Coagulation System in Peripheral Arterial Disease

Subjects: Peripheral Vascular Disease

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Peripheral artery disease (PAD) is a clinical manifestation of atherosclerotic disease with a large-scale impact on the economy and global health. Histopathological analysis and some clinical studies conducted on atherosclerotic plaques testify to the existence of different types of plaques. Likely, the role of coagulation in each specific type of plaque can be an important determinant in the histopathological composition of atherosclerosis and in its future stability.

peripheral artery disease coagulation atherosclerosis

1. Introduction

Peripheral artery disease (PAD) is a clinical manifestation of atherosclerotic disease with a large-scale impact on the economy and global health, affecting over 200 million people worldwide [1]. The term PAD refers to all arterial trees, except for the aorta and coronary arteries, as recently emphasized by Tran et al. [2]. The prevalence of PAD is approximately 12% in the adult population, with males being affected slightly more than females [3]. Even if symptoms and manifestations may be disabling, most patients can present an asymptomatic PAD. Due to the lack of characteristic signs and symptoms, these patients are often under-recognized and undertreated [4].

The goal of identifying the molecular pathways involved in both asymptomatic and symptomatic patients is to prevent the progression and complications of PAD and find subjects with a high risk for cardiovascular disease [5]

In fact, though asymptomatic patients do not have limitations in carrying out daily activities, they present an increased risk for major cardiovascular events [6]. A large international registry of patients found that 5.4% of patients with established PAD had a major cardiovascular event such as cardiovascular death, myocardial infarction, or stroke at one year, and 21% experienced these endpoints or hospitalization for an atherosclerotic event [7][8].

Despite the role played by platelets in the process of atherogenesis being well recognized, evidence has been increasing on the contribution of the coagulation system to the atherosclerosis formation and PAD development [9] [10].

In fact, the interaction between the activated platelet and the artery wall is a fundamental process for atherothrombotic disease, but it is also responsible for augmented fibrinogen concentrations, thrombin formation,

and fibrin turnover. The role of coagulation proteins in PAD pathogenesis is established not only in acute thrombotic complications but also in the stable stages of the disease, where fibrinogen and thrombin seem to be associated with the clinical severity [11]. The growing evidence concerning the central role of the coagulation cascade in the pathogenesis of PAD is also responsible for important repercussions for the therapeutic approach.

Given the implication of the hemostasis process and coagulative proteins in the pathophysiology of PAD, the use of anticoagulant therapy alone or in combination with antiplatelets has been considered as a potential antithrombotic option for antiplatelets alone.

2. Role of Coagulation in the Formation and Progression of Atherosclerosis

Coagulation is involved in thrombus formation and, therefore, in PAD progression. According to the composition, the thrombi can be categorized into acute or chronic (organized). Thrombus formation is driven by activated platelet and thrombin generation pathways. Acute thrombi are composed of red blood cells, fibrin, and platelets which adhere to the endothelial wall after the disruption of the atheromatic plaque and the exposure of the necrotic core. Chronic thrombus is defined by the presence of capillaries, smooth cells, connective tissue and inflammatory cells. While acute thrombi can be detected indiscriminately in advanced atherosclerotic and non-significant atherosclerotic lesions, chronic thrombi are observed more frequently in non-significant atherosclerotic plaque.

The disruption of an atherosclerotic lesion, exposing thrombogenic material to the blood, is the starting mechanism of the atherothrombotic events leading to plaque progression [12]. Several coagulation proteins have been implicated in proinflammatory conditions and atherosclerosis. The presence of tissue factor (TF) is considered the primary physiologic trigger of the coagulation cascade in atherosclerotic lesions: Wilcox et al. showed that TF was found on the membrane of macrophages and vascular smooth muscle cells, where it co-localizes with factor VII [13]. Furthermore, elevated TF levels have been found in patients with PAD. Abnormal TF levels have been detected mainly in early atherosclerotic lesions compared to stable advanced atherosclerotic plaque, suggesting a procoagulant state, especially in early stages of atherosclerosis, amplified by the reduction of inhibitor pathways of coagulation, as demonstrated by a higher TF/TF pathway inhibitor ratio in patients with early atherosclerosis [14].

Endogenous thrombin and thrombin–antithrombin complex values indicated a procoagulant profile of early atherosclerotic lesions compared to stable advanced atherosclerotic lesions. In subclinical atherosclerotic disease, a relation between TF and an increased carotid intimate media thickness has been documented as a marker of early atherosclerosis [14]. The presence of coagulation components, such as thrombin levels and thrombin/antithrombin complexes, in atherosclerotic lesions suggests the role of these clotting proteins in plaque thrombogenicity. The fact that coagulation proteins are more present in early atherosclerotic lesions compared to advanced atherosclerotic lesions supports an important role for these coagulation factors in the initial development of atherosclerosis rather than an involvement limited to thrombus formation in unstable plaques only [15].

These data might suggest a possible thromboembolic phenomenon in the peripheral arterial occlusion—above all, in infrapopliteal arteries—explaining the relatively lower incidence of chronic limb ischemia compared to PAD prevalence [16].

These data support the evidence of a procoagulant state in patients with peripheral artery disease, whose expression is more evident in the early stages, suggesting that thrombotic complications do not depend on the plaque size.

Furthermore, abnormal levels of thrombin, factor X, TF, and FXII have been detected in circulating blood. The expression of these proteins has also been noticed on the arterial wall, particularly in the early stages. This different expression might be attributed to the different plaque compositions. Indeed, early plaques are composed of inflammatory cells, producing procoagulant proteins, so the expression of coagulation factors in the vascular wall depends not only on the translocation from blood flow but also on the local production by the inflammatory cells. A change in plaque composition might explain why stable advanced atherosclerotic lesions, composed of fibrotic tissue surrounding the necrotic lipidic core, express fewer coagulation factors [17][18].

3. Plaque Composition and Vulnerability: Differences in Coronary and Peripheral Atherosclerotic Disease

The modified AHA classification [19] categorizes atherosclerotic plaques into adaptive intimal thickening (AIT), pathological intimal thickening (PIT), fibroatheroma (FA), and fibrocalcific plaque (FC). AIT is considered the expression of non-significant atherosclerosis, and it also includes atherosclerotic lesions composed of smooth cells without a lipid matrix. PIT refers to plaques with smooth cells and extracellular lipids, while fibrous caps surrounding lesions are classified as FA and calcified plaques are classified as FC; PIT, FA, and FC are classified as significant atherosclerosis.

CAD and PAD might be considered two distinct expressions of the same condition, but, although similar, they present different characteristics that are secondary to the peculiarities of the two vascular districts affected. Many factors, including anatomical features such as vessel size and tortuosity, local shear stress and inflammation on the arterial wall, and the presence of vasa vasorum, are responsible for a different composition of atherosclerotic plaques in coronary and peripheral arteries. In fact, coronary lesions are prevalently constituted from a central lipid-necrotic core composed of cholesterol (LRNC), oxidized LDL, and necrotic foam cells surrounded by a thin fibrotic cap, while the LEAD plaques present more frequently fibroproliferative and calcific lesions, without q lipid core and a prevalent composition of collagen, smooth cells, and calcification [20].

The different plaque composition is responsible for more vulnerability in the coronary than the peripheral arteries. Indeed, plaque stability depends on the percentage of fibrotic and lipidic components; therefore, connective tissue stabilizes atherosclerotic lesions, making complications, such as plaque rupture, less likely [21].

Many studies have analyzed the plaque composition in coronary and peripheral arteries with non-invasive imaging such as Magnetic Resonance, proving that only 25% of patients with LEAD had LRNC lesions, with a higher prevalence in smoking patients [22][23]. LRNC plaques are associated with a higher risk of LEAD complications, defined as a worsening ankle brachial index (ABI) and critical limb ischemia requiring intervention, [22] even if prior studies did not find any significant association between LNRC and ABI decline or lumen stenosis but rather only with local atherosclerotic severity [24].

The risk of complications also depends on the increase in inflammatory cells in the plaques. Recent evidence has demonstrated a major prevalence of macrophages and lymphocytes in the coronary and carotid lesions compared to the femoral plaques, supporting a less inflammatory process in peripheral circulation, as confirmed by a lower uptake of fluorodeoxyglucose in the femoral arteries compared to the carotid arteries in many studies using FDG-PET to determine inflammatory involvement in the atherosclerotic disease [25][26].

Histopathological studies have shown that atherosclerotic disease progression is related to local clotting formation. Some plaque components—in particular, cholesterol compounds—reveal marked thrombogenicity, promoting the activation of the coagulation cascade and the thrombus formation.

Previous studies demonstrated abnormal concentrations of coagulation factors, such as von Willebrand's factor, fibrinogen, and factor VIIa, as well as increased plasminogen activator inhibitor-1 and tissue-type plasminogen activator antigen in patients with CAD, promoting the hypothesis that an impaired balance between coagulation and fibrinolysis might be involved in coronary atherosclerosis. [27]. These data were confirmed in more recent studies, underlying the possible role of some clotting proteins as biomarkers of CAD. In fact, elevated levels of fibrinogen and soluble fibrin monomer complexes and decreased concentrations of prothrombin were identified in patients with CAD in comparison with healthy controls [28]. As opposed to cardiovascular events, which occur in the case of plaque rupture, peripheral ischemia is often associated with chronic thrombus formation in the absence of atherosclerotic lesions, indicating a possible procoagulant state in PAD. Coagulation plays an essential role in the initial processes leading to plaque formation but also in the growth of the atherosclerotic lesions and the progression of peripheral artery disease, as suggested by the finding of altered levels of coagulation factors in patients affected by PAD [16].

4. Endothelial Disfunction in Chronic Kidney Disease and the Risk of Lower Extremity Atherosclerosis

Patients with kidney disease are more often diagnosed with peripheral atherosclerosis than equivalents without renal dysfunction [29][30][31]. Chronic kidney disease (CKD) and atherosclerosis share the same risk factors (smoking, age, sex, comorbidities such as hypertension, diabetes, and hyperlipidemia) inducing vascular damage. Nevertheless, different studies have demonstrated that kidney dysfunction is associated with a higher risk of peripheral artery disease regardless of the classical risk factors for atherosclerosis [32][33][34][35][36].

There are two main mechanisms responsible for endothelial dysfunction in patients with chronic kidney disease. The first one is the activation of a proinflammatory state: indeed, patients affected by end-stage renal disease (ESRD) show elevated serum concentrations of acute phase proteins, such as C-reactive protein, IL-6, and TNF-alpha, demonstrating the activation of proinflammatory processes in kidney injury [37]. On the other hand, the reduced availability of molecules with vasodilatory action—in particular, nitric oxide (NO) bioavailability—induces the dysregulation of the vascular tone. Confirming these data, recent studies showed impairment in endothelium-dependent vasodilatation in ESRD [38].

Inflammation causes endothelial dysfunction, inducing the expression of adhesion molecules on the vascular wall and increasing the levels of TNF-alpha, which are responsible for the cytotoxic effect on the endothelial cells [39]. As the renal damage progresses, some soluble adhesion molecules, such as ICAM-1, VCAM-1, and MMP, are dismissed from endothelial cells and activate the NfkB pathway, with the final result of reducing the NO levels [40].

Oxidative stress is another mechanism that is decisive for endothelial dysfunction in chronic kidney disease: the interconnection between these two processes comes through increased levels of myeloperoxidase (MPO). Indeed, the activation of neutrophils in inflammatory processes determines the production of MPO, using NO as a substrate, and leads to lipid peroxidation through the generation of diffusible oxidants and oxidized-LDL (ox-LDL), whose levels in CKD are inversely related to endothelial function [41].

Moreover, oxidative stress leads to the production of the AGE (advanced glycation end-products), molecules whose action is to inhibit DDAH, and the degradation enzyme of asymmetric dimethylarginine (ADMA), a competitive inhibitor of L-arginine inducing the inactivation of eNOS (endothelial NO synthase), with a consequently reduced availability of NO [42].

Increased levels of AGE are detected in patients with chronic kidney disease.

In addition, the lower serum concentration of triiodothyronine induced by inflammation is another factor responsible for impaired ADMA levels in ESRD [43].

Other factors cause the lowering of NO availability in CKD patients. Hyperphosphatemia, vitamin D deficit, and FGF23 overexpression contribute to the inactivation of eNOS in renal damage; furthermore, the lower levels of NO in renal dysfunction are also the consequence of the reduced synthesis and transport of the precursor L-arginine [44][45][46][47].

A recent study by Batkoa et al. showed an elevated expression of thrombomodulin (TM) in patients with ESRD [48]. TM is a glycoprotein whose expression has been found on the endothelium covering atherosclerotic plaques and on the macrophages and smooth cells; TM is also released from endothelial cells after vascular damage [49][50]. The increased levels of TM are positively associated with TNFR2 (soluble tumor necrosis factor receptor type 2) and osteopontin (OPN) expression. TNFR2 activation induced by TNFalpha binding has a central role in the clotting pathway beginning, leading to arteriolar thrombosis [51], while osteopontin is a cytokine involved in

differentiating smooth muscle cells into an osteogenic phenotype, promoting vascular calcification and the progression of atherosclerotic disease [52][53]. OPN concentrations correlate with medial arterial calcifications, which are associated with a higher risk of cardiovascular and mortality risk in patients with CKD [54]. However, the mechanisms through which OPN and TNFR2 are related to increased levels of TM still need to be clarified.

Finally, increased concentrations of vWF (von Willebrand Factor) have been detected in patients with ESRD, suggesting a correlation between the coagulation system and thrombogenicity in kidney disease [55][56].

The interconnection between chronic kidney disease and endothelial dysfunction led to defining a new life-threatening clinical entity called malnutrition-inflammation-atherosclerosis (MIA) syndrome, in which the three aforementioned mechanisms synergistically concur to increase the cardiovascular risk and set the outcome of ESRD patients [57].

Based on these data, researchers can affirm that endothelial dysfunction in chronic kidney disease results from different processes leading to endothelial damage and dysregulation, which are responsible for accelerated atherosclerosis and a higher incidence of lower extremity atherosclerotic disease in patients with renal impairment.

About a quarter of patients with CKD with eGFR < 60 mL/min/1.73 m^2 suffer from peripheral artery disease, representing an independent risk factor for mortality and extended hospitalization, particularly in chronic limb ischemia [58].

The incidence of LEAD (Lower Extremity Atherosclerotic Disease) is higher in proportion with the degree of kidney damage: the risk of LEAD is 1.2–2.5 fold higher in patients with chronic kidney disease G3–G5, and the risk of lower limb complications needing amputation is more frequent in eGFR < 30 mL/min/1.73 m^2 in comparison with patients with normal renal function [59][60]. In addition, the risk is higher in patients undergoing dialysis because of the biochemical abnormalities leading to systemic inflammation, hypoalbuminemia, and hyperphosphatemia associated with chronic uremia [61][62].

The demonstration that CKD is a significant risk for LEAD is supported by data coming from a recent meta-analysis evaluating the outcome in patients with renal damage undergoing peripheral artery interventions in comparison with patients not affected by kidney disease: the study showed that target lesion revascularization (TLR), major amputations, and long-term mortality were most frequent in patients with CKD and, in particular, in ESRD, suggesting a pathogenic role of kidney dysfunction in the severity of peripheral atherosclerosis [63].

The data reported can lay the basis for the optimal clinical approach to patients with CKD who need to be evaluated for asymptomatic peripheral artery disease through the measurement of the ankle-brachial-index (ABI) to prevent the progression of lower extremity atherosclerosis and complications, even if ABI might be falsely normal in patients with ESRD and medial arterial calcification such that other diagnostic tools such as exercise ABI, the toe-brachial index, or duplex ultrasonography should be performed.

Lower extremity atherosclerosis in CKD is, therefore, the result of a complex interlacement of multiple processes resulting in vascular damage: for this reason, the management should include the participation of a multidisciplinary team, including a vascular surgeon, a physician, a wound care specialist, and a nephrologist, to perform the best diagnostic and therapeutic assessment of patients with peripheral atherosclerosis and chronic kidney disease.

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