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Cardiovascular disease in autoimmune disorders

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Abstract

Autoimmune disorders characterized by aberrant immune attacks on self-antigens are recognized to be significant risk factors for cardiovascular disease (CVD), which is a leading worldwide cause of death. Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and antiphospholipid syndrome (APS) are among the autoimmune conditions with strong associations with premature atherosclerosis, thrombosis, and cardiac dysfunction. This literature review merges the current evidence on the pathophysiological mechanisms linking autoimmune disorders to CVD, its diagnostic approach, clinical associations, and therapeutic implications. Systematic studies were conducted on PubMed, Scopus, and Web of Science using the following keywords: "autoimmune disorders" AND "cardiovascular disease," "systemic lupus erythematosus" AND "atherosclerosis," and "rheumatoid arthritis" AND "cardiac risk" for studies published between 2015 and 2025. The key mechanisms are chronic inflammation, endothelial injury due to autoantibodies, and dyslipidemia, and the presence of anti-phospholipid antibodies and elevated levels of cytokines in over 70% of SLE-related CVD. Diagnostic modalities, such as coronary artery calcium (CAC) scoring and cytokine profiling, are promising but are compromised by assay variability and concordant clinical presentation. Immunomodulating therapy, such as methotrexate and biologics, reduces the risk of CVD in RA by 20–30%, but efficacy is disorder-variable. This review identifies the critical intersection of autoimmunity and CVD, emphasizing the significance of standardized biomarkers, integrated risk assessment models, and future research in an attempt to maximize diagnosis and management.

Keywords: autoimmune disorders, cardiovascular disease, antiphospholipid syndrome, atherosclerosis, inflammation.

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1. Introduction and Background

Cardiovascular disease (CVD), which includes coronary artery disease (CAD), myocardial infarction, and stroke, is one of the leading causes of death globally and occurs at an estimated 17.9 million deaths annually [1]. Autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), antiphospholipid syndrome (APS), and Sjögren's syndrome, significantly increase CVD risk through the production of chronic inflammation, autoantibody-mediated injury, and metabolic deregulation [2]. The prevalence of CVD in autoimmune diseases is striking, with 5-10 times higher risk for myocardial infarction among SLE patients compared to the general population [3]. Similarly, RA is independently associated with a 50% increased risk of CVD-related mortality independent of conventional risk factors like hypertension and smoking [4].

The relationship between autoimmunity and CVD is complex and encompasses complex mechanisms, such as endothelial dysfunction, pro-atherogenic accelerated atherosclerosis, and thrombosis caused by autoantibody- and cytokine-mediated mechanisms [5]. Recent advances in biomarker research, for example, anti-phospholipid antibodies and interleukin-6 (IL-6) levels, have enabled risk stratification, while imaging modalities like coronary artery calcium (CAC) scoring offer early diagnosis [6]. However, there are limitations including variability of assays in biomarkers, convergence of autoimmune and cardiovascular symptoms, and limited data on long-term outcomes [7]. Emerging therapy such as biologics and Janus kinase (JAK) inhibitors has the potential to reduce CVD risk but needs further validation [8]. This review aims to integrate current evidence regarding the mechanisms, diagnosis, and treatment strategies for CVD in autoimmune disease, highlight areas of research needed and directions for the future.

1.1 Mechanisms linking autoimmune disorders to cardiovascular disease

1.1.1 Chronic inflammation

Chronic inflammation is a hallmark of autoimmune diseases and a key driver of CVD. In SLE, elevated pro-inflammatory cytokine levels, such as IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-alpha (IFN-α), facilitate endothelial dysfunction and plaque accumulation [9]. A 2022 study by Petri et al. found increased IL-6 levels

of greater than 5 pg/mL in 75% of SLE patients with premature atherosclerosis [10]. In RA, synovial inflammation extends to the systemic circulation, raising C-reactive protein (CRP) and increasing vascular stiffness, with 60% of patients showing elevated arterial stiffness indices [11]. APS is linked with thrombotic complications triggered by anti-phospholipid antibodies, which stimulate endothelium and platelets, raising CVD risk 3-fold [12].

1.1.2 Autoantibody-Mediated damage

Autoantibodies play a crucial role in CVD pathogenesis in autoimmune diseases. In SLE, anti-phospholipid antibodies (aPL), including anti-cardiolipin and anti-β2-glycoprotein I, are present in 70% of patients with CVD manifestations and promote thrombosis through endothelial homeostasis disruption [13]. Anti-double-stranded DNA (anti-dsDNA) antibodies present in 80% of SLE patients form immune complexes that accumulate in vessel walls, causing inflammation [14]. In RA, ACPA is linked to a 2-fold increase in ischemic heart disease risk, likely through immune complex-mediated endothelial damage [15]. New autoantibodies, such as anti-oxLDL, occur in 30% of APS patients and exacerbate atherosclerosis [16].

1.1.3 Metabolic dysregulation

Autoimmune diseases are associated with dyslipidemia and insulin resistance, raising CVD risk. In SLE, decreased HDL and elevated triglycerides in 50% of the patients are caused by IFN-α-induced suppression of lipid metabolism genes [17]. RA patients have a "lipid paradox" where low total cholesterol levels hide pro-atherogenic profiles, and oxidized LDL is present in 40% of the patients [18]. APS hypercoagulability, with added dyslipidemia, doubles acute coronary syndromes by 25% [19].

1.1.4 Diagnostic challenges

Detection of CVD in autoimmune diseases relies on biomarkers like CRP, IL-6, and aPL but is compromised by variability of assay sensitivity. ELISA for aPL, for example, is 85% sensitive but 70% specific in SLE [20]. Imaging tests like CAC scoring and carotid intima-media thickness (CIMT) detect subclinical atherosclerosis but are costly and not always accessible [21]. Overlap of autoimmune symptoms (e.g., fatigue, chest pain) and CVD presentations leads to delay in diagnosis, particularly in young patients with SL [22].

2. Clinical and prognostic implications

2.1 Clinical phenotypes

CVD presentations vary based on autoimmune disease. In SLE, accelerated atherosclerosis leads to preterm CAD, with 30% of patients below the age of 40 developing myocardial infarction [23]. RA involves diffuse coronary plaque and heart failure, with 20% of patients developing left ventricular dysfunction [24]. APS primarily leads to thrombotic occurrences like stroke and pulmonary embolism, with 40% of patients developing recurring thrombosis [25]. There is increasing evidence that Sjögren's syndrome facilitates CVD risk through microvascular dysfunction, which is detected in 15% of patients by abnormal myocardial perfusion imaging [26].

2.2. Prognostic significance

Biomarkers and imaging provide prognostic data. In SLE, persistently positive aPL titers are prognostic for a 3-fold increased recurrent CVD event risk [27]. In RA, high ACPA levels and CAC scores >100 are predictive of a 25% increase in risk of MACE at 5 years [28]. Longitudinal research shows that early immunosuppression in RA reduces CVD mortality by 20%, while delayed treatment in SLE increases death by 30% [29]. APS patients with triple-positive aPL (lupus anticoagulant, anti-cardiolipin, anti-β2-glycoprotein I) carry 50% higher mortality due to thrombotic complications [30].

2.3 Traditional vs. autoimmune-Related CVD

Traditional CVD risk factors (e.g., smoking, hypertension) augment autoimmune-associated CVD, while autoimmune mechanisms dominate in younger patients. For example, SLE patients under 30 years have a 10-fold risk of CVD independent of traditional factors [31]. Biomarker stratification and imaging for the differentiation of autoimmune-driven CVD are crucial for personalized management.

3. Mechanisms of autoimmune-Mediated Cardiovascular pathology

Autoimmune mechanisms foster CVD through distinct mechanisms. In SLE, IFN-α causes expression of adhesion molecules (e.g., VCAM-1) on endothelial cells, with recruitment of monocytes and plaque formation [32]. Anti-dsDNA immune complexes precipitate in coronary arteries, leading to complement activation and vascular injury [33]. In RA, ACPA and rheumatoid factor (RF) exist as immune complexes, which stimulate macrophages to produce matrix metalloproteinases that destabilize plaques [34]. In APS, aPL bind β2-glycoprotein I on endothelial surfaces, inducing a pro-thrombotic state via upregulation of tissue factor [35]. Emerging evidence suggests that oxidative stress, driven by anti-oxLDL antibodies, exacerbates endothelial dysfunction during autoimmune diseases [36]. Such mechanisms demonstrate the collaborative role of inflammation, autoimmunity, and metabolic dysregulation in CVD pathogenesis.

4. Diagnostic approaches

4.1 Biomarkers

Biomarker panels of IL-6, CRP, and aPL are central to CVD diagnosis in autoimmune diseases. Manzi et al.'s 2023 work developed a composite biomarker score based on IL-6, TNF-α, and aPL and could predict CVD events in SLE with 80% accuracy [37]. In RA, RF titers and ACPA are linked to CAC scores, giving 75% sensitivity for subclinical atherosclerosis [38]. Novel entrants anti-oxLDL and microRNAs (miR-146a) hold promise but require validation [39].

4.2 Imaging modalities

Imaging enhances CAC detection in autoimmune diseases. Techniques of CAC scoring by the use of computed tomography identify subclinical atherosclerosis in 50% of asymptomatic RA patients [40]. CIMT, when measured by ultrasound, is 70% sensitive in predicting stroke risk in APS [41]. Positron emission tomography with fluorodeoxyglucose identifies vascular inflammation in SLE, though excessive cost limits its application to research only [42].

4.3 Challenges

Biomarker assay and imaging protocol variation discourages diagnostic standardization. For example, ELISA for aPL is lab-dependent with 10–15% false positives due to non-specific binding [43]. Biomarker combination with imaging and clinical risk scores is required for improving diagnostic accuracy.

5. Therapeutic implications and Challenges

5.1 *Immunosuppressive therapies*

Immunosuppressive therapy reduces CVD risk in autoimmune disorders. First-line RA medication methotrexate lowers CVD mortality by 20–30% through reduced systemic inflammation [44]. Hydroxychloroquine in SLE lowers aPL titers and CVD events by 25% [45]. Biologics such as TNF-α inhibitors (e.g., adalimumab) improve endothelial function in RA, with 60% of patients showing reduced arterial stiffness [46]. APS-related thrombosis, however, requires anticoagulation (e.g., warfarin), with minimal effect of immunosuppression [47].

5.2 Emerging therapies

New therapies, such as JAK inhibitors (e.g., tofacitinib), work in RA and reduce IL-6 and CVD risk by 15% in trials [48]. Belimumab (a B-cell inhibitor) in SLE reduces immune complex formation, with preliminary data showing a reduction of 20% in CVD events [49]. Anti-oxidant therapies against oxLDL are studied but lack adequate clinical evidence [50].

5.3 Challenges

Therapeutic outcomes vary with autoimmune disease and CVD phenotype. For example, TNF-α inhibitors increase the risk of heart failure in RA patients with pre-existing cardiac disease [51]. Immunosuppression over the long term increases the risk of infection, which happens to 10–15% of SLE patients [52]. Designing disorder-specific treatment regimens and optimizing therapy duration are high priority.

6. Limitations and future directions

6.1 Current limitations

Variability in assays, small cohort sizes (50–150 patients in most studies), and retrospective study designs limit generalizability [53]. Longitudinal data on CVD outcomes in APS and Sjögren's syndrome are sparse [54]. There is overlap between autoimmune and CVD symptoms, so it is difficult to diagnose early in younger patients [55].

6.2 Future research

Prospective, multicenter studies with standardized biomarker and imaging protocols are needed to validate diagnostic tools. Integration of multi-omics data (genomics, proteomics, metabolomics) with machine learning has the potential to improve risk prediction. RCTs of new therapies, such as JAK inhibitors, are needed to establish efficacy and safety. Exploration of the role of the gut microbiota in inflammation regulation and CVD risk in autoimmune diseases is a new frontier [56].

6.3 Clinical implications

Routine biomarker profiling (e.g., aPL, IL-6) and imaging (e.g., CAC scoring) has to become standard in autoimmune patients under suspicion of CVD. Point-of-care diagnostics enabling rapid detection of biomarkers can reduce delays. Patient registries and biobanks would facilitate large-scale investigation and tailored approaches to personalized medicine.

7. Conclusions

Cardiovascular disease in autoimmune disease is a complex interaction of chronic inflammation, autoantibody-mediated damage, and metabolic derangement. SLE, RA, and APS are strongly associated with premature atherosclerosis and thrombosis, driven by biomarkers such as aPL and IL-6. Both diagnostic tests, such as CAC scoring and cytokine profiling, and imaging are very specific but are limited by standardization and availability. Immunosuppressive therapies reduce CVD risk, but new drugs such as JAK inhibitors require further validation. Standardized assays, composite risk models, and prospective studies are necessities for improving diagnosis and management, rendering precision medicine a cornerstone for the alleviation of CVD burden in autoimmune disease.

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