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Effects of Walking Exercise in Patients with Lower Extremity Peripheral Arterial Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Peripheral arterial disease (PAD) is a chronic condition that increases the risk of death and causes major clinical complications like reduced walking activity. Patients with peripheral artery disease (PAD)-related intermittent claudication (IC) are encouraged to engage in walking as an exercise therapy.

Aim and Objectives: This Systematic Review and Meta-Analysis to analyse the effects of walking exercise in patients with lower extremity PAD.

Methods: The databases were searches in Cochrane, PubMed, and Google Scholar databases up to August 2023. Randomized controlled trials (RCTs) comparing the effects of walking exercise in patients with PAD were included for systematic review and meta-analysis. The primary outcome measure was 6 minute walk distance and Ankle Brachial Index.

Keywords: used "Peripheral Arterial Disease" (PAD), "Walking exercises", "6 Minute Walk Distance" and "Ankle Brachial Index" (ABI). Standardized mean differences (SMDs) with 95% CI were calculated to compare outcome measures.

Results: A total of 1533 researches were searched but twelve studies with 1288 patients were included in this Systematic Review according to the inclusion criteria and seven studies were added in meta-analysis and assessed with very low to moderate risk of bias. The pooled results showed significant difference in Walking exercises with 6 minute walk distance SMD 203.55[95% CI 176.90 to 230.20; I^2=92%], P =< 0.00001) and there was no significant difference in Walking exercises with Ankle Brachial Index (SMD -0.04 [95% CI -0.08 to 0.01; I^2=57%], P= 0.11) in patients with PAD.

Conclusion: This review suggests that walking exercise therapy significantly improve the walking performance in patients with Lower Extremity Peripheral Arterial Disease

Keywords: "Peripheral Arterial Disease" (PAD), "Walking exercises", "6 Minute Walk Distance" and "Ankle Brachial Index" (ABI).

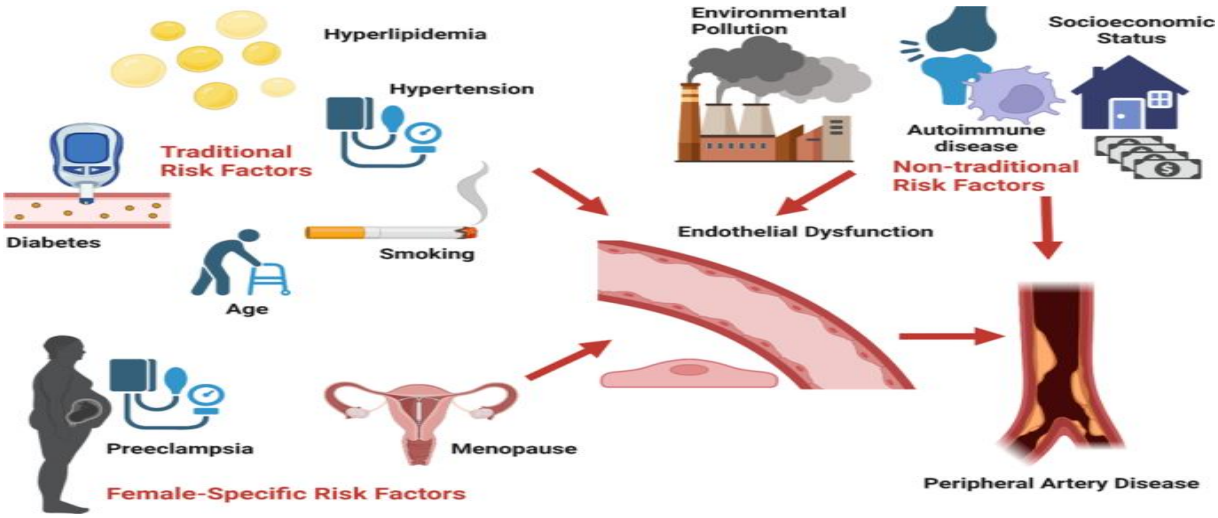
INTRODUCTION

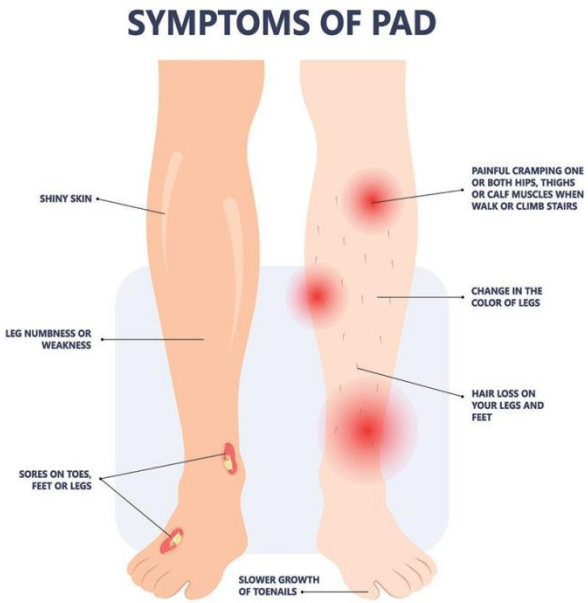
A persistent atherosclerotic /occlusive condition of the aorta and its branches that most usually affects the arteries supplying the legs and feet is known as peripheral arterial disease (PAD). Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis, characterized by progressive narrowing and occlusion of peripheral arteries, most frequently affecting the lower extremities. The disease leads to reduced blood flow and impaired oxygen delivery to skeletal muscles, resulting in pain, functional limitations, and diminished quality of life (McDermott & Criqui, 2001; Norgren et al., 2007). PAD is increasingly recognized as a major public health concern due to its strong association with cardiovascular morbidity and mortality. In the general population of adults over 40, the prevalence of PAD is around 5%; among people over 70, it rises to about 15% (Selvin et al., 2004).

Globally, PAD affects more than 200 million individuals, with prevalence rising significantly with advancing age and the presence of risk factors such as diabetes mellitus, hypertension, dyslipidemia, and smoking (Fowkes et al., 2013). Despite its high prevalence, PAD remains underdiagnosed and undertreated, particularly in low- and middle-income countries. Many individuals remain asymptomatic in early stages, while symptomatic patients typically present with intermittent claudication, defined as exercise-induced leg pain relieved by rest. In advanced stages, PAD may progress to rest pain, non-healing ulcers, critical limb ischemia, and limb loss (Hirsch et al., 2006; Aboyans et al., 2018).

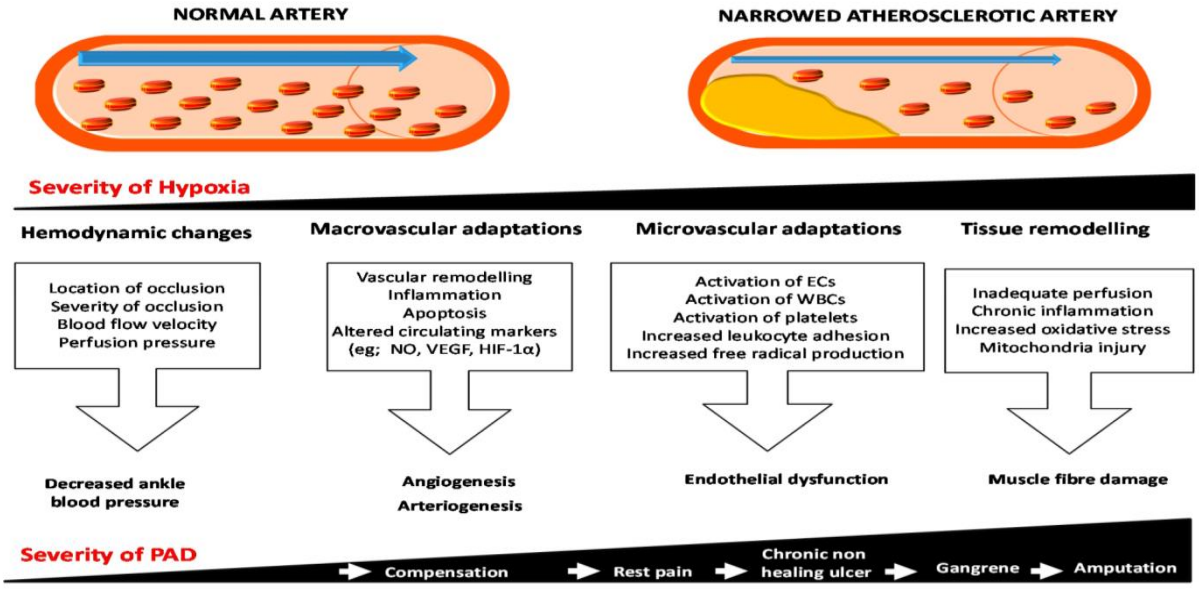
PAD is not only a localized disease of the lower limbs but also a marker of widespread atherosclerosis. Patients with PAD have a significantly increased risk of myocardial infarction, stroke, and cardiovascular death compared to individuals without the disease (Hirsch et al., 2006). The pathophysiological mechanisms underlying intermittent claudication include impaired blood flow, endothelial dysfunction, abnormal skeletal muscle metabolism, and reduced exercise tolerance, all of which contribute to decreased functional capacity (Hamburg & Creager, 2017).

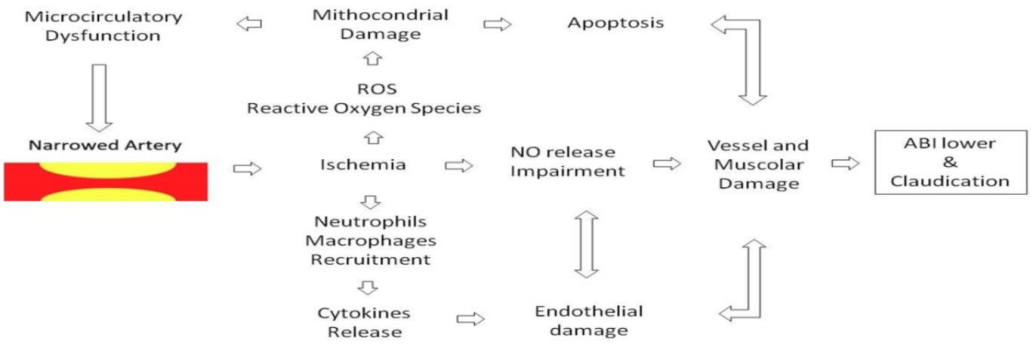
Risk Factors





Pathophysiology





Aim of the Study: This Systematic Review and Meta-Analysis to analyse the effects of walking exercise in patients with lower extremity PAD.

Need of the Study: However, the majority of the evaluations have considered research on exercise forms other than walking, such as dynamic leg exercise, lower limb resistance training, and even upper limb exercise, as well as studies on a subset of PAD patients. The advantages of walking exercise for PAD patients are not well understood.

MATERIAL AND METHODS

- Study Design
- A Systematic Review and Meta-Analysis
- Search Strategy
- PubMed,
- Google Scholar and Cochrane
- Time Duration
- 2013-2023
- Search Terms
- Peripheral Arterial Disease (PAD), Walking exercises, 6 Minute Walk Distance and Ankle Brachial Index (ABI)

- Search Results
- Total 1533 articles were searched and only12 studies fullfilled the inclusion criteria

Selection Criteria

Inclusion Criteria

- 1. Population: Peripheral Arterial Disease (mean age of 67.1 ± 9.4 years).
- 2. Intervention: Walking exercises.
- 3. Comparison: a comparator group performing low, medium, or high load exercise of the lower limb.
- 4. Outcomes: pre- and post-training measures of 6 Minute Walk Distance and Ankle Brachial Index (ABI).
- 5. Study design: Randomized controlled trial (RCTS).
- 6. Only English language articles were included.

Exclusion Criteria

- 1. Abstract, case studies , pilot studies and Non RCTs.
- 2. Articles other than English
- 3.Articles in which other than walking exercises intervention was used
- 4. Paid articles
- 5. Case reports and Case studies

PRISMA TABLE

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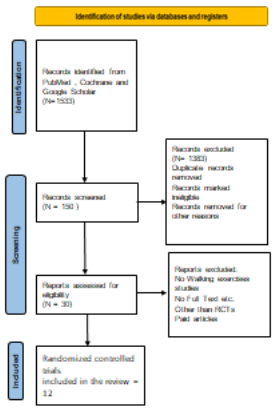

SUMMARY OF THE INCLUDED ARTICLES

Sr. No.	Title	Author's Name	No of participants	Intervention	Outcome measures	Results
1.	Effects of Exercise Mode on Arterial Stiffness in Symptomatic Peripheral Artery Disease Patients: A Randomized Crossover Clinical Trial	Evans et al., 2021	12	Group1. walking exercise, Group2. Resistance exercise, Group3. combined exercise, Group4. control session	AASI, Body mass index, ankle brachial index	A single bout of resistance exercise acutely reduces arterial stiffness in symptomatic PAD, while walking and combined exercise did

						not alter this variable.
2.	Impacts of aquatic walking on arterial stiffness, exercise tolerance, and physical function in patients with peripheral artery disease: a randomized clinical trial	Song et al., 2019	72	aquatic walking training group (AQ, n 35) or a control group (CON, n 37)	Arterial stiffness, ABI, V˙ O2max, 6MWD, handgrip strength,	These results suggest that aquatic walking exercise is an effective therapy.
3.	Effects of heated water-based versus land-based exercise training on vascular function in individuals with peripheral artery disease	Song et al., 2020	53	a LBET group (n 25) or HWET group (n 28)	ABI, 6MWD	These results suggest that HWET greater improvements
4.	Effects of Walking Exercise at a Pace With Versus Without Ischemic Leg Symptoms on Functional Performance Measures in People With Lower Extremity Peripheral Artery Disease: The LITE Randomized Clinical Trial	Michael et al., 2022	61	home-based walking exercise at a pace (24), home-based walking exercise at a pace(24), control group(13)	ABI	walking exercise at a pace significantly improved.
5.	Walking training at the heart rate of pain threshold improves cardiovascular function and autonomic regulation in intermittent claudication: A randomized controlled trial	Marcel et al., 2017	42	control Group, n = 20, and Walking Training Group ,n = 22	1) walking capacity, (2) resting cardiovascular function, (4) cardiovascular autonomic regulation	to increasing walking capacity, WT improved cardiovascular function
6.	A group-mediated, home-based physical activity intervention for patients with peripheral artery disease: effects on social and psychological function	Rejeski et al ., 2014		groups: a home-based group- control condition.	Six-minute walk test, Pain acceptance, ABI	The intervention group experienced greater improvement
7.	Effectiveness of a New Exercise Program after Lower Limb Arterial Blood Flow Surgery in Patients with Peripheral Arterial Disease: A Randomized Clinical Trial	Edita et al., 2014	117	intervention (n = 57) or a control group (n = 60).	6 MWT, ABI, and Study Short Form-36 of QoL	SEP and non-SET at home has yielded significantly better results .
8.	Heat therapy vs. supervised exercise therapy for peripheral arterial disease: a 12-wk randomized, controlled trial	Ashley et al., 2019	23	Supervised exercise (N=12), Heat group (N=11)	Functional Walk Tests, Tissue Oxygenation, Blood Pressure, Vascular function, Quality of life, ABI	There were no significant changes between heat and exercise in individuals with PAD.
9.	The effects of Crenotherapy and exercise in peripheral arterial occlusive disease.	Gennaro et al., 2017	98	an intensive training (group A); the crenotherapy (group B).	ABI, actual claudication distance (ACD), MWD and the intima-media thickness (IMT).	Our experience shows that crenotherapy has similar effects compared to traditional physical training in the treatment of PAOD,
10.	Effect of a Home-Based, Walking Exercise Behavior Change Intervention vs Usual Care on Walking in Adults With Peripheral Artery Disease: The MOSAIC	Lindsay et al., 2022	190	walking exercise (n = 95) or usual care (n = 95)	6-minute walking distance, Walking Estimated Limitation.	a home-based, walking exercise resulted in improved walking distance at 3 months.

	Randomized Clinical Trial					
11.	Effect of Low-Intensity vs High-Intensity Home-Based Walking Exercise on Walk Distance in Patients With Peripheral Artery Disease: The LITE Randomized Clinical Trial	Mary et al., 2021	305	low-intensity walking exercise (n = 116), high-intensity walking exercise (n = 124), or nonexercise control (n = 65)	6-minute walk distance,	These results do not support the use of low-intensity home-based walking exercise
12	Effect of Granulocyte-Macrophage Colony-Stimulating Factor With or Without Supervised Exercise on Walking Performance in Patients With Peripheral Artery Disease The PROPEL Randomized Clinical Trial	Mary et al., 2017	210	exercise + GM-CSF (n = 53), supervised exercise + placebo (n = 53), attention control + GM-CSF (n = 53), attention control + placebo (n = 51).	6-minute walk distance	Among patients with PAD, supervised treadmill exercise significantly improved 6-minute walk distance

PEDRO TABLE

S.No.	Eligibility Criteria	Rejeski et al., 2014	Ashley et al., 2019	Lindsay et al., 2022	Marcel et al., 2017	Edita et al., 2014	Michael et al., 2022	Song et al., 2020	Song et al., 2019	Gennaro et al., 2017	Mary et al., 2017	Evans et al., 2021
1	Specified eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Concealed allocation	No	Yes	Yes	Yes	No	Yes	No	No	No	No	No
4	Similar baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Subjects blinding	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
6	Therapists blinding	Yes	No	Yes	Yes	No	No	No	Yes	No	No	No
7	Assessors blinding	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
8	Measures of key outcomes from more than 85% of subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

9	Intention to treat analysis of one key outcome	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
10	Statistical comparisons between-groupof at least one key outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Variability for at least one key outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Total	10	10	11	11	9	8	8	9	8	7	8

RESULTS

- Data Analysis: To evaluate the effectiveness of walking exercise, mean changes from baseline to end of the study in 6 MWD and ABI were taken into consideration as the main outcome. The weighted mean difference and 95% confidence interval (CI) for the effects of walking exercise were used to generate and assess the mean difference with standard deviation for the outcome variables. The "Review manager (version 5.3) software" was used to do the meta-analysis.

- Only Seven articles were chosen for the quanlitative analysis (Meta-Analysis) out of twelve articles and twelve articles were included in the quatitative analysis (Systematic Review)

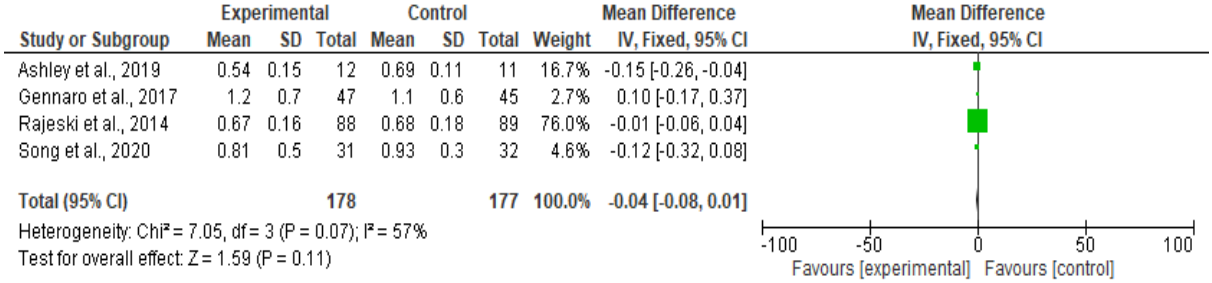

Fig. 1.Forest plot showing effect of Walking exercises on Ankle Brachial Index in Patient with Peripheral Arterial Disease

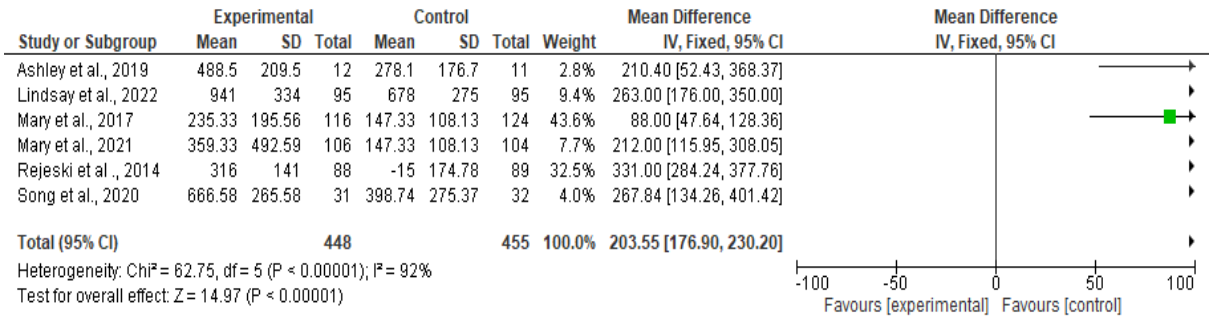

Fig. 2.Forest plot showing effect of Walking exercises on 6 minute walk Distance in Patients with Lower Extremity Peripheral Arterial Disease

- The walking exercise significantly improved 6-MWD SMD 203.55[95% CI 176.90 to 230.20; I^2=92%], P =< 0.00001). Further subgroup analyses suggested no significant difference in all stratifications, including differential PAD symptoms.

The walking exercise showed no significant differences in resting ABI and post-exercise ABI (SMD -0.04 [95% CI -0.08 to 0.01; I^2=57%], P= 0.11)

DISCUSSION

- The findings of the present meta-analysis indicated that compared with usual care, walking exercise improved 6-MWDin PAD patients with IC.

- Greater improvement in walking performance was observed in PAD patients with IC and no difference in improvement of walking performance was observed among different exercise program lengths and modalities. Intensive walking exercise had no effect on ABI and it did not increase the incidence of adverse events. For PAD patients without IC, improvements in 6-MWD after walking exercise. However, the differential efficacy of walking exercise in PAD with and without IC may be associated with the quality of the studies included and the different tools used to assess walking ability.

- Nevertheless, the 6-min walk test is closely correlated to real-life outdoor walking capacity, and is increasingly recognized as a meaningful outcome measure in patients with PAD.40,41 Further studies are required to address this issue.

- The mechanism by which walking exercise exerts beneficial effects on walking performance remains incompletely understood.54 There is accumulating evidence that improved collateral circulation may be involved.23,25 Significant increases in calf blood flow under resting, hyperemic, and maximal conditions have been demontrated after 6 months supervised treadmill training.

- **Conclusion:** This review suggests that walking exercise therapy should be a significant part of patients with PAD's standard of care in patients with Lower Extremity Peripheral Arterial Disease. Walking exercise may also be advised for PAD patients without IC, however more research is needed in this area are necessary to clarify this topic further. Moreover, early participation in vigorous walking activity can increase the therapeutic effect for PAD patients.

- Implications and Future Work: More precision in prescribing therapy intensity is required for future guidance, distinguishing between claudication pain severity and exercise therapy intensity in patients with symptomatic PAD.

- **Conflict of Interest** -None

- **Source of funding** – None

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