

Combined Effects of Low-Level Laser Therapy and Aerobic Exercise on Peripheral Arterial Function in Type 2 Diabetes Mellitus: A Randomized Trial

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ABSTRACT

Background: Peripheral arterial disease (PAD) in patients with type 2 diabetes mellitus (T2DM) is a significant factor contributing to impaired mobility and increased cardiovascular risk. While aerobic exercise remains a fundamental part of PAD rehabilitation, low-level laser therapy (LLLT) has been used as a promising adjunct to improve perfusion and promote angiogenesis.

Objective: To examine the combined effect of LLLT and aerobic exercise on peripheral arterial function, pain, and functional walking capacity in T2DM patients with PAD.

Patients and Methods: This randomized controlled trial enrolled 40 patients aged 55–65 years with T2DM and mild-to-moderate PAD. Participants were randomly assigned to two groups: Group A received LLLT (scan; 808 nm, 450 mW) in addition to moderate aerobic exercise, and Group B received aerobic exercise only. The intervention lasted for 12 weeks (3 sessions/week). Outcome measures included the ankle-brachial index (ABI), peak systolic velocity (PSV), pain assessed using a visual analog scale (VAS), and functional treadmill metrics, such as initial claudication distance, absolute claudication distance, time to initial and absolute claudication, and VO₂ max.

Results: Both groups showed significant improvements in ABI, PSV, VAS, and treadmill parameters ($p < 0.05$). Compared to Group B, Group A demonstrated significantly greater gains in ABI (20% vs. 13.6%), larger reductions in PSV (52.7% vs. 45.4%), and a bigger decrease in pain intensity (VAS: 48.8% vs. 29.2%). Treadmill performance improved significantly in both groups, with Group A achieving better outcomes in initial claudication distance, absolute claudication distance, and time to initial and absolute claudication ($p < 0.05$). Although VO₂ max improved in both groups, the difference between the groups was not statistically significant; however, group A showed a greater performance.

Conclusion: The combination of low-level laser therapy and aerobic exercise proved more effective than exercise alone in improving vascular function, relieving pain, and enhancing walking ability in diabetic patients with PAD.

Keywords: PAD; Photobiomodulation, Walking Capacity; Peak Systolic Velocity.

INTRODUCTION

PAD is a common and disabling complication of T2DM, primarily caused by systemic atherosclerosis and characterized by partial or complete occlusion of peripheral arteries, most commonly in the lower limbs. The global prevalence of PAD among individuals with T2DM has risen to 20–30%, particularly affecting older adults and low-to-middle-income populations. A 2024 multicenter screening study in the Middle East and North Africa region reported PAD prevalence of 28.3% among diabetic patients, with over 60% remaining undiagnosed until functional limitations or critical symptoms occur^(1,2).

PAD in T2DM is strongly associated with increased risks of cardiovascular mortality, lower-limb amputation, and functional decline. Intermittent claudication, the primary symptom of PAD, substantially reduces walking ability and QoL. Conventional management options, such as pharmacological therapy, revascularization, and structured exercise, are often underutilized, especially in resource-limited settings⁽³⁾.

Management of PAD primarily aims to improve patients' QoL by alleviating symptoms and reducing vascular morbidity and mortality⁽⁴⁾.

Medical management includes lipid-lowering therapy, antiplatelet and anticoagulant medications, peripheral vasodilators, blood pressure control, smoking cessation, and structured exercise programs⁽⁵⁾. Exercise therapy, in particular, may enhance walking performance in individuals with PAD by improving lower limb perfusion. This improvement is hypothesized to occur through increased availability of nitrite and nitric oxide, promoting vasodilation and enhanced blood flow⁽⁶⁾.

To encourage tissue regeneration, lessen inflammation, and ease pain. LLLT has a photochemical effect on biological systems, which means that the light is absorbed and results in a chemical change, as opposed to other medical laser techniques that depend on an ablative or thermal process⁽⁷⁾. To prevent burning or injury to the skin's surface, lasers can penetrate deeply into the skin⁽⁸⁾. For various clinical conditions, cold lasers have been improved to provide analgesia and hasten healing⁽⁹⁾.

By combining angiogenesis and osteogenesis, LLLT stimulates the production of blood vessels, collagen fibers, and bone tissue⁽¹⁰⁾.

This study aims to assess the combined effect of LLLT and aerobic exercise on peripheral arterial function,

pain relief, and walking capacity in patients with peripheral artery disease and type 2 diabetes.

PATIENTS AND METHODS

Study design

This randomized controlled trial was conducted from August 2024 to December 2024 at Agouza Police Hospital, Giza, Egypt.

Ethical Approval

The regional ethics commission gave the study its ethical approval. The protocol was approved by Cairo University and assigned (No.: P.T.RET 012 004935). The study was registered at ClinicalTrials.gov with the trial ID: NCT06827171. Before being enrolled, all patients gave their written informed permission. The study was conducted in accordance with the Helsinki Declaration.

Participants and Recruitment

Forty elderly patients aged between 55 and 65 years with T2DM complicated by peripheral artery disease (PAD) were recruited from the outpatient clinic of Agouza Police Hospital, Egypt.

Inclusion criteria included: (1) BMI of 25–29.9 kg/m²; (2) Glycated hemoglobin (HbA1c) between 7–9%; (3) T2DM duration of more than 5 years; and (4) PAD classified as mild to moderate according to Rutherford classification stages 1–3.

Exclusion criteria: history of hypo- or hyperglycemic coma; uncontrolled cardiovascular complications or ischemic heart disease; photosensitivity or known malignancy (contraindications to laser therapy); anemia; deep vein thrombosis (DVT) or acute thrombosis; cerebrovascular disease; Monckeberg's sclerosis or hemorrhagic conditions; resting limb pain; critical limb ischemia; diabetic foot or peripheral edema; asymptomatic PAD or diabetic neuropathy; history of minor or major limb amputation; and active smoking.

Procedure

Participants in this study were diagnosed with T2DM associated with PAD classified as mild to moderate according to Rutherford classification stages 1–3. All participants undergo baseline and post-intervention assessments at 12 weeks.

Participants were randomly assigned into two equal groups (Figure 1): Group A (Study Group): Received LLLT using a scanning laser device applied to the posterior tibial artery, followed by a structured aerobic exercise program, three sessions/week for twelve weeks, and **Group B (Control Group):** Received aerobic exercise only, following the same schedule as Group A (three sessions/week for 12 weeks). All patients continued to receive their prescribed medications, including hypoglycemic agents, antiplatelet agents, anticoagulants, antihypertensive agents, vasodilators, and analgesics. **Figure (1):** The study's consort diagram.

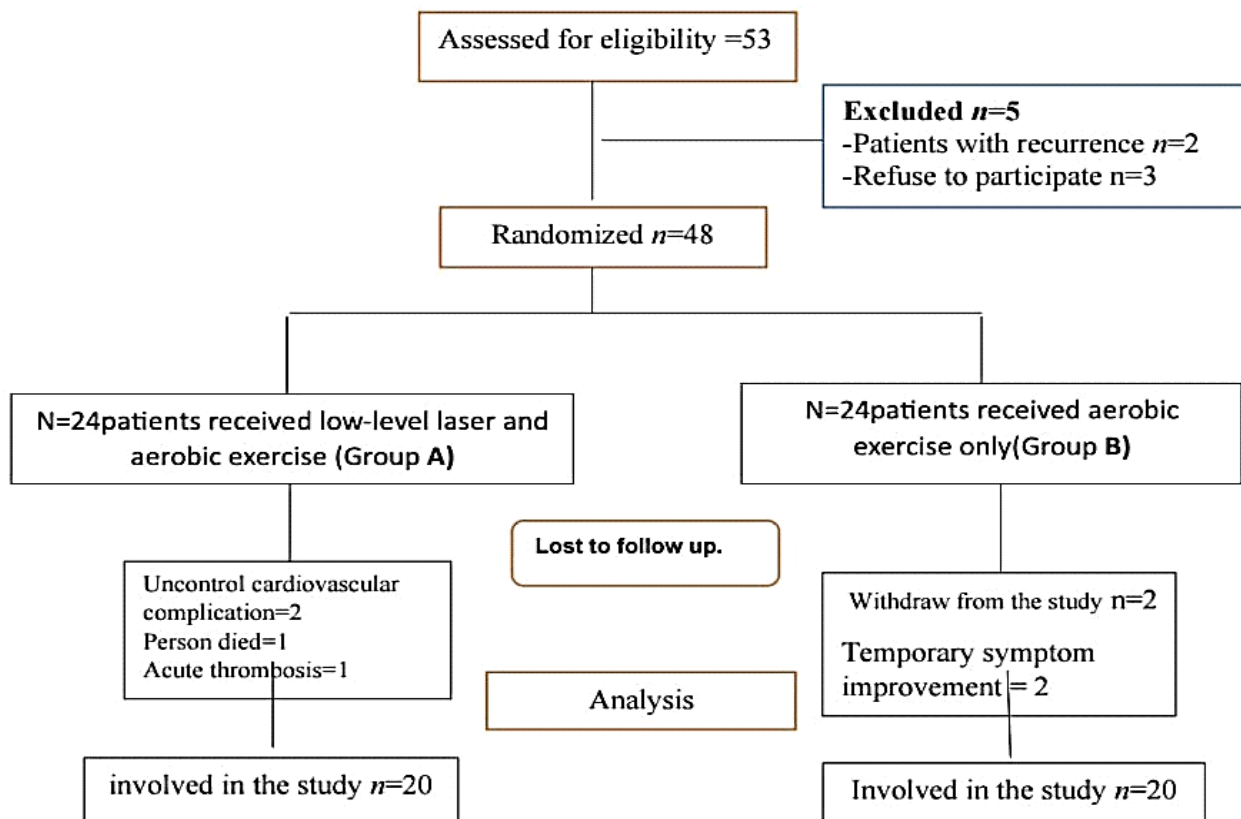


Figure (1): The study's consort diagram.

Low-Level Laser Therapy

LLLT using a scanning laser device (**Model:** ASTAR, SKW2-450&400, SK2_450&400, Made in Poland) was applied along the anatomical course of the posterior tibial artery, from the medial aspect of the popliteal fossa to the area behind the medial malleolus. **Laser parameters included a wavelength** of 808 ± 5 nm, **output power** of 450 mW, a red laser beam, beam divergence greater than $0.025 \text{ rad} \pm 0.005 \text{ rad}$, and a nominal ocular hazard distance (NOHD) exceeding 8 meters. Each session involved 10 minutes of application over the posterior tibial artery, with 3 sessions/week over a total treatment period of 12 weeks.

General consideration: Laser application was performed in a quiet, temperature-controlled room with the patient in a comfortable prone position. Eye protection for both the patient and the clinician was used during all sessions.

Aerobic Exercise Protocol: A structured treadmill walking program was designed to enhance walking distance, reduce claudication symptoms, and boost vascular function. Supervised treadmill exercises by trained physiotherapists occurred 3 times weekly; each session lasted 50 minutes, beginning with a 10-minute warm-up at low speed, followed by a main training phase of 30 minutes of walking with rest periods as needed due to claudication pain (graded walking approach), with exercise intensity set at 50% to 75% of VO_2 max. The session concluded with a 10-minute cool-down at a gradually decreasing speed.

Estimated VO_2 max using the Treadmill test through Modified Bruce Protocol. **Exercise intensity** started at 50% VO_2 max and progressed after 2 weeks to 75% VO_2 max over the 12-week period according to a symptom-limited protocol.

Claudication Consideration:

Patients were encouraged to walk **until the onset of claudication pain**, then rest as needed until the pain subsided before resuming walking. This "walk-rest-walk" pattern is aligned with clinical guidelines for PAD rehabilitation,

Outcome measures

To evaluate the clinical and functional outcomes of the intervention, the following validated assessment tools were used:

1- Peak Systolic Velocity (PSV) via Duplex Ultrasonography

Duplex ultrasonography was used to evaluate arterial blood flow and determine the level of stenosis. A high-resolution duplex scanner (Model: Sony Deutschland GmbH, Hedelfinger Strasse 61, 70327) measured peak systolic velocities (PSV) in the posterior tibial artery following a standardized protocol from the common femoral artery to the pedal arteries. Normal PSV in the tibial artery ranges from 40 to 60 cm/sec. Interpretation of PSV measurements (11,12),

- Less 30% increase in PSV with preserved triphasic waveform indicates mild disease (<20% stenosis)

- A 30–100% increase in PSV with bidirectional or reverse flow suggests moderate disease (20–50% stenosis).
- A100% increase in PSV, loss of reverse flow, and monophasic waveform indicate severe disease (50–99% stenosis).

2-The Ankle-Brachial Index

The Ankle-Brachial Index (ABI) serves as a non-invasive screening tool for lower extremity arterial disease. ABI is calculated by dividing the systolic blood pressure at the ankle by the systolic pressure at the brachial artery, using a handheld sphygmomanometer. An ABI less than 0.90 or greater than 1.40 is considered abnormal and indicative of PAD (2,13).

3- Visual Analog Scale (VAS): Pain intensity was assessed immediately after the treadmill test using the VAS, a 10-cm line where participants marked their perceived pain level. Pain was categorized as follows: 0–4 mm: No pain; 5–44 mm: Mild pain; 45–74 mm: Moderate pain; 75–100 mm: Severe pain (14,15).

4-Modified Bruce Protocol: Functional walking capacity was evaluated using the Modified Bruce Treadmill Protocol on a KETTLER Holding GmbH treadmill, following the guidelines of the American College of Sports Medicine (16) and the Society for Physiotherapists' recommendations. Patients underwent a graded treadmill test with the following **stages:** Stage I, 1.7 mph at 0% incline for 3 minutes; Stage II, 1.7 mph at 5% incline for 3 minutes; and Stage III, 1.7 mph at 10% incline for 3 minutes.

The following measurements were recorded from the treadmill test

- **Initial Claudication Distance (ICD):** Distance walked before pain onset.
- **Absolute Claudication Distance (ACD):** Maximum walking distance before needing to stop due to pain.
- **Initial Claudication time and Absolute Claudication time.**
- **Estimated VO_2 max:** calculated using the total time (T) on the treadmill test using the following equation.

$\text{VO}_2 \text{ max (ml/kg/min)} = 14.76 - (1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$, where T is the total exercise time in minutes; T^2 is the square of the total exercise time; T^3 is the cube of the total exercise time (17).

Statistical analysis

SPSS software version 22 was used to perform all statistical analyses. A comparison of the features between the two groups, including age, weight, height, and BMI, was conducted using an unpaired t-test. Chi^2 test was employed for the comparison of gender. Subsequently, MANOVA was performed to compare the variables between groups. The normality of the data was assessed using the Kolmogorov–Smirnov test. Additionally, Levene's test was applied to examine data homogeneity. The significance level for all statistical tests was set at $P < 0.05$.

RESULTS

A total of 40 patients were randomly allocated into two groups, with 20 patients in each group. According to **table 1**, there is no significant difference in the participants' characteristics, including age, weight, height, BMI, and gender ($p > 0.05$).

Table (1): Comparison of characteristics between groups A and B.

		Group A (n:20) Study		Group B (n:20) Control		p-value	t-value
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$		
Age (years)		60.1±3.4		60.6±3.1		0.599	0.530
Height (cm)		168.3±11.2		170±10.3		0.610	0.514
Weight (kg)		79.2±11.9		79.1±9.6		0.965	0.044
BMI (kg/m²)		27.8±1.6		27.3±1.3		0.224	1.236
		N	%	N	%	p-value	X ² -value
Gender	Male	11	55%	13	65%	0.519	0.417
	Female	9	45%	7	35%		

Table 2 shows a significant improvement in ABI in both groups, with no baseline difference ($P = 0.693$). Post-intervention, Group A showed a significantly greater improvement than Group B ($P = 0.035$), with a 20% increase compared to 13.6%.

The findings showed that PSV decreased significantly toward normal in both groups, with no significant differences between them pre- or post-intervention. However, Group A showed a greater percentage reduction (52.7%) than Group B (45.4%), indicating a more favorable improvement in blood flow.

Moreover, regarding the VAS outcomes, no significant difference existed between groups at baseline, but a significant difference emerged post-intervention. Study Group A showed a greater pain reduction (48.8%) compared to Control Group B (29.2%).

Table (2): Comparison between groups A and B regarding the ABI, PSV, and VAS.

		Group A (Study) (n:20)	Group B (Control) (n:20)	Comparison between groups	
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	F-value	P-value
ABI	Pre-intervention	0.8±0.06	0.81±0.07	0.158	0.693
	Post-intervention	0.96±0.02	0.92±0.07	4.795	0.035*
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	20%	13.6%		
PSV (cm/s)	Pre-intervention	97±10.9	93±9	1.602	0.213
	Post-intervention	45.9±9.5	50.8±6	3.597	0.066
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	52.7%	45.4%		
VAS	Pre-intervention	75.7±14.7	73.9±14.5	0.144	0.707
	Post-intervention	38.95±11.9	52.3±16.2	8.860	0.005*
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	48.8%	29.2%		

*: Significance, **ABI**: Ankle Brachial Index, **PSV**: Peak Systolic Velocity, **VAS**: Visual Analog Scale.

The results showed that the initial claudication distance, initial claudication time, absolute claudication distance, and absolute claudication time were significantly improved in both groups. Additionally, significant differences appeared after the intervention between the groups. Superiority was demonstrated for the study group A, which revealed a greater mean difference in all measures (115.8m, 3.6min, 171.6m, 3.5min, respectively) compared to the control group B (76m, 2.6min, 128.3m, 2.9min, respectively) (**Table 3**).

Table (3): Comparison between groups A and B regarding initial claudication distance and time, absolute claudication distance and time

		Group A (Study) (n:20)	Group B (Control) (n:20)	Comparison between groups	
		$\bar{x} \pm SD$	$\bar{x} \pm SD$	F-value	P-value
Initial Claudication Distance (m)	Pre-intervention	136.1±45.1	126.9±45.9	0.409	0.526
	Post-intervention	251.9±59	202.9±46.6	8.463	0.006*
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	85.1%	59.9%		
Time for initial claudication (minutes)	Pre-intervention	3.5±1	3.1±0.8	2.750	0.105
	Post-intervention	7.1±1.2	5.7±1	20.349	P<0.001*
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	102.9%	83.9%		
Absolute claudication distance (m)	Pre-intervention	193.2±59	179.9±46.5	0.610	0.440
	Post-intervention	364.8±72.8	308.2±64.2	6.808	0.013*
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	88.8%	71.3%		
Time for Absolute claudication (minutes)	Pre-intervention	5.2±0.9	5.2±0.6	0.038	0.846
	Post-intervention	8.7±1.1	8.1±0.7	4.413	0.042*
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	67.3%	55.8%		

\bar{x} : Mean, SD: Standard deviation, p-value: Probability value. *: Significance.

The results showed that VO₂ max significantly increased in both groups. Additionally, there were no significant differences between the two groups before or after the intervention. However, Group A exhibited a higher percentage change in VO₂ max (36.4%) compared to Group B (31.6%) (Table 4).

Table (4): Comparison between groups A and B regarding VO₂ max.

		Group A (Study) (n:20)	Group B (Control) (n:20)	Comparison between groups	
		$\bar{x} \pm SD$	$\bar{x} \pm SD$	F-value	P-value
VO₂ max (ml/kg/min)	Pre-intervention	19.2±2.8	18.7±2.7	0.290	0.594
	Post-intervention	26.2±3.1	24.6±2.5	2.944	0.094
	Comparison within group	P<0.05*	P<0.05*		
	Percentage of change (%)	36.4%	31.6%		

*: Significant.

DISCUSSION

This study contributes significantly to the growing body of evidence supporting multimodal rehabilitation programs. The integration of LLLT with aerobic exercise yielded superior outcomes in **vascular health** (ABI, PSV), **pain modulation** (VAS), and **functional capacity** (claudication distances, time, and VO₂ max) compared to aerobic training alone in patients with T2DM complicated with PAD.

Laser therapy enhances ATP synthesis and reduces oxidative stress by enhancing the efficiency of the electron transport chain in mitochondria. It also activates transcription factors, suppresses inflammatory factors, and influences neurotrophic factors such as brain-derived neurotrophic factor and nerve growth factor⁽¹⁸⁾.

Laser irradiation also influences cell biology by modulating transcription factors. One of the most well-known transcription factors, whose activity is

affected by LLLT, is nuclear factor-kappa B (NFκB). NFκB controls many cellular functions such as migration, proliferation, inflammation, and stress responses. This protein complex remains inactive until stimulated, at which point it becomes active⁽¹⁹⁾.

The appropriate dose of LLLT radiation activates the enzyme, enhancing its proliferative and anti-inflammatory potential⁽²⁰⁾. However, exceeding the radiation dose leads to increased oxidative stress and substantial activation of NF-κB⁽²¹⁾.

Nitric oxide regulates inflammatory processes and the immune response of cells. This effect is achieved through multiple mechanisms that influence cell signaling systems, including cGMP and G-protein, as well as cAMP, JAK/STAT, and MAPK-dependent signal transduction pathways. NO may also alter the activity of transcription factors and the expression of other mediators of inflammation⁽²²⁾.

The increase in mitochondrial membrane potential

($\Delta\Psi_m$) after LLLT is one of the most well-documented effects of laser light on cell function. This effect is also observed through other mitochondrial retrograde signaling mechanisms, such as ROS, pH, and NO⁽²³⁾. It has been shown that this mechanism is responsible for the pro-proliferative effect of LLLT. LLLT causes the phosphorylation of tyrosine kinase receptors (TPKR) due to these changes in mitochondrial retrograde signaling, which stimulates the MAPK/ERK kinase signaling pathway, leading to increased cell proliferation⁽²⁴⁾.

The findings in the study group (Group A) revealed significant improvements across outcomes such as a VO₂ max by 36.4% increase, with multiple mechanisms involved, including initial claudication distance, initial claudication time, absolute claudication distance, and absolute claudication time (85.1%, 102.9%, 88.8%, and 67.3%, respectively). Furthermore, the ABI increased significantly by 20%, while PSV showed a substantial reduction of 52.7%.

These results align with findings by **Ahmad *et al.***⁽²⁵⁾ who demonstrated that GaAlAs laser acupuncture at selected acupoints significantly alleviated claudication symptoms and improved functional performance in older men with PAD. Their study also reported a significant increase in the 6-minute walking distance (6-MWD) from 214 ± 60 m to 318 ± 77 m ($p < 0.001$).

This aligns with the conclusions drawn by **Kumar Cg *et al.***⁽²⁶⁾ in their study, which showed a significant reduction in pain using the VAS scale (6.47 ± 0.84 to 1.21 ± 0.78, $p < 0.001$) in patients with painful peripheral diabetic neuropathy.

The results are also consistent with **Silajiya *et al.***⁽²⁷⁾ who demonstrated the effectiveness of combined LLLT and aerobic exercise in treating venous leg ulcers (VLUs). The study noted improvements in VO₂ max of 17.18%.

However, our findings are consistent with those of **Amoli *et al.***⁽²⁸⁾ who reported that Tecar (Transfer of energy capacitive and resistive) + laser therapy yielded significantly better outcomes than laser therapy alone, particularly in terms of tibial motor nerve conduction velocity (MNCV) and ABI values after three months. While improvements were also observed in the laser group, the combination therapy appeared superior for peripheral neuropathy in the lower limb.

The control group (Group B), which received aerobic exercise only, also demonstrated significant improvements: VO₂ max increased by 31.6%; improvements in initial claudication distance, initial claudication time, absolute claudication distance, and absolute claudication time were recorded as 59.9%, 83.9%, 71.3%, and 55.8%, respectively; ABI increased by 13.6%; and PSV decreased by 45.4%.

These outcomes are consistent with those of **Fassora *et al.***⁽²⁹⁾ who concluded that light-to-moderate aerobic exercise was more effective than vigorous exercise intensity in improving maximum walk distance and pain-free walk distance. However, vigorous

exercise elicited greater gains in VO₂ peak. Furthermore, **Xiao *et al.***⁽³⁰⁾ confirmed that supervised exercise training (SET) improves cardiovascular function and walking capacity in patients with intermittent claudication, with significant increases in VO₂ peak and walking distance.

In line with **Almutairi *et al.***⁽³¹⁾ our findings also support the role of aerobic exercise in improving cardiovascular fitness in patients with T2DM. In the study, aerobic exercise led to reductions in fasting blood glucose, HbA1c, and resting heart rate, along with an increase in VO₂ max.

CONCLUSION

This study confirms that combining low-level laser therapy with aerobic exercise significantly improves peripheral circulation, reduces pain, and enhances walking performance in patients with type 2 diabetes and mild to moderate PAD. However, both groups showed improvement; the combined treatment produced better results across most clinical and functional measures. These findings support using LLLT as a powerful addition to PAD rehabilitation programs.

LIMITATIONS

Lacks long-term evaluation of vascular outcomes and symptom recurrence, limited to 40 participants; results may not apply to broader populations or more severe stages of PAD. The effects of LLLT might vary depending on the application site; only the posterior tibial artery was targeted. Additionally, the study did not assess inflammatory or angiogenic markers (e.g., VEGF, NO), which could support mechanistic interpretations.

RECOMMENDATIONS

Long-term, large-scale studies are necessary to evaluate the sustainability of combined LLLT and exercise benefits over time, including the prevention of symptom recurrence and disease progression. Additionally, assess the combined effect of Tecar (Transfer of energy, capacitive and resistive) as a new therapy alongside aerobic exercise on PAD. Future trials should incorporate inflammatory biomarkers or angiogenesis markers to support these mechanisms. Explore the application of LLLT to different anatomical sites, such as the anterior tibial artery, in future studies.

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