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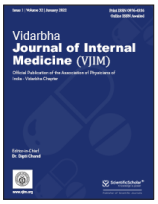

Review Article

Systemic Lupus Erythematosus and Atherosclerosis

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ABSTRACT

Disorders likely 'inflammatory' in nature are known to be linked to accelerated atherosclerotic processes that increase the chances of cardiovascular disease. Systemic lupus erythematosus (SLE) is a well-known autoimmune disease for its ability to affect any organ and cause morbidity. One such major cause of morbidity and mortality in SLE is premature coronary heart disease. Inflammation is considered to be the main pathogenesis of atherosclerosis and an important risk factor for vascular disease. Many clinical trials and studies of epidemiological and pathogenesis-related factors revealed that there is a common link between the pathogenesis of autoimmune diseases such as SLE, causing inflammatory responses similar to those seen in atherosclerosis. In the following review article, we will describe how SLE, inflammation and its traditional risk factors, promotes atherosclerosis.

Keywords: Systemic lupus erythematosus, Autoimmune disease, Inflammation, Cardiovascular disease, Atherosclerosis

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that is known to affect young females of the reproductive age group. There is a major cardiac involvement in cases of SLE, all the components of the heart, such as pericardium, conduction system, myocardium, valves and coronary arteries are involved due to the inflammatory response of the body.[1,2] The involvement of coronary arteries disease (CAD) was described much later than other manifestations. CAD in SLE patients can result from various different pathophysiologic mechanisms such as atherosclerosis, arteritis, thrombosis, embolisms and coronary artery spasm, leading to reduced blood flow.[2] SLE patients may present with myocardial infarction at a young age. It has been revealed that fatal myocardial infarction has been reported to be 50 times higher in patients with SLE than in other control subjects of the same age and gender.[1-3] Hence, lupus is now considered to be an independent risk factor for atherosclerosis development.

ENDOTHELIAL INFLAMMATION AND ATHEROSCLEROSIS

Inflammation and atherosclerosis have been linked for decades, yet the underlying mechanism of immune-activated inflammation is still unknown. C-reactive protein (CRP) has been the strategic marker for the involvement of inflammation in cardiovascular disease (CVD). Antigen-antibody complexes have shown a crucial role in atherogenesis.[4] The endothelial luminal surface – a single layer of cells, acts as a direct interface between the blood and local tissues. It is known to perform functions such as cell adhesions, coagulation, inflammation and the permeability barrier. Endothelium is very potent in producing and reacting to other local active mediators that process the inflammatory cells to the sites of damaged tissues. The dysfunction of the endothelial layer is a key event in atherogenesis development and precedes the formation of atherosclerotic lesions.[5] Chronically increased levels of inflammatory factors may cause inflammation of the endothelium that subsequently damages the endothelial lining. In the initial stages of atherosclerosis, monocytes and T cells are deployed, but to cross the endothelium, adhesion molecules must be expressed in the inner layers of the endothelium. Many adhesion molecules promote adhesions to monocytes, including intercellular adhesion molecule1, vascular adhesion molecule1 and selectins. These adhesion molecules are surface proteins that are regulated by transcription factors, which then induce tumour necrosis factor (TNF) such as alpha-TNF-1, interleukin-1 (IL-1) and CRP interactions. CRP levels can be used to measure the inflammation in autoimmune diseases and can help estimate the level of atherogenesis in a normal population. Elevated CRP levels have pro-atherogenic

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properties, which are capable of activating the complement system, which influences the endothelial production of monocyte chemotactic protein 1 which follows the secretion of endothelin-1 and IL-6 and upregulates the adhesion molecules. This mediates the macrophage uptake of LDL and stimulates monocyte production of tissue factor.[5] Many studies have shown that there is a strong association between markers of inflammation and an increased risk of future CVD events. As a result, CRP levels have been considered part of the main and independent risk factor assessment scale for the risk of myocardial infarction and stroke without the presence of other traditional risk factors.

ATHEROSCLEROSIS AND AUTOANTIGENS

It has been found that many auto antigens and antibodies are involved in the pathogenesis of atherosclerosis. Heat shock proteins (HSPs), oxidised low-density lipoproteins (oxLDL) and 2-glycoprotein-I are directly involved in the process of atherosclerosis.

HSPS

Heat Shock Proteins (HSPs) act as molecular chaperones and assist in the folding of misfolded proteins, thereby preventing their aggregation. HSPs have a protective role under normal physiologic conditions. These proteins get expressed when there is a significant amount of stress factor, which is expressed directly on endothelial cells to maintain the viability of the targeted cells and thus may be sometimes eradicated by autoimmunity. These stress factors involve hypertension, oxidative stress, smoking and many others. Anti-HSP65 antibody titres correlated strongly with severity of coronary atherosclerosis. Many patients with anti-HSP65 antibodies were found to be at increased risk of future cardiovascular events. Patients with sonographic evidence of carotid atherosclerotic lesions have significantly elevated levels of anti-HSP65.[6] HSPs are known to be over expressed in patients of SLE.

ANTI-OXLDL

LDL is seen to be accumulated in macrophages; this has molecules such as phospholipids, triglycerides and cholesterol. LDL gets trapped in subendothelial space and gets oxidised, which later promotes early atherogenesis. OxLDL has been shown to cause inflammation in macrophages and vascular walls. It induces the activation of monocytes and T cells and helps endothelial cells to adhere to one another; also converting the macrophages into foam cells that participate in forming atherosclerotic lesions. Anti-oxLDL antibodies are abundant in patients developing atherosclerosis. Many patients having peripheral vascular disease have high levels of anti-oxLDL autoantibodies.[7,8] Elevated levels of anti-oxLDL antibodies are also found in patients with autoimmune diseases, including rheumatoid arthritis, SLE and APS.

ANTI-PHOSPHOLIPID (APL) ANTIBODIES

APL antibodies are a heterogeneous group of autoantibodies targeting different phospholipid-binding protein antigens. These autoantibodies include lupus anti-coagulant, anti-cardiolipin, anti-beta 2 glycoprotein 1 (anti-β2GP1) and anti-prothrombin antibodies. APL antibodies dysregulate the normal cellular activities and are associated with thrombosis (venous, arterial and microvascular), pregnancy complications (e.g., obstetric failure, pre-eclampsia and eclampsia) and non-specific manifestations (e.g., thrombocytopenia, heart valve disease, chorea, livedo reticularis/racemosa and nephropathy). High APL antibodies can occur in isolation or in association with underlying autoimmune diseases such as SLE. Anti-β2GP1 antibodies and their target β2GP1 demonstrate a strong correlation with thrombosis. β2GP1 is found in atherosclerotic lesions. It is known to colocalise with CD4 lymphocytes. T cells binding to the β2GP1 cause an increase in atherosclerosis, which suggests that β2GP1 is the target autoantigen in atherosclerosis.

ATHEROSCLEROSIS AND SLE

SLE is predominantly found in the reproductive age group of females, with a variety of clinical manifestations. A bimodal curve of mortality for SLE is observed, where early deaths (<1 year after diagnosis) were attributable to kidney disease and infection, while later deaths were associated with CVD.[9] The risk of CVD is higher in SLE patients compared to healthy controls. Due to their lower risk at baseline, the relative risk for CVD is highest in premenopausal women with SLE, they have been shown to be 50 times more likely to experience myocardial infarction than their age-matched counterparts.[10] With treatments for SLE and disease control becoming more effective, CVD is now a leading cause of death in SLE patients. Autopsy reports by Bulkley and Roberts revealed that there was a high incidence of atherosclerosis in young women with SLE, which was 50% more than that of deceased patients who died without SLE. SLE-related risk factors for accelerated atherosclerosis include dyslipidaemia, disease activity and duration, autoantibodies, nephritis and circulating immune complexes. It must be considered that other traditional risk factors such as diabetes and hypertension may affect atherosclerosis development and may increase the atherosclerosis-related risk in SLE by several folds.[2]

CARDIOVASCULAR RISK FACTORS IN SLE

The occurrence of ischaemic heart disease in the condition of SLE is between 8% and 16% in reported studies. Use of non-invasive methods has shown that atherosclerosis can be found in 28–40% of SLE patients. This was linked to patients' increasing age, disease duration, hypertension and smoking.

Treatment use of corticosteroids may also be added as a non-traditional risk in SLE patients that may also elevate the levels of lipids in the blood, cause hypertension and obesity. In comparison between the SLE patients and controls, there were high concentrations of plasma homocysteine and triglycerides in SLE patients.[11,12]

MANAGEMENT

SLE needs to be treated early. If a premenopausal woman has SLE, she is very prone to having CVD and atherosclerosis. 99mTc-sestamibi myocardial perfusion SPECT investigation must be done for SLE patients to detect the cardiovascular involvement with even non-specific clinical complaints. In a case study, this technique was able to detect the cardiac-related abnormalities in 27 of the 33 SLE patients.[13-17] Aggressive risk reduction with weight, blood pressure and hyperglycaemia control is advocated. Smoking should be stopped. HCQS treatment reduces the lipid levels in SLE; however, dyslipidaemia must be aggressively treated with statins as well.

CONCLUSION

There is increasing evidence of the role of immune-mediated atherogenesis in SLE. This may provide an explanation for the premature vascular disease in SLE patients. SLE-related immune factors have been found in all the stages of the atherogenesis and even in the thrombotic event. Hence, these patients should be treated aggressively for SLE and the associated traditional risk factors, because they are at high risk of developing CAD.

Authors' contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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