

The effect of supervised exercise on biomarker levels in individuals with peripheral arterial disease - a systematic review

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Back ground

Atherosclerosis is a chronic inflammatory process involving the arterial endothelium leading to stenosis, contributing to the pathophysiology of intermittent claudication (IC). Cardiovascular risk factors enhance the progression of the inflammatory process leading to increased morbidity and mortality at least 50% at 10 years. Patients with IC are at high risk of coronary and cerebrovascular events. The systemic inflammatory response damages the endothelium, initiating release of several vasoactive mediators leading to further damage.

Several studies have shown the beneficial effect of supervised exercise (SE) on walking distance and general cardiovascular health. Furthermore, the effect of exercise on inflammatory and non-inflammatory markers has been widely studied.

Aim

The aim of this systematic review is to examine the effect of SE on inflammatory and non-inflammatory biomarkers in patients with IC.

Methods

A comprehensive search of the published literature was conducted in accordance with PRISMA guidelines (11). Cochrane, Embase and MEDLINE databases were systematically searched using the Ovid interface for articles published from 1949 to 2016 reporting the impact of supervised exercise of 2 weeks duration or more on biomarker levels in patients with intermittent claudication. The following key words were used in the mesh search: ('lower limb arterial disease' OR 'ischemia' OR 'extremities' OR 'IC leg' OR 'PAD' OR 'PVD', OR 'AOD') AND ('metabolome' OR 'metabonomics' OR 'proteomics' OR 'biomarker') AND ('exercise therapy' OR 'exercise' OR 'walking' OR 'exercise test' OR 'physical exertion').

Inclusion criteria

SE for a minimum of 2 weeks duration
Patients with IC symptoms proven of peripheral arterial disease aetiology
Human studies

Exclusion criteria

SE for less than 2 weeks duration
Non-human animal studies
Review articles

Results

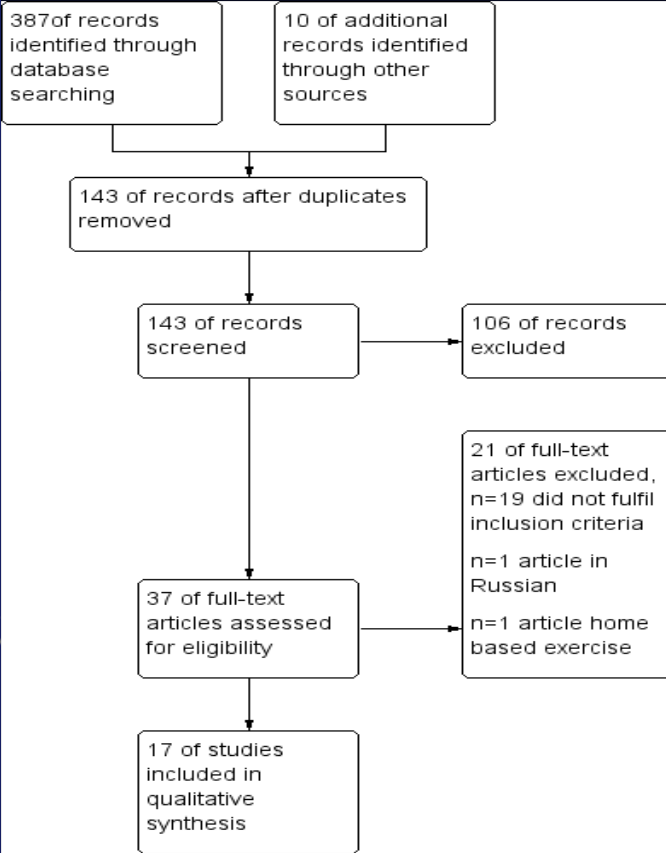
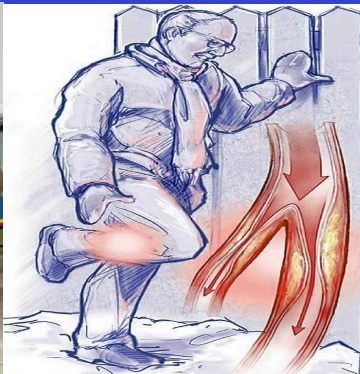


Figure 1: PRISMA diagram, flow chart of literature search



Conclusion

➤ SE has reduced biomarkers involved in the process of atherosclerosis

- I. CRP, VCAM-1, ICAMP-1
- II. Fibrinogen receptors, ADMA, TREM-1, SAA, E-selectin & acylcarnitine
- III. LDL and TC.

➤ SE increased Beneficial biomarker which play a role in improving the blood flow

- I. Lactate & plasma nitrite
- II. HDL
- III. EPC
- IV. ACR (urinary albumin creatinine ratio)

First Author	Year	RCT	n	Type of biomarker	Key Findings	MF	Duration of follow-up	Frequency of exercise	SE / Control	Grade
Delaney	2015	Yes	35	Protein	NO →, ADMA ↓	(25:9)	12 weeks	2/wk	(18:17)	Strong
Schlager	2012	Yes	53	Protein	CRP, IL-6, P-selectin, fibrinogen, prothrombin fragment 1&2 & monocyte platelet aggregate ↔	(33:20)	12 months	2/wk	(27:26)	Strong
Mika	2011	Yes	68	Lipoprotein	HDL ↑, LDL ↓ & TC ↓, fibrinogen & haematocrit ↔	(60:8)	3 months	3/wk	(34:34)	Strong
Andrew	2008	Yes	60	Protein	Lactate ↑	(42:18)	3 months	2/wk	(30:30)	Strong
Nawaz	2001	Yes	52	Protein	Neutrophils ↑, von Willebrand factor, E-selectin ↔	(21:5)	6 weeks	2/wk	(26:15)	Strong
Saxton	2008	Yes	104	Protein	CRP, ICAM & VCAM ↔, Stress proteins (HSP 60 & HSP 70) & E-selectin ↔	(48:14)	6 months	2/wk	(62:30)	Strong
Hobbs	2007	Yes	34	Protein	Thrombin-antithrombin complex & prothrombin fragments 1&2 ↔	(27:7)	6 months	2/wk	(7:9)	Strong
Zwierska	2005	Yes	104	Protein	Lactate ↑	(83:21)	6 months	2/wk	(104:33)	Strong
Schlager	2011	Yes	40	Protein	EPC ↑, ADMA ↓, SDF-1 & VEGF ↔	(13:7)	6 months	2/wk	(20:20)	Strong
Tisi	1997	Yes	67	Protein	ACR ↑, SAA ↓ & CRP ↓, fibrinogen ↔	(46:21)	12 months	1/wk	(22:17), n=28 angioplasty	Moderate
Allen	2010	Yes	33	Protein	Plasma nitrite ↑		3 months	3/wk	(15:18)	Moderate
Saetre	2011	No	29	Protein	ICAM-1, ↓VCAM-1 ↓ & E-selectin ↓	(16:13)	8 weeks	2/wk	(29:0)	Weak
Turton	2002	No	46	Protein	CD11b, neutrophil elastase, malonaldehyde & TAC ↔	(35:11)	6 months	1/wk	(46:22)	Weak
Collins	2013	Yes	55	Lipoprotein	TG ↓ & TC ↓, HDL, LDL, ICAM, VCAM, CRP & IL-6 ↔	(22:8)	6 months	1/wk	(30:20)	Strong
Murphy	2011	Yes	111	Lipoprotein	HDL & LDL ↔, Fibrinogen ↓	(21:22)	6 months	3/wk	(43:22)	Strong
Arosio	2000	No	24	Glycoprotein	Fibrinogen receptor IIb/IIIa ↓, p-selectin,vcam,TC,fibrinogen↔,	(24:0)	14 days	Daily	(12:12)	Weak
Hiatt	1989	Yes	19	Protein	Acylcarnitine ↓	(19:0)	3 months	3/wk	(10:9)	Strong

Table 1 summarises the impact of supervised exercise programme on the blood biomarkers

ACR: Urinary albumin creatinine ratio. sVCAM: Vascular adhesion molecule. sICAM: Intracellular adhesion molecule. CRP: C-reactive protein. IL-6: Interleukin-6. EPC: Epithelial progenitor cell. VEGF: Vascular endothelial growth factor. HDL: High density lipoprotein. LDL: Low density lipoprotein. TC: Total cholesterol. NO: Nitric oxide. MPA: Monocyte platelet aggregate. SDF-1: Stromal cell derived factor-1. ADMA: Asymmetric dimethylarginine. MDA: Malonaldehyde. TAC: Total antioxidant oxidant. SAA: Serum amyloid protein, HSP: Heat shock protein