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Lipid apheresis and rheopheresis for treatment of peripheral arterial disease

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Abstract

Lipid apheresis is an effective lipid-lowering treatment in drug unresponsive severely hypercholesterolemic patients with coronary artery disease. It results in symptomatic improvement, reduces progression of coronary atherosclerosis, and decreases coronary event rates. These effects are partly caused by aggressive lipid lowering itself and partly by unselective removal of high molecular weight proteins leading to improved hemorheology. This review summarizes current available data on the proposed mechanisms by which lipid apheresis acts anti-atherosclerotic and improves ischemic symptoms. Based on this, it discusses the putative effects of lipid apheresis on restoring pathophysiological processes involved in the development of symptoms of peripheral arterial disease and critical limb ischemia. The available clinical experience with lipid apheresis and rheopheresis in treating patients with peripheral arterial disease is then critically reviewed and put into the context of currently available treatment options.

Keywords: Peripheral arterial disease; Critical limb ischemia; Diabetic foot syndrome; Lipid apheresis; Rheopheresis; Blood rheology

1. The clinical problem

Peripheral arterial occlusive disease (PAD) is mainly due to atherosclerotic obstruction of the major arteries of the lower extremities, and rarely the upper extremity. It is one manifestation of the systemic disease atherosclerosis, which also affects the coronary and cerebral vascular territory. The prognosis quoad vitam of patients with PAD is determined by their high risk of suffering coronary or cerebrovascular events. Cardiovascular mortality of patients with PAD is as high as cardiovascular mortality of patients who already suffered their first myocardial infarction [1]. Long-term prognosis of vascular surgery patients is even significantly worse than long-term prognosis of patients with coronary heart disease (CHD) [2]. The prognosis quoad extremitatem in patients with PAD is determined by the severity of the hemodynamic impairment of the affect leg. PAD patients who are either asymptomatic or experience symptoms of intermittent claudication with compensated peripheral hemodynamics at rest (Fontaine stages I and II) rarely progress to critical limb ischemia and finally amputation. In contrast, the affected extremity of patients presenting with critical limb ischemia (CLI), i.e. rest pain and/or ischemic ulcers or gangrene, and markedly reduced peripheral perfusion even at rest (Fontaine stages III and IV), is threatened by amputation if restoration of blood flow is not possible. Amputation significantly reduces quality of life, rarely allows continuation of living independent lives, and increases mortality in PAD patients [3].

Risk factors for PAD are the same as for CHD or cerebrovascular disease (CVD) and include age, male gender, cigarette smoking, arterial hypertension, diabetes, hypercholesterolemia and hyperhomocysteinemia [4]. In addition, elevated fibrinogen levels seem to contribute to the development of PAD and CLI [3].

Patients with diabetes and patients on chronic hemodialysis due to end-stage renal disease are especially prone to the development of PAD and CLI: diabetic patients have a four-fold increased risk for PAD and are more susceptible to CLI [5]. Diabetic foot syndrome is a frequent complication of long-standing type 2 diabetes, and usually due to a combination of macrovascular PAD, microvascular disease of the skin and muscle, and neuropathy. Diabetic foot ulcers are a major cause of hospital admittance for people with diabetes preceding 84% of all nontraumatic lower leg amputations in this growing population [6]. Furthermore, atherosclerotic vascular disease affecting peripheral arteries is a major cause of morbidity and mortality in patients

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undergoing hemodialysis [7], and is dramatically increased if there is coexistence of diabetes and end-stage renal disease. The amputation rate is close to 200 per 1,000 patient years for hemodialysis patients with diabetes [8].

Treatment of patients with PAD is first directed at controlling cardiovascular risk factors to reduce general cardiovascular risk. Improving symptoms in patients with intermittent claudication by exercise training, pharmacotherapy, and endovascular or surgical revascularization is aimed at improving quality of life. Revascularization, whenever feasible, is the treatment of choice in patients with CLI aimed at saving the limb threatened by amputation. Only half of patients with CLI, however, are suitable for revascularization due to technical reasons (i.e. distal or diffuse obstruction unsuitable for revascularization) or due to comorbidity not allowing complex surgical procedures [3]. Treatment with vasoactive prostaglandins or, more recently, gene therapy or stem cell therapy directed at stimulating angio- and/or arteriogenesis in the affected limb, may lead to temporary limb salvage in some patients. Despite ongoing improvement in endovascular or surgical techniques for revascularization and in conservative treatment options, one year after presentation with CLI only around one quarter of patients is alive without CLI, 30 percent of patients have lost a limb, 20 percent of patient live with continuing CLI, and 25 percent have died [3]. The prognosis is even worse in diabetic patients and in patients with end-stage renal disease [8].

There is urgent need for additional treatment options that are able to improve the prognosis of patients with CLI, both quoad vitam and quoad extremitatem.

2. Pathophysiology of ischemic lesions in critical limb ischemia and the diabetic foot syndrome

The pathophysiology of intermittent claudication and ischemic lesions in PAD, CLI and/or the diabetic foot syndrome is a combination of atherosclerotic obstruction of large conductance vessels (macrocirculation) of the leg (i.e. the iliac, femoral, popliteal, and crural arteries) together with impaired microcirculation leading to reduced capillary blood flow and reduced oxygen and nutritional supply to muscle and skin of the affected leg, finally leading to ischemic ulcers and tissue loss.

Obstruction of larger arteries by atherosclerotic lesions leads to decreased blood flow and perfusion pressure in distally located vascular territories, leading to decreased shear rates. Furthermore atherosclerosis impairs endothelial function in large vessels and in microcirculation. This affects nutritional capillaries in the microcirculation of muscle and skin. Blood flow over the capillary bed and therefore delivery of oxygen and nutrition to muscle and skin is driven by the pressure difference between arterioles and venules, and influenced by the diameter of the capillary bed and blood viscosity. This relation can be described by the Hagen–Poiseuille equation [9]. If blood flow is reduced due to arterial obstruction and if impaired endothelial function does not allow vasodilation of capillaries and thereby does not compensate decreased pressure difference, blood viscosity becomes more important as a determinant of blood flow over the capillary bed. As blood behaves like a non-Newtonian fluid blood viscosity increases exponentially at low shear rates due to high molecular weight proteins and erythrocyte aggregation. Viscosity of blood is further increased in patients with atherosclerosis as fibrinogen levels are often elevated. All together, these mechanisms decrease capillary blood flow and thereby oxygen and nutritional supply to muscle and skin, which finally may lead to the development of ischemic symptoms and lesions [10].

Table 1
Proposed immediate and chronic effects of lipid apheresis in atherosclerotic vascular disease

Rapid Reponses: Improvement of endothelial function in macro- and microcirculation
Activation of vasodilatory substances and increase in the bioavailability of endogenous vasodilatators
Reduction in susceptibility of LDL to oxidation and suppression of oxidative stress
Improvement of blood rheology
Inhibition of activation of the coagulation system
Continued Effects: Antiatherogenic effects
Suppression of progression of atherosclerotic lesions
Regression of atherosclerotic lesions
Development of new collaterals by stimulation of neoangiogenesis

3. Putative mechanisms by which apheresis may affect the course and symptoms of PAD

LDL apheresis leads to functional improvement of macro- and microcirculation during the very early stages of treatment, and continued treatment may produce antiatherogenic effects in patients with atherosclerotic vascular disease, such as PAD. These effects are due to aggressive cholesterol lowering but may also be caused by other effects, such as lowering of plasma fibrinogen levels and other at least partly unknown mechanisms (Table 1).

3.1. Inhibition of the progression of atherosclerotic lesions

It is well established that continuous aggressive cholesterol lowering by lipid apheresis decreases the progression of coronary atherosclerosis and reduces cardiac events in hypercholesterolemic patients with established CAD who do not respond sufficiently to drug treatment [11, 12]. Furthermore, lipid apheresis has been shown to prevent or retard the development of coronary atherosclerosis in patients with homozygous familial hypercholesterolemia [13, 14]. It also reduces the progression of peripheral atherosclerotic vascular disease [11], as discussed below.

3.2. Increase in blood supply to the skeletal muscle and improvement of endothelium-dependent vasodilator responses

Impaired endothelium-dependent vasodilation has been demonstrated in patients with atherosclerosis and in conditions predisposing to the development of atherosclerosis, such as the presence of cardiovascular risk factors (diabetes, hypercholesterolemia, arterial hypertension, smoking, and hyperhomocysteinemia). Endothelial dysfunction is notable early in the course of atherosclerotic vascular disease even before structural vascular changes are established. It is both a mediator of the future development of atherosclerotic lesions and a consequence of established vascular disease.

LDL alters vasomotion by impairing the signal transduction between cell surface receptors and nitric oxide (NO) production, by inhibiting NO synthase activity, and by inactivating NO released from endothelial cells. Repeated LDL apheresis produces an increase in peak blood flow to the calf and forearm during reactive hyperemia as determined noninvasively by a strain-gauge plethysmograph [15]. Therefore, more flow is available in conditions of high oxygen demand, such as exercise. This may be due to an improvement of rheological properties of blood by apheresis [15, 16]. Furthermore, removal of native and oxidized LDL by LDL apheresis in hypercholesterolemic humans improves endothelium-dependent vasodilatation in the forearm by augmenting vasodilator responses to acetylcholine with increased production of NO [17], and improves coronary vasodilatory capacity [18, 19]. This is also observed in patients with endstage renal failure on chronic hemodialysis suffering from PAD. Although these patients have severely impaired endothelium-dependent vasodilator responses before apheresis, repeated LDL apheresis, significantly increased endothelium-dependent vasodilation after 12 weeks from 1.6 ± 0.6% to 4.7 ± 1.0%. Endothelium-independent, nitroglycerin induced vasodilation remained unchanged [20]. A single LDL apheresis using a dextran sulfate cellulose column resulted in increased circulating levels of NO and nitrosylhemoglobin irrespective of changes in bradykinin release [21].

An increase in endothelium-dependent vasodilator function due to an increase in bioavailable nitric oxide, an increase in blood supply to skeletal muscle, and an improvement in rheological properties may contribute both to symptomatic improvement in patients with PAD and claudication or ischemic rest pain and to slowing the progression of atherosclerotic lesion development.

Whether or not LDL apheresis or rheopheresis alters microvascular reactivity has not been systematically studied so far. Stulc et al. [22] have shown that hyperlipidemic subjects with established coronary artery disease have impaired skin microvascular reactivity after postischemic and thermal stimulation compared to healthy subjects as assessed by laser Doppler flowmetry. Intensive lipid lowering by statins, however, did not affect impaired skin microvascular reactivity.

To date no solid data are available which demonstrate that LDL apheresis reduces proinflammatory changes of the endothelium or the vessel wall, which are an important component of the development of atherosclerotic lesions. In contrast, LDL apheresis by either direct adsorption of lipoproteins in whole blood by adsorption onto polycrylate-coated polyacrylamide beads (DALI) or by a reciprocative double column adsorption system including dextran sulfate cellulose columns did not result in lowering of soluble ICAM-1, VCAM-1, and E-selectin levels after a single apheresis session or during chronic treatment up to 6 months [23].

3.3. Endothelial cell-specific growth factors and endothelial progenitor cells

VEGF (vascular endothelial growth factor) plays an important role in angiogenesis [24] as an endothelial cell-specific mitogen, angiogenic inducer and mediator of vascular permeability. IGF-1 (insulin-like growth factor 1) is a growth-promoting, anabolic polypeptide, known to participate in regeneration of injured vascular endothelium [25, 26].

Kobayashi et al. [27] examined whether or not VEGF or IGF-1 may contribute to the favorable effects of LDL apheresis on ischemic limbs in PAD patients. They treated 16 patients with PAD (half of them with CLI) including 9 with diabetes and 11 undergoing hemodialysis by LDL apheresis using dextran sulfate adsorption columns twice a week for 5 weeks. VEGF and IGF-1 plasma levels were measured before and 3 months after LDL apheresis. LDL apheresis led to a significant improvement of hemodynamic parameters like ankle brachial blood pressure index (ABI) and improved ischemic symptoms in 11/16 patients. This went along with a significant increase in VEGF (from 262 ± 171 to 441 ± 175 pg/mL) and IGF-1 (from 144 ± 67 to 190 ± 138 ng/mL) levels, together with a significant decrease in fibrinogen levels. There is some concern, however, on the accuracy of the data presented [28]. VEGF and IGF-1 levels were analyzed partly from plasma and partly from serum samples, and conditions for sample storage and preanalytic preparations were not standardized, which raises some methodological concern and might have introduced some artificial variance. Before firm conclusions can be drawn, these data have to be reproduced using more rigid and reliable analytical conditions.

3.4. Improvement of blood hemorheology

Under conditions of decreased perfusion pressure over the capillary bed and impaired capillary vasodilation, blood viscosity becomes the most important determinant of microcirculatory blood flow. Plasma concentrations of high molecular weight proteins such as α-2-macroglobulin and fibrinogen as well as total cholesterol concentrations are strongly and positively correlated with plasma viscosity [29]. By eliminating not only LDL particles but also other

high molecular weight proteins lipid apheresis and rheopheresis decrease plasma viscosity [10, 15, 30] and thereby may improve hemorheology in microcirculation.

4. Clinical experience with apheresis in peripheral arterial occlusive disease and the diabetic foot syndrome

The clinical experience with lipid apheresis and rheopheresis in patients with PAD has been reported in several case series and observational studies during the last 15 years. The only controlled clinical trial published so far is a subgroup analysis of the LDL-Apheresis Atherosclerosis Regression Study (LAARS) [11]. Despite the lack of high quality clinical trials in this field, this review tries to summarize and discuss the potential use and benefit of apheresis in different patient populations affected by PAD with differing severity. It also points out uncertainties and need for further research.

4.1. Effect of lipid apheresis on the progression of atherosclerotic vascular disease in peripheral arteries

Lipid lowering treatment using statins has been shown to lower the progression rate of PAD, to increase walking distance in patients with intermittent claudication, to reduce cardiac events following noncardiac vascular surgery, and to increase patency rates following infrainguinal arterial bypass grafting [31]. Whether or not more intense lipid lowering therapy using LDL apheresis has an effect on the progression of PAD has been studied in a controlled trial that was part of the LDL-Apheresis Atherosclerosis Regression Study (LAARS) [11]. 41 men with primary hypercholesterolemia and extensive coronary artery disease were either treated by continuous LDL apheresis using dextran sulfate cellulose adsorption in combination with simvastatin or simvastatin only. End points were changes in systolic ABI at rest and during hyperemia and measurement of blood flow velocities in the common femoral artery by using Doppler spectrum analysis at 1 and 2 years compared to baseline.

In the simvastatin-only group, the number of patients with hemodynamically significant stenoses in arteries of the lower extremities increased from 6 to 13 during two years of follow-up, mainly due to an increase of lesions in the femoropopliteotibial tract (from 4 to 11). The number of patients with abnormalities of the aortoiliac tract increased from 5 to 7. In the apheresis group, the total number of patients with hemodynamically significant lesions decreased from 9 to 7, representing a decrease of patients with aortoiliac lesions from 4 to 1, and with infrainguinal lesions from 8 to 6. 90% of patients in the apheresis group (18/20) compared to only 38% of patients in the simvastatin-only group (8/21) showed stable or improving findings during two years on treatment. One patient in each group required peripheral revascularization. Significant correlations were found between the worsening or improvement of peripheral hemodynamic measurements and absolute changes from baseline in levels of total and LDL cholesterol, apolipoprotein B and lipoprotein(a).

This trial showed that more aggressive lipid lowering using LDL apheresis in combination with simvastatin in severely hyperlipidemic patients is effective in preventing the progression of atherosclerotic vascular disease in peripheral arteries as well as in the coronary circulation compared to pharmacological treatment only. These findings further indicate that atherosclerosis is a systemic disorder, and intense risk factor modification is effective in preventing the progression of the disease in all vascular territories, including peripheral arteries.

4.2. Effect of lipid apheresis on symptoms of intermittent claudication in hyperlipidemic patients

In Japan, LDL apheresis is an approved treatment covered by health insurances for patients with drug-resistant hyperlipidemia and symptomatic PAD unsuitable for surgical or endovascular intervention and in whom pharmacological treatment had failed.

Agishi et al. [32] reported their experiences using LDL apheresis in this setting. 33 hypercholesterolemic patients (mean LDL-cholesterol 161 ± 31 mg/dL) with symptomatic PAD (Fontaine's class II: 39.3%, Fontaine's class III and IV: 60.7%) were treated by LDL apheresis using dextran sulfate adsorption columns ten times over a period of three months. This resulted in lowering of LDL cholesterol below 140 mg/dL in all cases. Authors reported an improvement in clinical symptoms of claudication in 27 of 31 patients (87.1%). Foot pain at rest ameliorated in 7 of 13 patients (53.8%) and lesion size decreased in 3 of 5 patients (60%) with ischemic foot ulcers. Hemodynamic parameters like ABI improved in 14 of 20 patients (70%) and digital plethysmography findings in 6 of 7 patients. Symptoms remained improved for more than 1 year after stopping the course of LDL apheresis. Interpretation of these findings, however, is significantly restricted by the fact that authors did neither describe the methods of assessing walking distance and intensity of pain, nor the magnitude of improvement observed. A control group was not included.

More recently, treatment of another series of 31 patients (47-86 years, 20 men) with hypercholesterolemia (total cholesterol ≥ 220 mg/dL) after dietary treatment and medication and symptomatic PAD (Fontaine's stage II: 26; III: 4; IV: 1) using the same apheresis system as above was described (P-LAS trial) [33]. An average of 9.6 ± 0.8 LDL apheresis sessions was performed during a period of 7 ± 1 weeks. Patients were assessed before and one week after completion of the treatment course using objective and standardized tests. A control group was not included.

ABI increased in 60% (26/43) of the affected legs, with an average 15% increase from 0.66 ± 0.03 to 0.76 ± 0.03 ($p < 0.001$). The maximum tolerated walking distance during a standardized treadmill test increased in 70% (16/23) of patients by an average of 30 m (20%) from 160 ± 19 to

190 ± 23 m ($p < 0.001$). Rest pain improved in all 5 patients with Fontaine's class III or IV as indicated by a decrease in the use of analgesics. The minor improvement in walking distance is comparable to the improvement seen with supervised exercise training [34] and with lipid lowering by statins [31], and seems to be less pronounced than the improvement seen with modern pharmacotherapy for claudication like cilostazol in combination with training [3, 35], although both treatment modalities were not compared directly. Cilostazol, which is currently the most potent drug for improving walking distance in PAD patients, was not available at the time the study by Agishi et al. [32] had been performed.

Taken together, currently there is no scientific evidence that lipid apheresis may be efficient to improve walking distance in PAD patients with hypercholesterolemia at a clinically relevant magnitude and superior to best medical treatment currently available. The number of treated patients with CLI is too small to draw any conclusions for this subgroup of PAD patients. There is urgent need for controlled clinical trials on the effect of lipid apheresis compared to best medical treatment including statins and cilostazol in hypercholesterolemic patients with PAD before this treatment option can be applied more widely.

4.3. Effect of lipid apheresis or rheopheresis in patients with critical limb ischemia

Two pilot observational studies describe the effect of either repeated H.E.L.P. treatments [30] or rheopheresis sessions [36] in patients with CLI that experienced a deterioration of their PAD despite standard approaches using both conservative and interventional therapies and were threatened to undergo major amputations. It is described that 13 major amputations in 12 patients could be avoided and surgery limited to necrosectomy only after treatment with 18 sessions of H.E.L.P. each. Together with a decrease in total and LDL cholesterol levels, repeated H.E.L.P. significantly improved hemorheology parameters such as fibrinogen levels, plasma and whole-blood viscosity, as well as red cell transit time. Only four out of twelve patients with CLI treated by series of up to twelve rheopheresis sessions are reported to experience a clinical benefit such as complete regression of rest pain. Interpretation of the results of the latter study, however, is hampered by the fact that inclusion criteria did not use generally accepted criteria for CLI [3] and included patients with ankle pressure above 50 mmHg and/or toe pressures above 30 mmHg into treatment.

4.4. Effect of lipid apheresis in diabetic hemodialysis patients

Atherosclerotic vascular disease affecting peripheral arteries is a major cause of morbidity and mortality in diabetic patients undergoing hemodialysis. The amputation rate reaches up to 14 per 100 patient years for hemodialysis patients with diabetes [7]. Endovascular or surgical revascularization is technically unsuitable in a large portion of chronic hemodialysis patients due to the predominance of distal obstructions, and when technically feasible, associated with a worse patency rate and prognosis compared to patients with normal renal function [37]. Conservative treatment with vasoactive prostaglandins, which reduces amputation rate in patients with CLI and normal renal function, is less effective in patients with end stage renal disease. Therefore patients with PAD on chronic hemodialysis are a difficult to treat patient population at high risk of limb loss.

Several small series have been published that aimed at describing short term clinical effects of 9 to 16 sessions of lipid apheresis over 3 months using dextran sulfate adsorption [20, 38-41] or membrane double filtration [42] in PAD patients on chronic hemodialysis unsuitable for surgical or endovascular revascularization and in whom pharmacological treatment with vasoactive prostaglandins had failed. Details of the studies are summarized in Table 2. Neither of these series included a control group. Outcome parameters are heterogeneous and not standardized, ranging from subjective estimates of rest pain, coldness and numbness of the leg without standardized and evaluated questionnaires, over changes in Fontaine's stages of PAD without concurrent hemodynamic classification (which is unreliable in diabetic patients and patients with chronic renal failure due to a high prevalence of peripheral polyneuropathy) to changes in ABI values (measured either by standard methodology or by newly developed automatized methods that had not been validated). Due to the short observation period data on limb salvage and amputation free survival are not available.

Taken together, these observations showed that walking distance improved [38, 40] or remained stable [20] in 50 to 80% of patients, in whom this parameter was assessed. More encouraging, rest pain improved and ischemic ulcers healed in up to 80% of patients with CLI reported in the different series. Hemodynamic parameters, when reported, improved in patients responding to therapy. These observed treatment effects are encouraging, but there is urgent need for well planned controlled trials with standardized hemodynamic assessment, objective endpoints and extended follow-up in these otherwise difficult to treat patients.

4.5. Effect of lipid apheresis and rheopheresis in patients with the diabetic foot syndrome

Two larger series of patients with diabetic foot syndrome treated by apheresis have been reported [43, 44]. Klingel and colleagues [43] treated 8 patients with non-healing lesions for more than 2 months under standardized wound care caused by severe ischemic diabetic foot syndrome (6 × Wagner stage 2, 2 × Wagner stage 4 or 5) with seven rheopheresis treatments (Diamed, Cologne, Germany) over a period of 11 weeks. The target for each single treatment was filtration of 100% of patient's plasma volume. Patients were evaluated before (week 0), one week after the last

Table 2
Reported series on the short term effects of lipid apheresis using dextran sulfate adsorption (DSA) or membrane differential filtration apheresis (MDF) in patients with PAD requiring maintenance hemodialysis

Reference	Method of apheresis	N of patients described	Stages of PAD according to Fontaine's classification	Outcome	Remarks
[38, 39]	DSA	12	Grade II: n = 6 Grade III: n = 6	Objective parameters: ↑ Walking distance (from 60 ± 48 to 150 ± 151 m) ↑ ABI (from 0.35 ± 0.12 to 0.45 ± 0.16) Subjective parameters: ↓ pain, numbness and coldness in the affected leg	No differentiation between patients at Fontaine's grade II and III
[37]	DSA	19 with ESRD among 28	Grade II: n = 15 Grade III: n = 6 Grade IV: n = 7	Objective parameters: ↑ ABI (from 0.69 ± 0.29 to 0.85 ± 0.24) Subjective parameters: 53.6% of patients: doubling of walking distance 14.3% of patients: improvement of foot ulcers 82.1% of patients: improvement of foot chillness or numbness ABI increased from 0.69 ± 0.29 to 0.85 ± 0.24 3 months after LDL apheresis	Follow-up examination and questionnaire after 3 months Automatized and non-validated measurement of ABI No standardized treadmill walking test No data on ulcer healing
[40]	DSA	8	Grade II: n = 5 Grade III: n = 3	Objective parameters: ↑ ABI (from 0.83 ± 0.15 to 0.92 ± 0.17) Subjective parameters: 6/8 improvement in Fontaine's stage of PAD (2/3 patients with grade III at entry)	High ABI at baseline (no comments on prevalence of mediasclerosis among patients)
[19]	DSA	11	Grade II: n = 5 Grade III: n = 5 Grade IV: n = 1	Subjective parameters: Grade II: stable disease Grade III+IV: ↓ rest pain in 5/6 patients ↓ Fontaine stage in 3/6 patients Worsening in 1/6 patients	Evaluation of clinical symptomas by visual analog scores after the 10th apheresis
[41]	MDF	5	Grade IV: n = 5	Objective parameters: 5/5 suspension of analgetic therapy 4/5 complete ulcer healing Subjective parameters: 5/5 complete resolution of pain after three weeks of rheopheresis	Methods for assessing treatment effects not described

ESRD: end stage renal disease requiring hemodialysis, DSA: dextran sulfate adsorption, MDF: membrane differential filtration apheresis

rheopheresis (week 12), and at the follow-up examination 3 months after the last treatment (week 24). 4/6 patients with Wagner stage 2 lesions improved clinically, resulting in complete healing in 2/4, and requiring no amputation in any of these patients during follow-up. Lesions remained unchanged in two patients requiring minor amputation. The two patients entering the study with more severe lesions (Wagner stage 4 and 5) deteriorated and required major amputations. In the patients in whom rheopheresis was associated with healing of foot ulcers, this went along with a pronounced increase in $tcPO_2$, whereas the patients that deteriorated during the trial phase did not respond to treatment by an increase in $tcPO_2$. Hemodynamic characterization of patients has not been performed.

Rietzsch and colleagues [44] used a different approach. They treated 17 diabetic patients with septic foot lesions (Wagner stages 3-5) and severe angiopathy, which did not qualify for revascularization, by H.E.L.P apheresis. All patients showed signs of systemic infection (leucocytosis, lymphadenitis), were at high risk for amputation, and had plasma fibrinogen levels > 6 g/L. All patients underwent H.E.L.P apheresis to remove low-density lipoproteins, other lipoproteins, and fibrinogen, until fibrinogen levels were stabilized at 3 g/L, or until infection was controllable. The number of H.E.L.P treatments ranged from 1 to 7 per patient. At the stage of fibrinogen stabilization, necrotic tissue was removed surgically, and the patients were followed up for 2 to 73 months. During follow-up ulcers were treated according to the stage of wound healing, and surgical interventions were applied when indicated. Necrosis could be confined in sixteen patients. Minor toe amputations were required in 8 patients, and forefoot removal in four patients. Three patients underwent major amputation. Two patients died from myocardial infarction during follow-up. Treatment of these patients required an intense inpatient health care of 111 days on average.

These two series indicate an interesting difference of different methods of apheresis. Whereas patients with advanced diabetic foot syndrome complicated by infections, which are difficult to treat and usually require major amputations, did not respond to rheopheresis [43], they responded to H.E.L.P. apheresis combined with thorough wound care. Whether or not H.E.L.P. is more effective than rheopheresis in this clinical situation is not possible to decide. It is remarkable, however, that all 12 patients with CLI treated with H.E.L.P. as described in the series by Walzl [30] responded to treatment, whereas only 4 out 12 patients with CLI reported in the series by Klingel [36] showed clinical improvement. Before firm conclusions can be drawn, more patients with comparable inclusion criteria have to be treated by the different techniques of apheresis.

5. Conclusions

Taken together, the data presented show that

1 lipid apheresis is effective in preventing the progression of atherothrombotic vascular disease in the coronary, cerebral and peripheral arterial vascular bed in severely hypercholesterolemic patients. As patients with PAD are at the same risk for cardiovascular mortality as patients with CAD, lipid apheresis may be indicated in patients with severe hypercholesterolemia unresponsive to drug treatment and atherosclerotic vascular disease in any vascular territory, including peripheral arteries. This conclusion is supported by controlled clinical studies [11-14].
2 Currently, there is insufficient evidence that lipid apheresis is as efficient as modern drug therapy in treating symptoms of intermittent claudication in hyper- or normocholesterolemic PAD patients unsuitable for revascularization [32, 33]. Controlled trials comparing best medical treatment to lipid apheresis are necessary in PAD patients unsuitable for revascularization before this treatment option can be recommended to patients with PAD who are not threatened by CLI.
3 First case reports are encouraging and suggest that lipid apheresis using H.E.L.P., dextran sulfate adsorption or membrane double filtration techniques may be beneficial in difficult to treat patients with limb threatening severe peripheral angiopathy, such as diabetic patients on chronic hemodialyis or patients with diabetic foot syndrome [20, 30, 38-42, 44]. Rheopheresis seemed to be less effective [36, 43]. Well planned controlled trials of lipid apheresis vs. best medical treatment with standardized hemodynamic and wound stage assessment, objective endpoints and extended follow-up periods are urgently needed in these otherwise difficult to treat patients with end-stage renal disease and critical limb ischemia and in patients with diabetic foot syndrome unsuitable for revasularization, as these patients otherwise have limited treatment options for limb and thereby life salvage**.**

Conflicts of interest

There are no conflicts of interest

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