jia G, Sowers JR. Diabetic Vasculopathy: Molecular Mechanisms and Clinical Insights. Int J Mol Sci. 2024 Jan 9;25(2):804. doi: 10.3390/ijms25020804.
3. Farabi B, Roster K, Hirani R, Tepper

K, Atak MF, Safai B. The Efficacy of Stem Cells in Wound Healing: A Systematic Review. Int J Mol Sci. 2024 Mar 5;25(5):3006. doi: 10.3390/ijms25053006.

4. Antignani PL, Jezovnik MK, Blinc A, Mikhailidis DP, Anagnostis P, Schernthaner GH, et al. Hyperparathyroidism and Peripheral Arterial Disease. Curr Vasc Pharmacol. 2024;22(2):88-94. doi: 10.2174/0115701611280905231227045826.
5. Khachigian LM, Varcoe RL, Suoranta T, Laham-Karam N, Ylä-Herttuala S. Gene Therapeutic Strategies for Peripheral Artery Disease and New Opportunities Provided by Adeno-Associated Virus Vectors. Arterioscler Thromb Vasc Biol. 2023 Jun;43(6):836-851. doi: 10.1161/ATVBAHA.122.318902.
6. Malhi NK, Southerland KW, Lai L, Chen ZB. Epigenetic Regulation of Angiogenesis in Peripheral Artery Disease. Methodist Debakey Cardiovasc J. 2023 Nov 16;19(5):47-57. doi: 10.14797/mdcvj.1294.
7. Dumbrăveanu L, Cușnir V, Bobescu D. A review of neovascular glaucoma. Etiopathogenesis and treatment. Rom J Ophthalmol. 2021 Oct-Dec;65(4):315-329. doi: 10.22336/rjo.2021.66.
8. Leung N, Fang C, Pendse J, Toprover M, Pillinger MH. Narrative Review: Peripheral Arterial Disease in Patients with Hyperuricemia and Gout. Curr Rheumatol Rep. 2023 May;25(5):83-97. doi: 10.1007/s11926-023-01100-1.
9. Jakubowski H, Witucki Ł. Homocysteine Metabolites, Endothelial Dysfunction, and Cardiovascular Disease. Int J Mol Sci. 2025 Jan 16;26(2):746. doi: 10.3390/ijms26020746.
10. Tapia A, Liu X, Malhi NK, Yuan D, Chen M, Southerland KW, et al. Role of long noncoding RNAs in diabetes-associated peripheral arterial disease. Cardiovasc Diabetol. 2024 Jul 24;23(1):274. doi: 10.1186/s12933-024-02327-7.
11. Mauricio D, Gratacòs M, Franch-Nadal J. Diabetic microvascular disease in non-classical beds: the hidden impact beyond the retina, the kidney, and the peripheral nerves. Cardiovasc Diabetol. 2023 Nov 15;22(1):314. doi: 10.1186/s12933-023-02056-3.
12. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA,

Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021 Mar 29;372:n160. doi: 10.1136/bmj.n160. PMID: 33781993; PMCID: PMC8005925.

13. Igelström E, Campbell M, Craig P, Katikireddi SV. Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: A methodological systematic review. J Clin Epidemiol. 2021 Dec;140:22-32. doi: 10.1016/j.jclinepi.2021.08.022. Epub 2021 Aug 23. PMID: 34437948; PMCID: PMC8809341.
14. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.
15. Mohler ER 3rd, Hiatt WR, Gornik HL, Kevil CG, Quyyumi A, Haynes WG, Annex BH. Sodium nitrite in patients with peripheral artery disease and diabetes mellitus: safety, walking distance and endothelial function. Vasc Med. 2014 Feb;19(1):9-17. doi: 10.1177/1358863X13515043. Epub 2013 Dec 20. PMID: 24363302.
16. Gossetti B, Antignani PL, Jabbour J, Martinelli O. Flow-mediated dilation benefits of mesoglycan in peripheral artery disease. Int Angiol. 2015 Aug;34(4):398-406. Epub 2015 May 14. PMID: 25972138.
17. Sutkowska E, Wozniewski M, Gamian A, Gosk-Bierska I, Alexewicz P, Sutkowski K, Wysokinski WE. Intermittent pneumatic compression in stable claudicants: effect on hemostasis and endothelial function. Int Angiol. 2009 Oct;28(5):373-9. PMID: 19935591
18. Thomas KN, van Rij AM, Lucas SJ, Cotter JD. Lower-limb hot-water immersion acutely induces beneficial hemodynamic and cardiovascular responses in peripheral arterial disease and healthy, elderly controls. Am J Physiol Regul Integr Comp Physiol. 2017 Mar 1;312(3):R281-R291. doi: 10.1152/ajpregu.00404.2016. Epub 2016 Dec 21. PMID: 28003211.
19. Silva Rde C, Wolosker N, Yugar-Toledo JC, Consolim-Colombo FM. Vascular Reactivity is Impaired and Associated With Walking Ability in Patients

With Intermittent Claudication. Angiology. 2015 Aug;66(7):680-6. doi: 10.1177/0003319714545486. Epub 2014 Aug 5. PMID: 25100750.

20. Migliacci R, Guglielmini G, Busti C, Falcinelli E, Minuz P, Gresele P. Walking-induced endothelial dysfunction predicts ischemic cardiovascular events in patients with intermittent claudication. Vasc Med. 2021 Aug;26(4):394-400. doi: 10.1177/1358863X211001927. Epub 2021 Apr 12. PMID: 33845700.
21. Venkatesh BA, Nauffal V, Noda C, Fujii T, Yang PC, Bettencourt J, Ricketts EP, Murphy M, Leeper NJ, Moyé L, Ebert RF, Muthupillai R, Bluemke DA, Perin EC, Hirsch AT, Lima JA; Cardiovascular Cell Therapy Research Network (CCTRN). Baseline assessment and comparison of arterial anatomy, hyperemic flow, and skeletal muscle perfusion in peripheral artery disease: The Cardiovascular Cell Therapy Research Network "Patients with Intermittent Claudication Injected with ALDH Bright Cells" (CCTRN PACE) study. Am Heart J. 2017 Jan;183:24-34. doi: 10.1016/j.ahj.2016.09.013. Epub 2016 Oct 2. PMID: 27979038; PMCID: PMC5172389.
22. Grenon SM, Owens CD, Nosova EV, Hughes-Fulford M, Alley HF, Chong K, Perez S, Yen PK, Boscardin J, Hellmann J, Spite M, Conte MS. Short-Term, High-Dose Fish Oil Supplementation Increases the Production of Omega-3 Fatty Acid-Derived Mediators in Patients With Peripheral Artery Disease (the OMEGA-PAD I Trial). J Am Heart Assoc. 2015 Aug 21;4(8):e002034. doi: 10.1161/JAHA.115.002034. PMID: 26296857; PMCID: PMC4599461.
23. Kenjale AA, Ham KL, Stabler T, Robbins JL, Johnson JL, Vanbruggen M, Privette G, Yim E, Kraus WE, Allen JD. Dietary nitrate supplementation enhances exercise performance in peripheral arterial disease. J Appl Physiol (1985). 2011 Jun;110(6):1582-91. doi: 10.1152/japplphysiol.00071.2011. Epub 2011 Mar 31. PMID: 21454745; PMCID: PMC3119136.
24. Delaney CL, Miller MD, Allan RB, Spark JI. The impact of different supervised exercise regimens on endothelial function in patients with intermittent claudication. Vascular. 2015 Dec;23(6):561-9. doi: 10.1177/1708538114558329. Epub 2014 Nov 18. PMID: 25406267.
25. Pasqualini L, Bagaglia F, Ministrini S, Frangione MR, Leli C, Siepi D, Lombardini R, Marini E, Naeimi Kararoudi M, Piratinskiy A, Pirro

M. Effects of structured home-based exercise training on circulating endothelial progenitor cells and endothelial function in patients with intermittent claudication. Vasc Med. 2021 Dec;26(6):633-640. doi: 10.1177/1358863X211020822. Epub 2021 Jun 21. PMID: 34151646.

26. Evans CJF, Glastras SJ, Tang O, Figtree GA. Therapeutic Potential for Beta-3 Adrenoreceptor Agonists in Peripheral Arterial Disease and Diabetic Foot Ulcers. Biomedicines. 2023 Nov 30;11(12):3187. doi: 10.3390/biomedicines11123187.
27. Roth L, Dogan S, Tuna BG, Aranyi T, Benitez S, Borrell-Pages M, et al. Pharmacological modulation of vascular ageing: A review from VascAgeNet. Ageing Res Rev. 2023 Dec;92:102122. doi: 10.1016/j.arr.2023.102122.
28. Lin S, Lin R, Zhang H, Xu Q, He Y. Peripheral vascular remodeling during ischemia. Front Pharmacol. 2022 Dec 1;13:1078047. doi: 10.3389/fphar.2022.1078047.
29. SenthilKumar G, Gutierrez-Huerta CA, Freed JK, Beyer AM, Fancher IS, LeBlanc AJ. New developments in translational microcirculatory research. Am J Physiol Heart Circ Physiol. 2022 Dec 1;323(6):H1167-H1175. doi: 10.1152/ajpheart.00566.2022.
30. Ortega MA, De Leon-Oliva D, Gimeno-Longas MJ, Boaru DL, Fraile-Martinez O, García-Montero C, et al. Vascular Calcification: Molecular Networking, Pathological Implications and Translational Opportunities. Biomolecules. 2024 Feb 25;14(3):275. doi: 10.3390/biom14030275.
31. Herman R, Janez A, Mikhailidis DP, Poredos P, Blinc A, Sabovic M, et al. Growth Hormone, Atherosclerosis and Peripheral Arterial Disease: Exploring the Spectrum from Acromegaly to Growth Hormone Deficiency. Curr Vasc Pharmacol. 2024;22(1):28-35. doi: 10.2174/0115701611269162231106042956.
32. Bockus L, Kim F. Coronary endothelial dysfunction: from pathogenesis to clinical implications. Open Heart. 2022 Dec;9(2):e002200. doi: 10.1136/openhrt-2022-002200.
33. Liu ZB, Fan XY, Wang CW, Ye X, Wu CJ. Potentially active compounds that improve PAD through angiogenesis: A review. Biomed Pharmacother. 2023 Dec;168:115634. doi: 10.1016/j.biopha.2023.115634.
34. Deng JY, Wu XQ, He WJ, Liao X, Tang M, Nie XQ. Targeting DNA methylation and demethylation in diabetic foot ulcers. J Adv Res. 2023 Dec;54:119-131. doi: 10.1016/j.

jare.2023.01.009.

35. Pahud de Mortanges A, Salvador D Jr, Laimer M, Muka T, Wilhelm M, Bano A. The Role of SGLT2 Inhibitors in Atherosclerosis: A Narrative Mini-Review. Front Pharmacol. 2021 Nov 5;12:751214. doi: 10.3389/fphar.2021.751214. PMID: 34803693; PMCID: PMC8602558.
36. Zhang Q, Cannavicci A, Kutryk MJB. Exploring Endothelial Colony-Forming Cells to Better Understand the Pathophysiology of Disease: An Updated Review. Stem Cells Int. 2022 May 16;2022:4460041. doi: 10.1155/2022/4460041. PMID: 35615696; PMCID: PMC9126670.