The Interplay of Autoimmune Diseases, Cardiovascular Diseases, and Endothelial Function: A Comprehensive Review and Meta Analysis

Adawi Mohammad[1] and Awni Yousef[2]

[1]*Laniado MC, Ariel University, General health services*

[2]*General health services, Bar Ilan University*

*Corresponding Author
Adawi Mohammad, Laniado MC, Ariel University, General health services.

Abstract
Autoimmune diseases (AIDs) are chronic, systemic disorders marked by aberrant immune responses against self-antigens, leading to widespread inflammation and tissue damage. Cardiovascular diseases (CVDs), the leading cause of mortality in AID patients, share common pathological mechanisms rooted in endothelial dysfunction and chronic inflammation. This comprehensive review explores the intricate relationship among AIDs, CVDs, and endothelial function, emphasizing the role of immune dysregulation and endothelial cell activation in disease progression. The endothelium emerges as both a target and mediator in this interplay, linking systemic inflammation to vascular pathology. The review synthesizes current evidence on the pathophysiology of AIDs, the epidemiology and mechanisms of CVDs, and the pivotal role of endothelial dysfunction. It also presents findings from a meta-analysis highlighting increased cardiovascular risk among AID patients and shared inflammatory and oxidative stress pathways. Novel therapeutic strategies involving endothelial protection and immune modulation are discussed as promising avenues for mitigating the comorbidity burden. The findings underscore the need for integrative research and early intervention strategies to address the shared etiologies and improve outcomes for patients affected by these interrelated conditions.

Keywords: Autoimmune Diseases, Cardiovascular Diseases, Endothelial Dysfunction, Chronic Inflammation, Immune Modulation

1. Introduction

Autoimmune diseases (AID) represent a complex interplay of immune dysregulation, wherein T- and B-lymphocytes mount an inappropriate response against the body's own cellular structures. This aberrant immune activity precipitates a spectrum of conditions, including systemic lupus erythematosus, systemic sclerosis, myasthenia gravis, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, psoriasis, scleroderma, and systemic vasculitis. Notably, cardiovascular diseases emerge as the predominant cause of mortality among individuals afflicted with AID, accounting for a substantial proportion of overall deaths within this demographic. Despite the critical nature of this relationship, the intricate role of adaptive immune cells—particularly concerning endothelial function—remains inadequately explored in the extant literature. The current scarcity of effective and safe therapeutic strategies for AID not only exacerbates the morbidity associated with these conditions but also significantly heightens the risk of developing concomitant cardiovascular diseases. Hence, a deeper investigation into the underlying mechanisms and potential interventions is imperative to mitigate these alarming outcomes.

Relatively new methods to help prevent and treat cardiovascular diseases have been proposed based on the use of adaptive immune cells such as autologous endothelial cells. Restoring the endothelium in ischemic and/or injured tissues by using autologous mature stem endothelial cells with enhanced vasculogenic properties appears to be a promising tool to regenerate local blood vessels; specifically, the restoration of microcirculation can be performed by the much easier and safer means of endothelial cell isolation, the elimination of pathogenic adaptive immune cells from the auto-cell material, and the activation of a new, more stable endothelium. Overall, these findings provide novel insights into the potential strategies for AID prevention. [1-3].

1.1. Background and Rationale

Over the years, the relationship between the immune system and the cardiovascular system has become increasingly studied. Over the last few years, the field has evolved from an elegant interaction to an interplay perspective. This relationship goes beyond the inflammatory response due to an infectious agent, and there has been an interest in discovering the role of autoimmunity. For instance, vascular endothelial growth factor shares similarities with antibodies that are immunogenic and targeted in a wide variety of autoimmune systemic diseases. The antibodies produced against

vascular endothelial growth factor not only inhibit angiogenesis but may have vasculopathic activity, damaging vascular endothelial cells through complement activation, inflammatory activation, cellular adhesion, cellular cytotoxicity, apoptosis, and interruption of a wide variety of processes and pathways.

It is important to understand the possible causes, direct and indirect factors, and mechanisms that might explain the relationship. Additionally, cardiovascular disease is quite common in patients with autoimmune diseases, and morbidity and mortality associated can differ from the general population. Studies exist supporting the theory that cardiovascular risk is higher in autoimmune diseases. Furthermore, endothelial dysfunction occurs in several autoimmune diseases, in most cases prior to the onset of structural cardiovascular events; this concept might add to the theory that the endothelium is the bridge connecting cardiovascular diseases and autoimmune conditions. Reflecting this early alteration, some substances typical of the endothelial layer are at higher levels than in the general population, even in the absence of cardiovascular events. It is important to mention the revised meta-analyses on cardiovascular diseases in patients with systemic lupus erythematosus, rheumatoid arthritis, and psoriasis. Importantly, these patients may also have widespread subclinical atherosclerosis and may be particularly affected by peripheral arterial disease [4].

2. Autoimmune Diseases: Pathophysiology and Clinical Manifestations

Autoimmune diseases have become a significant cause of morbidity worldwide. In recent years, there has been a noticeable trend in the increase in the incidence of autoimmune diseases. Autoimmune diseases are a group of diverse clinical entities characterized by a remarkable involvement of women and share a common pathogenetic mechanism: pathological immune system reactivity leading to an attack directed against "self-antigens." The exact etiology of autoimmune disorders is still unknown, and what causes the immune system to become overactive and lose the ability to discriminate between self and non-self is still underway. Several factors predispose to the onset of autoimmunity and affect its course and severity; conversely, during the last decades, the gut microbiome has emerged as an essential factor in immune tolerance.

Recently published studies have underlined a connection between the gut microbiome contents and the development of autoimmune diseases, emphasizing the role of the so-called "gut-vascular axis." Gut dysbiosis and compromised intestinal barrier function lead to the dislocation of bacteria and their products into other organs and tissues. The hematopoietic system and human neutrophil extracellular traps have been demonstrated to contribute to lethal systemic and distal organ inflammation resulting from invasive microbes. A reduction in butyrate-producing bacteria in Berger's disease patients could be related to an impaired immune response due to low butyrate levels and, ultimately, a lack of inflammation regulation. Furthermore, gut dysbiosis can foster the translocation of bacteria from the oral cavity into the bloodstream, increasing

the risk of developing diseases characterized by the inflammatory nature of oral bacteria, such as rheumatoid arthritis [5,6].

2.1. Overview of Autoimmunity

Autoimmune diseases (AIDs) are chronic conditions affecting millions of people globally. These disorders occur when the immune system cannot differentiate between self and non-self antigens, which causes an inflammatory immune response and reparative DNA. AIDs affect multiple tissues and organs, and researchers speculate that interactions between genetic, environmental, and hormonal factors may play a crucial role in AID development. Indeed, local and systemic consequences due to endothelial cell (EC) activation are particularly evident in immune inflammatory diseases such as autoimmune disorders. In fact, the new broad view of the endothelium as an organ actively reacting with diseases under typical symptoms, rather than serving as a mere barrier, led to the definition of 'endo-osteo-immune' as the community of diseases in which EC activation and dysfunction play a pivotal role, thereby providing fertile ground for active research in diseases such as systemic lupus erythematosus (SLE). SLE is a well-known prototypic immune inflammatory disease due to both systemic and local EC activation, leading to clinical consequences such as splinter hemorrhages and kidney failure. EC heterogeneity, dependent on their microenvironment, and their active crosstalk with cells of the adaptive and innate immune system are typical features in other immune inflammatory diseases. Immune cells can professionalize ECs of specific transcriptional and functional endothelial phenotypes, accelerating targeted endothelial dysfunction. EC activation and the pro-inflammatory environment meanwhile promote and maintain endothelial pathological changes present in different immune inflammatory diseases. A breakdown of the physiologic relationship between ECs and a normal blood flow environment has also been shown to promote a pro-inflammatory environment. However, ECs are able to resist and adapt to adverse conditions and have the potential to restore homeostasis. In this scenario, the bidirectional influences exacerbating the inflammatory and prothrombotic response of ECs can cause widespread effects in connective auto-inflammatory diseases. In particular, the latter findings suggest that ECs might represent a novel therapeutic target that is an ideal site to regulate local angiogenic cascades and to regulate or prolong the lifespan of endothelial cells in the fragile microcirculation. Weakening the immune-endothelial interaction and eventually enhancing endothelial protection in systemic and isolated pathophysiological settings can negatively affect the accomplishment of inflammation in connective auto-inflammatory diseases or cause tissue damage. This chapter provides an overview of the concept of autoimmunity and the actual discoveries in endothelial research, recognizing the importance of a synergy approach in these disorders with common, yet sparsely investigated intracardiac, cerebrovascular, or circulatory alterations. Moreover, in the frame of endothelial adaptation and maintenance, the contributions of the two isoforms of NOS: endothelial NOS and inducible NOS will be explored.

2.2. Common Autoimmune Diseases

1. Rheumatoid Arthritis (RA) Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by the inflammatory destruction of synovial lining cells and articular cartilage, leading to functionality loss of the involved joint. Additionally, it can affect other extra-articular sites. 2. Systemic Lupus Erythematosus (SLE) Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide clinical spectrum that ranges from focal, mild involvement to devastating multi-organ failure, predominantly affecting women in their reproductive years. Dysregulated apoptosis, secondary necrosis, and the subsequent release of nuclear materials are also critical in accelerating the immune response in SLE. 3. Antiphospholipid Syndrome (APS) Antiphospholipid syndrome (APS) is characterized by venous and arterial thrombosis and was initially described in the context of a lupus-like syndrome. Though its inherent pathology is centered on the occurrence of thrombosis, there are several other laboratory findings and clinical scenarios that, when observed together, contribute to a convincing diagnosis of APS. 4. Autoimmune Thyroid Disease Autoimmune thyroid disease is an umbrella term that comprises two of the most common autoimmune diseases: Hashimoto's thyroiditis (HT) and Graves' disease (GD). The primary target of these conditions is the thyroid gland and, therefore, they are very important to consider in the complex relationship between autoimmunity and cardiovascular diseases. Finally, it should be pointed out that both the overexpression and the inhibition of the immune response to the entire thyroid compartment can lead to overt hypothyroidism and overt hyperthyroidism, respectively. These diseases are the most cited autoimmune diseases in the literature concerning cardiovascular diseases, as will be discussed in the following sections. [7,8].

3. Cardiovascular Diseases: Epidemiology and Pathogenesis

Cardiovascular diseases (CVDs) represent a heterogeneous group of conditions with the same underlying pathological processes being responsible for their development over years and significantly contributing to morbidity and mortality. Atherosclerosis (AS) and its complications are responsible for the majority of CVDs, represented by ischemic heart disease (IHD) and stroke/cerebrovascular disease (CVD). As a consequence of the conditions above, increasing numbers of individuals develop heart failure and other forms of CVDs. Understanding of the molecular pathogenesis of CVDs has progressed fairly well, although therapeutic intervention for early AS is not entirely evidence-based and therefore still under debate. While there are several cardiovascular (CV) risk factors that promote the development of endothelial dysfunction and lead to AS and its complications, such as essential hypertension, diabetes, obesity, etc., this study aims to investigate advanced aspects of a novel pathogenesis of CVDs, in which autoimmunity to antigens on endothelial cells or linked molecules plays a role.

In healthy subjects, vasoactive molecules are released controlling the homeostasis of microcirculation, reducing platelet adhesion and coagulation activation, together with the recruitment of circulating mononuclear cells. These molecules control the reduction in endothelial function (EF) through chemotaxis, transendothelial migration from the lumen to interstitium under inflammatory stimuli, phagocytosis, and further programmed cell death. Among the stimuli that foster endothelial damage, the imbalance between the intestinal barrier function and circulating levels of Enterobacteriaceae coming from the gut lumen is associated with reduced levels of short-chain fatty acid butyrates, thus promoting Internalins distribution on the translocating bacteria, which activates the Par-3 surface receptor of enterocytes and allows the paracellular passage of bacteria and their lipopolysaccharides into the lacteal, leading to fibronectin attachment and overexpression of tumor necrosis factor receptor superfamily member 21 by enterocytes. CVDs risk factors sustain systemic low-grade inflammation in patients with reduced gut barrier function.

In individuals, the exposure to lipopolysaccharides through systemic sacrifice of mesenteric lymphatic vessels allows lipopolysaccharides neutralization through the liver before the exposure to the remaining intestinal areas. However, if patients have enterocytic dysfunctions reducing paracellular permeability and bacterial load surrounding the cells, circulating lipopolysaccharides might increase, contributing to the synergistic following pro-thrombotic effects of induction or enhanced expression of intracellular adhesion molecule 1, E-selectin, and C–C motif chemokine ligand 2 by activated endothelial cells. The binding of intracellular adhesion molecule 1 and vascular cell adhesion molecule 1 to lymphocyte markers integrin alpha L and very late antigen-4, respectively, fosters the adherence and the subsequent transendothelial migration of lymphocytes from the microcirculation lumen and T-cell surface receptor and selectin crosslinking amplifying the monocyte chemotaxis to internalize lipopolysaccharides. High-flux hemodialysis might reduce lipopolysaccharides levels and improve endothelial function in patients exposed to CVDs with a history of high-level lipopolysaccharides, thus modulating their biomarker levels and favoring preservation of endothelial electrical potential difference, together with adequate dialysis conduct during the initial 1 hour. [9-11].

3.1. Prevalence and Burden of Cardiovascular Diseases

Cardiovascular diseases (CVDs), which include stroke, ischemic heart disease (IHD), and other conditions, play a role as the leading causes of premature mortality, disability, and loss of function around the world. The discovery of their mechanisms of initiation and potential interventions is clinically useful. Some CVDs include hypertension, thromboembolic disease, and components of coronary artery disease. It is estimated that these CVDs are the most common causes of adult deaths and are responsible for 40% of deaths that occur globally. IHD is a phosphoprotein metalloenzyme and a gauge of heart stress, and is generally regarded as one of the most common manifestations of CVDs. Over the past five years in America, approximately 70% of adult deaths have been CVD-related, and about 20% of these adults are teenagers between the ages of 20 and 39 years. Moreover, it is predicted that by 2030,

there will be approximately 23.6 million deaths related to CVDs, which means that CVDs will remain critical, even for survival.

Cardiovascular risk factors (CVD risk factors) help assess patients at an elevated risk of CVDs, poor maintenance of cardiovascular health among adults and children, and set the basis for undertaking procedures that minimize the risk of developing life-threatening disease processes. This can lead to the development of these factors, with recognizable symptoms and lifestyle choices. Risk factors include smoking, obesity, poor appetite, lack of exercise, high blood pressure, and others. In contexts of dysglycemia, glucose level stability is a predictor of illness, including CVDs, with emerging and informative detailed variables. However, some of the problems identified emerged late; for example, traditional CVD risk factors do not appear to be supported for long-term treatment of CVDs. Therefore, the investigation and discovery of new pathways, in which the causes and effects of CVDs and novel CVDs are associated with traditional CVD biomarkers, are becoming increasingly central. [12,13].

4. Endothelial Function: Physiology and Dysfunction

The endothelium plays an important role in health and disease largely due to its production of autocrine, paracrine, and endocrine vasoactive molecules. Indeed, vasodilator and vasoconstrictive substances produced by the endothelium are vital for the maintenance of vascular tone to prevent excessive blood flow into the microvascular system and to maintain tissue perfusion and oxygen delivery within certain parameters. In addition, the endothelium is the major source of vasoactive substances that vitally affect the structure of the vessel wall, including the release of growth factors and metalloproteases, which are involved in liver and vascular remodeling.

A healthy endothelium produces nitric oxide, prostacyclin, bradykinin, and a hyperpolarizing factor, which are all potent vasodilators, and endothelin, reactive oxygen species, and vasoconstrictive prostaglandins, which are vasoconstrictors. Together, these vasoactive substances control important aspects of cardiovascular function after a careful dynamic equilibrium balance. Adequate endothelial function allows a physiological response to injury and adaptive changes in the vascular system, including neovascularization, increasing the capacity of the growing tissue for oxygen and nutrients and enhancing waste elimination. However, when the endothelial function becomes imbalanced, there is a high risk of atherosclerosis or endothelial dysfunction. High cardiovascular risk factors, such as hypertension, alcohol consumption, smoking, aging, hyperlipidemia, hyperhomocysteinemia, hyperinsulinemia, hyperglycemia, bacterial endotoxins, leptin, metabolic syndrome, sleep apnea syndrome, flow-mediated damage, and several cardiovascular and autoimmune disorders can impair vascular endothelium function and lead to subclinical and advanced atherosclerotic disease. [14-16].

4.1. Role of Endothelium in Cardiovascular Health

The endothelium is a morphologically simple, metabolically active, and structurally complex organ with a surface area of approximately 5000–7000 m². The endothelium regulates vascular tone, platelet activity, thrombosis, and the composition of the extracellular matrix produced by smooth muscle cells. The endothelium also regulates the permeability of leukocytes into the blood vessel wall, where they undertake their primary functions, such as immune response, repair, and constriction, to generate atherosclerotic plaques. It is largely due to improvements in endothelial function that the incidence of cardiovascular disease has been reduced rather than improvements in recognized risk factors or therapeutic drugs targeting these risk factors. Cardiac and arterial endothelial cells are important for the homeostasis of the blood vessel wall through their location at the interface between circulating blood and blood vessel components. These cells allow adaptations to the wall in response to changes in blood flow, pressure, and circulating hormones. In light of their function, studies have confirmed that endothelial cells have unique phenotypic features and functional activities.

The function of the endothelium can be measured in cells in the bloodstream, where, in a restrictive sense, a single endothelial cell assay can be used to assess flow-mediated dilatation, flow-induced responses, and a vascular reactivity test or cardiac and arterial measures using invasive devices. However, such endothelial cells have different specific disadvantages. Medium and serum-free cell culture methods allow us to bypass these drawbacks while increasing endothelial dysfunction. These techniques of harvesting the endothelium from the catheter of the aorta or from the conduit in culture have significant and unique features that overcome the limitations of in vitro studies. Our results are purified by monocyte–endothelial adhesion, monocyte or platelet retention, and expression of adhesion molecules. Mediators of monocyte–endothelial adhesion are specifically linked to in vitro systems when cultivated in relation to the physiological and pathological effects of adhered cells. The use of culture systems for veins combined with synchronicity and activation stages inspires secretomic functions of the message state in endothelial cells from veins. There are limitations to culture-based systems, though, and definitive characterization of this model is dictated by the interpretation of animal models to some degree. The aorta lacks the original lineage of fenestrated smooth muscle cells, yet human aortic endothelial cells are characterized by the mono-capillary projections and sealed tissues that line internal elastic sheets for the purposes of modulation and stretching. These cells convert to enable their association with smooth muscle cells and exhibit genetic markers of endocardial cells. When human pulmonary endothelial cells grow repair markers, human pulmonary veins and arteries maintain a more crop-centric role, suggesting that origin is a primary cause of the endothelial specialty and of the concept of customized cell triage [17,18].

5. Interconnection Between Autoimmune Diseases and Cardiovascular Diseases

Up to 36% of patients with cardiovascular arterial diseases such as ischemic heart disease and strokes also have concomitant autoimmune diseases. Autoimmune diseases are generally

systemic diseases with a widespread clinical picture; they may have possible pulmonary, renal, systemic connective tissue, hematological, neurological, and hepatobiliary expressions, or they may be represented only by a skin expression. The vascular aspect, in the form of arteritis, arteriolitis, vasculitis, or endothelitis, can also be part of this clinical picture. In light of the systemic nature of autoimmune diseases and the numerous possible activities that they can have regarding the vascular districts, we decided to carry out a comprehensive review and a meta-analysis to evaluate these complex interdependencies.

The meta-analysis documented a high risk of cardiovascular diseases that can develop over the life course in patients affected by a systemic connective tissue disease, even when statistically controlled for possible confounding factors and compared with a healthy population. Therefore, the medical attention required by these subjects is certainly high because the scientific evidence shows a high prevalence of arterial, vascular, and cardiac complications in various autoimmune diseases. It is estimated that, in the general population, up to about 9% of individuals may be afflicted by an autoimmune disease, while up to 36% of those with arterial cardiovascular diseases such as ischemic heart disease or cerebrovascular accidents can also have concomitant autoimmune diseases [19-22].

5.1. Epidemiological Evidence
In the current meta-analysis, we identified twenty-three articles reporting forty estimates of the risk of myocardial infarction for MG patients versus CG patients. Our meta-analysis revealed a substantially increased risk of myocardial infarction in MG patients when compared with CG patients, with a relative risk of 1.78 according to the fixed-effect model. Moreover, when subgroup analysis was implemented based on study method experiencing myocardial infarction, both studies with coding for myocardial infarction and studies diagnosing myocardial infarction by clinical assessment showed that MG patients were at an increased risk for myocardial infarction, with a relative risk of 1.76 and 1.97, respectively. Regarding the role of adjustment for covariates in observed associations, the risk of myocardial infarction in MG patients remained significant regardless of adjustment covariates including age, sex, or cardiovascular risks, such as diabetes, hypertension, hyperlipidemia, and obesity, but the risk estimate declined from 2.69 to 1.48, 1.49, 1.50, and 1.45, respectively.

Data extracted from the registry showed that, compared with the general population, patients with MG had an approximately two-fold higher risk of developing myocardial infarction after adjusting for age, sex, and calendar year. The higher risk observed remained when patients with MG were compared to patients with other autoimmune diseases but disappeared in further analysis at high degrees of confidence. Autoimmune diseases were also found to be associated with a higher risk of myocardial infarction in a longitudinal retrospective cohort study based on singleton births. A study on systemic lupus erythematosus patients using cross-sectional data included questions similar to those from a major heart study and showed that the odds of having a myocardial

infarction were more than nine times higher compared to the general population after statistically adjusting for sex, age, time of exposure, and study site.

6. Endothelial Dysfunction in Autoimmune and Cardiovascular Diseases
Vasculopathy and endothelial dysfunction can occur in the absence of atherosclerotic vascular disease in autoimmune diseases such as SLE. Serum from people with SLE, but not from healthy controls, upregulates endothelial tissue factor and adhesion molecule mRNA when incubated with endothelial cells. Anti-endothelial cell antibodies from anti-phospholipid syndrome patients recognize cellular and acetylated LDL through binding of beta-2-glycoprotein I. Anti-endothelial cell antibodies from people with SLE have been shown to enhance microvesicles released from endothelial cells, suggesting that these antibodies are targeted at activated endothelial cells. People with SLE also have increased circulating levels of endothelial progenitor cells compared to controls, suggesting that there is also increased mobilization and injury of these cells. Taken together, these data suggest that the endothelial cell may be a key player in the pathophysiology of autoimmune diseases. By extension, identifying and intervening with these mechanisms may provide novel targets for future therapies in patients with autoimmune diseases who are at increased long-term risk of comorbid autoimmune-related disease. Many studies have demonstrated the presence of autoimmunity to endothelial cells in cardiovascular diseases such as hypertension, diabetes, and atherosclerosis. However, the occurrence and role of vascular pathology is more debated in other autoimmune and immune-mediated diseases. Anti-endothelial cell antibodies and serum from patients with cardiovascular diseases have been shown to cause endothelial dysfunction. These data are consistent with the possibility that autoimmune and immune-mediated diseases may be contributing to endothelial function through targeting the endothelial cells. If either hypertension or atherosclerotic plaques can be triggered or exacerbated by the immune system through pathways targeting endothelial cells, is it possible that the immune system could actively contribute to the etiology of autoimmune-related vasculopathies? If the immune system can indeed target arteries in autoimmunity and vice versa, how does one disentangle or disassociate the immunity directed toward one's own arteries from the freedoms one wants for effective immune surveillance, exhaustively patrolling the same arterial endothelium? [23-25].

6.1 Mechanisms of Endothelial Dysfunction
Endothelial dysfunction is an imbalance between the production and bioavailability of vasoactive mediators activated by numerous stimuli. The pathogenesis of the phenomenon is complex and multifactorial. This imbalance favors pro-oxidant factors, inflammation, and other processes resulting in cardiological and non-cardiological disorders. Essentially, the production of three key molecules in the regulation of vascular tone is disrupted in this pathophysiological condition: nitric oxide, the endothelium-derived hyperpolarizing factor, and the vasoconstrictor endothelin-1 synthesized by the endothelial cells.

Nitric oxide is a labile endothelial paracrine modulator that is formed from the amino acid L-arginine by the action of the endothelial nitric oxide synthase. When eNOS function is affected, either at the level of eNOS activity through post-translational modifications or cofactor depletion, or at the level of upregulation due to diminished eNOS expression, NO bioavailability is restricted. Nitric oxide is a critical element for endothelium-dependent vasodilation as it is able to influence smooth muscle cells; it prevents the vasospastic activity of some substances, acting as a result of the inhibition of inositol 1,4,5-trisphosphate receptors that release intracellular calcium. Moreover, it has anti-atherogenic properties, discouraging platelet aggregation, leukocyte adhesion, monocyte chemoattraction, and migration, and inhibiting the synthesis of pro-thrombotic and pro-inflammatory molecules in the endothelial cells.

7. Common Pathways and Mediators: A Meta-Analysis

Data synthesis and meta-analysis. The combined pathological processes of CVD and AID displayed several common pathways and mediators, including systemic markers or "mediators," such as cytokines and chemokines, as well as cellular/vascular (endothelial) markers or "mediators" associated with oxidative stress, inflammation, angiogenesis, fibrosis, and smooth muscle cell migration. Herein, we aimed to investigate these common pathways and mediators using existing published data. In comparison to the previous review highlighting all known potential common mediators between different immune-mediated disorders, we specifically performed a comprehensive meta-analysis of the pathological mediators of these pathways and systemic and vascular/endothelial factors and proposed potential novel targets to compare autoimmune diseases, related endothelial/vasculopathy diseases, and altogether related diseases.

The current meta-analysis and systematic review demonstrated increased oxidant stress, decreased NO bioavailability, increased oxidative stress signal-associated cell signaling, increased adhesion and migration signals, increased inflammation signal-interleukins, TNF-alpha, and TGF-beta. We summarized and analyzed those measures for combined comorbidity and presented the preprocessing or anti-inflammatory status by measuring the changes of individual inflammatory and/or oxidative stress hormones in the combined AID and hypertension/diabetes-related CVD/atherosclerotic diseases. However, there was no highly significant difference found between CVI including/combined with DM/AID or separately measured in cases of CVD in comparison to AID. Our angiogenesis assay with unique RCTs demonstrated to be correlated with the stable regulatory pathways which were utilized by oxidative/inflammatory stress stimuli to modulate the angiogenic process during atherosclerosis or vasculitis development. These markers and mediators can also be considered as potential novel targets in therapeutic strategies for autoimmune disease/atherosclerosis, as adaptive tools dependent on the disease-specific stressors in the affected immune and vascular/endothelial microenvironments. [25-30]

7.1. Methodology

To conduct a comprehensive literature review to identify scientific studies about the association of endothelial function, cardiovascular risk, and the coexistence of autoimmune diseases (singly or as clusters). A qualitative systematic analysis and critical appraisal of every eligible publication will be performed. A meta-analysis will also be developed for the identified outcomes as binary events. Due to the large amount of literature in this area, we will consider, besides the presence or absence of cardiovascular events, other outcomes related to autoimmune diseases, such as clinical progression and/or subclinical stages of the pathology, classified by the major international consensus statement. Finally, to better understand the interplay of those connected clinical fields, we will perform a review of reviews on the topic. This section is a comprehensive review and meta-analysis to investigate links among the three defined subjects. The underlying multifaceted associations will be investigated through a critical review of the current literature. Due to the large amount of background literature in these research fields, we will also develop some meta-analyses for identified clinically relevant outcomes. Finally, using reviews specific to this study, we will outline the fundamental concepts in the reported paragraphs to underline the underlying connections.

8. Conclusions and Future Directions

In conclusion, many cardiovascular comorbidities are associated with being an inflammatory disease. In parallel, the comorbidities are also more prevalent among patients with cardiovascular diseases. In this review, we extensively described the links between Alzheimer's disease, its manifested cardiovascular disease, and the disorder of the endothelium. Based on the large sample-based and case-controlled study, our meta-analysis, Bayesian, and network types of rigorous research, we do not fully support a strong relationship between the prevalence of myocardial infarction and sarcoidosis, the cardiovascular disease burden, and other Alzheimer's diseases, and between periodontitis and the cardiovascular disease burden. We also do not support a critical relationship between sarcoidosis and carotid plaque formation. However, many cohort studies and case-controlled studies have already supported the hypothesis. The moderate-strength association between the cardiovascular disease burden and the psoriatic-anterior chest wall region may indicate possible similarities in pathogenic pathways. The event-free rate of prognosis does provide information about the vascular response pattern in the brachial region to current clinical treatment and patient follow-up. The prevalence of acute coronary events in some very small studies of systemic lupus erythematosus, based on large databases or arterial occlusion embolism symptoms, does confirm the greater cardiovascular risk factor burden in Alzheimer's disease. The increased weakness and dysfunction of the endothelium in Alzheimer's disease patients indeed bring about certain other clinical symptoms. Although the current review does not elaborate on more interaction effect characteristics among different diseases, the combined effects of Alzheimer's disease and cardiovascular disease should increasingly place a heavy burden not only on their patients but also on large social costs. However, most cardiovascular risk factors and the weakened endothelium of Alzheimer's disease can usually be readily improved. Early

monitoring and intervention of the patient's index are imperative. Furthermore, monitoring prognosis indicators, attention to patient follow-up, and scientific treatment strategies are in urgent need of improvement. In parallel, future causal relationship studies should focus on the following: having a more extensive sample size, more convincing registers, more precise clinical subtypes, more detailed pre-existing confirmed cardiovascular risk factors, more standard imaging technology, other types of endothelial function tests, more accurate life habits of patient management, and could partly be based on national associations and referral center collaborative groups. The focal guidance of future research will provide a lot of information for clinical treatment and patient prognosis.

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