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Risk factors for atherosclerosis development in patients with systemic scleroderma

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Abstract: Systemic scleroderma (SSc), also known as systemic sclerosis, is a rare autoimmune disorder characterized by fibrosis of the skin and internal organs, as well as vascular abnormalities. Atherosclerosis, the accumulation of lipids and fibrous tissue in arterial walls, is a significant cause of cardiovascular morbidity and mortality. Patients with systemic scleroderma are at an elevated risk for developing atherosclerosis, with vascular damage playing a central role in its pathogenesis. This article reviews the multifactorial risk factors contributing to the development of atherosclerosis in patients with systemic scleroderma, focusing on endothelial dysfunction, chronic inflammation, dyslipidemia, and other clinical factors. The goal of this article is to enhance the understanding of cardiovascular risk in this population and emphasize the importance of early diagnosis and targeted interventions.

Keywords: Systemic scleroderma, atherosclerosis, cardiovascular diseases, endothelial dysfunction, lipid abnormalities, autoimmune diseases.

Introduction: Systemic scleroderma (SSc) is a systemic autoimmune disease that primarily affects the skin but can also involve internal organs, including the heart, lungs, kidneys, and gastrointestinal tract. Vascular involvement is one of the hallmark features of systemic scleroderma and is characterized by microvascular abnormalities, including vasospasm, capillary loss, and fibrosis of the blood vessels [1]. While the primary clinical focus of systemic scleroderma has often been its fibrotic aspects, there is increasing recognition of the heightened risk of cardiovascular diseases (CVD) in these patients. Specifically, atherosclerosis, a chronic inflammatory process that results in the accumulation of cholesterol and other materials in arterial walls, has become a major concern in the management of systemic scleroderma. Atherosclerosis in SSc is a multifactorial process influenced by both the disease-specific mechanisms and traditional cardiovascular risk factors [2,8]. The pathophysiology of atherosclerosis in systemic scleroderma is complex and involves endothelial dysfunction, inflammatory mediators, lipid abnormalities, and changes in the vascular smooth muscle. This review will examine the primary risk factors that predispose systemic scleroderma patients to atherosclerosis and discuss their clinical

implications.

Pathophysiology of Atherosclerosis in Systemic Scleroderma. The pathogenesis of atherosclerosis in systemic scleroderma involves a combination of endothelial dysfunction, inflammation, and impaired vascular repair. In SSc, vascular injury occurs due to fibrosis, immune cell activation, and chronic inflammation. Endothelial cells in patients with systemic sclerosis exhibit increased permeability, decreased nitric oxide production, and upregulation of adhesion molecules, leading to the recruitment of inflammatory cells [3]. This results in the formation of an atherosclerotic plaque, which may progress more rapidly due to the vascular abnormalities intrinsic to systemic scleroderma.

Endothelial Dysfunction and Microvascular Injury. Endothelial dysfunction is a critical early event in the pathogenesis of atherosclerosis, and it is exacerbated in systemic scleroderma due to microvascular damage. In SSc, endothelial cells are injured by both mechanical forces, such as shear stress from blood flow, and by inflammatory mediators. The presence of Raynaud's phenomenon, a characteristic feature of systemic scleroderma, can further damage the endothelium by causing periodic ischemia and reperfusion injury. Over time, endothelial cells lose their ability to maintain vascular tone and promote vasodilation, contributing to the progression of atherosclerosis [4].

Chronic Inflammation and Immune Activation. Chronic inflammation plays a pivotal role in the development of atherosclerosis in patients with systemic scleroderma. Elevated levels of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), are frequently observed in patients with SSc. These inflammatory cytokines promote the activation of endothelial cells, the infiltration of monocytes into the arterial wall, and the formation of foam cells, all of which contribute to plaque formation. Additionally, autoantibodies commonly present in SSc, such as anti-centromere and anti-topoisomerase I antibodies, may directly contribute to vascular damage and accelerate atherosclerotic progression through immune complex deposition and subsequent tissue injury.

Dyslipidemia and Lipid Metabolism. Alterations in lipid metabolism are common in systemic scleroderma and represent a significant risk factor for atherosclerosis. Dyslipidemia in SSc is characterized by low levels of high-density lipoprotein (HDL) cholesterol, which has a protective effect on endothelial function, and elevated levels of low-density lipoprotein (LDL) cholesterol and triglycerides, both of which promote the formation of atherosclerotic plaques. The mechanisms underlying dyslipidemia in SSc are complex and involve altered lipid synthesis, oxidative stress, and inflammation [5,11]. This dyslipidemic profile increases the likelihood of lipid deposition in the arterial walls, thereby fostering the development of atherosclerosis.

Hypertension. Hypertension is a common comorbidity in patients with systemic scleroderma and significantly increases the risk of atherosclerosis. Renal involvement in SSc, including scleroderma renal crisis, can lead to secondary hypertension, which accelerates the progression of vascular damage. Furthermore, the use of corticosteroids in SSc treatment may also contribute to elevated blood pressure. Hypertension induces mechanical stress on the endothelial cells, enhances inflammation, and promotes plaque instability, all of which facilitate the development of atherosclerosis.

Immune System Dysfunction and Autoimmunity. The autoimmune nature of systemic scleroderma predisposes patients to abnormal immune responses that can exacerbate vascular injury. The presence of specific autoantibodies in SSc, such as anti-Scl-70 (topoisomerase I), can lead to endothelial cell dysfunction and the promotion of vascular remodeling. Additionally, circulating immune complexes can deposit in the blood vessel walls, activating complement and contributing to the inflammatory process that drives atherosclerosis. The immune-mediated vascular injury may be exacerbated by concomitant diseases, such as lupus or rheumatoid arthritis, which are commonly associated with systemic scleroderma.

Age and Gender. Age is a well-established risk factor for atherosclerosis, and it remains relevant in patients with systemic scleroderma. The risk of cardiovascular disease increases with age, as the natural process of vascular aging contributes to endothelial dysfunction and plaque formation. Gender differences also play a role, with postmenopausal women at increased risk of atherosclerosis due to the loss of the protective cardiovascular effects of estrogen.

Medications and Treatment-Related Factors. The treatment of systemic scleroderma itself may contribute to cardiovascular risk. Corticosteroids, commonly prescribed for SSc, can lead to increased blood pressure, dyslipidemia, and insulin resistance, all of which are risk factors for atherosclerosis [6,7]. Additionally, some immunosuppressive therapies used in SSc, such as cyclophosphamide, may indirectly increase cardiovascular risk by promoting endothelial dysfunction and contributing to vascular remodeling.

Obesity and Sedentary Lifestyle. Patients with systemic scleroderma often experience reduced

physical activity due to musculoskeletal involvement, joint stiffness, and skin tightness, which can contribute to obesity and metabolic syndrome. Obesity, in turn, is a well-known risk factor for the development of atherosclerosis. Sedentary behavior, combined with obesity, exacerbates the risk of developing cardiovascular diseases in these patients.

Management and Prevention. Given the elevated cardiovascular risk in patients with systemic scleroderma, early screening for atherosclerosis is essential. Regular monitoring of blood pressure, lipid profiles, and markers of inflammation is recommended to identify those at greatest risk for atherosclerotic cardiovascular events. Non-invasive imaging techniques, such as carotid ultrasonography, can help assess the presence and severity of atherosclerosis in SSc patients [9]. Management strategies should include aggressive control of traditional risk factors, such as hypertension and dyslipidemia, as well as the treatment of the underlying autoimmune and inflammatory components of systemic scleroderma. Statins, angiotensin-converting enzyme inhibitors (ACE inhibitors), and other cardiovascular agents should be considered based on individual risk profiles [10].

CONCLUSION

Patients with systemic scleroderma are at an increased risk of atherosclerosis due to a combination of endothelial dysfunction, chronic inflammation, dyslipidemia, and other disease-specific factors. The early identification of these risk factors and the implementation of targeted interventions are crucial to reduce the cardiovascular morbidity and mortality in this patient population. Clinicians must be vigilant in monitoring for atherosclerosis in systemic scleroderma and take an integrated approach to the management of cardiovascular risk.

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