

Mechanism of Early Atherosclerosis in Systemic Lupus Erythematosus

Caimei Wang¹, Lanke Xu², Xiaoling Liu^{3,*}, Jinhuan Deng¹, Guofei Mao¹, Yi Sun²

¹Department of Laboratory Medicine, Affiliated Hospital of Guilin Medical College, Guilin, 541001, China

²Guilin Medical College, Guilin, 541000, China

³Department of Endocrinology, Affiliated Hospital of Guilin Medical College, Guilin, 541001, China

*Corresponding author: 50923965@qq.com

Keywords: Systemic Lupus Erythematosus; Atherosclerosis; Disorder of Lipid Metabolism; Immune Mechanism

Abstract: Systemic lupus erythematosus (SLE) is a diffuse connective tissue disease characterized by immune inflammation, which often has multiple system involvement. The late cause of death is coronary atherosclerosis (AS) and its complications. Early atherosclerosis in SLE patients may be related to related microvascular damage and dysfunction caused by long-term immune disorders and lipid metabolism disorders.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes the formation of diseased autoantibodies and immune complexes and mediates organ and tissue damage. Clinically, there are often manifestations of multiple system involvement, most commonly occurring in women of reproductive age, ranging from 15 to 45 years of age, with a female: male ratio of 7 to 9:1. With the significant improvement of diagnosis and treatment measures, the prognosis of this disease has significantly improved compared to before. However, with the extension of survival, cardiovascular system diseases are one of the important reasons for the increased mortality rate of this disease. Atherosclerosis is the most important pathological basis for the occurrence of cardiovascular and cerebrovascular diseases. Its harm to patients has become increasingly prominent, and has been widely valued [1]. Therefore, intervening in the risk factors for the occurrence and development of cardiovascular diseases in SLE patients is an important means to improve their quality of life and disease prognosis. This article reviews the pathogenesis of atherosclerosis in SLE patients, so as to improve the prognosis of patients and reduce adverse outcomes of coronary heart disease.

2. Epidemiology of early atherosclerosis in SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease that involves multiple organs. According to epidemiological surveys in multiple regions of the United States, the prevalence rate of SLE is 14.6-12.2 per 100000 people; A one-time survey of a large sample (>30000 people) in China

shows that the prevalence rate of SLE is 70 per 100000 people, while among women, it is as high as 113 per 100000 people [2]. Based on the total population of about 1.38 billion in China in 2013, the number of SLEs in China is nearly 1 million. In 1976, Urowitz et al. first proposed that the mortality curve for SLE presented a "double peak" pattern, that is, in the early stage, most people died of severe infection and lupus activity, while in the late stage, they mainly died of cardiovascular and cerebrovascular diseases. In recent years, it has been reported that SLE patients are several times more likely to have atherosclerosis related diseases than normal people, and they often show atherosclerosis in important organs and vessels in young and middle-aged people. Early atherosclerosis in SLE patients has been recognized. European and American countries have successively established a prospective cohort to study the atherosclerosis in SLE, and provide evidence for clinical intervention by exploring the natural course and mechanism of SLE with atherosclerosis. Cardiovascular and cerebrovascular diseases have been identified as an important factor in the increased mortality rate of SLE patients. The establishment of the Chinese SLE Treatment and Research group CSTAR has provided significant support for the study of early atherosclerosis in domestic SLE patients. Asanuma et al. found that SLE patients without a previous history of coronary heart disease have a significantly higher probability of developing coronary artery calcification compared to normal individuals [3]. Hao Yanjie and others analyzed that among SLE patients without previous coronary heart disease history, 38% of carotid intima-media thickening and 17% of carotid atherosclerotic plaque formation [4]. As early as 1999, Manzi S et al. found that the incidence of carotid artery plaques was 21% in SLE patients under 35 years old, and 100% in patients over 65 years old [5]. These research results show that early atherosclerosis in SLE patients may be related to related microvascular damage and dysfunction caused by long-term immune imbalance. Therefore, early detection and prevention of atherosclerosis have important clinical significance for the prognosis of SLE.

3. Lipid metabolism disorder and early atherosclerosis in SLE

Disorder of lipid metabolism refers to the abnormal increase or decrease of cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, extremely low density lipoprotein, and apolipoprotein in the body. More and more evidence shows that SLE patients are prone to abnormal lipid metabolism, which is mainly manifested by the significant increase in the levels of triglycerides, low-density lipoprotein and very low-density lipoprotein, while the level of high-density lipoprotein is significantly reduced. A prospective cohort study found that [6], even after adjusting the baseline level of Framingham risk of subjects, SLE patients still had an additional risk of 7.5 to 17 times coronary atherosclerotic heart disease. An observation of SLE patients with an average follow-up of 12 years found that the incidence rate of coronary atherosclerotic heart disease in patients with normal cholesterol was 3%, while the incidence rate of coronary atherosclerotic heart disease in patients with hypercholesterolemia was 24% [7]. Hyperlipidemia significantly promotes the development of atherosclerosis in SLE patients, but the mechanism of early atherosclerosis in traditional cardiovascular diseases is unknown, which is currently believed to be related to the following factors.

3.1. Changes in structure and function of HDL in inflammatory state

It is well known that "healthy" high-density lipoprotein (HDL) has anti atherosclerosis effect, the main mechanism is the reverse transport of cholesterol [8]. In inflammatory state, HDL structure and function change, which is manifested as inflammation, oxidation promotion, and impairment of cholesterol reverse transport function, and may participate in early atherosclerosis in SLE. At present, it is believed that the following factors are involved in the formation of early atherosclerosis:

① Impaired cholesterol reverse transport function: Runda et al. found that SLE through ABCG1 (ATP binding cassette transporter G1) and ABCA1 (ATP binding cassette transporter A1) mediated HDL cholesterol reverse transport function is impaired by using radioisotopes in vitro, which is unrelated to the HDL-C concentration of SLE patients.[9] ② Antioxidant dysfunction, MPO (myeloperoxidase) is the main source of active oxygen in the body, while PON1 (serum paraoxonase 1) protects high-density lipoprotein from oxidation, mediates phagocytosis of macrophages, and reduces atherosclerosis. Both exist in HDL, and changes in MPO and PON1 in HDL in SLE patients lead to antioxidant dysfunction.[10-11] In vitro experiments have shown that PON3 has a stronger antioxidant capacity than PON1. [12] Some scholars have used targeted proteomics methods to compare the 18 proteins rich in HDL of patients with and without SLE with carotid plaque, and found that PON3 has been depleted in HDL of patients with SLE with carotid plaque. This explains the mechanism of the decline and loss of HDL antioxidant activity of SLE from the structural plane. The inflammatory and immune mechanism of SLE patients can cause the circulating immune complex to damage endothelial cells, and can also cause the structural change of HDL. The anti-atherosclerosis effect of HDL-C is inhibited in the microenvironment, leading to an increased risk of cardiovascular events in SLE. Reducing the risk of CVD through early inhibition of inflammatory environment and lifestyle intervention may be a risk factor for early atherosclerosis and a potential therapeutic target.

3.2. Elevated levels of low density lipoprotein

Rodriguez M et al. found that the increase of low-density lipoprotein level may be an independent risk factor of subclinical atherosclerosis in SLE through case-control studies. Ahmad HM et al found through a cohort study of 60 SLE patients that the percentage of oxidized low-density lipoprotein in the SLE group with carotid plaque was significantly higher than that in the SLE group without carotid plaque. They further showed through multivariate logistic regression analysis that the risk ratio of the percentage of oxidized low-density lipoprotein in the SLE group with carotid plaque compared with that in the SLE group without carotid plaque was 6.13 ($P < 0.001$), The results of this study suggest that the percentage of oxidized low-density lipoprotein in the circulation level is a risk factor for SLE patients to develop atherosclerosis complications. Other researchers also reported that oxidized low-density lipoprotein is an independent risk factor for late atherosclerosis in SLE patients, and the continued high level of oxidized low-density lipoprotein in SLE patients will promote vascular endothelial damage, and further increase subclinical atherosclerosis in patients. However, the increasing mechanism of low-density lipoprotein oxidation is still unclear, and it may be that SLE patients provide an oxidative environment for low-density lipoprotein oxidation, such as reactive oxygen species and related lipoproteins. A large number of literature shows that triglyceride, apolipoprotein B/apolipoprotein A, triglyceride/high-density lipoprotein in SLE patients are significantly higher than those in the control group, and triglyceride, low-density lipoprotein and triglyceride/high-density lipoprotein levels are positively correlated with the active stage of SLE disease, which may be jointly involved in atherosclerosis in SLE patients. The above research shows that SLE patients are prone to lipid metabolism disorder, and long-term abnormal blood lipids increase the risk of atherosclerosis in SLE patients, but its specific molecular mechanism needs further study.

3.3. Decrease of apolipoprotein AI and increase of apolipoprotein E

Apolipoprotein AI (apoA I) has the function of clearing tissue lipids and anti-atherosclerosis. Some studies have found a significant decrease in apoA I in SLE patients, which may be related to the presence of specific anti apoA I antibodies. Apolipoprotein E (apo E) is a polymorphic protein that

participates in the transformation and metabolism of lipoproteins. The concentration of Apo E is positively correlated with plasma triglyceride content. Its physiological functions include: (1) being a ligand for LDL receptors, as well as for hepatocyte CM residue receptors, which are closely related to lipoprotein metabolism ApoE has polymorphism, which determines that individual blood lipid level is closely related to the occurrence and development of atherosclerosis; (2) It is involved in the activation of enzymes that hydrolyze fat, in immune regulation, and in the regeneration of nerve tissue. Some studies have found that Apo E is significantly higher in patients with lupus compared to normal controls, and is associated with disease activity.

4. Autoimmunity and early atherosclerosis in SLE

4.1. Cytokines and early atherosclerosis in SLE

SLE is a disease characterized by autoimmune and inflammatory reactions. TNF α is present in human endothelial and smooth muscle cells at all stages of AS, high levels of TNF- α in SLE patients is associated with high triglycerides and coronary artery calcification scores. In addition, TNF- α can inhibit the positive regulatory effect of key metabolic enzymes, including lipoprotein lipase LPL, on AS, exacerbating lipid metabolism disorders in SLE patients. TNF- β it may inhibit the formation of atherosclerotic plaque. Jackson and other researchers found that activity of TGF- β 1 in SLE patients decreased and lymphocyte apoptosis increased. Many epidemiological studies have shown that the level of FIB in SLE patients has significantly increased in the early stages of AS without significant clinical symptoms. Although studies support that cytokines play a role in accelerating the pathogenesis of atherosclerosis, these specific mechanisms are still not fully understood.

4.2. Autoantibodies and early atherosclerosis in SLE

There are multiple autoantibodies in the blood of SLE patients, some of which may lead to the development of cardiovascular disease. Autoantibodies known to be related to the occurrence of AS in SLE include anti phospholipid antibodies (a PL), anti regulatory protein antibodies, anti lipoprotein lipase antibodies, antioxidant low density lipoprotein (ox LDL) antibodies, Ro-52 antibodies, and anti heat shock proteins (HSP) antibodies. Ames [6] et al. reported that there is a correlation between anticardiolipin antibody Ig G and carotid intima-media thickness (cIMT) in patients with idiopathic antiphospholipid syndrome, suggesting that anticardiolipin antibodies can accelerate the occurrence and development of AS. Ox LDL promotes the progression of atherosclerosis mainly by increasing the accumulation of lipids under vascular endothelial cells. Ro-52 antibody is associated with EPC/CAC dysfunction and IL-18 levels, and may play a role in the progression of cardiovascular disease in SLE. T cells activated by HSP can stimulate B cells to produce anti HSP antibodies. Previous studies have shown that anti HSP60/65 antibodies can induce endothelial cell apoptosis, thereby inducing AS. The highly activated immune function and the production of autoantibodies in SLE patients increase their risk of CVD, especially the occurrence of AS, which is an important factor in the increased mortality of SLE patients.

SLE patients have a significantly increased risk of cardiovascular disease, and have become a high-risk group of cardiovascular diseases. Although immune mechanism and lipid metabolism disorder play an important role in accelerating carotid atherosclerosis in SLE patients, there is no specific treatment for atherosclerosis at present, and its mechanism and treatment need to be further explored.

Acknowledgment

Supported by the Health Commission of Guangxi Zhuang Autonomous Region (Z20190303).

References

- [1] Tselios K1, Gladman DD, Sheane BJ, et al. All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013)[J]. *Ann Rheum Dis*. 2019, 78(6):802-806.
- [2] Guidelines for diagnosis and treatment of systemic lupus erythematosus, Rheumatology Branch of Chinese Medical Association, *Chinese Journal of Rheumatology*, 2010, 14 (5) 342-346.
- [3] Asanuma Y, Oeser A, Shintani AK, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus[J]. *N Engl J Med*, 2003, 349(25): 2407-2415.
- [4] Hao Yanjie, Dong Yi, Zhang Zhuoli, et al. Study on risk factors of subclinical atherosclerosis in systemic lupus erythematosus [J]. *Chinese Journal of Rheumatology*, 2009, 13 (12): 816-818.
- [5] Manzi S, Selzer F, Sutton-Tyrrell K, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus[J]. *Arthritis Rheum*, 1999, 42(1):51-60.
- [6] Al Husain A, Bruce IN. Risk factors for coronary heart disease in connective tissue disease[J]. *Ther Adv Musculoskel Dis*, 2010, 2(3):145-153.
- [7] Bruce IN, Urowitz MB, Gladman DD, et al. Natural history of hypercholesterolemia in systemic lupus erythematosus [J]. *J Rheumatol*, 1999, 26(11):2137-2143.
- [8] Hafiane AI, Kellett S, Genest J. Treatment options for low high-density lipoproteins [J]. *Curr Opin Endocrinol Diabetes Obes*, 2014, 21:134-139.
- [9] Ronda N, Favari E, Borghi MO, et al. Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus[J]. *Ann Rheum Dis*, 2014, 73: 609-615.
- [10] McMahan M, Skaggs BJ, Sahakian L, et al. High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidised lipids[J]. *Ann Rheum Dis*, 2011, 70: 1619-1624.
- [11] McMahan M, Skaggs BJ, Grossman JM, et al. A panel of biomarkers is associated with increased risk of the presence and progression of atherosclerosis in women with systemic lupus erythematosus[J]. *Arthritis Rheumatol*, 2014, 66:130-139.
- [12] Hahn B. H, Grossman J, Ansel BJ. Altered lipoprotein metabolism in chronic inflammatory states: proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis[J]. *Arthritis Res Ther*, 2008, 10(4): 213.