Etiology of Peripheral Arterial Disease

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Peripheral artery disease (PAD) affects more than 230 million people worldwide. PAD patients suffer from reduced quality of life and are at increased risk of vascular complications and all-cause mortality. Despite its prevalence, impact on quality of life and poor long-term clinical outcomes, PAD remains underdiagnosed and undertreated compared to myocardial infarction and stroke. PAD is due to a combination of macrovascular atherosclerosis and calcification, combined with microvascular rarefaction, leading to chronic peripheral ischemia. Novel therapies are needed to address the increasing incidence of PAD and its difficult long-term pharmacological and surgical management.

peripheral artery disease PAD intimal hyperplasia

1. Introduction

Peripheral artery disease (PAD), defined as “all arterial diseases other than coronary arteries and aorta”, affects more than 230 million people worldwide [1][2].

PAD is primarily due to the development of atherosclerotic plaques, leading to progressive narrowing of the vessel lumen. Limb symptoms include leg pain, cramps, fatigue, and muscle weakness during physical activity. At rest, blood flow remains sufficient to meet basal oxygen requirements and patients are free of symptoms. However, during exercise, the increased oxygen supply to the lower limb is impaired, leading to moderate ischemia, which the patient experiences as cramping pain. The patient usually stops walking until the pain subsides. Alternating cycles of walking and resting, known as intermittent claudication (IC), is the cardinal clinical manifestation of PAD [3]. Patients with IC have a reduced walking distance, leading to an inability to perform daily activities and a reduced quality of life [1][4][5]. However, IC may be present in only 10–35% of patients, whereas 40–50% of PAD patients have a wide range of atypical leg symptoms, and 20–50% of patients are asymptomatic [4][5][6]. The femoral and popliteal arteries are the most common sites of atherosclerotic disease in patients with PAD. Approximately 80–90% of patients with symptomatic PAD have some combination of femoropopliteal occlusive disease [4][5][7].

In late-stage PAD, ischemia worsens as the arteries become completely occluded, leading to chronic limb-threatening ischemia (CLTI). CLTI is characterized by resting muscle pain, ulceration, and gangrene, and a significant reduction in quality of life. In addition, PAD and CLTI patients are at increased risk of developing vascular occlusive disease and all-cause mortality, as atherosclerosis usually develops throughout the vasculature. Notably, the 1-year incidence of all major cardiovascular events is 30% higher in patients with PAD than in those

with coronary or cerebral artery disease [8]. Without surgical revascularization, 25% of CLTI patients die within one year of initial diagnosis and 40% of CLTI patients undergo limb amputation within three years [9][10]. Venous bypass surgery and endovascular approaches such as angioplasty with or without stenting and endarterectomy are the main treatment for CLTI. The disease presentation and the patient's general health and comorbidities determine the choice between open surgery and endovascular approaches.

Acute limb ischemia (ALI) is another severe manifestation of PAD, defined by sudden, severe hypoperfusion of the limb, usually due to thromboembolism. Symptoms may include pain, pallor, pulselessness, poikilothermia, paresthesias and paralysis, with loss of sensation and motor function in severe cases. Although ALI can occur in the absence of significant peripheral atherosclerosis due to distant plaque rupture, it is common in the setting of PAD.

2. Current Management of PAD and CLTI

The main risk factors for the development of PAD are age, smoking, and diabetes. Hyperlipidemia and hypertension are also risk factors for PAD, although the predictive value of these parameters does not appear to be as strong as for the primary risk factors. The presentation of PAD varies considerably and includes four categories: asymptomatic, claudication, critical limb ischemia, and ALI. PAD patients are classified according to the Fontaine or Rutherford classification systems.

- **Fontaine**
- Stage I—No symptoms
- Stage II—Intermittent claudication subdivided into:
- Stage IIa—Without pain on resting, but with claudication at a distance of greater than 650 feet (200 m)
- Stage IIb—Without pain on resting, but with a claudication distance of less than 650 feet (200 m)
- Stage III—Nocturnal and/or resting pain
- Stage IV—Necrosis (death of tissue) and/or gangrene in the limb
- **Rutherford**
- Stage 0—Asymptomatic
- Stage 1—Mild claudication
- Stage 2—Moderate claudication

- Stage 3—Severe claudication
- Stage 4—Rest pain
- Stage 5—Minor tissue loss with ischemic nonhealing ulcer or focal gangrene with diffuse pedal ischemia
- Stage 6—Major tissue loss—Extending above transmetatarsal level, functional foot no longer salvageable

Asymptomatic PAD patients with evidence of atherosclerosis who do not have typical claudication symptoms (Fontaine I or Rutherford 0) are offered risk reduction strategies to decrease cardiovascular risk factors depending on symptom severity, lipid levels, and the presence of comorbidities such as diabetes, smoking and hypertension. Thus, current guidelines for the management of PAD are preventive strategies such as diet and lifestyle modification, including supervised exercise, smoking cessation and pharmacotherapy tailored to individual risk factors [1][8][11][12][13][14]. All patients with PAD should receive statin medication. Antihypertensive therapy should be administered to hypertensive patients to reduce the risk of myocardial infarction (MI), stroke, heart failure, and cardiovascular death. Antiplatelet therapy with aspirin or clopidogrel alone may be considered in asymptomatic patients, and should always be administered to symptomatic PAD patients. After assessment of bleeding risk, further anti-coagulant therapies (Rivaroxaban) may be considered for symptomatic PAD patients as they significantly reduce the risk of stroke, myocardial infarction, and ALI [1][11][12][15][16].

For patients with lifestyle-limiting claudication or CLTI (Fontaine IIb—IV; Rutherford 4–6), who are poor responders to medical and/or exercise therapy, surgical revascularization remains the only option when possible. Venous bypass surgery and endovascular approaches such as angioplasty, stenting and atherectomy are the main methods. The choice between open surgery and endovascular approaches depends on the presentation of the disease and the patient's general health and comorbidities. Whenever possible, autogenous vein is the conduit of choice for open revascularization so that bypass surgery is limited to patients with "good" veins [7][17]. All patients with CLTI should be given antithrombotic and lipid-lowering therapies, as well as counseling on smoking cessation, diet, exercise, and preventive foot care. Additional antihypertensive, and glycemic control therapies should be given appropriately [1][11][12].

Without surgical revascularization, 25% of CLTI patients die within one year of initial diagnosis and 40% of CLTI patients undergo limb amputation within three years [9][10]. Up to 25% of CLTI patients are ineligible for revascularization and amputation is often the only option [18]. When possible, surgery may be suboptimal for symptom relief, and 20% of PAD patients have "failed revascularization". Furthermore, PAD patients, especially those with CLTI, carry a high risk of post-op complications, including ALI, often leading to limb loss, disability, and death [12][19]. Even if the procedure is technically successful, residual microvascular disease remains and the outcomes after amputation stay poor [12][20].

3. Etiology of PAD

Atherosclerosis in lower limb arteries is the main cause of PAD [21], but emerging evidence suggests that medial calcification also contributes to the disease, especially in lower limb PAD. Microvascular disease is also emerging as a potential contributor to the progression of PAD and a clinically relevant sign of PAD severity.

3.1. Atherosclerosis

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of fatty cholesterol streaks in arterial trees. Several pathophysiological processes are involved in this disease, including endothelial cell (EC) dysfunction, inflammation, lipid accumulation, and vascular smooth muscle cell (VSMC) proliferation and migration (reviewed in detail in [22]).

The disease is initiated by EC dysfunction. Located at the interface between the blood and the vessel wall, EC maintain a non-thrombogenic surface. In arteries, high shear stress and laminar blood flow maintain EC function and secretion of anti-thrombotic and vasodilator agents, mainly nitric oxide (NO) and prostacyclins [23]. Disturbed arterial flow patterns observed at bifurcations and curved sections of arteries create regions of low shear stress that induce EC dysfunction or “endothelial activation”. These weak points in the vasculature are the sites of primary occlusion by atherosclerotic plaques. Endothelial dysfunction or injury results in reduced production of NO and hydrogen sulfide (H_2S), two gasotransmitters that maintain healthy vascular function. Impaired EC function promotes vasoconstriction, platelet aggregation and the accumulation of oxidized low-density lipoproteins (LDL) in the vessel wall. Monocytes attracted to the inflamed vessel wall differentiate into macrophages, which engulf large amounts of LDL particles and become foam cells to form the fatty streaks typical of early atherosclerotic lesions. Foam cells undergo apoptosis and form a lipid core within the vessel wall, exacerbating inflammation. The VSMC composing the media layer of vessels are highly plastic. Upon chronic inflammation, VSMC switch to a “synthetic” phenotype, characterized by a loss of contractile markers. Recent lineage-tracing studies revealed that VSMC dedifferentiate into intermediate multipotent cell type, often referred to as mesenchymal stem cells (MSC). These cells may give rise to adipocytes, myofibroblasts, macrophage-like cells and fibro/osteochondrogenic cells [24][25][26][27]. Of note, VSMC-derived macrophages perform nonprofessional phagocytosis and contribute to the population of foam cells in atherosclerotic plaques [28][29]. Altogether, proliferating immune cells and reprogrammed VSMC promote matrix remodeling and the development of a fibrous cap overlying the lipid core.

Overall, atherosclerosis is driven by dyslipidemia and vascular chronic inflammation [27][30]. Macrophages are the primary immune cells involved in atherosclerosis, but over the years evidence has accumulated of a coordinated inflammatory immune response involving T- and B-lymphocytes in the progression of atherosclerotic plaques [27]. It should also be noted that all the cell types found in atheromatous plaques can secrete pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factors alpha (TNFα) and chemokine monocyte chemoattractant protein-1 (MCP-1/CCL2). Activated T-helper 1 (Th1) lymphocytes produce interferon gamma (IFNγ), which promotes phagocytosis and formation of foam cells. B2 lymphocytes also secrete mediators that can aggravate atherogenesis. In contrast, other immune cells including M2 macrophages, B1 lymphocytes and Th2 lymphocytes can produce anti-inflammatory mediators to alleviate inflammation [27][30]. In addition, activated EC secrete lipid-

derived pro-inflammatory molecules called eicosanoids, including prostaglandins, leukotrienes, and thromboxanes, which also play a major role in the pathophysiology of atherosclerosis [31][32].

Despite decades of research and although dyslipidemia and inflammation are known to be the major pathophysiological features leading to atherosclerosis, the exact pathways and mechanisms remain to be elucidated.

3.2. Vascular Medial Calcification

PAD is commonly described as an atherosclerotic disease. However, for lower limb artery disease, recent clinical data suggest that researchers underestimated the role of medial arterial calcification in PAD (recently reviewed in detail in [33][34]). Thus, the etiology of PAD, particularly in the arteries below the knee, may differ from that of the coronary and femoral arteries.

Two types of vascular calcification exist, intimal calcification (VIC) and medial calcification (VMC), also referred to as medial arterial calcification (MAC) [33][34]. VIC is a common feature of advanced atherosclerotic lesions and a risk factor for rupture. In contrast, VMC/MAC develops independently of atherosclerosis, but is a common feature of arterial disease associated with aging [35]. It is found in up to 40% of patients with advanced chronic kidney disease [36][37][38][39], and histological studies show that up to 70% of occluded arteries below the knee feature VMC and intimal thickening, but no atherosclerotis [40]. In their recent study, Jadidi et al. used machine learning to identify age, creatinine, body mass index, coronary artery disease and hypertension as the strongest predictors of calcification. They further confirmed that distal vessel segments (iliofemoral vs. aortic) calcify first. In this study of an American cohort, they estimated that up to 80% of people had VMC by the age of 40 [35].

VMC is characterized by the accumulation of calcium (Ca^{2+}) phosphate and the formation of hydroxyapatite crystals, leading to hardening of the medial layer [37]. It is particularly prevalent in patients with chronic kidney disease, especially diabetic patients, due to impaired phosphate homeostasis [34][38][39]. Different stages/severities of arterial calcification have been described by histopathologists, ranging from punctate to nodular calcification, and finally bone formation [33].

VIC in atherosclerosis lesion is well characterized. It is due to ectopic vascular osteogenesis via phenotypic reprogramming of contractile medial VSMC into synthetic mesenchymal VSMC, which then differentiate into osteochondrogenic VSMC, leading to bone formation [34]. VMC in lower limb arteries has not been so well studied. The presence of osteogenesis vs. hydroxyapatite deposition and their respective contribution to VMC in PAD and CLTI patients remain unknown, and may differ depending on the vascular bed [37][38][39]. VMC increases the risk of complications during vascular interventions and worsens their outcomes [33][34][41]. Further work is required to define the process underlying medial calcification in the absence of atherosclerosis, evaluate its impact on PAD and CLTI, and eventually target it for treatment.

3.3. Microvascular Dysfunction

PAD is usually recognized as a macrovascular disease. However, several recent studies indicate that artery occlusion in PAD is often accompanied by microvascular disease. Microvascular dysfunction (MVD) refers to the impairment of capillary function and number. Usually, peripheral microvascular endothelial function is evaluated using laser speckle contrast imaging, which allows assessment of cutaneous microcirculation. The incidence of MVD is particularly high in diabetic patients. Thus, 20 to 30% of PAD patients, and up to 70% of CLTI patients have diabetes [10]. Of note, diabetic patients have a five-fold increased risk of developing CLTI, and diabetic CLTI patients have up to five-fold more incidence of adverse outcomes and amputations [9][10][42]. Given the strong association between diabetes complications and MVD, clinical studies also tend to define MVD as the presence of nephropathy, retinopathy, or neuropathy. Clinical studies revealed a strong association between MVD and risk of heart failure in diabetic patients, independent of traditional heart failure risk factors including coronary artery disease [43][44][45]. MVD is also a common phenomenon in PAD patients, which feature impaired cutaneous microcirculation throughout the progression of PAD, often leading to reduced capillary density in CLTI patients. In PAD patients, MVD can contribute to the progression of the disease and the development of complications such as ischemic pain, tissue hypoxia, and impaired wound healing [10]. A recent study also found a positive correlation between microvascular endothelial function and impaired cognitive performance in PAD patients [46]. MVD can also worsen the outcome of surgical procedures as it reduces the ability of the blood vessels to respond to the increased blood flow after revascularization, which impairs healing, leading to a higher risk of complications.

Additionally, recent studies suggest that MVD may be used to assess PAD severity. In a recent meta-analysis, the Chronic Kidney Disease Prognosis discovered that albuminuria, a marker of nephropathy, strongly correlates with the incidence of amputation [47]. This study advocates that even at mild-to-moderate stages, chronic kidney disease and MVD may be a major risk factor for PAD. In a similar study, a stronger association was found between retinopathy and the incidence of PAD/CLTI, than between coronary heart disease or stroke and PAD/CLTI [48].

Mechanistically, MVD is not due to the formation of atherosclerosis plaque and/or occlusion of vessels. MVD is due to EC apoptosis and progressive loss of capillaries, which plays a major role in the development and progression of diabetic complications (diabetic retinopathy, nephropathy, and neuropathy). Patients with familial hypercholesterolemia also feature impaired endothelial-dependent vasodilatation [49].

Overall, MVD contributes to PAD, but is seldom considered in diagnostic and therapeutic approaches. There is currently no specific therapy for MVD. However, the good news is that current PAD therapeutic strategies focused on optimizing risk factors (management of diabetes, and hypercholesterolemia), and lifestyle modifications (physical exercise, smoking cessation, and weight loss), improve vascular fitness, including microvascular function. For instance, several clinical studies demonstrated that exercise promotes microvascular function in disease states [50][51][52][53][54]. Although solid evidence is still lacking, statins may also provide benefits to endothelial function and against MVD [55][56]. Pre-clinical studies also showed that anti-diabetic therapies, metformin especially, may preserve/restore endothelium function [57][58][59][60]. Understanding the mechanisms underlying MVD in PAD patients and finding new treatments and therapeutics targeting MVD specifically may help reduce symptoms and improve quality of life.

Overall, PAD is due to a combination of macrovascular atherosclerosis and calcification, associated with a rarefying microvasculature, leading to impaired vascular function and a complex inter-individual response to treatment and revascularization interventions.

3.4. Intimal Hyperplasia: The Unmet Challenge of Post-Operative PAD Management

Bypass surgery and endovascular revascularization, which includes angioplasty, stenting and atherectomy, are recommended for patients with lifestyle-limiting claudication who do not respond to medical and/or exercise therapy. Unfortunately, the vascular trauma associated with surgical revascularization eventually leads to secondary occlusion of the injured vessel, a process called restenosis. For open surgical procedures such as bypass and endarterectomy, the rate of restenosis at 1-year ranges from 20 to 30% [61]. For endovascular approaches, the rate of re-occlusion after balloon angioplasty and stenting ranges from 30 to 60% depending on the location [62]. Restenosis has various causes, such as secondary growth of atherosclerotic lesions or inward remodeling. However, the most common cause is intimal hyperplasia (IH). IH is a well-known complication of all types of vascular surgery. The progressive growth of a neointimal layer causes both an outward and inward remodeling of the vessel wall, resulting in luminal narrowing and ultimately impaired perfusion of downstream organs.

IH begins as a physiological healing response to injury to the blood vessel wall [63][64]. Like atherosclerosis, IH is initiated by EC injury, which promotes vasoconstriction, platelet aggregation and recruitment/activation of resident and circulating inflammatory cells. Inflammation leads to the reprogramming of VSMC and fibroblasts into proliferating and migrating cells that form a neointimal layer between the intima and the internal elastic lamina. This new layer is mainly composed of VSMC-derived cells expressing various markers of mesenchymal (stemness) or osteochondrogenic phenotype and secreting abundant ECM [64][65][66].

All current strategies to limit IH, such as paclitaxel and sirolimus, target cell proliferation. Paclitaxel is a chemotherapeutic agent that stabilizes microtubules, thereby preventing mitosis [67]. Sirolimus inhibits the mammalian target of rapamycin (mTOR), a master regulator of cell growth and metabolism [65]. However, targeting cell proliferation to reduce IH also impairs re-endothelialization. Endothelial repair is critical to limit inflammation, remodeling and IH. Poor endothelial repair also prolongs the need for antithrombotic therapy.

The increasing number of PAD and CLTI patients in need of surgical vascular repair, combined with difficult long-term pharmacological and surgical management, calls for novel therapies to promote endothelial repair while inhibiting VSMC phenotypic switch, fibrosis, and VMC. The gaseous vasodilator molecule H_2S has interesting properties in this respect.

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