Atherosclerosis risk in antiphospholipid syndrome

The antiphospholipid syndrome is characterized by a clinical phenotype that mimics several aspects present in general atherosclerosis. This association has been supported by the identification of similar biologic pathways that are activated in both conditions. The inflammatory and immune profiles found in these two types of patients are reinforced by the common vascular dysfunction present in general atherosclerosis and in antiphospholipid syndrome. However, these concepts are not matched by the anatomical findings present in both conditions. This suggests that although atherosclerosis may have an important role in antiphospholipid syndrome, the direct pro-thrombotic nature of this condition may be responsible for the majority of the manifestations seen in these patients.

KEYWORDS: antiphospholipid syndrome ▪ atherosclerosis ▪ inflammation ▪ thrombosis

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The antiphospholipid syndrome (APS) was recognized in the early 1980s as an autoimmune acquired thrombophilia characterized by thrombosis of both venous and arterial territories, and/or pregnancy morbidity. The small vessels are not spared and their involvement is particularly relevant in patients with catastrophic APS [1]. This syndrome has also been associated with other manifestations that include thrombocytopenia, cardiac valvular disease, renal thrombotic microangiopathy, hemolytic anemia and cognitive impairment [2]. The classification criteria for APS, updated in 2006, include at least one clinical (mostly thrombotic events) and one laboratorial criterion (anticardiolipin [aCL] or anti-β2-glycoprotein I [GPI] antibodies), provided that the time lag between the occurrence of the clinical and laboratorial features is no shorter than 12 weeks and no longer than 5 years [3]. The term antiphospholipid antibody is erroneous since these antibodies do not recognize phospholipids but rather plasma proteins (β2-GPI, prothrombin [4], annexin V [5], high- and low-molecular-weight kininogens [6] and phospholipid microparticles present in the circulating plasma) [7]. Those plasma proteins bind to anionic phospholipids and β2-GPI can also bind to other negatively charged molecules, such as heparin, DNA, oxidized low-density lipoprotein (oxLDL) and apoptotic cells [8,9]. β2-GPI is the most important antigenic target for antiphospholipid antibodies [10,11], but many other molecules can be implicated in the genesis of APS. A deregulated activation of complement, platelets, endothelial cells and monocytes, and a compromised fibrinolysis are currently recognized as key players in the thrombotic phenomena associated with APS [12]. Endothelial microparticles associated with vascular dysfunction have also been identified as another important mechanism, present in many steps of thrombus formation [13].

Regarding atherosclerosis, it is no longer seen as an age-related process with passive accumulation of lipids in the vessel wall but instead as a dynamic and complex biochemical and anatomical process. It is characterized by alterations in the lipoprotein metabolism, activation of the immune system and the consequent proliferation of smooth muscle cells, atheroma formation and arterial narrowing.

Atherosclerosis should in fact be regarded as a chronic inflammatory process, with inflammation and autoimmunity at the forefront of the initiation, progression and rupture of the atherosclerotic plaque [14,15]. The concept that a possible role for systemic inflammation in atherogenesis has been vindicated by the observation that anti-inflammatory interventions can protect the endothelium resulting in attenuation of the atherosclerotic process [16,17]. Furthermore, patients suffering from chronic inflammatory diseases have accelerated atherosclerosis, and the high level of inflammation to which patients with autoimmune diseases are exposed may induce and accelerate endothelial cell injury. Furthermore, biomechanic shear forces enhanced by classic cardiovascular risk factors,

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such as hypertension, hypercholesterolemia, diabetes and smoking, have been associated with endothelium dysfunction [18]. In fact, the earliest manifestation of atherothrombosis can be the result of a disturbance on the physiologic pattern of blood flow at arterial bending and bifurcation sites.

Endothelium is a dynamic autocrine and paracrine organ. It regulates anti-inflammatory, mitogenic and contractility activities of the vessel wall, as well as the hemostatic process within the vessel lumen. Nitric oxide is the major molecule involved in these processes. A dysfunctional endothelium, characterized by an imbalance of oxidative stress, facilitates the migration of these cells to the vessel wall, oxidation and uptake of circulating lipoproteins by monocytes, and the concomitant proliferation of smooth muscle cells. The expression of adhesion molecules (ICAM and VCAM) induces the binding of monocytes to the endothelial wall [19]. Those same areas, when submitted to shear stress forces, are susceptible to permeation and subendothelial accumulation of ApoB-containing lipoproteins, such as LDL and remnant lipoproteins, where they become targets for oxidative and enzymatic attack. After monocyte endothelial binding takes place, the blood cells are internalized and differentiated into macrophages. Retained pro-atherogenic LDL will lead to an enhancement in selective leukocyte recruitment and attachment to the endothelial layer, thus contributing to their transmigration across the endothelium into the intima. Lipoprotein uptake promotes the accumulation of lipid droplets in the cytoplasm of macrophages, transforming them into foam cells. By secreting additional extracellular matrix molecules, foam cells are in the core of a vicious cycle, with subsequent lipoprotein retention and cell recruitment. Among these are collagen-secreting myofibroblasts responsible for the fibrous cap, a subendothelial scar-like structure that contains the atherosclerotic lesion. Progressively, atherosclerosis grows and evolves from asymptomatic atherosclerotic lesions to atheroma plaques with increased risk of disruption and possible hemodynamic repercussion [20]. Within those plaques, apoptotic macrophages become necrotic, perpetuating inflammation and forming necrotic cores. These plaques, often called vulnerable or unstable, may rupture, exposing pro-coagulant and pro-thrombogenic molecules into the intima. Platelets recognize specific ligands in the ruptured atherosclerotic plaque or eroded endothelial lining, initiating platelet activation and aggregation. This leads to thrombosis and to the clinical manifestation of the atherothrombotic disease. From this summarized description, we can assume that a large temporal gap between initiation of atherosclerosis and thrombus formation exists. Thus, the initial phase of inflammation is silent and premature, and subclinical atherosclerosis can be long-lasting.

Increasing evidence suggests a high prevalence of atherosclerosis in APS patients. This assumption is mainly supported by common physiopathologic mechanisms that have been recognized. Whether this is enough to define a clear relationship between atherosclerosis and the syndrome is still under debate. This article summarizes the existent knowledge regarding possible links between atherosclerosis and APS.

Atherosclerosis & APS: what are the common features?

The association between APS and atherosclerosis was probably suggested for the first time by Shortell *et al.* in the 1990s [21]. More recent experimental studies as well as human observations suggested a link between premature atherosclerosis and APS [22–24], with both cellular and humoral immune responses being the common factors. Despite the possible relevance of plasma lipids, in the context of APS the main trigger would be an over reactive immune system. Thus, the relationship between atherosclerosis and APS is not exclusively related with traditional cardiovascular risk factors [25]. Instead, it is suggested that antiphospholipid antibodies may themselves induce pro-atherogenic immune responses, such as an increased oxidative status, endothelial activation and decreased fibrinolysis.

An important question is whether patients with primary APS differ from those with secondary APS associated with systemic lupus erythematous regarding the atherosclerotic burden. There are relatively few studies addressing this question. Belizna *et al.* studied intima media thickness (IMT), arterial stiffness, and the presence of plaques in APS patients and controls to evaluate the risk of atherosclerosis [26]. The study showed significant changes in all those parameters in patients with both primary APS and secondary APS in relation to controls, but with no relevant differences between the two study groups, suggesting that atherosclerosis could be an intrinsic finding in APS patients. Even when disease duration and the magnitude of complications are considered, no differences were found in any of these parameters for both groups [27].

A recent study demonstrated that traditional risk factors for cardiovascular disease are similar between patients with primary and secondary APS, although low levels of high-density lipoprotein (HDL) were found more frequently in patients with primary APS [28].

What are the common features between classical atherosclerosis & the vascular disease found in APS?

Lipid pathways

The primary lipid components of atherosclerosis are lipoproteins. Among these, LDL and HDL assume a central role.

High-density lipoproteins are thought to have an anti-atherothrombogenic effect by stimulating endothelial nitric oxide and inhibiting oxidant stress and inflammation [29], thus preventing LDL oxidation. LDL is the most pro-atherogenic lipoprotein owing to its ability to capture free radicals, becoming itself a powerful pro-oxidant.

High-density lipoprotein has several other anti-atherogenic properties, including the transport of cholesterol from peripheral tissues to the liver. The concept that macrophage cholesterol efflux has a significant role in cardiovascular disease prevention was recently suggested by the finding of a strong inverse association between HDL-mediated cholesterol efflux from macrophages and both carotid IMT and the likelihood of coronary heart disease [30]. These effects were shown to be independent of HDL-cholesterol level. Nevertheless, low levels of HDL increase the cholesterol burden in the arterial wall and macrophage-driven inflammation, and are strongly associated with an enhanced risk of coronary artery disease. Inflammation and other conditions that increase the risk of coronary disease involve the conversion of HDL to a dysfunctional form that is no longer cardioprotective [31], and instead acquire a pro-inflammatory and pro-oxidant phenotype promoting atherosclerosis [32,33]. Regardless of all these data, the underlying mechanisms are still unclear, and no widely accepted methods for determining HDL function in humans have been described. One possible mechanism for HDL dysfunction may be increased glycation with ApoA-I multimerization and decreased phospholipid content [34]. Furthermore, the importance of the humoral response towards HDL has been explored in APS [32,35]. It was demonstrated that the atheroprotective effects of HDL are largely impaired in patients with APS [36]. IgG anti-HDL present in these patients may hamper the antioxidant and anti-inflammatory effect of HDL favoring low-grade inflammation and enhanced oxidation in thrombotic APS [37]. LDL is the major cholesterol-carrying lipoprotein in plasma and may exist in different forms. oxLDL injures cells in artery walls, and HDL is able to inhibit LDL-induced cytotoxicity [38,39]. Small dense LDL, when compared with its larger, normal sized counterpart, is more easily oxidized, has a higher affinity for extracellular matrix and is subject to a higher degree of retention in the arterial wall [40–42]. In addition, small dense LDL has reduced binding to LDL receptors [43] and a longer 'half-life'. These facts can potentially lead to a greater degree of structural modification, which further increase its atherogenic profile.

Lipid peroxidation is a major feature of chronic inflammatory diseases, including APS [44,45]. Ames *et al.* found for the first time a positive correlation between a lipid peroxidation marker (F2-isoprostanes) and aCL titers [46]. The same group latter reinforced the relevance of oxidative stress in this context [45]. HDL-associated ApoA-1 has known anti-inflammatory properties [47,48] by promoting reverse cholesterol transport from macrophages *in vivo* [49], as well as by blocking contact-mediated activation of monocytes by T lymphocytes. Its anti-atherosclerotic actions rely mostly on the stabilization of the paraoxonase (PON)-1 enzymatic activity [50,51] and in the regulation of cholesterol homoeostasis by promoting the reverse cholesterol transport.

Paraoxonase-1 prevents the formation of lipid peroxidation products, such as oxLDL, that play a major role in endothelial cell dysfunction, monocyte chemotaxis, foam cell formation and plaque rupture [52]. Higher PON-1 activity is associated with a lower incidence of major cardiovascular events [53]. In APS, an inverse relationship between aCL antibodies and PON-1 has been described, which makes this pathological pathway an important factor. IgG autoantibodies against ApoA-1 have been found in APS and systemic lupus erythematosus, as well as in acute coronary syndromes [54]. A recent study demonstrated that they can be markers of plaque instability [55].

Immunologic intervenients

The involvement of macrophages and dendritic cells, activation of T cells, CD40–CD40 ligand interactions, endothelial dysfunction, oxidative stress, and an increase of cell adhesion molecules and platelet activation are common findings in both general atherosclerosis and APS [56,57].

As suggested by its importance as an antigenic target for antiphospholipid antibodies, β2-GPI plays a major role in atherosclerosis in APS. George *et al.* [58] have demonstrated, by immunohistochemical staining, that human atherosclerotic lesions display β2-GPI.

This glycoprotein is able to bind to negatively charged molecules such as heparin and oxLDL [8,59], and also apoptotic cells [60]. When interacting with specific antibodies, β2-GPI has a high affinity for both endothelial cells and activated platelets, which can be inhibited by annexin V. Matsuura *et al.* demonstrated that β2-GPI can bind to oxLDL and form oxLDL/β2-GPI complexes *in vitro* [61]. These complexes have been detected in patients with chronic inflammation and autoimmune diseases with a relevant atherothrombotic burden [62]. It has been suggested that the interaction of oxLDL with β2-GPI represents an antioxidant mechanism by blocking oxLDL deleterious effects. This is mainly accomplished by promotion of the clearance of oxLDL from the circulation. oxLDL/β2-GPI complexes are associated with disease severity and increased risk for adverse outcomes in patients with acute coronary syndromes [62]. It appears that stable oxLDL/β2-GPI complexes can promote the macrophage uptake and degradation of oxLDL and its intracellular accumulation [59]. β2-GPI is uptaken by macrophages via scavenger receptors only when complexed to oxLDL or with phosphatidylserine-containing vesicles. Furthermore, oxLDL/β2-GPI complexes increase the surface expression of CD36 and FcγRI. It is believed that this process facilitates the presentation of β2-GPI epitopes by macrophages or dendritic cells to autoreactive T cells [63], ultimately leading to the production of anti-β2-GPI antibodies in APS.

The pathogenic role of those antibodies has been demonstrated in mice models for thrombosis [64]. Interestingly, IgG antibodies directed against domain I of β2-GPI are more strongly associated with thrombosis and obstetric complications than those detected using the standard anti-β2-GPI antibodies [65].

Additionally, oxLDL/β2-GPI complexes were also shown to be antigenic targets for autoantibodies present in APS. IgG anti-oxLDL/β2-GPI antibodies have been shown to have a positive predictive value for venous (92%) and arterial (88.9%) thrombosis in patients with secondary APS [66]. An important finding that contributes to explain premature atherosclerosis in APS is the increased uptake of oxLDL/β2-GPI complexes by macrophages in the presence of anti-oxLDL/β2-GPI antibodies [59,67,68].

Antiphospholipid syndrome should not be regarded as an inflammatory disorder in the traditional sense. Nevertheless, higher levels of plasma C-reactive protein (CRP) have been found in these patients [69]. Furthermore, CRP has the ability to bind to phosphorylcholine moieties on apoptotic cells and oxLDL, constituting a very primitive form of innate immunity. CRP was also shown to enhance binding of oxLDL to macrophages via Fcγ receptors [70]. It is associated with a higher risk of cardiovascular disease, and elevated levels of CRP independently predict residual or recurrent symptoms in a cohort of antiphospholipid-positive patients with neurological manifestations (mainly stroke and transient ischemic attacks) [71]. The theoretical relevance of oxLDL, β2-GPI, oxLDL/β2-GPI complexes and IgG anti-oxLDL/β2-GPI complex antibodies has been demonstrated in *in vitro* and *in vivo* studies, but many interactions still remain unidentified.

Atherosclerosis versus thrombosis in APS

Some authors have tried to find an association between atherosclerosis and thrombotic complications in APS [72]. However, it is difficult to draw definite conclusions given the wide range of mechanisms involved. In addition, while the thrombotic events that are consequent to atherosclerosis are usually associated with intima disruption in the plaque zone, in the context of APS, thrombosis occurs in a greater proportion than would be expected in relation to the anatomic atherosclerosis burden. Given the pro-coagulant and pro-thrombotic state in this syndrome, there may be factors that contribute to an increased instability of the atheroma plaque in its early stages. Furthermore, it was demonstrated that thrombotic phenomena can occur long before the plaque ruptures [73].

The main risk factors for arterial thrombotic events in APS are lupus anticoagulant, hypertension, hyperhomocysteinemia, and hormone-replacement therapy or oral contraception. For venous thrombosis in APS, the principal risk factors are hypertriglyceridemia, hereditary thrombophilia and aCL IgG greater than 40 IU [74]. Other identified risk factors are hypercholesterolemia and concomitant autoimmune disease [75]. Thus, in addition to their mutual physiological mechanisms, arterial and venous thrombosis are associated by their common atherosclerosis risk factors.

Recent studies tried to determine if the factors provoking atherosclerotic lesions in arteries can also be responsible for deterioration of the veins [76], as venous thrombosis is frequent in APS, but the results are conflicting. Taking this discrepancy into consideration, it could be argued that thrombotic events in APS patients seem to be more related to thrombogenesis *per se* than to atherosclerosis.

Antiphospholipid antibodies promote activation of platelets (mainly if a previous thrombotic event had occurred), induce endothelial dysfunction (increasing the production of tissue factor, von Willebrand factor, tissue plasminogen activator, placental growth factor and soluble ICAM-1) and bind to enzymatic domains of serine proteases (e.g., thrombin, activated C protein, plasmin, tissue plasminogen activator and FIXa) [77], interfering with coagulation and fibrinolysis. Specific antibodies present in APS can also interfere directly with clotting (e.g., anti-FXa antibodies) [78] and fibrinolysis (e.g., antiplasminogen antibodies) [79]. Additionally, angiogenesis is implicated in APS-related thrombotic events: VEGF levels are higher in APS patients with arterial thrombosis. VEGF enhances the production of tissue factor by monocytes, and VEGF pathways are inhibited by β2-GPI [80]. Venous thrombosis in APS has also been associated with elevated plasma levels of stromal cell-derived factor-1 and PIGF [81].

Assessment of atheroma in APS patients

The ideal biomarker for atherosclerosis should mirror the extent of the atherosclerotic burden, be noninvasive, have a good sensitivity and specificity, predict disease in asymptomatic individuals and be available for widespread application. The diagnosis of atherosclerosis in the various vascular beds is usually made by the presence of symptoms. Presymptomatic screening could identify subclinical disease, emphasizing the increased need for aggressive treatment of atherothrombotic risk factors. Two questions then arise: what instruments are available for measuring the atherosclerotic burden in APS patients? Is there an association between these tests and clinical outcomes? Different laboratorial and imaging techniques are considered surrogate markers of the atheroma burden: the IMT in carotid arteries, vascular stiffness and the presence of atherosclerosis.

The available tools to assess atherosclerosis can be classified as anatomical, physiological and biological. The standard test to assess atherosclerosis since its inception is IMT and it is considered a marker of subclinical atherosclerosis. In the general population, IMT is a strong predictor of coronary artery disease [82,83]. When comparing patients with primary APS to sex- and age-matched controls, a greater IMT in primary APS was found [72]. In patients over 40 years of age compared with younger patients with APS and to patients with other thrombophilias, a greater IMT in primary APS patients was also detected [84]. Furthermore, high levels of both plasma homocysteine and IgG aCL antibodies are apparently independent predictors of IMT [85]. However, these are still conflicting results. Jiménez *et al.* showed that plaque prevalence in patients with primary APS is similar to that of controls [86], whilst Bilora *et al.* concluded that atherosclerosis was not a feature of primary APS by demonstrating the inexistence of an association between aCL and the presence of atherosclerotic lesions in that cohort [87].

The impact of atherosclerosis on hemodynamics can be assessed by the ankle brachial index (ABI), which is a good predictor for peripheral vascular disease, stroke and cardiovascular events in middle-aged and older populations. Barón *et al.* demonstrated an abnormal ABI in 19% of patients with primary APS compared with 4% in controls ($p = 0.026$) [88]. Interestingly, they did not find a correlation between abnormal ABI and traditional cardiovascular risk factors, nor with the presence of antiphospholipid.

Endothelial dysfunction can be assessed by biochemical analysis of markers of endothelial damage and activation. Furthermore, clinical assessment of endothelial dysfunction is possible by monitoring the vasodilator response evoked by increased flow shear (flow-mediated vasodilatation [FMD]) [89]. Diminished FMD in the brachial artery is an indicator of cardiovascular risk and considered to be a marker of atherosclerosis [90]. Stalc *et al.* proved that mean FMD is significantly lower in APS than in controls ($8 \pm 5\%$ vs $15 \pm 6\%$, $p < 0.001$) [91]. There was a correlation between the baseline diameter of the brachial artery and duration of the disease (-0.56, $p < 0.05$), between the concentration of VCAM-1 and FMD (-0.35, $p < 0.05$) and between ICAM-1 and FMD (-0.41, $p < 0.05$). Bilora *et al.* demonstrated that FMD of the brachial artery was significantly lower in patients than in controls ($6.3 \pm 5.2\%$ vs 18.2 ± 2.7; $p < 0.005$) and that FMD was significantly reduced in patients with IgM

aCL antibodies [92]. Further, in a recent study by Cugno *et al.* [93], APS patients displayed endothelial dysfunction in the absence of other detectable traditional risk factors for atherosclerosis. Plasma levels of soluble adhesion molecules (e.g., s-ICAM-1, s-VCAM-1 and s-E-selectin), soluble thrombomodulin, von Willebrand factor, tissue plasminogen activator and circulating endothelial cells were higher and brachial artery FMD was impaired in 40 selected APS patients and 40 age- and sex-matched healthy subjects. Interestingly, the same investigators also reported normal IMT values and lack of plaques in carotid arteries in patients with primary APS, which contradicts the hypothesis of accelerated atherosclerosis. Still, one can assume that the endothelial dysfunction is responsible for an atherosclerotic process only detectable after a more prolonged follow-up period. Alexanderson *et al.* evaluated endothelial function in patients with primary APS by assessing myocardial flow reserve and endothelial-dependent vasodilation index using PET [94]. The study confirmed an increase in endothelial dysfunction, an early marker of atherosclerosis, in these patients.

Charakida *et al.* published an interesting study combining some possibly important tools for assessing atherosclerosis patients with primary APS [36]. They studied 77 women with positive APS and 77 controls matched for age and cardiovascular risk. Carotid IMT, FMD, pulse wave velocity and PON-1 activity were measured in all patients, as well as the anti-inflammatory and antioxidant properties of HDL. The results were as follows: women with APS had greater IMT and pulse wave velocity compared with controls (mean [SD]: 0.75 [0.16] vs 0.64 [0.09] mm; $p < 0.001$; and 9.2 [1.6] vs 8.5 [1.8] m/s; $p = 0.04$) and lower flow-mediated dilatation (6.2% [4.1%] vs 9.6% [4.2%]; $p < 0.001$). PON-1 activity was inversely associated with IMT and pulse wave velocity in women with APS but not in the control group. This study is perhaps one of the best in establishing a link between biochemical and functional characterization of APS vasculopathy.

Globally, it seems that in APS, atherosclerosis should only be assessed by functional and biological tests, as anatomical measures do not correctly estimate the atherosclerosis burden in these patients.

Despite the establishment of an increased IMT of patients with APS, a question remains: are the differences found significant when compared with other populations? Taking this into account, Ames *et al.* found that IMT measures of carotid bifurcation of patients with APS with a mean age of 49 years were 0.693 ± 0.171, with a mean IMT of 0.556 ± 0.162 mm across the studied population [95]. As a simple comparison, patients with diabetes mellitus, a major cause of atherosclerosis, have a much thicker carotid artery intima. Sigurdadottir *et al.* found that newly diagnosed patients with diabetes and patients with established diabetes may have an average IMT of 0.85 ± 0.0315 mm and 0.87 ± 0.0315 mm, respectively [96]. Thus, although a head-to-head comparison cannot be made, even in the studies that showed an increased IMT in patients with APS, those values were not even close to the magnitude that has been found in other populations with atherosclerosis-associated diseases.

Arterial stenosis in APS

Atherosclerosis is a common cause of arterial stenosis in the general population. Many observational studies have demonstrated the association between APS and arterial stenosis affecting different territories. Evidence of the involvement of renal, celiac, mesenteric, intracerebral and limb arteries has been reported [97–100]. Interestingly, these case reports in patients with APS document arterial stenosis with features that are different from patients with general atherosclerosis or fibromuscular dysplasia: the stenosis is regular, well defined and only partial. Histologically, a predominance of fibro-elastic thickening of the intima and smooth muscle hyperplasia appears to exist [101]. In addition, some reported cases of arterial stenosis associated with APS diminish with anticoagulation. Thus, it appears that arterial stenosis in APS is mostly dependent on factors different from the ones found in traditional atherosclerosis, and maybe the traditional tests to assess atherosclerosis-related stenotic lesions are not adequate to study APS patients. Measuring the size of the atheroma plaque may not be enough and new tools to assess the plaque phenotype are needed. There is hope that ultrasonography methods and high-resolution MRI will be useful tools [102].

Perspectives on the treatment of atherosclerosis in APS

The increasing necessity for screening and aggressive treatment of traditional cardiovascular risk factors has led to the use of drugs with immunomodulatory or immunosuppressive

actions, in addition to classic antithrombotic and antiplatelet therapies. Of all the drugs that have been proposed, two emerge as strong candidates to be included in the baseline treatment of this syndrome: statins and hydroxychloroquine.

Statins

In the last two decades, an increasing number of pleotropic actions of hydroxyl-3-methylglutaryl coenzyme A inhibitors (statins) has been reported. Current understanding of its actions goes beyond cholesterol lowering, and includes immunomodulatory properties that have directed attention has been directed towards their potential as therapeutic agents for the treatment of autoimmune diseases.

Statins can reduce the adhesiveness of endothelial cells promoted by anti-β2-GPI antibodies, thus diminishing endothelial activation [103]. They can also reduce the expression of certain adhesion molecules, such as CD11 and LFA-1 on leucocytes [104] and ICAM-1 and P-selectin on endothelial cells [105]. Furthermore, these drugs have been associated with an improvement of fibrinolytic activity and a decrease of platelet aggregation [106]. A recent pilot study of fluvastatin in patients with this condition demonstrated that 40 mg of fluvastatin per day was able to decrease concentrations of both inflammatory and thrombogenic mediators [107].

As a consequence of cumulative data supporting immune-related benefits from the use of statins, it has been suggested that these drugs should be administered to APS patients regardless of their cholesterol levels, but specifically designed efficacy trials are needed to support this decision.

Hydroxychloroquine

Several mechanisms have been proposed to explain the beneficial effects of hydroxichloroquine, such as the reduction of proteolysis and antigen presentation [108], the inhibition of T-cell receptor and B-cell antigen receptor-induced calcium signaling [109], and the inhibition of Toll-like receptor signaling [110]. Hydroxychloroquine also reduces the binding of antiphospholipid antibody–β2-GPI complexes to phospholipid bilayers [111], reverses platelet activation induced by human IgG antiphospholipid antibodies [112] and contributes to the reduction of antiphospholipid antibody-induced thrombosis [113]. These findings raise the possibility that hydroxychloroquine may be an alternative approach to treating APS.

Final comments

The APS is characterized from a clinical point of view by the presence of thrombotic events that could represent an expression of atherosclerosis-associated clinical features. Furthermore, there are a number of common biologic findings that suggest that APS could be a form of accelerated atherosclerosis. Vascular function has also been assessed and arteries from patients with APS seem to be dysfunctional in a similar way to the ones found in the non-APS population. However, despite the striking similarity of mechanisms present in the pathogenesis of APS and general atherosclerosis, the real burden of anatomical disease is still a matter of controversy since many clinical studies failed to show a significant presence of anatomical changes in patients with APS. Some argue that atherosclerosis is not a predominant pathological phenomenon in APS, and that thrombosis related to thrombophilia is more important. In fact, perhaps atherosclerosis is not occurring as fast in APS patients as it has been proposed initially: thrombosis is much faster.

Future perspective

The APS is characterized by an activation of major pathways associated with endothelium dysfunction and thrombogenesis. These pathways are linked to an increased rate of thrombosis and admittedly atherosclerosis. Nevertheless, the activation of such mechanisms is dependent on initiating factors that have not been established in either APS or general atherosclerosis.

Identifying those factors that trigger APS might be as important as pinpointing the key structures or mechanisms that induce the full cascade of events.

Future research should focus on the recognition of the most important events that activate the nonreturn pathways seen in atherogenesis. In parallel, the identification of the possible external variables that lead to the beginning of the disease, as well as the definition of the phenotypes that make subjects vulnerable to that particular trigger are crucial for the identification of a definitive treatment.

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Executive summary

- Antiphospholipid syndrome has been recognized as an atherosclerosis-associated disease.
- This association is based on the coincidence of multiple pathways identified in both conditions.
- Endothelium dysfunction induced by inflammation and immune activation leads to vascular disease, already demonstrated at a biologic and functional level.
- In antiphospholipid syndrome, the anatomic evidence for atherosclerosis is not so compelling, suggesting that thrombosis itself might play a more relevant and direct part in the progression of disease.

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