

# Influence of endovascular treatment on the vascular endothelium in patients with peripheral arterial disease: a systematic review

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## Abstract

*Peripheral arterial disease (PAD) is a major public health problem. Endothelial dysfunction represents an important mechanism in the development and progression of atherosclerosis, in part attributable to inflammation, platelet and smooth muscle activation, and arterial stiffening. The aim of this study was to explore the impact of lower limb revascularization on endothelial function in patients with PAD. We performed a comprehensive search of the academic literature using the PubMed and Embase databases to screen suitable records. Following the application of our search strategies, a total of eight studies were included in this review. Despite the limited available evidence, the dearth of academic literature suggests that revascularization has a positive effect on endothelial functioning. The effects of endovascular revascularization on endothelial functioning in patients with PAD are subject to further research.*

**Key words:** peripheral artery disease; endothelial function; endovascular therapy; systematic review

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## Introduction

Atherosclerotic peripheral arterial disease (PAD) is a major public health concern that affects more than 200 million people worldwide [1]. The estimated lifetime prevalence of PAD is 19%, 22%, and 30% in White, Hispanic, and Black populations, respectively [2, 3]. In 3–4% of patients, amputation is inevitable [1].

Endothelial dysfunction represents the key pathophysiological event in the development and progression of atherosclerosis [4] due to inflammation, platelet, and smooth muscle activation, and arterial wall stiffening.

Several diagnostic tools for peripheral atherosclerosis have been developed, including the use of markers for endothelial dysfunction. These include flow-mediated dilatation (FMD), the reactive-hypere-

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mia index (RHI), and arterial pulse waveform analysis (aPWA) [5, 6]. The majority of patients with clinically symptomatic lower limb atherosclerosis are now treated with percutaneous transluminal angioplasty (PTA), which normalizes blood flow and might have a beneficial effect on endothelial functioning. In turn, better endothelial functioning is associated with faster peripheral perfusion recovery after exercise in patients with intermittent claudication and slower progression of new atherosclerotic lesions [7].

The role of endothelial dysfunction in the pathogenesis of PAD is well-known. In contrast, the effect of angioplasty on endothelial function is less clear. In addition, very few studies have included patients with atherosclerotic lower limb ischemia [8–14]. The goal of this systematic review was to appraise the effects of angioplasty on endothelial functioning in patients with PAD.

## Material and methods

### Data sources and search strategy

This systematic review was conducted in compliance with the PRISMA guidelines [15]. A comprehensive literature search was undertaken using PubMed and Embase databases. The search strategy included three domains of MeSH terms and keywords combined using “AND,” whereas each domain was created using “OR.” The first domain contained terms related to endovascular treatment; the second contained terms related to vascular disease; and the third contained terms related to the definition of PAD. Search results were then imported into Mendeley (mendeley.com) for the selection of appropriate studies and removal of duplicates. All databases were systematically searched by six independent researchers using identical search terms. Eligible studies were screened based on titles and abstracts in accordance with the inclusion and exclusion criteria. Full-text articles were then obtained and screened. Investigators independently examined all studies to decide on which ones to include in this review. Any discrepancies were resolved via consensus.

### Study eligibility

We included case-control and cohort studies that prospectively or retrospectively analyzed patients with lower extremity PAD. Lower extremity involvement was confirmed based either on an ankle-brachial index (ABI) below 0.90, or patients having undergone interventions for this condition as indicated in their medical records. Furthermore, only studies that investigated the influence of endovascular procedures on endothelial function were included.

### Data extraction

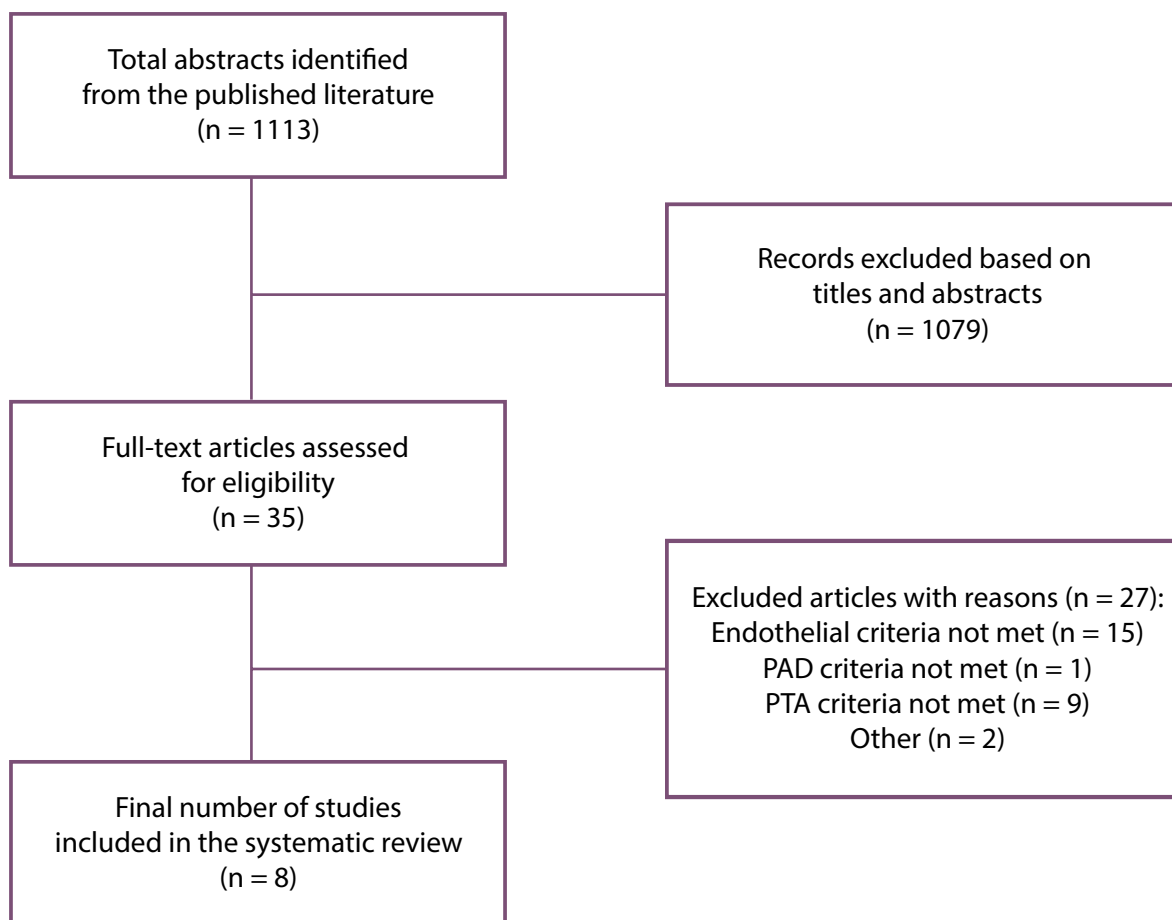
Six authors were divided into three groups; extracted studies were also divided into three groups. Each group of studies was independently assessed by two authors, who performed the literature search, selected the studies, extracted the data, and assessed the quality of the studies. Data were systematically extracted from the full-text articles. Multiple studies based on the same sample, or duplicate publications of the same study, were also checked for additional data. The following data were categorized: first author name, publication year, location of investigation, study design, and population (total number of patients, age, sex, illness progression, type of endovascular equipment used, duration of follow-up, study outcome, results, and conclusions).

## Results

The full search identified 1113 hits, of which 1078 were excluded after the title and abstract inspection. The remaining 35 articles were screened by full-text inspection, leading to the exclusion of another 27 articles (Fig. 1). The remaining eight articles were analyzed, as summarized in Table 1. Among these studies, one was published in 2005, one was published in 2008, and the remaining six were published between 2010 and 2020. In total, three studies originated from Switzerland, two studies originated from Poland, one study originated from the United States of America, one study from Finland, and one study from Austria. Seven studies had a case-control study design, of which all were retrospectively analyzed. One study was conducted as a prospective, randomized controlled trial.

### Patient characteristics

A total of 466 PAD patients were enrolled across all studies included in this review, with an average age ranging between  $63.5 \pm 9.03$  and  $71.5 \pm 8.5$  years. In total, 395 patients were classified as claudicants, while 68 patients had chronic limb-threatening ischemia. Endothelial function was analyzed in most of the studies based on FMD, RHI, and intima-media thickness (IMT). In two studies, the analysis was based only on arterial stiffness parameters [10, 11]. Endovascular procedures in all studies included the use of balloon catheters and stents when indicated. One study [12] compared the DCB (Drug-Coated Balloon) to POBA (Percutaneous Old Balloon Angioplasty). The results of PTA were analyzed based on the occurrence of restenosis (i.e. a decrease in lumen diameter to less than 50% based on Doppler ultrasound), pain-free walking distance (PFWD), maximal walking distance (MWD), Rutherford scale, ABI (ankle-brachial index — change at least by



**Figure 1.** PRISMA flow chart

0.1) and TBI (toe-brachial index — change at least by 0.1). The duration of the follow-up period length ranged between 30 days and 12 months.

### Flow-mediated dilatation

Of the eight studies, four compared FMD before and after PTA, as summarized in Table 2. Hafner and colleagues [9] measured FMD at baseline ( $3.53 \pm 3.56\%$ ). They compared FMD in patients with and without restenosis. No baseline differences in FMD were found between patients with and without restenosis ( $3.55 \pm 3.64\%$  vs.  $3.52 \pm 3.48\%$ ;  $p = 0.716$ ). There was however no significant change in FMD from baseline to 12-month follow-up ( $3.34 \pm 4.18\%$ ,  $p = 0.710$ ) [9]. Kaczmarczyk et al. [14] found significant, but transient, improvements in FMD after PTA, with a subsequent drop in FMD over a 6-month follow-up period ( $4.1 \pm 2.9\%$  at baseline vs.  $4.88 \pm 2.9\%$  at 1 month vs.  $3.4 \pm 2.5\%$  at 6 months,  $p = 0.04$ ). Husmann et al. [16] measured FMD in patients undergoing PTA compared to those treated conservatively. The authors found a significant increase in FMD after PTA compared to baseline ( $4.96 \pm 1.86\%$  at baseline vs.

$6.44 \pm 2.88\%$  at 1 month,  $p = 0.02$ ). Pawlaczyk and colleagues [8] measured FMD in three patient groups: those treated with PTA, those who underwent bypass, and those treated with exercise only. They reported a significant improvement in FMD in the PTA group over the course of the study ( $3.88 \pm 1.92\%$  at baseline vs.  $6.69 \pm 2.23\%$  after 3 months,  $p < 0.01$ ).

### Reactive-hyperemia index

Two studies [12, 14] included in this review primarily compared RHI values before and after PTA, as summarized in Table 2. Shafe et al. [12] measured RHI after endovascular revascularization in two groups of patients: DCB-treated patients and POBA with stenting-treated patients. There was a significant increase in the RHI after revascularization compared with values before revascularization, whereas the RHI did not change significantly during the 90-day follow-up period ( $1.43 \pm 0.20$  before revascularization,  $1.58 \pm 0.21$  after revascularization, and  $1.57 \pm 0.22$  during the follow-up,  $p < 0.01$ ). Kaczmarczyk and colleagues proved no change in RHI values related to PTA ( $1.7 \pm$

0.7 before PTA vs.  $1.7 \pm 0.9$  after 1 month vs  $1.6 \pm 0.5$  after 6 months of follow-up,  $p = 0.62$ ) [14].

### Intima-media thickness

In total, three studies examined the relationship between PTA and its effects on restenosis using IMT values, as summarized in Table 2. Hafner et al. [9] compared IMT between patients with and without restenosis [9]. The authors found a trend towards a lower IMT in the patient group without restenosis

( $0.277 \text{ mm} \pm 0.138 \text{ mm}$ ) compared to the group with restenosis ( $0.314 \pm 0.145 \text{ mm}$ ), although this was not statistically significant. Using a cut-off level of 0.21 mm for IMT, a statistically significant association between increased IMT and restenosis was however evident ( $p = 0.009$ ). Kaczmarczyk et al. [14] found that baseline IMT decreased significantly six months after PTA administration ( $0.96 \pm 0.29 \text{ mm}$  before PTA vs.  $0.93 \pm 0.26 \text{ mm}$  after six months follow-up,  $p < 0.01$ ). There was however no relationship between IMT and re-

**Table 1.** Summary of included studies

Author [year]	Country	Study type	Participants	Inclusion criteria	Exclusion criteria	PAD diagnostic criteria	Intervention (number of patients)	Follow-up [months]	Parameters of endothelium
Hafner et al. 2010	Austria	Prospective study	128; CLI/non-CLI = 0/128	Intermittent claudication no history of revascularization procedures on the affected side	Acute myocardial infarction, unstable angina pectoris or stroke, uncontrolled hypertension, decompensated congestive heart failure, pregnancy, life expectancy lower than 1 year, contraindications for anticoagulation and/or antiplatelet therapy, wound infection	Symptoms, digital subtraction angiography	PTA (n = 128), Stent implantation (n = 28)	12	FMD NMD IMT
Husmann et al. 2008	Switzerland	Prospective open, randomized controlled trial	33; CLI/non-CLI = 0/33	Symptomatic PAOD (R2-3) due to femoropopliteal obstruction	History of lower limb or coronary revascularization, an acute ischemic event within the last 3 months, chronic inflammatory disorders, moderate or severe renal insufficiency, severe liver disease, incompressible tibial arteries, persistent claudication after angioplasty	Clinical examination, ABI, color duplex sonography	PTA (n=17); Conservative treatment (n=16)	1	FMD
Jacomella et al. 2013	Switzerland	A prospective, non-randomized, controlled trial	61; CLI/non-CLI = 0/61	Symptomatic PAD (R2-3) $\geq 6$ months without improvement during non-supervised walking exercise and substantial limitation in walking capacity affecting patient's quality of life	R4-6, cardiac arrhythmia, chronic inflammatory vascular disorders, failed revascularisation defined as more than 50% residual stenosis after the procedure	Symptoms	PTA (n = 61)	3	Alx
Kaczmarczyk et al. 2020	Poland	Prospective study	72; CLI/non-CLI = 30/40	CLI, stable PAD (R2,3)	End-stage kidney disease, age $> 85$ years, pain related to limb ischemia not allowing to obtain a horizontal position, patients with incompressible tibial arteries	Clinical examination, ABI, TBI, color duplex sonography, angiography	PTA (n = 72), stent implantation if necessary	12	FMD RHI, IMT, aPWA

Author [year]	Country	Study type	Participants	Inclusion criteria	Exclusion criteria	PAD diagnostic criteria	Intervention (number of patients)	Follow-up [months]	Parameters of endothelium
Pawlaczyk et al. 2016	Poland	a prospective, non-randomized study	79; CLI/non-CLI = 0/79	Symptomatic PAD, R3, patency of the popliteal artery along with at least 2 of 3 arteries in the ischemic limb, full arterial patency within the non-affected lower extremity	Previous vascular surgery, angioedema, true or dissecting aneurysms of any artery, cancer, neurological disorders, inflammatory disorders, allergies, chronic venous insufficiency, kidney failure requiring RRT, neurogenic diabetic ulcers, poorly controlled or untreated arterial hypertension, extensive skin lesions, current use of phlebotropic agents, steroids or immunosuppressants	duplex Doppler ultrasound, Angio CT, ABI	PTA with stenting (n = 30); bypass (n = 29); treadmill training (n = 20)	3	FMD NMD
Peltokangas et al. 2018	Finland	Prospective study	24; CLI/non-CLI = 0/24	ABI < 0.9 or ABI > 1.3, symptomatic PAD, stenosis in SFA based on MRI angiography, planned PTA of the SFA	Pacemaker, risk of treatment interference by participation in the trial	Symptoms, ABI < 0.9 or ABI > 1.3, MRI angiography	PTA of the SFA (n = 24; 26 limbs)	1	Pulse wave analysis
Shafe et al. 2020	Iran, USA	A prospective, non-randomized study	86; CLI/non-CLI = 49/37	Symptomatic PAD (R2-5), R2-3 with symptoms > 3 months (with conservative treatment); ABI < 0.9; TBI < 0.7	Thrombotic lesions, lesions only within BTK segments, access via the upper limb	Symptoms, ABI < 0.9; TBI < 0.7	DCB (n = 46); POBA with stent implantation (n = 40)	3	RHI
van der Loo et al. 2005	Switzerland	Prospective study	29; CLI/non-CLI = 1/28	Planned femoropopliteal PTA (Fontaine stages II–IV)	Non-atherosclerotic diseases, bypass graft lesions, concomitant stent implantation, patients in whom the procedure was primarily not successful, history of carotid thrombendarterectomy, carotid stenting or carotid stenosis > 50%	Angiography, duplex ultrasonography	Femoro-popliteal PTA (n = 29)	6	IMT wall shear stress

nosis after the 12-month follow-up period. Van der Loo et al. [13] evaluated the relationships between PTA and restenosis with IMT. The authors found no relationship between the occurrence of restenosis and baseline IMT (IMT 0.89 mm [0.77–1.03 mm]) without restenosis vs. 0.86 mm (0.81–0.90 mm) with restenosis).

### Studies assessing arterial stiffness parameters

In total, three studies included in this review examined the influence of PTA on arterial stiffness [10, 11, 14]. Peltokangas et al. [11] found that PTA causes

only small, non-significant changes to PW-derived parameters for the treated limb immediately after treatment [11]. However, changes in amplitude ratios, time differences, and area ratios for the treated lower limb reached statistical significance between the follow-up visit and post-treatment state, as well as between the pre-treatment and follow-up visit. Jacomella and colleagues [10] compared arterial stiffness parameters between patients treated with PTA and those managed conservatively [10]. Their study found that revascularization was associated with a significant reduction in

**Table 2.** Comparison of parameters of endothelial functions before and after PTA

	References	Number of patients	Follow-up [months]	Before PTA [mean ± SD]	After PTA [mean ± SD]	p-value	
FMD (%)	Hafner 2010	128	12	3.53 ± 3.56	3.34 ± 4.18	0.710	No differences
	Husmann 2008	17	1	4.96 ± 1.86	6.44 ± 2.88	0.02	↑
	Kaczmarczyk 2020	72	6	4.1 ± 2.9	3.4 ± 2.5	0.04	↓
	Pawlaczyk 2016	30	3	3.88 ± 1.92	6.69 ± 2.23	< 0,01	↑
PW-derived parameters	Jacomella 2013*	61	3	31.5 ± 1.1	28.8 ± 1.1	0.01	↓
	Kaczmarczyk 2020**	72	6	67.4 ± 12.9	65.6 ± 15.6	0.8	No differences
	Peltokangas 2018***	24	1	0.52 (0.45–0.57)#	0.34 (0.27–0.44)#	< 0,001	↓
RHI	Kaczmarczyk 2020	72	6	1.7 ± 0.7	1.6 ± 0.5	0.62	No differences
	Shafe 2020	86	3	1.43 ± 0.2	1.58 ± 0.21	0.0001	↑
IMT [mm]	Hafner 2010	128	12	No restenosis group 0.256 ± 0.133 Restenosis group 0.326 ± 0.134	NA		
	Kaczmarczyk 2020	72	6	0.96 ± 0.29	0.93 ± 0.26	0.006	↓
	van der Loo 2005	29	6	No restenosis group 0.90 (0.85–0.97)# Restenosis group 0.89 (0.84–0.93)#	No restenosis group 0.89 (0.77–1.03)# Restenosis group 0.86 (0.81–0.90)#		No differences  No differences

\*Augmentation Index

\*\*Pulse pressure

\*\*\*Ratio of the amplitude of diastolic wave B and the systolic maximum

#Data given as medians (interquartilranges)

FMD — Flow-Mediated Dilatation; PW — Pulse Wave; RHI — Reactive Hyperaemia Index; C-IMT — Carotid Intima-Media Thickness; B-IMT — Brachial Intima-Media Thickness; Alx — Aortic Augmentation Index

Alx (Augmentation Index) from  $31.5 \pm 1.1$  to  $28.8 \pm 1.1$  after 3 months ( $p = 0.01$ ). In contrast, there was no significant change in Alx in the conservatively treated group from baseline to follow-up ( $29.9 \pm 1.1$  to  $29.9 \pm 1.1$ ,  $p = 0.83$ ). Kaczmarczyk et al. [14] showed that most of the measured arterial stiffness parameters (pulse pressure, augmentation index, central augmentation index, central augmentation pressure, and central augmentation index-HR75) decreased after PTA, and showed a consistent decrease at the 6-month follow-up, although this was not statistically significant [14]. Other parameters, like ejection duration, subendocardial viability ratio [SEVR], stiffness index, and reflection index, showed a non-significant decrease after PTA. However, all measures except SEVR increased from baseline during the 6-month follow-up.

## Discussion

The aim of our study was to determine whether endovascular procedures, the most frequent method of revascularization, improve endothelial function in patients with PAD.

Endothelial dysfunction plays a key role in the pathophysiology of atherosclerosis and contributes to an increased risk of developing lower limb ischemia [17, 18] as well as other adverse cardiovascular sequelae [19]. Heiss et al. [19] called endothelial function a “barometer” for cardiovascular health, and suggested it could be a useful tool for assessing the effectiveness of novel treatment strategies. Multiple comorbidities in PAD patients, including obesity, hypercholesterolemia, hypertension, and diabetes, might in fact be related to endothelial dysfunction. All efforts focused on the im-



provement of endothelial parameters should therefore benefit patients by reducing overall cardiovascular risk.

Endothelial dysfunction disrupts the balance between vasodilation and vasoconstriction. Nitric oxide (NO) is a potent vasodilator and decreased NO bioavailability in PAD patients is strongly correlated with poor FMD [19]. The use of brachial artery FMD has been reported since 1992. It is now the most common method used to assess endothelial functioning in clinical research [20]. Several other non-invasive tests have since been developed in order to assess endothelial function. In 2002, reactive hyperemia-peripheral arterial tonometry (RH-PAT) was first described as a method for assessing peripheral vascular endothelial function. The use of RHI since then has increased rapidly [21].

FMD assesses the endothelial response to shear stress in the brachial artery as a result of hyperemia, whereas RHI corresponds to actual hyperemia. The Framingham Heart Study reported no statistically significant relationships between signals obtained using RH-PAT compared to FMD, suggesting that they reflect distinct aspects of vascular function [22]. Several studies have investigated the relationship between cardiovascular events and endothelial function. Nonetheless, the number of studies comparing FMD and RHI as predictors of adverse cardiovascular events is limited [23–25]. In a systematic review and meta-analysis, Matsuzawa et al. [26] found that both FMD and RHI have significant value in the prediction of future cardiovascular events after adjustment for other risk factors.

Carotid-femoral pulse wave velocity (cf-PWV) is another non-invasive method used to assess endothelial function and is considered the gold standard for estimating regional arterial stiffness. Arterial stiffening increases systolic and pulse pressure, promotes left ventricular hypertrophy and dysfunction, and impairs the capacity for myocardial perfusion [27]. It is an independent predictor of all-cause and cardiovascular mortality in PAD patients [28]. Indeed, arterial stiffening is associated with most cardiovascular disease endpoints, including heart disease, stroke, and chronic kidney disease. The studies included in this review suggest that revascularization might have a positive effect on endothelial function; however, this topic remains unclear, due to a small number of available studies.

Hafner et al. [9] found no significant effect for FMD as a predictor of restenosis 12 months after PTA treatment. The authors however suggested that the selective enrolment of participants with advanced PAD might have affected their results. In contrast, three studies [8, 14, 16] revealed significant improvement in FMD one to three months after successful revascularization. Kaczmarczyk and co-workers [14] also described the transience of this effect, with a significant decrease in

FMD evident after six months [14]. Husmann et al. [16] described the beneficial effects of endovascular revascularization, which restored blood flow and increased tissue perfusion, in turn making walking training possible [16].

Studies included in this review that examined the RHI did not provide cohesive data. Shafe and colleagues [12] compared RHI measured before and after drug-coated balloons angioplasty and bare-metal stent placement. Improvements in RHI persisted for at least 3 months, irrespective of which intervention was used. In contrast, Kaczmarczyk et al. [14] reported a decrease in RHI directly after PTA and six months later, however, results were not statistically significant. Three studies included in our review [10, 11, 14] assessed the influence of PTA on arterial stiffness parameters, of which two showed a favorable effect on endothelial function. However, Kaczmarczyk et al. [14] found no effect of PTA on arterial stiffness parameters.

In a recent systematic review conducted by Normahani and colleagues [29], the authors evaluated the effect of lower limb revascularization on endothelial function. Their review focused on the impact of revascularization as a whole (surgical and endothelial) on various vascular measures, including perfusion (assessed using laser Doppler method, transcutaneous pressure of oxygen [TcPO<sub>2</sub>], and heat washout technique), flow (evaluated using ABI) and finally endothelial function (evaluated by using FMD, endothelin (ET)-1, NO concentrations, plasma soluble intercellular adhesion molecules (sICAMs), soluble vascular adhesion molecules (sVCAMs), C-reactive protein (CRP), lymphocyte CD11a/CD18, and neutrophil CD11b/CD18, among others) [29].

We however limited our focus to endovascular treatment and restricted our review to the most reliable markers of endothelial function. This approach simplified the review process and allowed the core message to be highlighted.

## Conclusions

In conclusion, findings from this review suggest that revascularization might have a positive effect on endothelium function in patients with PAD. Further investigations focused on the assessment of endothelial function after endovascular revascularization might have therapeutic implications. Further research is needed to develop new methods of revascularization and materials used during this procedure which might have a positive and permanent effect on endothelial function.

## Conflict of interests

None.

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