

Atherosclerosis in Autoimmune Rheumatic Diseases—Mechanisms and Clinical Findings

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Abstract Atherosclerosis is one of the major entities leading to morbidity and mortality in the western world. It is known now that atherosclerosis cannot be explained merely by the presence of the Framingham traditional risk factors and that autoimmunity takes a significant role in its pathogenesis. It is also known that individuals with autoimmune diseases demonstrate increased incidence of cardiovascular manifestations and subclinical atherosclerotic disease. The mechanisms for the assumed accelerated atherosclerosis in diseases such as systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, and systemic sclerosis include the classical risk factors, but may also be due to chronic inflammatory processes and immune dysregulation. Autoantibodies, autoantigens, pro-inflammatory cytokines, and infectious agents play a role in that process. Involvement of autoimmunity in the pathogenesis of accelerated atherosclerosis in rheumatic diseases and the common pathway that leads to this condition may lead to significant change in prevention of treatment.

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Introduction

Rheumatic diseases constitute a diverse group of conditions characterized by autoimmunity and chronic systemic inflammation. They are also associated with increased mortality compared to the general population [1, 2]. Due to the significant progress in the treatment of these patients, their long-term survival has improved, allowing comorbid conditions and late sequela of disease to become more apparent [3], with atherosclerosis playing a major role [3, 4].

Atherosclerosis is a widespread pathologic process of medium to large arteries responsible for cardiovascular disease (CVD), such as myocardial infarction (MI) and stroke—amongst the main etiologies for morbidity and mortality in the western world [5, 6]. The nature of atherosclerosis and cardiovascular disease was considered degenerative, and cardiovascular morbidity was believed to be attributed to “traditional” risk factors, such as high blood pressure, cigarette smoking, hypercholesterolemia, diabetes mellitus, obesity, left ventricular hypertrophy, family history, and estrogen replacement therapy [7]; however, growing evidences show that atherosclerosis cannot be fully explained by these traditional factors alone [8], and recent data support the assumption that atherosclerosis is an inflammatory autoimmune disease [4].

The role of inflammation in atherosclerosis

All arms of the immune system take part in atherosclerosis formation.

The involvement of cellular immunity

Immunohistologic observations revealed that the primary cells to appear in the arterial intima in future atherosclerosis sites are lymphoid cells [8]. T cells are abundant in the atherosclerotic plaques, and TH1 lymphocytes with their pro-inflammatory cytokines (TNF- α , IFN- γ , IL-2) dominating over TH2 lymphocytes, releasing anti-inflammatory mediators such as IL-4, IL-5, and IL-10 [8]. They appear in the arterial intima as early as in 1-year-old children in lesions called “fatty streaks” [8]. Cytotoxic CD8⁺ T cells also take present in atheromatous lesions, but are less abundant [8].

The T cell significance in atherosclerosis is implied by animal studies in which depletion of CD4⁺ and CD8⁺ T cells reduced fatty streak formation in C57BL/6 mice and another study showing 73% reduction in aortic fatty streak lesions in the offspring of homozygous apolipoprotein E knockout (APOE^{-/-}) mice, crossed with immunodeficient homozygous SCID MICE compared with immunocompetent Apo E ^{-/-} mice [4].

Balance shift toward Th1 domination, in turn, contributes to the production of T-cell-derived cytokines that favor smooth muscle cell migration and proliferation and, as a consequence, extension of the atheromatous plaque [9]. Patients with acute coronary syndromes have a subtype of CD4⁺ T cells lacking the co-stimulatory molecule CD28. These cells have a tendency to produce IFN- α , which is a potent monocyte activator. Moreover, CD4⁺ CD28^{null} cells invade unstable plaque, contributing to reduced collagen synthesis and killing endothelial cells by their cytotoxic capability, further weakening the fibrous cap [10].

Macrophages also contribute to the plaque formation. Their differentiation is associated with the upregulation of receptors for innate immunity, including scavenger receptors that mediate endocytosis of particles, such as oxLDL, thus promoting foam cell formation, and toll-like receptors (TLRs), which initiate a cascade of macrophage activation and release of vasoactive molecules such as nitric oxide (NO), reactive oxygen which induces oxidation and toxicity of lipoproteins, endothelins, eicosanoids, and proteolytic enzymes, all of which lead to the destabilization of plaque and increased risk for its rupture [6]. Endothelial cells, mast cells, and dendritic cells also have a role in atheromatous plaque formation through their TLR receptors, but their contribution is not fully understood [6].

Autoantigens

Oxidized low-density lipoprotein (OxLDL) is a molecule generated by lipid peroxidation of polyunsaturated fatty acids in the phospholipids and cholesteryl esters. During this process, reactive aldehydes are produced, which, by

binding to lysine and histidine residues in the apolipoprotein B (ApoB) component of LDL, produce immunogenic neoepitopes [6]. In fact, OxLDL is a huge molecule composed of multiple autoantigens with different properties, some of them aggravating atherosclerosis, but others may suppress atherogenesis [4]. The antigens are presented by dendritic cells and macrophages, giving rise to clonal expansion of OxLDL specific T cells and autoantibodies. These cells constitute 10% of T cells in human atheromatous plaques and are also found in the circulation [10].

Increased OxLDL antibodies are found in patients with early-onset peripheral vascular disease, carotid atherosclerosis, and coronary artery disease (CAD), being predictive of progression of atherosclerosis to MI and death [6].

Another autoantigen is β 2GPI, a polypeptide that binds to negatively charged molecules and plays a part in the clearance of apoptotic cells and inhibition of coagulation. It is considered to be the autoantigen in antiphospholipid syndrome (APS). β 2GPI is found in atherosclerotic lesions and colocalizes with immunoreactive CD4⁺ lymphocytes [11]. Patients with atherosclerosis and other inflammatory conditions display autoantibodies against it. Immunization with this polypeptide results in accelerated atherosclerosis in mice [6].

Heat shock proteins (HSPs) are a family of proteins well conserved across species [4]. HSP60 is expressed by vascular cells in response to stressful events such as infections, fever, cytokines, oxidative stress, and mechanical injury. HSPs facilitate refolding of denatured proteins and loading of immunogenic peptides to major histocompatibility class I and II molecules. It is assumed that the endogenous HSP60 becomes immunogenic as a consequence of molecular mimicry of HSPs expressed by pathogens such as *Chlamydia pneumonia* and *Helicobacter pylori*. The antibodies formed against HSP60 and 65 mediate lysis of stressed endothelial cells in vitro and are elevated in patients with cardiovascular disease [11]. There are also data showing the existence of oligoclonal T cells within atherosclerotic plaques that can recognize hHSP60 specifically, in contrast to T cells more distant from the lesion [12].

Dying cells in the atherosclerotic plaque can die via apoptotic or necrotic pathway. Cells going through apoptosis are removed by dendritic cells and macrophages, a process involving an anti-inflammatory response, without causing injury to the surrounding tissue. In contrast to that, the process of necrosis or the delayed uptake of apoptotic cells induces activation of inflammatory response and a higher risk for development of autoimmunity [10].

Inflammatory markers

CRP is an acute phase protein and a marker of systemic inflammation. There is inconsistency of data regarding the association between atherosclerosis and levels of CRP [13],

with evidences supporting higher levels of CRP as a marker to increased burden of atheromatous plaque [14]. A possible mechanism of CRP's active role in atherosclerosis is assumed to be via activation of the complement system and induction of pro-inflammatory cytokines such as IL-6 [15–16]. Other studies, in human and animal models, failed to show that connection [17, 18].

The active role of inflammatory markers, including fibrinogen, metallic metalloproteinase-9, TNF- α , IL-6, and many others, is still indefinite, with further research warranted [13].

Infections

There are several pathogens implicated as contributors to the process of atherosclerosis, among them *C. pneumonia*, *Mycoplasma pneumonia*, and *H. pylori*, cytomegalovirus (CMV), Epstein–Barr virus, and herpes simplex virus type 1 [6]. The most established evidence attributed to CMV. Its seropositivity correlates with atherosclerosis, restenosis after coronary angioplasty, and transplant vascular stenosis. CMV targets endothelial cells and induces expression of intercellular adhesion molecule 1 (ICAM-1) and several chemokines. CMV also induces autoimmunity through the mechanism of molecular mimicry: Sera of patients with CAD show high prevalence of antibodies against an 11-amino acid epitope of HSp60 molecule, which shares homology with hCMV-derived proteins. These antibodies recognize molecules present on the surface of stressed and unstressed endothelial cells, causing endothelial damage [19].

H. pylori is another ubiquitous pathogen associated with atherosclerosis. It is assumed that the heat shock protein 60 of Hp origin shares a close similarity to human HSP60, especially in the Glu¹⁴¹–Leu¹⁶⁰ sequence. This similarity contributes to the generation of autoantibodies and further generation of vascular damage [20].

Accelerated atherosclerosis in SLE

Systemic lupus erythematosus (SLE) is an autoimmune multi-systemic disease involving all body organs. It is well established that SLE involves early atherosclerosis. Moreover, it is now considered the leading cause of morbidity and mortality of these patients. Epidemiological data show an estimated 50-fold increased risk of MI in SLE women in the age group of 35 compared with age- and sex-matched controls [21] (6%–10% prevalence of cardiovascular events, with 1.5% annual incidence) [22–24]. SLE has a bimodal mortality pattern, with an early phase attributed to the disease activity and the late phase to cardiovascular manifestations [25]. A study comparing intima-media thickness (IMT) by B-mode ultrasound, as a marker of the

presence of atheroma, between SLE women with a history of CVD with age-matched SLE women without CVD and controls showed higher IMT levels in SLE patients with history of CVD compared to SLE patients without this history, thus supporting the role of atheromatous plaque rather than thrombosis in vascular occlusion. However, no difference was found between IMT levels of SLE patients without CVD and controls [26]. More recent studies demonstrated higher incidence of plaques in SLE patients compared to controls [27, 28]. Using carotid ultrasound to evaluate plaque burden, increased presence of atherosclerotic plaque in SLE patients was demonstrated compared to controls [27]. Another method being used to evaluate the atherosclerotic burden is high-resolution computed tomography (CT), which also helped to prove higher incidence of atherosclerosis in SLE patients [29].

Risk factors for atherosclerosis in SLE

The risk factors for atherosclerosis in SLE are a combination of traditional and non-traditional risk factors. The former includes hypertension [30] as well as diabetes mellitus, high levels of very low-density lipoproteins (VLDL)-cholesterol triglycerides and homocysteine [30, 31, 35, 33]. Another important risk factor to be considered is smoking [32, 33]. The use of antidepressants was also associated with increased risk for atherosclerosis [34]. Older age at diagnosis and longer disease duration account for higher risk [27, 35], although disease duration in other studies is not associated with increased risk of CVD [26]. Other possible risk factors are higher damage index score, absence of use of cyclophosphamide and hydroxychloroquine, absence of anti-Sm antibodies [27], and renal disease and failure, which are associated with lipid peroxidation [36]. Given the fact that women are the main “candidates” for SLE, being pre- or postmenopausal, may influence the risk for developing cardiovascular disease [31].

Autoantibodies

OxLDL It was demonstrated that OxLDL levels are higher in SLE patients. Titers of IgG anti-OxLDL are higher in hypertensive SLE patients than in normal controls, and there is a good correlation between the values of IMT and the titers of this antibody. IgG antibodies to OxLDL seem to have a role in the development of subclinical atherosclerosis in SLE patients, while IgM is considered to have a protective role [37].

β 2GPI both IgG and IgM levels of antibodies against this protein are elevated in SLE atherosclerosis, but the increased levels do not seem to correlate with IMT [38].

HSP60/65 Levels of antibodies against HSP60/65 are elevated in patients, but no correlation between their levels and IMT is demonstrated [38].

OxLDL/ β 2GPI complexes and anti-oxLDL/ β 2GPI The levels of this complex are elevated in the circulation of SLE patients, with no association to disease activity. It might be related to chronic vascular inflammation and oxidative stress in autoimmune diseases. IgG anti-oxLDL/ β 2GPI is significantly elevated in SLE patients, especially those with APS. It is also correlated with renal disease in SLE, most probably because of increased oxidative stress. No correlation was found between the antibodies and subclinical atherosclerosis in SLE [38].

Other autoantibodies Antibodies against Smith antigen and RNP and aCL antibodies are associated negatively with atherosclerosis, and antibodies against endothelial cells (aECs) do not show clear association to atherosclerosis in the context of SLE [39].

Dyslipidemia

The “lupus pattern” of dyslipoproteinemia consists of low high-density lipoprotein (HDL), raised triglycerides (TGs), unchanged or modestly elevated LDL, and raised lipoprotein(a) (LP(a)). Strong correlation is described between elevated TGs and low HDL to disease activity. It is assumed that dyslipoproteinemia in SLE is influenced by the pro-inflammatory cytokine TNF- α . TNF- α causes increase in TGs and in VLDL. HDL is atheroprotective through reverse cholesterol transport, antioxidant properties, and HDL-associated apolipoprotein A-1-which can decrease levels of TNF- α . The decrease in its levels contributes to the elevated risk of atherosclerosis in SLE [39]. Elevated TGs can also be the consequence of elevated levels of the antibody to lipoprotein lipase (anti-LPL) in SLE patients, which is associated with increased triglyceride levels, disease activity (SLEDAI), erythrocyte sedimentation rate, and CRP levels [39].

Role of medications

Glucocorticoids have a pivotal role concerning atheroma formation; their effects on lipid metabolism (elevations of total cholesterol, ApoB, and TGs, especially when used in high concentrations), blood pressure, and glucose metabolism have the potential to promote atherosclerosis [40]. There are evidences supporting the association between glucocorticoid treatment and increased cardiovascular risk [38], while another study showed lower prevalence of carotid plaques associated with treatment of low levels of glucocorticoids without being exposed to cyclophosphamide. This positive effect might be the result of a better disease control [27].

Antimalarias exert a positive effect through their control over inflammation, improvement of lipid profile, and lowering the cholesterol level [41].

Accelerated atherosclerosis and rheumatoid arthritis

Rheumatoid arthritis (RA) is another systemic autoimmune disease associated with reduced life expectancy, as demonstrated by standardized mortality ratios of 0.87:3 [42] or as shown by 2.5 years decrease in life duration among women suffering from RA [43]. The main cause of cardiovascular disease mortality among RA patients is ischemic heart disease (IHD) [42]. The relative risk of cardiovascular disease in RA is lower than that documented for SLE, and the link between RA and stroke seems to be weaker than the link between stroke and SLE [44]. It is not clear whether the increased mortality from IHD in these patients is a consequence of accelerated atherosclerosis, or, alternatively, the result of delayed diagnosis due to the possible masking of IHD symptoms by disease features [9]. Examinations of carotid IMT shows greater values of IMT in RA patients compared to controls, both in established [45, 46] and new onset disease [47]. Advanced age is considered a strong risk factor [48], but cannot stand by itself [47]. When comparing the “traditional” Framingham risk factors of patients with RA to the general population, it can be seen that patients with long-standing disease have higher risk score compared to early disease patients or control subjects, as opposed to SLE patients who share similar scores in comparison to controls [49]. The differences in the Framingham risk scores are attributed to higher rates of smoking and higher values of systolic blood pressures among patients with long-standing disease [49]. Cigarette smoking is a risk factor for the development of RA and has a dose-dependant relationship with disease severity and rheumatic factor production; however, it was not proven to increase mortality from CVD in these patients [50]. The presence of the novel autoantibodies anti-cyclic citrullinated peptides (anti-CCP), which might be associated with smoking, is correlated with subclinical atherosclerosis in RA [51].

Dyslipidemia

There are no well-established evidences for the features of lipid profile in RA. The assumed profile characteristic of RA is of decrease and increase in small LDL level alterations which are most probably due to a secondary effect of inflammation rather than primary metabolic alterations of RA [51].

Chronic inflammation is characterized by release of collagen breaking mediators, which has a role in the destabilization of atherosclerotic plaques. These mediators are also responsible for the erosion of bone and cartilage into the RA joint. That is why a disease more diffuse, with

involvement of the lungs and vasculitis, is associated with higher CVD mortality [51].

Endothelial dysfunction is considered as a pathological stage prior to atherosclerosis and can be assessed by the measurements of flow-mediated vasodilatation (FMD), which is an endothelium-dependent dilatation, versus nitrate-mediated dilatation (NMD), which is endothelium-independent. Recent data demonstrate low values of FMD, with preserved values of NMD among RA patients compared to controls. The low values of FMD correlates with higher cIMT values, age, and anti-double-stranded DNA (dsDNA) levels. It is also associated with several other inflammatory markers such as the possible involvement of anti-CCP, anti-dsDNA, Lp(a), cytokines, and PON-1 activity, providing support to the assumption that endothelial dysfunction in RA is a result of chronic inflammation [52].

Autoantibodies are associated with elevated risk to atherosclerosis in patients with SLE; however, the same antibodies that are assumed to play a role in SLE do not correlate with increased risk of atherosclerosis in RA patients, as is demonstrated by a recent study. Anti-Hsp 60, anti-Hsp 65, anti- β 2GPI, anticardiolipin (aCL), anti-CCP, or anti-lipoprotein lipase (anti-)LPL were studied, with only anti-CCP being elevated in RA. Patients positive to these antibodies did not show elevated IMT [53], CRP, and ESR levels.

This difference is not demonstrated between inactive RA patients and controls. These proteins—native and oxidized—are thought to be acute phase reactants and to contribute to accelerated atherosclerosis [54].

CD4+CD28 T cells, as was mentioned above, relate to increased risk of atherosclerosis. They are elevated in RA patients, contribute to endothelial dysfunction in them, and to atherosclerosis as a late consequence [50].

Accelerated atherosclerosis in antiphospholipid syndrome

Antiphospholipid syndrome is a prothrombotic state characterized by recurrent thrombosis—arterial and venous—recurrent pregnancy loss, and the presence of antiphospholipid antibodies (aPL) [50].

Clinical evidence for prediction of vasculopathy in APS include ankle brachial index (ABI)—a method used to assess risk for developing peripheral vascular diseases. Patients with APS showed abnormal ABIs [55].

Elevated values of IMT are found in APS [56]. High levels in these patients associated with increased incidence of stroke [57]. Other studies implied endothelial dysfunction in these patients by demonstrating reduced FMD in aPL-positive patients [57]. These data are inconsistent with

another recent study documenting normal FMD values similar to of age- and sex-matched controls, suggesting normal endothelial function, and opposed the assumption regarding the vasculopathy of APS as of atherosclerotic nature rather than thrombotic [58].

Many studies were performed in order to establish the role of APS antibodies in the development of atherosclerosis; analysis of patients positive to aPL show increased risk of venous thrombosis associated with lupus anticoagulant positivity as opposed to peripheral artery thrombosis which was related to aPL positivity alone, establishing the role of aPL in atherosclerosis [58].

Other proatherogenic factors in APS consist of anti-HDL antibodies, oxLDL, β 2GPI, antibodies against the complex oxLDL/ β 2GPI, and antibodies against HSP60/65 [50]. Evidence for aPL as a proatherogenic factor is conflicting; some work demonstrate its connection to myocardial infarction, while others fail to do so [59, 60].

Accelerated atherosclerosis in SSc

Systemic sclerosis (SSc) is a systemic autoimmune disease featured by widespread vascular damage, which was believed, until recently, to consist mainly of microvascular damage [61]. New evidence suggests the possible existence of atherosclerosis (which is a medium–large arterial disease) in SSc; however, these data are inconsistent [62]. There are reports of myocardial perfusion defects by single photon emission CT analysis and impaired coronary flow reserve evaluated by transthoracic echocardiography [62–64], but there is yet no clear evidence of plaque. Cerebrovascular disease, in contrast to lupus, is not demonstrated [62].

Noninvasive methods were used to assess subclinical atherosclerosis in SSc, including IMT and IBPI, with contradicting results [65, 66]. Studying other variables such as traditional risk factors, disease duration, patients' age, the presence of anticentromer or antitopoisomerase antibodies, ANA, and the type of SSc (limited and diffuse and abnormalities in lung function tests), shows that only patients' age is associated to increase risk of atherosclerosis, an association opposed by some studies [67, 68].

Evaluations of endothelial dysfunction in SSc patients, through measurements of FMD and NMD, show impaired carotid FMD, with preserved values of NMD data supporting the assumption of increased tendency to accelerated atherosclerosis [67].

Mechanisms of accelerated atherosclerosis in SSc:
Autoantibodies

HSPs There is inconsistency of data regarding the presence of increased titers of these antibodies with SSc [68, 69],

with the finding of positive correlation between the presence of IgM anti HSP-65 antibodies and increased carotid IMT in them [68].

Antibodies against OxLDL Not all the works demonstrate increased titers of these antibodies [70], and others show elevations of them specifically in the limited [71] or diffuse cutaneous form [72].

aPL There is evidence suggesting association of elevated aPL, including aCL, lupus anti-coagulant, and β 2GPI with increased rates of clinical manifestations of vasculopathy and severity of capillary involvement in SSc patients [73]. Again, some works fail to show the connection [74].

ACE polymorphism

Angiotensin-converting enzyme (ACE) polymorphism is the result of insertion/deletion. The resultant genotypes are DD, II-homozygote, and the DI, which is heterozygote. The DD allele is associated with highest circulating ACE levels, II with the lowest. There is evidence suggesting association of the DD phenotype, increased IMT, endothelial dysfunction, and cerebrovascular disease. This association might be explained by decreased bradykinin activity, resulting in a reduction of the receptor-mediated release of NO by carriers of this allele. D allele is more frequent among SSc patients, and its carriers develop more severe vascular injury [75, 76].

Lipid profile

The lipid profile in SSc is characterized by low HDL levels, together with normal LDL levels, and raised Lp(a). The reduced protective effects of HDL [77] and the raised levels of Lp(a), which, together with CRP acts as an acute phase reactant, contribute to propagation of inflammation and promotion of atherosclerosis [78].

Infections hCMV antibodies are elevated in SSC, probably due to sharing of homologous epitope with Topoisomerase-I and by the mechanism of molecular mimicry, resulting in activation of autoreactive B cell clones, further resulting in apoptosis and endothelial damage [79].

Conclusions

The recent years changed our concept of atherosclerosis from a merely degenerative disorder to inflammatory autoimmune disease in which all parts of the immune system take a role [80–84]. The well-known Framingham “traditional” risk factors of atherosclerosis could not give a

full explanation for its etiologies and progression, and autoantigens, oxidative stress, chronic inflammation, and infectious agents were added to the equation.

Another observation was the increased incidence of atherosclerosis in rheumatic diseases, with the failing attempts to explain this finding with the traditional risk factors, which, with exception of RA, were similar to age- and sex-related controls.

Immune mechanisms proposed to explain the accelerate atherosclerosis in rheumatic diseases are almost similar in the autoimmune diseases studied, with domination of autoantibodies to HSP60/65, OxLDL, β 2GPI, OxLDL/ β 2GPI complex, dyslipidemias, and oxidative stress and others. Evidence of accelerated atherosclerosis and the suggested etiologies above are being established, with SLE, RA, and APS showing stronger evidence than other rheumatic diseases such as SSc. This inconsistency of data is partly associated with the small size of populations studied.

Establishing the role of the immune system in the generation of atherosclerosis is of high importance because of its potential influence regarding the treatment. Assuming immune etiologies for accelerated atherosclerosis in rheumatic diseases, emphasis should be made to control disease activity and inflammation or to modulate pathways related to proatherogenic pathways. Larger scale studies should be executed, taking into account both traditional and novel risk factors to atherogenesis in autoimmune disease.

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