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REVIEW

Endothelial activation, endothelial dysfunction and premature atherosclerosis in systemic autoimmune diseases

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ABSTRACT

Atherosclerosis may be considered an inflammatory disease characterised by the development of atherosclerotic plaques and ischaemic cardiovascular events. Increased prevalence of cardiovascular morbidity and mortality due to (premature) atherosclerosis has been observed in patients with autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Wegener's granolumatosis. This increased prevalence cannot be explained by the presence of the traditional cardiovascular risk factors such as hypertension, hyperlipidaemia, diabetes mellitus and smoking. Therefore, other risk factors must be present in patients with systemic autoimmune disease. Although the mechanisms have not been fully unravelled, endothelial cell (EC) activation through autoantibodies seems to be one of the factors involved. EC activation results in EC dysfunction. It is supposed that chronic EC dysfunction, as present in patients with systemic autoimmune disorders, contributes to the development of premature atherosclerosis and results in an increased prevalence of cardiovascular disease.

INTRODUCTION

The endothelium is a physical barrier between the blood and the underlying tissues. Healthy endothelial cells (EC) are essential for the maintenance of vascular homeostasis since they synthesise and express different vasoactive substances and molecules. EC are responsible for the continuous adjustment of vascular tone, control of blood pressure, regulation of leucocyte traffic from blood to tissues and the maintenance of antithrombotic and anticoagulant balance in flowing blood. They are also involved in the control of growth, development and differentiation of the vessel wall, and solute flux and fluid permeability across the vessel wall. Furthermore, EC are involved in platelet adhesion and aggregation, and blood coagulation and fibrinolysis.[1]

The vascular tone is controlled by synthesis and secretion of two vasodilators, (prostacyclin (PGI_2) and nitric oxide (NO), endothelium-derived hyperpolarising factor, CO and the vasoconstrictors endothelin-1, thromboxane A2 and endoperoxidase. The careful balance between these mediators provides minute-by-minute control of tone and blood pressure. Leucocyte migration is controlled by expression of adhesive molecules capable of attracting and firmly attaching leucocytes after stimulation with thrombin, cytokines or endotoxins. The main transmembrane proteins involved in the capture and rolling of leucocytes are P-selectin, E-selectin, L-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1).

A network of events that involves interaction of thrombin with EC controls platelet function, coagulation and fibrinolysis and contributes to the maintenance of normal blood fluidity by anticoagulant and antiplatelet effects. This process includes synthesis and secretion of NO, PGI_2, platelet-activating factor (PAF) and von Willebrand factor (vWF), and an increase in solute permeability between EC. For control of fibrinolysis, EC secrete tissue plasminogen activator (tPA) and its inhibitor plasminogen activator inhibitor-1 (PAI-1).

Loss or dysregulation of these homeostatic mechanisms, due to activation of EC, characterises EC dysfunction and results in an inflammatory response leading to atherosclerosis.[2] The inflammatory response is reflected by elevated

levels of high-sensitivity C-reactive protein (hsCRP) and seems to be a promising marker of atherosclerotic activity.[3,4] Prospective studies in the general population have shown that levels of hsCRP, but also of other acute-phase reactants like interleukin-1, are related to the future risk of cardiovascular disease.[5-7]

ENDOTHELIAL CELL ACTIVATION

EC can be activated by stimulation with different agents such as interleukin-1, several autoantibodies and modified low-density lipoproteins (LDL).[8] EC activation is characterised by five main changes: loss of vascular integrity, increased expression and shedding of leucocyte adhesion molecules, change in phenotype from antithrombotic to thrombotic, production of several cytokines, and upregulation of HLA molecules. These changes allow EC to participate in the inflammatory response. The enhanced expression of adhesion molecules and chemoattractants provides an environment for leucocyte adhesion and migration of these cells into the vessel wall. Thrombosis can occur. Furthermore, activation of leucocytes leads to release of enzymes, cytokines, chemokines and growth factors resulting in a cascade of events accumulating in smooth muscle cell proliferation and formation of plaques.[2,9]
In systemic autoimmune diseases like systemic lupus erythematosus (SLE) as well as in vasculitides such as Wegener's granulomatosis, inflammation of many organ systems can occur. The presence of EC activation has been demonstrated indirectly by the elevation of circulating levels of soluble adhesion molecules, thrombomodulin and NO.[10-18] Furthermore, surface protein expression of VCAM-1, ICAM-1 and E-selectin on EC is increased.[19]
The nature of this EC activation is unknown. It has been suggested that next to the presence of the classical risk factors for atherosclerosis, disease specific factors are involved. In particular, autoantibodies directed to phospholipids, endothelial cells, double-stranded DNA (dsDNA) and ribonucleoproteins (nRNP) can induce EC activation *in vitro*.[20-24] Also antineutrophil cytoplasmic antibodies (ANCA) are implicated in EC activation, although presumably to a lesser extent.[25] Most relevant seems the presence of antibodies to oxidised LDL (oxLDL) and to HSP65. Antibodies to these antigens are increased in patients with accelerated atherosclerosis and those directed to HSP65 have been shown to be an independent risk factor for cardiovascular disease.[26,27] Increased levels of anti-oxLDL antibodies have been found in patients with systemic vasculitis.[28] Next to the presence of EC-activating antibodies, also disturbances in the lipid spectrum, including increased levels of lipoprotein (a), elevated levels of total cholesterol and triglycerides, and elevated plasma levels of circulating oxLDL have been found in patients with SLE.[29,30] Parts of the changes in the lipid spectrum are possibly explained by the presence of antibodies to lipoprotein lipase (LPL) as the presence of these antibodies is strongly correlated with total serum triglycerides, apolipoprotein B and apolipoprotein E concentrations.[31]

ENDOTHELIAL CELL DYSFUNCTION

The EC activation and the inflammatory vessel wall damage in systemic autoimmune diseases and systemic vasculitis may result in EC dysfunction. EC dysfunction can be measured by pulse-wave analysis (PWA) or flow-mediated vasodilation (FMD). PWA is a technique in which large and small artery compliance is estimated from analysis of the peripheral arterial waveform. The radial artery is measured with a tonometer. Increased vascular stiffness is a sign of EC dysfunction and correlates with invasive tests of arterial compliance.[32] Large and small artery compliance is calculated from the recorded waveform. Reduced arterial compliance has been shown to predict coronary events and mortality in patients with hypertension.[33] Recently, in a small group of 18 RA patients, free of traditional cardiovascular risk factors, PWA measurement showed a marked decrease of arterial compliance. In the same patient group, FMD was normal, suggesting that PWA is probably a more sensitive marker of vascular dysfunction in RA.[34,35]
FMD determines with ultrasound the capability of the brachial artery to dilate after the occlusion of the forearm by inflation of a pneumatic tourniquet. Deflation of the tourniquet increases blood flow to the distal part of the forearm, inducing an endothelium-dependent vasodilatation. The results obtained are then compared with results obtained after nitroglycerine (NTG) sublingually, resulting in endothelium-independent vasodilation. EC dysfunction is present when only the EC-dependent vasodilation is impaired. The technique has been validated and the results obtained have been shown to relate to the extent and severity of coronary artery disease.[36,37] In a small group of patients with primary systemic necrotising vasculitis (n=24) endothelial function was assessed by FMD as described above. Indeed, in these patients endothelium-dependent FMD was severely impaired compared with age- and sex-matched controls ($p<0.0001$).[38] Endothelium-dependent FMD was impaired in patients with active disease in particular and improved after suppression of the inflammation in all seven patients with active vasculitis who where measured before and after treatment ($p=0.016$). In SLE patients endothelium-dependent FMD was analysed cross-sectionally in 69 patients. Also in these patients endothelium-dependent FMD was significantly impaired compared with controls, even in the subgroup of patients without coronary artery disease risk factors ($p<0.001$).[39]

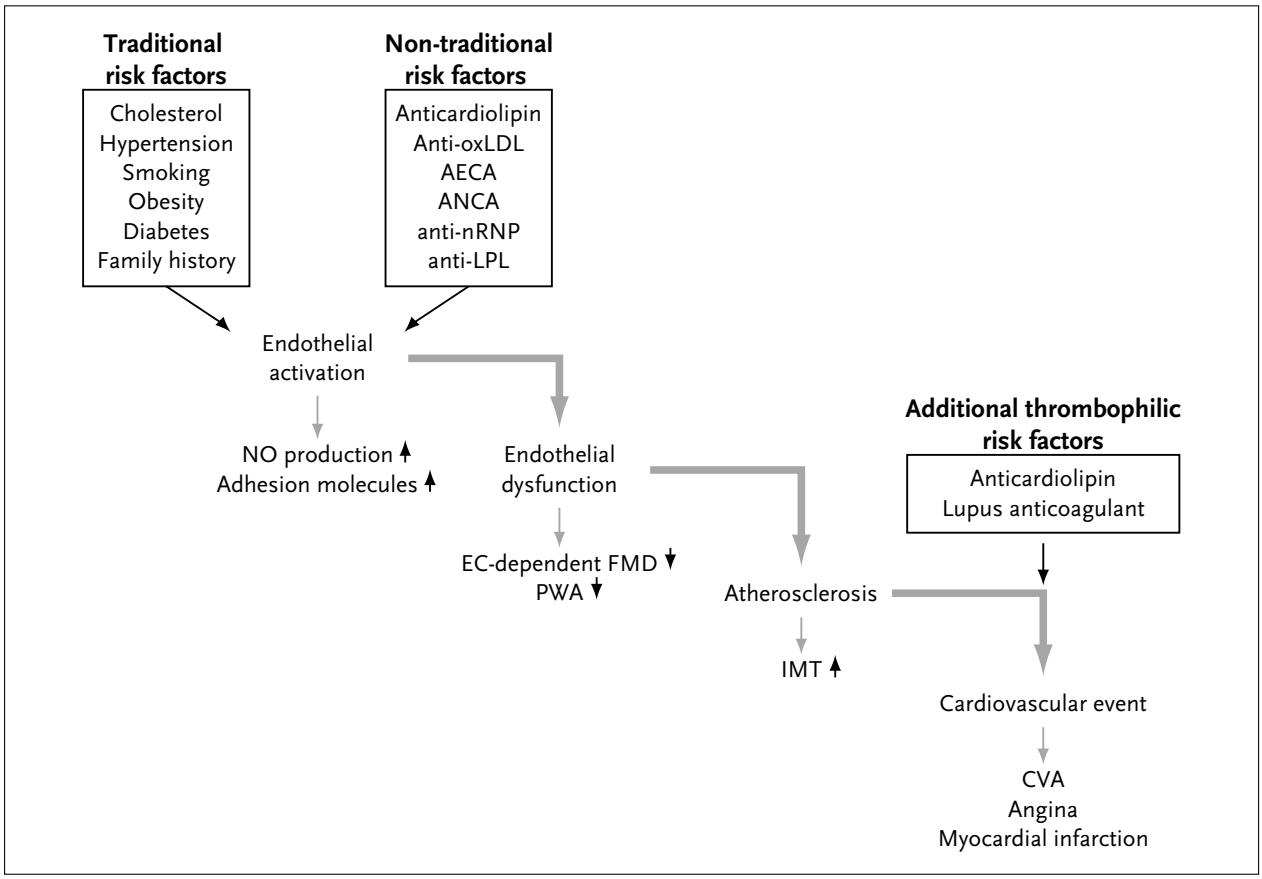

Figure 1

Simplified schematic view of the development of cardiovascular disease in patients with systemic autoimmune disease

Anti-ox LDL = antibodies to oxidised LDL; AECA = antiendothelial cell antibodies; ANCA = antineutrophil cytoplasmic antibodies; anti-nRNP = antibodies to nuclear ribonucleoprotein; anti-LPL = antibodies to lipoprotein lipase, NO = nitric oxide; FMD = flow-mediated vasodilation; PWA = pulse-wave analysis; IMT = intima-media thickness. Next to the traditional cardiovascular risk factors additional factors are involved in EC activation. EC activation results in EC dysfunction that can be measured using PWA or FMD. Severe, or chronically impaired EC dysfunction results in premature atherosclerosis. Atherosclerotic plaques can be detected by measuring IMT in the carotid artery. These lesions are thrombogenic and might therefore cause thrombosis or plaque rupture and overt cardiovascular disease. Also in the process of thrombosis additional risk factors play a role in patients with autoimmune disease. Especially the presence of thrombophilic factors like antiphospholipid antibodies increase the risk of cardiovascular disease.

Interestingly, the endothelium-dependent dilation was not related to disease duration, cumulative prednisone dose, use of antimalarial agents, anticardiolipin antibody, Raynaud's phenomenon or presence of vasculitis.

ATHEROSCLEROSIS

It can therefore be hypothesised that EC dysfunction, as present in patients with systemic autoimmune disorders, reflects EC activation and when severely and/or chronically impaired results in the development of premature atherosclerosis. Indeed, next to the studies showing impaired FMD in systemic vasculitis and in SLE, studies have been performed to evaluate whether premature atherosclerosis could be detected in these patients.

Studies of carotid and intima-media wall thickness (IMT) in unselected SLE patients showed that 40% of the patients had at least one focal plaque and a high risk for cardiovascular disease.[40] It is of interest to note that traditional risk factors seem to be insufficient to explain the increased prevalence of atherosclerosis and cardiovascular disease found in SLE patients.[41] The mortality due to myocardial infarction in SLE patients compared with age- and sex-matched controls are increased up to 50-fold.[42] In patients with rheumatoid arthritis the clinical findings are comparable, although less impressive. The risk of death from cardiovascular disease in RA patients is doubled.[43,44] Similarly to the findings in SLE patients, in rheumatoid arthritis patients without a history of atherosclerosis or its complications, IMT was significantly greater than in age- and sex-matched controls.[45]

INTERVENTION

HMG-coenzyme A-reductase inhibitors (statins) are potent lipid-lowering drugs. Next to their cholesterol-lowering capacity they have other effects. Statins are able to reduce the expression of adhesion molecules on monocytes and diminish their adhesion to EC.[46,47] Meroni *et al.* demonstrated that the presence of statins during incubation of human umbilical vein endothelial cells with antiphospholipid antibodies prevented EC activation *in vitro*.[48] In addition, the potentially beneficial effects of statins have also been demonstrated *in vivo*. After six months of therapy with statins patients showed a significant increase in coronary flow reserve and maximum coronary flow using pharmacological stress with dypridamole.[49] Also in patients with essential hypertension, long-term, effective blood-pressure reduction resulted in improvement in the impaired FMD of the brachial artery.[50] These results are promising. Whether similar effects will be reached in patients with systemic autoimmune disease and the increased risk profile for developing cardiovascular disease can be changed beneficially has to be demonstrated.

CONCLUSION

In summary, we propose that systemic autoimmune diseases and systemic vasculitis are associated with EC activation, during active disease in particular. This EC activation *in vivo* is related to parameters of EC dysfunction. It is suggested that chronic EC dysfunction in patients with systemic autoimmune diseases and systemic vasculitis will prove to be an independent additional risk factor that contributes to the development of atherosclerosis. The presence of EC dysfunction could explain the increased prevalence of premature atherosclerosis found in these patients. For clinicians it is important to realise that it seems possible to influence EC dysfunction and endothelium-dependent vasodilation. Randomised, controlled, intervention studies in patients with systemic autoimmune disease aiming at a reduction of the cardiovascular risk profile, including decrease in EC dysfunction, and development of premature atherosclerosis are eagerly awaited.

NOTE

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