Health & Medical Sciences Volume: 3, Number 1, 2025, *Page*: 1-9

Pathophysiology of Atherosclerosis Formation in Autoimmune Diseases: Rheumatoid Arthritis, Systemic Lupus Erythematosus, Primary Sjögren's Syndrome, and Antiphospholipid Syndrome

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DOI:
https://doi.org/10.47134/phms.v3i1.556
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Received: 02-11-2025
Accepted: 13-11-2025
Published: 29-11-2025

Abstract: This study aimed to systematically examine the autoimmune mechanisms contributing to atherosclerosis development in patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjögren's syndrome, and Antiphospholipid Syndrome. The focus was on identifying immunological pathways, inflammatory mediators, and vascular changes that accelerate atherosclerosis in these autoimmune conditions. A systematic scoping review was conducted following established scoping review guidelines. Peer-reviewed studies on immune-mediated processes, endothelial dysfunction, lipid changes, or cardiovascular outcomes in autoimmune diseases were sourced from PubMed, Scopus, and Web of Science, screened via electronic searches and predefined inclusion criteria. Data extraction focused on immune cell involvement, cytokine profiles, mechanisms of vascular injury, and indicators of atherosclerotic progression.The results demonstrated that chronic systemic inflammation is a central mechanism driving accelerated atherosclerosis in autoimmune diseases. Activated immune cells, particularly monocytes, macrophages, and T lymphocytes, were consistently reported to infiltrate the vascular endothelium, promoting endothelial dysfunction and intimal thickening. Pro-inflammatory cytokines such as tumor necrosis factor-alpha and interferon-gamma were frequently associated with increased expression of adhesion molecules, oxidative stress, and foam cell formation. Altered lipid metabolism, including increased levels of oxidized low-density lipoprotein, further contributed to plaque development. In Antiphospholipid Syndrome, autoantibody-mediated endothelial injury and thrombogenic processes were prominent, while immune complex deposition and complement activation were key contributors in Systemic Lupus Erythematosus. Overall, the findings indicate that immune dysregulation and persistent inflammation substantially increase cardiovascular risk in patients with autoimmune diseases, underscoring the need for targeted anti-inflammatory and immunomodulatory strategies to reduce atherosclerotic burden.

Keywords: Autoimmune Diseases; Atherosclerosis; Chronic Inflammation

Introduction

Autoimmune is a diverse group of conditions characterized by abnormal reactivity of B cells and T cells to the normal constituent of the host. The disease is widespread and affects individuals of all ages, especially women (Atehortúa et al., 2019; Zegkos et al., 2016). Autoimmunity has a mechanism that unites these conditions in a single category, but their clinical manifestations vary widely (Tselios et al., 2017). Autoimmune diversity is particularly striking from one disease to another, with the difficulty of achieving a diagnosis for patients who come with alarming signs and symptoms that can arise from different etiologies, each of which may require a different and sometimes different management approach (Yennemadi et al., 2024).

Autoimmunity represents a diverse range of persistent diseases that can target particular organs or span various body systems. These disorders typically involve shared pathways, including genetic influences, sex-based variations, external triggers, disruptions in physiological processes, and specific subtypes illustrated by the concept of autoimmune tautology (Fomicheva et al., 2021; Yennemadi et al., 2024). Atherosclerosis, once viewed as an age-related degenerative disorder, now emerges as an autoimmune-inflammatory condition driven by infections, inflammation, altered lipoprotein metabolism, immune activation, smooth muscle proliferation, arterial narrowing, and atheroma formation (Fomicheva et al., 2021; Yennemadi et al., 2024).

Atherosclerosis involves subendothelial buildup of lipids, immune cells (monocytes/macrophages, T lymphocytes), autoantibodies, autoantigens, and cytokines (TNF-α, IFN-γ), thickening the intima, narrowing arteries, reducing blood flow, and causing plaque rupture and cardiovascular events. Increased rates *C-reactive protein* has been shown to be an independent risk factor for *Cardiovascular disease* (Gómez-Bernal et al., 2023; López-Pedrera et al., 2019; Qi et al., 2023). In atherosclerosis, autoantibodies, T cells, and B cells have been shown to worsen or improve the disease. The most common autoimmune causes of cardiovascular are *Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjögren's syndrome, Antiphospholipid Syndrome* where these diseases cause oxidation of low-density lipoproteins (LDL) which is one of the causes of the formation of atherosclerosis which initially experiences endothelial dysfunction (DeMizio & Geraldino-Pardilla, 2020; T. Liu et al., 2020; Urowitz et al., 2020).

The initial trigger for atherosclerosis, endothelial dysfunction, arises from conventional and unconventional risk factors linked to autoimmune diseases. These include free radicals from smoking and type 2 diabetes (T2DM)—often intensified by steroids—plus high angiotensin II levels that drive smooth muscle growth, raise peripheral resistance, oxidize LDL cholesterol, and elevate plasma homocysteine. Angiotensin II increases endothelial receptors for OxLDL, stimulates the absorption of OxLDL, and promotes formation *reactive oxygen species* (ROS) OxLDL-mediated and endotic cell apoptosis (Benacka et al., 2017; Bolla et al., 2023; Kosher et al., 2024).

The objective of this study is to systematically analyze and synthesize existing evidence on the immunological mechanisms linking autoimmune diseases to atherosclerosis development, particularly in Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjögren's syndrome, and Antiphospholipid Syndrome. This research aims to identify key

immune pathways, inflammatory mediators, and endothelial dysfunction processes that accelerate atherosclerotic progression in autoimmune conditions. From a research perspective, the expected outcomes include the consolidation of current scientific knowledge, identification of research gaps, and formulation of an integrated conceptual framework that may serve as a reference for future experimental, clinical, and translational studies. From the stakeholder perspective, including clinicians, healthcare policymakers, and public health practitioners, the findings are expected to provide evidence-based insights to support early cardiovascular risk stratification, optimization of immunomodulatory therapy, and development of preventive strategies tailored to patients with autoimmune diseases. Ultimately, this study seeks to contribute to improved clinical decision-making and to inform multidisciplinary approaches aimed at reducing cardiovascular morbidity and mortality in autoimmune populations.

Methodology

This study is a non-experimental observational study with a systematic scoping review design that aims to summarize, identify, assess, criticize, and interpret findings from various previous studies related to autoimmune processes in the formation of atherosclerosis. The scope and focus of the research questions were determined using the PICOS (Population, Intervention, Comparison, Outcome, Study) framework so that the research questions were clear and directed, while the study selection reporting process was carried out following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and evaluated using the PRISMA checklist. The study population is all articles/journals indexed in five databases PubMed, ScienceDirect, Nature Portfolio, Cochrane Library, and The Lancet that discuss the association between autoimmunity and atherosclerosis. The sample is in the form of secondary data obtained through keyword search according to eligibility criteria, then identification stages, title and abstract screening, free full text search, and risk assessment of bias until an included article is obtained. Inclusion criteria include articles published in 2015–2025, discussing autoimmunity and atherosclerosis, as well as human research; while the exclusion criteria include articles other than English or Indonesian and articles whose full text cannot be accessed. The sample size is determined from the number of articles that meet all stages of selection, with a sampling technique using purposive sampling based on consideration of the suitability of criteria so that the data produced is representative in describing the influence of autoimmune processes on the formation of atherosclerosis.

The framework of this research was prepared based on the PICOS approach. The population in this study was patients with autoimmune diseases, which was the main focus in the various studies analyzed. This study did not involve specific interventions or comparison groups, as it aimed to examine the natural conditions of autoimmune patients as reported in the literature. The observed outcome was the risk of atherosclerosis formation in patients with autoimmune diseases, which was identified through various clinical indicators and previous research findings. To obtain a comprehensive and evidence-based picture, this study uses original research from studies related to cross-sectional and cohort

design, so as to provide a deeper understanding of the relationship between autoimmune disease and atherosclerosis risk based on published empirical findings

Result and Discussion

Atherosclerosis is classically understood as a degenerative vascular disease characterized by a buildup of lipids on the walls of the arteries, which ultimately leads to a narrowing of the lumen of the blood vessels and increases the risk of cardiovascular events such as myocardial infarction and stroke. However, modern understanding has shifted this paradigm by positioning atherosclerosis as a progressive chronic inflammatory disease that involves complex interactions between endothelial cells, the innate and adaptive immune systems, lipids, as well as various inflammatory mediators (T. Liu et al., 2020; Park et al., 2016). The atherosclerosis process begins with endothelial dysfunction that increases the permeability of the blood vessel walls to low-density lipoproteins (LDL), especially oxidized LDL (oxLDL). OxLDL triggers endothelial activation, increased expression of adhesion molecules such as ICAM-1 and VCAM-1, as well as the recruitment of immune cells such as monocytes and T lymphocytes to the intima layer of blood vessels. Migrating monocytes differentiate into macrophages and phagocytosis oxLDL so that they form foam cells as a characteristic of early atherosclerotic lesions (Gómez-Bernal et al., 2023; López-Pedrera et al., 2019; Qi et al., 2023).

Over time, innate and adaptive immune responses play a role in maintaining local inflammatory states on the walls of blood vessels through the activity of macrophages, T cells, and dendritic cells that produce a variety of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ, and interferon type I. These inflammatory mediators contribute to plaque progression, increased atherosclerotic plaque instability, and the risk of cardiovascular events acute (Fomicheva et al., 2021; Weber et al., 2023; Yennemadi et al., 2024). Therefore, atherosclerosis is now understood as part of the spectrum of systemic inflammatory diseases, in which inflammation plays a central role from the stage of initiation, progression, to plaque destabilization. Chronically released proinflammatory cytokines cause sustained endothelial activation, migration and retention of immune cells, as well as impaired vascular function, so that the process of atherosclerosis takes place progressively and chronically (Fomicheva et al., 2021; Yennemadi et al., 2024).

Autoimmune diseases are a group of diseases due to the failure of the immune system to maintain tolerance to self-antigens, thus triggering persistent immune activation involving autoreactive T cells, autoantibody-producing B cells, the formation of immune complexes, as well as the release of inflammatory mediators in the long term, which makes it included in the category of chronic inflammatory diseases (Atehortúa et al., 2019; Tselios et al., 2017; Zegkos et al., 2016). Systemic chronic inflammation in autoimmune diseases not

only damages major target organs such as the joints in rheumatoid arthritis (RA) or the kidneys in systemic lupus erythematosus (SLE), but also has systemic impacts on the cardiovascular system, which is the main pathophysiological basis of the link between autoimmune disease and atherosclerosis(DeMizio & Geraldino-Pardilla, 2020; Urowitz et al., 2020). Clinical evidence suggests that patients with autoimmune diseases have a significantly increased risk of cardiovascular events, even after being controlled against traditional risk factors, so autoimmune inflammation is seen as an independent risk factor for atherosclerosis and plays a role in the occurrence of accelerated atherosclerosis(Cooksey et al., 2018; Dalbeni et al., 2020; Hannawi et al., 2020; Popescu et al., 2023). In conditions such as SLE, RA, primary Sjögren's syndrome, and antiphospholipid syndrome, persistent inflammation, autoantibodies, and chronic immune activation contribute directly to endothelial dysfunction, oxidative stress, and atherosclerotic plaque progression, so atherosclerosis in autoimmune diseases cannot be viewed as a mere secondary complication, but rather as an integral part of the systemic manifestations of chronic inflammation (Kolitz et al., 2019; Mahmoudi et al., 2017).

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease that mainly affects the synovial joints and is characterized by persistent inflammation, tissue damage, and impaired joint function. Pathophysiologically, RA is caused by dysregulation of the immune system with the involvement of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which play an important role in the diagnosis and progression of the disease(Romo-Cordero et al., 2023). In addition to being articular, RA is a systemic disease that affects blood vessels through prolonged chronic inflammation, thereby significantly increasing the risk of cardiovascular disease (CVD)(S. Liu et al., 2023). RA patients have a higher risk of developing coronary heart disease and stroke due to endothelial dysfunction and accelerated atherosclerosis, which contributes to increased cardiovascular mortality and decreased life expectancy of up to 5–18 years compared to the general population (Benagiano et al., 2019; Huang et al., 2025).

The progression of RA to atherosclerosis occurs through sustained immune activation (Kay et al., 2016). This systemic inflammation leads to endothelial dysfunction and vascular damage that accelerates the atherosclerosis process.16,30 High RA disease activity has been shown to correlate with increased carotid intima-media (BMI) thickness and carotid plaque formation as an indicator of subclinical atherosclerosis(González-Sierra et al., 2023).

In RA patients, carotid intima-media thickness (CIMT) serves as a common marker for subclinical atherosclerosis. Higher BMI values in RA patients reflect an increased cardiovascular risk and correlate with chronic systemic inflammation and disease activity (Giles et al., 2021). In addition, the prevalence of carotid plaques in RA is reported to be higher than in the general population, especially in patients with traditional cardiovascular risk factors aggravated by chronic inflammation (Kolitz et al., 2019).

Carotid plaque formation in RA is accelerated by the interaction of systemic inflammation and cardiovascular risk factors, in which macrophages play a central role through the formation of foam cells and the release of inflammatory mediators (Kay et al.,

2016; Kolitz et al., 2019). Approximately 77% of RA patients are reported to have thickened carotid arteries, which increases the risk of stroke and coronary heart disease (Dimitroulas et al., 2017). TNF-α and IL-6 proinflammatory cytokines speed up plaque growth and vascular instability.

Macrophage dysfunction is an important mechanism linking autoimmune inflammation of RA with atherosclerosis. Activated macrophages absorb oxidized LDL and differentiate into foam cells, as well as produce proinflammatory cytokines that exacerbate endothelial dysfunction and plaque progression(Romo-Cordero et al., 2023). The presence of ACPAs, specifically anti-CCPs, is associated with increased BMI, carotid plaque formation, and higher cardiovascular risk, regardless of traditional risk factors.8,25,28,31 DMARDs and biologic therapies that control systemic inflammation have been shown to slow the progression of subclinical atherosclerosis in RA(Weijers et al., 2020).

Overall, Rheumatoid Arthritis is a systemic autoimmune disease that contributes significantly to the acceleration of atherosclerosis through chronic inflammatory mechanisms, endothelial dysfunction, macrophage activation, and the role of autoantibodies, thereby increasing the risk of cardiovascular events and worsening the long-term prognosis of RA patients.

Conclusion

Although atherosclerosis is generally considered a degenerative disease of aging, recent research suggests that autoimmune inflammation and endothelial dysfunction may accelerate this process. The chronic inflammatory processes that occur in autoimmune diseases lead to the activation of the immune system, the production of autoantibodies, and the formation of atherosclerotic plaques that can increase the risk of heart disease and stroke. Therefore, a better understanding of the mechanisms linking autoimmunity to atherosclerosis is essential to develop more effective therapies to reduce cardiovascular risk in patients with autoimmune conditions. Proper management of systemic inflammation and endothelial dysfunction in autoimmune patients can help slow the progression of atherosclerosis and prevent more serious cardiovascular complications.

Future studies are recommended to employ longitudinal and interventional designs to elucidate the causal relationship between autoimmune inflammation, endothelial dysfunction, and atherosclerosis progression, as well as to evaluate the role of immunological biomarkers and immunomodulatory therapies. Clinically, routine cardiovascular risk screening and a multidisciplinary approach integrating systemic inflammation control with atherosclerosis prevention are strongly recommended for patients with autoimmune diseases

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