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The Effect of Lower Limb Revascularization on Flow, Perfusion, and Systemic Endothelial Function: A Systematic Review

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Abstract

Peripheral arterial disease (PAD) is associated with reduced lower limb blood flow and tissue perfusion. The consequent reduction in vessel wall shear stress as well as ischemia–reperfusion injury has also been associated with systemic endothelial dysfunction and inflammation. We aimed to explore the impact of lower limb revascularization on (1) lower limb blood flow, (2) tissue perfusion, and (3) systemic endothelial function. We performed a systematic literature search using the MEDLINE, Embase, and Web of Science databases. Eligible studies measured changes in lower limb blood flow, perfusion, or systemic endothelial function following revascularization for the treatment of symptomatic PAD. We found 19 eligible studies, which were limited by considerable heterogeneity. Current evidence suggests that revascularization has a positive effect on flow, perfusion, and systemic endothelial dysfunction. Any changes may take a number of weeks to become apparent. There is a need for well-designed studies to explore the association between flow, perfusion, and endothelial dysfunction.

Keywords

systemic endothelial function, flow, perfusion, revascularization, peripheral arterial disease

Introduction

Peripheral arterial disease (PAD) is a chronic atherosclerotic process that causes narrowing or occlusion of peripheral arteries, particularly in the lower limbs.[1] Although the majority of patients remain asymptomatic, symptomatic progression often manifests as intermittent claudication (IC) or, in severe cases, chronic limb-threatening ischemia (CLTI).[2] Chronic limb-threatening ischemia is associated with a particularly poor prognosis, with an estimated annual amputation and mortality rate of 12% and 25%, respectively.[3] Much of the associated mortality risk associated with PAD is attributable to the increased risk of myocardial infarction and stroke, for which PAD is an independent risk factor.[4,5]

The management for PAD is multimodal. Conservative treatment centers around the optimization of cardiovascular (CV) risk factors. Patients with short distance claudication or CLTI are offered open or endovascular revascularization, with the aim of improving blood flow and tissue perfusion, in order to prevent limb loss and improve symptomatology. Observational studies have demonstrated higher healing rates in patients with CLTI and tissue loss undergoing revascularization as compared with those undergoing conservative management.[6] Additionally, PAD is associated with systemic endothelial dysfunction and inflammation, which can accelerate existing CV disease.[7-10] This is thought to be the result of reduced vessel wall shear stress and repeated ischemia–reperfusion injury.[11] Therefore, it is postulated that achieving improvements in flow and perfusion with revascularization may improve systemic endothelial function and also lead to a wider protective effect to the CV system.[8]

Flow, perfusion, and systemic endothelial function may well be closely related. However, this is a relatively recent concept with little evidence supporting it. In order to effectively investigate this association in future studies, we must first better understand the effect of revascularization on each of these parameters. Therefore, the aim of this systematic review is to explore the impact of revascularization on (1) lower limb blood flow, (2) tissue perfusion, and (3) systemic endothelial function.

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Methods

Eligibility Criteria

Observational studies of patients undergoing revascularization for CLTI or claudication in which lower limb flow, tissue perfusion, or systemic endothelial function were measured. All eligible studies were included. Conference abstracts, protocol papers, and studies involving animals were excluded.

Search

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations, an electronic database search was conducted using MEDLINE, Embase, and Web of Science to include articles from January 1, 1956, to November 30, 2019, written in English. Reference lists were examined from the retrieved full-text articles. In our search strategy, we used the following key terms: "lower limb," "bypass," "angioplasty," "revascularization," "haemodynamics," "perfusion," "pressure," "flow," "velocity," "microcirculation," and "endothelial function." Search results were then imported into Covidence (Covidence.org) for duplicate removal and study selection. Titles and abstracts were independently reviewed by 2 investigators (S.K. and P.N.). Full-text articles were then reviewed, and data collected on the methods, participants, intervention, outcomes, and findings. Disagreements were resolved through discussion between all the authors.

Outcomes

We collected data relating to changes in lower limb blood flow, perfusion, or systemic endothelial function following revascularization. No specific limitation was set on the surrogate measures for these outcomes of interest. For the purpose of this review, surrogates of flow were defined as any measure (direct or indirect) of lower limb macrovascular blood flow. Surrogates of perfusion were defined as any measure of lower limb tissue perfusion or microvascular function. Accepted measures of systemic endothelial function included biochemical markers of inflammation and endothelial function as well as brachial flow-mediated dilatation (FMD).

Results

Our initial search identified 4642 papers. Of these, 63 publications were selected for full-text review based on their title and abstract (Figure 1). A full-text screening resulted in the final selection of 19 studies; 13 of these studies reported the effect of revascularization on flow (Table 1), 9 articles reported tissue perfusion measurements (Table 2), and 5 articles reported on systemic endothelial function (Table 3). Key findings are presented in Figure 2.

Description of Studies

Only 1 study was a randomized controlled trial.[11] Of the remaining studies, 15 were prospective and 3 were retrospective. Sample sizes ranged from 9 to 85, with a total number of 707 participants across all studies. A total of 697 limbs underwent endovascular or open bypass revascularization, and 86 participants participated as controls in 5 studies (angiography [n = 31], exercise treatment [n = 16], best medical therapy [n = 20], and healthy volunteers [n = 12]). A total of 261 patients with IC and 375 patients with CLTI were included across the studies. A total of 316 (43.8%) patients had diabetes mellitus (DM) and 4 studies recruited only patients with DM. Studies that included patients with DM and non-DM reported separate results for each group. Mean age of patients in the included studies ranged between 47 and 94 years, with 65% men and 36% women. Study duration ranged from 14 days to 48 months.

Studies Assessing Flow

Thirteen studies reported ankle brachial pressure indices (ABPIs) after revascularization.[11,20,23,24,13,22,18,21,17,31] Nine of these studies reported significant improvement in initial ABPI.[20,22,18,21,17,12,14,16,19] Overall, success in improving flow was lower in patients with CLTI compared to patients with IC at 1 to 12 months follow-up; Savolainen et al[16] performed revascularization on 55 cases (26 CLTI and 21 IC) and reported a better outcome in patients with IC compared to patients with CLTI. Alback et al[19] reported 83% and 66% rate of hemodynamic success at 1-month follow-up in patients with IC and CLTI, respectively.

A randomized controlled trial compared percutaneous transluminal angioplasty (PTA) with best medical treatment in 17 patients with IC and reported significant increase in ABPI in the PTA group only (0.63-1.05; $P = .0004$).[15]

Borozan et al[23] observed a 72% initial ABPI improvement in 34% of patients with IC treated with PTA, followed by a significant deterioration of flow during the follow-up period. Continued hemodynamic success was maintained in 37%, and overall long-term success was 27% during a mean follow-up of 16 months. The average time to deterioration in ABPI following PTA was 14 months.

Flanigan et al[24] observed an immediate improvement in ABPI in only 62% of patients with IC treated with PTA, despite achieving 93% immediate anatomical success. Only 48% of patients maintained hemodynamic success during a mean follow-up duration of 9 months.

Pawlaczyk and colleagues[13] measured flow in 3 groups of patients: bypass (group 1, n = 30), PTA (group 2, n = 29), exercise only (group 3, n = 20). They reported a significant improvement in mean ABPI in groups 1 and 2 at 90 days post-procedure (mean ABPI: 0.57 and 0.59 in groups 1 and 2, respectively, improved to 0.75 in both groups; $P < .049$). No change in ABPI values was observed in the exercise group (group 3).

Studies Assessing Tissue Perfusion

We identified 8 studies that measured changes in perfusion after PTA and bypass in 162 patients (CLTI, n = 122; IC,

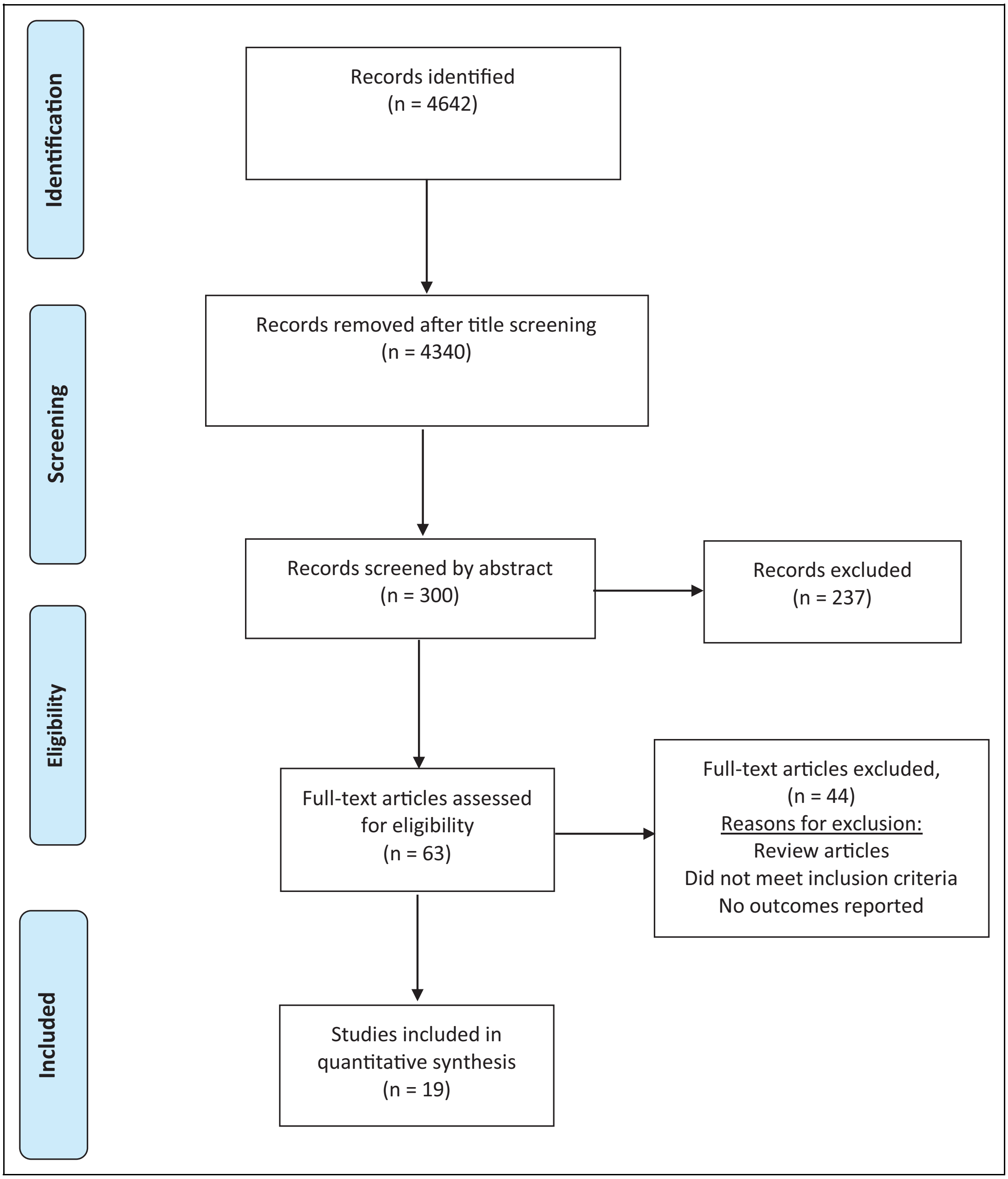

Figure 1. PRISMA systematic review flow diagram.

n = 40; DM, n = 85) using 3 different methods (laser Doppler method, transcutaneous pressure of oxygen [$TcPO_2$], and heat washout technique).[22,18,21,17,12,26,25,27] All 8 studies observed an improvement in perfusion when compared with preintervention measurements, regardless of the method of perfusion assessment. Kim et al[25] reported an increase in mean $TcPO_2$ from 12.7 $\pm$ 8.9 to 43.6 $\pm$ 24.1 mm Hg ($P < .01$) at 1 week post-PTA. Jacobs et al[21] reported an increase in mean $TcPO_2$ from 36 $\pm$ 14 to 59 $\pm$16 mm Hg at rest. They also demonstrated an increase in $TcPO_2$ in reactive hyperemia from 19 $\pm$ 15 to 58 $\pm$ 32 mm Hg post-op ($P < .001$).[21] Osmundson et al[22] provided separate results following open revascularization for patients with DM and non-DM with CLTI. In the DM group, mean $TcPO_2$ in the horizontal position improved from 15 to 50 mm Hg and mean $TcPO_2$ with the leg elevated improved from 4 to 40 mm Hg. In the non-DM group, the corresponding values were 23 to 60 and 5 to 47 mm Hg.

Wagner et al[18] demonstrated that improvements in perfusion may take as long as 6 weeks to manifest following endovascular revascularization (mean $TcPO_2$: prior to revascularization 32 mm Hg, at completion 34 mm Hg, 37 mm Hg 1 day following revascularization, and 45 mm Hg 6 weeks following revascularization). Saucy et al[17] (n = 10) reported a significant increase in skin blood flow (SBF) on the treated side 10 days post-bypass (hindfoot from 148 $\pm$ 58 to 203 $\pm$ 83 perfusion units [PU] and forefoot from 135 $\pm$ 67 to 202 $\pm$ 86 PU,

Table 1. Effect of Revascularization on Lower Limb Blood Flow.

Author, year	Design	Country	Participants	Measurement	Intervention	Results
Rother et al,[12] 2016	Prospective study	Germany	*n patients:30* *n limbs: 30* *IC/CLTI: 0/30* *DM/non-DM: 21/9*	ABPI	PTA: 30 patients	Mean ABPI from 0.50 to 0.94 (*P* < .001). Overall flow from 19.96 to 32.01 AU (*P* < .001).
Pawlaczyk et al,[13] 2016	Prospective nonrandomized study	Poland	*n patients:79* *n limbs: 79* *IC/CLTI: 0/79* *DM/non-DM: 18/61*	ABPI	Bypass: 29 PTA: 30 Supervised exercise: 20	Mean ABPI from 0.57 and 0.59 in bypass and PTA patients, respectively, improved to 0.75 after both interventions (*P* < .049). No change in ABPI values postexercise.
Zhan et al,[14] 2012	Retrospective study	The United States	*n patients:* 85 *n limbs:* 109 *IC/CLTI:* 0/85 DM/non-DM:85/0	ABPI	Bypass: 31 PTA: 78	Mean ABPI from 0.51 to 0.86 (*P* < .0001) in PTA group and 0.50 to 0.90 (*P* < .0001) in bypass group.
Husmann et al,[15] 2008	Prospective, open, randomized, controlled trial	Switzerland	*n patients:33* *n limbs: 33* *IC/CLTI: 33/0* *DM/non-DM: 4/29*	ABPI	PTA: 17 limbs Best medical treatment: 16 limbs	Mean ABPI from 0.63 to 1.05 (*P* = .0004) in PTA group. No change was observed in the best medical treatment group.
Savolainen et al,[16] 2007	Retrospective study	Switzerland	*n patients:* 55 *n limbs:* 55 *IC/CLTI:* 29/26 DM/non-DM: 19/36	ABPI	Profundaplasty: 55 limbs	Mean ABPI from 0.60 to 0.70 (*P* < .05).
Saucy et al,[17] 2006	Prospective study	Switzerland	*n patients:10* *n limbs: 10* *IC/CLTI: 0/10* *DM/non-DM: 3/7*	ABPI Duplex scan	Bypass: 10 limbs	Mean ABPI from 0.4 to 0.8 (*P* = .002).
Wagner et al,[18] 2003	Prospective controlled trial	Germany	*n patients:65* *n limbs: 34* *IC/CLTI: 15/19* *DM/non-DM: 15/19*	ABPI	PTA: 34 limbs	Mean ABPI from 0.59 to 0.82 (*P* < .05).
Alback et al,[19] 1998	Prospective observational study	Finland	*n patients:* 95 *n limbs:* 102 *IC/CLTI:* 52/50 DM/non-DM: 36/59	ABPI	PTA: 102 limbs	Mean ABPI from 0.32 to 0.88 in IC group and from 0.33 to 0.83 in CLTI group. Hemodynamic success rate was lower in patients with CLTI (64%) compared to patients with IC (74%) at 1 to 24 months follow-up.
Belkin et al,[20] 1992	Retrospective study	The United States	*n patients:* 9 *n limbs:* 9 *IC/CLTI:* 0/9 DM/non-DM: 7/2	ABPI	Bypass to isolated tibial artery segment (ITAS) Bypass to intact tibial artery Bypass to pedal artery	ITAS group: Mean ABPI from 0.26 to 0.75 (*P* = .0015). Bypass to intact tibial artery group: Mean ABPI from 0.26 to 0.98 (*P* = .0001). Pedal artery bypass group: Mean ABPI from 0.26 to 1.02 (*P* = .0005).
Jacobs et al,[21] 1990	Pilot study	Netherlands	*n patients:21* *n limbs: 21* *IC/CLTI: 12/9* *DM/non-DM: 3/18*	ABPI TP	Bypass: 21 limbs	Mean ABPI from 27% improved to 60% after surgery (*P* < .001).

(continued)

Table 1. (continued)

Author, year	Design	Country	Participants	Measurement	Intervention	Results
Osmundson et al,[22] 1988	Prospective observational study	The United States	*n patients:* 20 *n limbs:* 24 *IC/CLTI:* 3/18 DM/non-DM: 10/10	ABPI	Bypass: 24 limbs	Mean ABPI from 0.45 to 0.82 in DM subgroup, 0.48 to 0.81 in non-DM group.
Borozan et al,[23] 1985	Prospective observational study	The United States	*n patients:* 28 *n limbs:* 34 *IC/CLTI:* 18/16 DM/non-DM: NS	ABPI	PTA: 34 limbs	Success was defined as an increase in the ABPI $\geq$ 0.15 or normalization of the index ($\geq$0.90), measured at the closest level distal to the site of dilatation. Initial hemodynamic success observed in 16 (72.7%) of 22 iliac dilatations Long-term success was maintained in only 6 (27.6%).
Preston Flanigan et al,[24] 1982	Prospective observational study	The United States	*n patients:* 28 *n limbs:* 29 *IC/CLTI:* 18/11 DM/non-DM: NS	ABPI	PTA: 29	Initial hemodynamic success was observed in 62% of the procedures, which included 11 of 17 iliac, 6 of 7 superficial femoral, and 1 of 3 popliteal artery dilations (mean increase in ABPI was 0.25, 0.2, 0.23, respectively). Hemodynamic improvement was not observed in neither of the peroneal artery nor graft dilatations.

Abbreviations: ABPI, ankle-brachial pressure index; AU, arbitrary units; CLTI, chronic limb-threatening ischemia; DM, diabetes mellitus; IC, intermittent claudication; NS, not stated; PTA, percutaneous transluminal angioplasty; TP, toe pressure.

Table 2. Effect of Revascularization on Lower Limb Perfusion.

Author, year	Design	Country	Participants	Measurement	Intervention	Results
Rother et al,[12] 2016	Prospective study	Germany	*n patients:30* *n limbs: 30* *IC/CLTI: 0/30* *DM/non-DM: 21/9*	Combined LD and tissue spectrometry	PTA: 30 patients	Results of direct and indirect revascularization were similar, and relevance of angiosomes-targeted intervention on the level of microcirculation was not verified. Mean sO_2 from 45.73% to 62.39% ($P < .001$).
K m et al,[25] 2011	Pilot study	Korea	*n patients:23* *n limbs:29* *IC/CLTI: 0/29* *DM/non-DM: 23/0*	$TcPO_2$	PTA: 29 limbs	Mean $TcPO_2$ from 12.7 $\pm$ 8.9 mm Hg increased to 43.6 $\pm$ 24.1 mm Hg ($P < .01$) 1 week post-PTA.
Saucy et al,[17] 2006	Prospective study	Switzerland	*n patients:10* *n limbs: 10* *IC/CLTI: 0/10* *DM/non-DM: 3/7*	LDI TP	Bypass: 10 limbs	Skin blood flow in hindfoot increased from 148 $\pm$ 58 to 203 $\pm$ 83 PU and forefoot from 135 $\pm$ 67 to 202 $\pm$ 86 PU ($P = .001$) on the treated side. SBF in hindfoot decreased from 208 to 133 PU and the forefoot from 250 to 176 0.94 PU ($P = .001$) on the untreated side.
Wagner et al,[18] 2003	Prospective controlled trial	Germany	*n patients:65* *n limbs: 34* *IC/CLTI: 15/19* *DM/non-DM: 15/19*	$TcPO_2$	PTA: 34 limbs	Mean $TcPO_2$ from 32 to 34, 37, and 45 mm Hg, immediately, at 1 day, and at 6 weeks post-PTA, respectively.
Arora et al,[26] 2002	Prospective Controlled trial	The United States	*n patients:47* *n limbs: 13* *IC/CLTI: 0/13* *DM/non-DM: 35/12*	LDI	Bypass: 13 patients with diabetes with CLTI and neuropathy	Response to heat from 289% increased to 427%; response to acetylcholine increased from 6% to 26%, measured in volts ($P < .05$). After surgery, DI group vs D and C groups ($P < .0001$).
Midttun et al,[27]1999	Prospective open study	Denmark	*n patients:11* *n limbs: 11* *IC/CLTI: 11/0* *DM/non-DM: 0/11*	Heat washout method to measure blood flow rate	Bypass: 10 limbs PTA: 1 limb	Before bypass blood flow rate (ratio of 50 cm down/heart level) was 31.7 (27.9/46.1) mL/100 g/min at heart level which increased by a factor of 1.79 (1.50/1.87) when the toe was lowered to 50 cm below heart level, 57.0 (50.1/73.8) mL/100 g/min. After reconstruction, resting blood flow rate at heart level was 51.8 (47.2/94.8) mL/100 g/min, and at 50 cm down blood flow rate was 65.6 (49.1/74.0) mL/100 g/min. The ratio of 50 cm down/heart level was 0.93 (0.77/1.52).
Jacobs et al,[21] 1990	Pilot study	Netherlands	*n patients:21* *n limbs: 21* *IC/CLTI: 12/9* *DM/non-DM: 3/18*	$TcPO_2$ Intravital capillary microscopy	Bypass: 21 limbs	Mean $TcPO_2$ before revascularization was 36 $\pm$ 14 and increased to 59 $\pm$ 16 mm Hg at rest and at reactive hyperemia from 19 $\pm$ 15 to 58 $\pm$ 32 mm Hg post-op ($P < .001$).
Osmundson et al,[22] 1988	Prospective observational study	The United States	*n patients:* 20 *n limbs:* 24 *IC/CLTI:* 3/18 DM/non-DM: 10/10	$TcPO_2$	Bypass: 24 limbs	DM group: Mean $TcPO_2$ in horizontal position improved from 15 to 50 mm Hg and with leg elevated, from 4 to 40 mm Hg. Non-DM group: Mean $TcPO_2$ in horizontal position improved from 23 to 60 mm Hg, and with leg elevated from 5 to 47 mm Hg following revascularization.

Abbreviations: CLTI, chronic limb-threatening ischemia; DM, diabetes mellitus; IC, intermittent claudication; LD, laser Doppler; LDI, laser Doppler imaging; PU, perfusion units; PTA, percutaneous transluminal angioplasty; SBF, skin blood flow; sO_2, oxygen saturation; $TcPO_2$, transcutaneous pressure of oxygen; TP, toe pressure.

Table 3. Effect of Revascularization on Systemic Endothelial Function.

Author, year	Design	Country	Participants	Measurement	Intervention	Results
Pawlaczyk et al,[13] 2016	Prospective non-randomized study	Poland	*n patients:79* *n limbs: 79* *IC/CLTI: 0/79* *DM/non-DM: 18/61*	FMD NMD SBF	Bypass: 29 PTA: 30 Supervised exercise: 20	Mean FMD improved from 3.88% to 6.69% ($P < .01$) post-bypass and 4.27% to 4.8% ($P = .049$) post-PTA No change in FMD values in the supervised exercise group.
Unal et al,[28] 2011	Prospective study	Turkey	*n patients:54* *n limbs: 54* *IC/CLTI: 54/0* *DM/non-DM: 18/36*	FMD Blood test (NO, IL-6, TNF-α, CRP)	Bypass: 54 limbs with fem-pop occlusion only.	Mean FMD 9.2% ± 2.1% to 16.2% ± 4.5% ($P < .01$). Serum concentrations of NO, IL-6, TNF-α, and CRP post-bypass is 36.5 ± 8.2 mg/mL, 43.9 ± 8.8 nmol/L, 13.3 ± 1.6 mg/mL, and 13.5 ± 1.8 mg/L, respectively ($P < .05$). NO and FMD correlation ($r_s = 0.588$; $P = .0001$).
Tsai et al,[29] 2009	Pilot study	Taiwan	*n patients:21* *n limbs: 21* *IC/CLTI: 0/21* *DM/non-DM: 21/0*	Blood test (NO, ET-1, CRP, CD11/CD18)	Bypass: 21 limbs	Mean ET-1 from 2.2 to 2.0 and 2.2 at 1 unit and 7 days post-bypass, respectively. Mean NO from 3.5 to 2.5 and 3.4 μmol/L. sICAM, sVCAM, and CRP were pre-bypass 1406.2 ± 839.7 ng/mL, 344.3 ± 121.8 ng/mL, and 53.4 ± 46.7 μg/mL; after 1 day 1415.9 ± 722.6, 332.3 ± 112.1, and 64.6 ± 54.9; at 7 days 1224.9 ± 632.8, 398.5 ± 126.9, and 48.3 ± 45.7, respectively. Expressions of lymphocyte CD11a/CD18 and neutrophil CD11b/CD18 were before bypass 48.2% ± 18.0% and 3.1% ± 2.0%, at 1 day 42.4% ± 12.0% and 2.9% ± 1.3%, at 7 days 43.5% ± 12.3% and 3.5% ± 1.1%, respectively.
Husmann et al,[15] 2008	Prospective, open, randomized, controlled trial	Switzerland	*n patients:33* *n limbs: 33* *IC/CLTI: 33/0* *DM/non-DM: 4/29*	FMD Blood test (WBC count, CRP, fibrinogen)	PTA: 17 limbs Best medical treatment: 16 limbs	Mean ABPI from 0.63 to 1.05 ($P = .0004$) in PTA group. Mean FMD 4.96 to 6.44% ($P = .02$). WBC and platelet count and inflammatory mediators 7.6 to 6.89 × 10^6/mL ($P = .03$) after PTA. No change was observed in these parameters in the best medical treatment group.
Danielsson et al,[30] 2006	Prospective study	Sweden	*n patients:21* *n limbs: 21* *IC/CLTI: 0/21* *DM/non-DM: 8/13*	Blood test (WBC, platelet, CD11b, CD18, ICAM-1, VCAM-1)	Bypass: 21 limbs	WBC and granulocyte count decreased in ulcer group, but no change in activation of WBC was observed. Decrease in sICAM-1 and increase in VCAM-1 were reported mostly in the ulcer group.

Abbreviations: CLTI, chronic limb-threatening ischemia; CRP, C-reactive protein; DM, diabetes mellitus; ET, plasma endothelin; FMD, flow-mediated dilatation; IC, intermittent claudication; IL-6, interleukin-6; NMD, nitroglycerin-mediated dilation; NO, nitric oxide; PTA, percutaneous transluminal angioplasty; SBF, skin blood flow; sICAM, soluble intercellular adhesion molecules; sVCAM, soluble vascular adhesion molecules; TNF-α, tumor necrosis factor α; WBC, white blood cell.

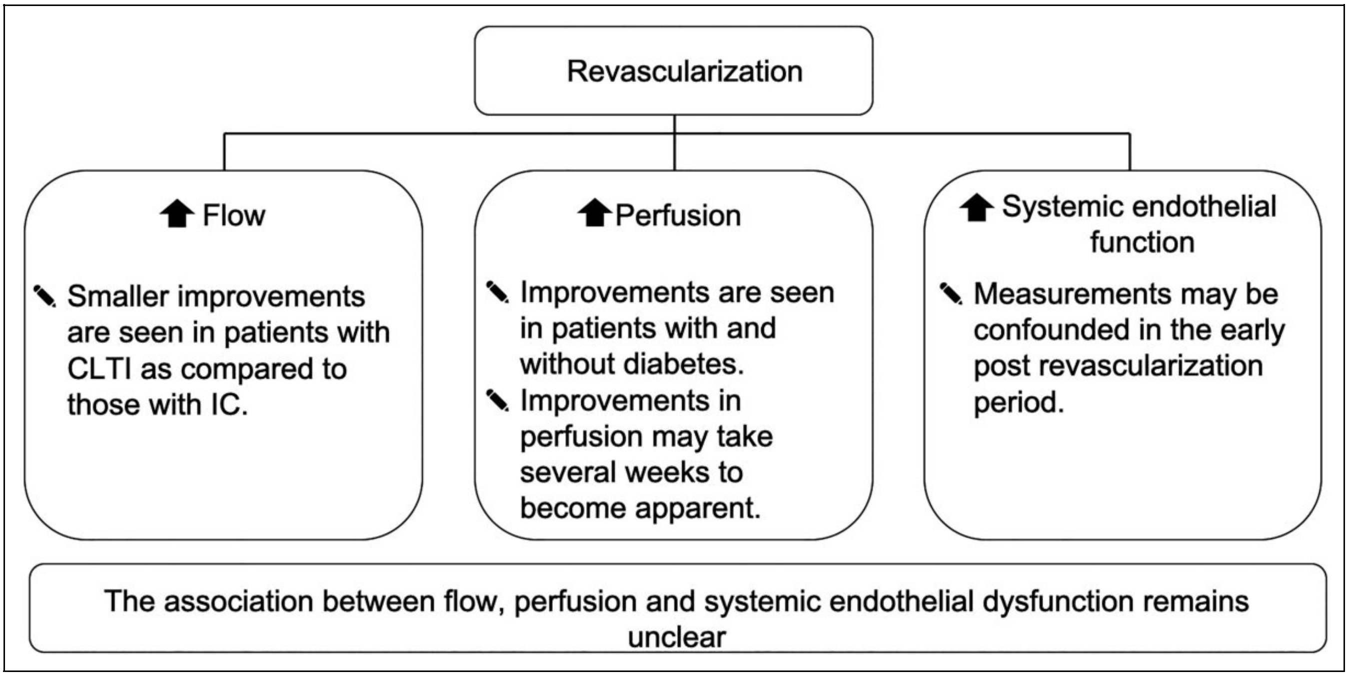

Figure 2. Summary of key findings. CLTI indicates chronic limb-threatening ischemia; IC, intermittent claudication.

$P = .001$). Interestingly, they observed a statistically significant decrease in SBF on the untreated side at 10 days postoperation (hindfoot from 208 to 133 PU and the forefoot from 250 to 176 0.94 PU, $P = .001$). No decrease in flow was observed on the untreated side. The mechanism behind the decrease in SBF was not clear. However, the authors hypothesized that it may be due to a neuromediated vasoconstriction of microvascular networks. In this study, the authors reported a significant increase in flow as measured by toe pressures ($P = .001$) on the treated side and demonstrated a good correlation between SBF and toe pressure (ie, perfusion and flow).

Rother et al[12] measured microcirculatory changes (using laser Doppler tissue spectrometry) continuously during and immediately following tibial PTA in 30 patients with CLTI (20 diagnosed with DM) at different angiosome regions of the index foot and reported a statistically significant increase in microcirculation in all patients with overall mean oxygen saturation (sO_2) improvement of 62.4%. They also compared directly and indirectly revascularized angiosomes and found no difference between the 2 groups in either flow or sO_2 parameters postintervention. This suggests that changes in tissue perfusion following revascularization are global and not restricted to angiosome-defined borders.

Arora et al[26] compared the post-bypass vasodilatory response (using laser Doppler imaging to measure vasodilation of the foot skin in response to heat and to iontophoresis of 1% acetylcholine and 1% sodium nitroprusside) in 13 patients with diabetic neuropathy and CLTI (group DI) with 3 different groups of patients who did not undergo revascularization (diabetic neuropathy without CLTI [group DN, n = 15], no neuropathy or ischemia [group D, n = 7], and healthy individuals [group C, n = 12]). The response post-bypass was considerably improved when compared with baseline measurements (response to heat: 289% increased to 427%; response to acetylcholine: 6% increased to 26%, measured in volts $P < .05$). However, the post-bypass response was comparable with the CLTI without neuropathy group and it was still significantly lower ($P < .0001$) when compared with no neuropathy and healthy groups despite a successful revascularization.

Studies Assessing Systemic Endothelial Function

Overall, 5 (165 limbs) studies reported the impact of revascularization on systemic endothelial function.[15,31,13,28-30] Tsai et al[29] investigated the effect of bypass surgery on plasma endothelin (ET)-1 and nitric oxide (NO) concentrations, plasma soluble intercellular adhesion molecules (sICAMs), soluble vascular adhesion molecules (sVCAMs), C-reactive protein (CRP), lymphocyte CD11a/CD18, and neutrophil CD11b/CD18 before and at 1 and 7 days postsurgery in 21 diabetic patients. They found no significant change in any of these parameters.

Danielsson et al[30] investigated the effect of revascularization on white blood cell (WBC) and platelet count, expression of CD11b/CD18 on granulocytes and monocytes, and CD41 on platelets and soluble endothelial markers (sICAM-1 and VCAM-1, soluble E-selectin and soluble P-selectin) 4 weeks following bypass. They found a decrease in WBCs and granulocyte counts 4 weeks postrevascularization in the subgroup of patients with ulcers and gangrene. They also noted a decrease in the endothelial marker ICAM-1 and increase in VCAM-1. No significant changes were seen in patients with rest pain, but no tissue loss (n = 8).

Three studies measured FMD to evaluate the effect of revascularization on systemic endothelial function. Flow-mediated dilatation is the expression of the change in diameter of brachial artery after a period of arm ischemia, which indicates the endothelial response to shear stress. Pawlaczyk and colleagues[13] measured FMD in 3 groups of patients ($n = 79$) with severe IC: bypass (group 1), PTA (group 2), and exercise only (group 3). They reported a significant improvement in FMD in groups 1 and 2, 90 days postprocedure (mean FMD: 3.88%-6.69%, $P < .01$; and 4.27%-4.8%, $P = .049$, respectively). No change in FMD values was observed in the exercise group (group 3).

Unal et al reported significant increase in FMD values in 54 patients with IC 4 weeks post-bypass (9.2% $\pm$ 2.1% to 16.2% $\pm$ 4.5%; $P < .01$) as well as considerable decrease in serum concentrations of interleukin-6, tumor necrosis factor α, and CRP post-bypass (36.5 $\pm$ 8.2 mg/mL, 43.9 $\pm$ 8.8 nmol/L, 13.3 $\pm$ 1.6 mg/mL, and 13.5 $\pm$ 1.8 mg/L, respectively, $P < .05$). They also reported significant positive correlation between FMD and serum NO ($r = 0.51$; $P = .0093$).[28]

A randomized controlled trial compared PTA with best medical treatment in 17 patients with IC and reported a significant increase in FMD (4.96%-6.44%; $P = .02$) and a statistically significant decrease in WBC (7.6-6.9 $\times 10^6$/mL; $P = .03$) at 4 weeks post-PTA revascularization.[15] No change was observed for CRP or fibrinogen. No change in these parameters was observed in the best medical treatment group.

Discussion

Currently, lower limb revascularization is performed to increase limb perfusion by improving flow. Peripheral arterial disease has also been strongly associated with systemic endothelial dysfunction and inflammation,[32,33] but the effect of revascularization on these parameters remains unclear. This is the first systematic review to explore the effect of revascularization on flow, perfusion, and systemic endothelial dysfunction.

The results from the limited number of studies in this review suggest that improvement in perfusion following revascularization is comparable when considering patients with and without DM.[22] Patients with DM and neuropathy are at highest risk of microcirculatory dysfunction.[34] However, Arora et al[26] suggest that foot perfusion and response to heat and acetylcholine can be significantly improved with revascularization in patients with diabetic neuropathy, although the response appears to be inferior to that for patients without DM and those with DM without neuropathy.

Included studies suggest that the likelihood of improving flow is lower in patients with CLTI compared to those with IC.[21,17] Reasons for this observation are likely multifactorial and may relate to the often multilevel and complex anatomy of disease in patients with CLTI and also the limitations in methods used to assess flow, such as the confounding effect of calcification on ABPI measurements.[35]

When considering PTA, anatomical success may not always translate into hemodynamic success. Flanigan et al[24] reported a 93% anatomical success but only 62% hemodynamic success immediately post-PTA. Clearly defined flow or perfusion end points may better translate to clinical benefit, although this remains to be investigated. Importantly, as observed in a number of studies in this review, improvements in perfusion may take weeks to become apparent.[23] Studies measuring systemic endothelial dysfunction using FMD were typically performed at least 4 weeks following revascularization. When considering systemic endothelial dysfunction following bypass surgery, measurements in the first few weeks may also be confounded by inflammation related to the operation. Additionally, patients may require hemodynamic support following the procedure, which may further confound measurements of flow, perfusion, and systemic endothelial dysfunction. This may offer an explanation for the conflicting results regarding the effect of revascularization on biochemical markers of systemic endothelial dysfunction. Although a number of studies found significant reductions in biochemical markers,[15,28,30] Tsai et al[29] only performed measurements 7 days following bypass surgery and did not observe such changes.

The magnitude of improvements in ABPI and FMD following revascularization seems to be equivocal for bypass and PTA.[13] However, there is paucity of long-term follow-up data regarding the effect of revascularization on flow, perfusion, and systemic endothelial dysfunction. The limited available evidence suggests that deterioration in flow parameters such as ABPI is common even in claudicants, with an average time to deterioration of approximately 14 months after revascularization.[23,24]

Although one study assessed the correlation between flow and perfusion,[13] none of the studies directly assessed the association between flow or perfusion with systemic endothelial dysfunction. Pawlaczyk et al and Husmann and colleagues did demonstrate improvements in flow and FMD but did not assess the correlation between them.[13,15]

One study suggested that improvements in systemic endothelial dysfunction measured with FMD are only observed in those with tissue loss.[30] However, other studies, assessing systemic endothelial dysfunction in patients with IC and CLTI, with and without tissue loss, noted improvements when measurements were taken a few weeks following revascularization.[31,13] There are a number of mechanisms that may be contributing to improvements in systemic endothelial function, including healing ulcers, increase in shear stress, and a reduction in inflammation secondary to a decrease in ischemia–reperfusion injury.[15] However, studies included in this review do not adequately investigate this hypothesis. Importantly, they lack direct measures of flow (eg, Duplex ultrasound and strain gauge plethysmography) and local endothelial function proximal and distal to the site of revascularization. Future studies should address these limitations in order to further our understanding of the association between flow, perfusion, and systemic endothelial function.

Limitations

There is a paucity of recent evidence on this topic as most studies were conducted over a decade ago. Studies were also limited by small sample size, short follow-up period, and significant heterogeneity in methodology including inclusion criteria, revascularization approach, outcome metrics, and measurement technique. The latter is particularly relevant to the assessment of FMD, which can only be reliably measured if standard protocols are followed. The included studies did not report FMD methodology in sufficient detail or reference up-to-date FMD assessment guidelines.[36] Additionally, none of the studies controlled for optimization of medical therapy such as initiation of statin therapy or level of physical activity, which may change postrevascularization due to improved IC and influence flow, perfusion, and systemic endothelial function measurements. Furthermore, none of the included studies provided a meaningful assessment of the association between flow, perfusion, and systemic endothelial function following revascularization.

Conclusion

Current evidence suggests that revascularization has a positive effect on flow, perfusion, and systemic endothelial dysfunction. There is a need for well-designed studies to explore the association between flow, perfusion, and systemic endothelial dysfunction.

Authors' Note

All authors contributed to (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Pasha Normahani and Sodabeh Khosravi are the first authors.

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