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Relationship between cardiovascular disease and Rheumatoid Arthritis – A review

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ABSTRACT
Systemic autoimmune disease rheumatoid arthritis is characterised by increased cardiovascular disease morbidity and death. Shared inflammatory mediators, post-translational modifications of peptides/proteins and subsequent immune responses, changes in the composition and function of lipoproteins, increased oxidative stress, and endothelial dysfunction are some of the mechanisms that link rheumatoid arthritis and cardiovascular disease. The best methods of risk classification, prevention, and therapy in the setting of rheumatoid arthritis are still unclear, despite advances in our knowledge of these processes and their intricate interactions with traditional cardiovascular risk factors. In addition to managing rheumatoid arthritis-specific risk factors such increased disease activity, a multimodal strategy to lessen the burden of cardiovascular disease is needed. The mechanisms tying these illnesses together as well as the impact of rheumatoid arthritis treatments appear to vary. If there are superior treatments for rheumatoid arthritis in terms of preventing cardiovascular disease, further study is required to confirm this. In the end, risk stratification and the discovery of novel targets for the significant reduction of cardiovascular risk in this patient population will benefit from knowing the distinct pathways for cardiovascular disease in rheumatoid arthritis.

I. INTRODUCTION

A systemic, autoimmune condition called rheumatoid arthritis affects 0.5–1.0% of people worldwide [1]. Asymmetrical inflammatory polyarthritis is what defines it, although extra-articular symptoms are also frequent and indicate a bad prognosis. Cardiovascular disease has been the subject of extensive research due to its prevalence and relevance to patients' morbidity and survival. This has led to a better understanding of the mechanisms linking rheumatoid arthritis and cardiovascular disease as well as improved cardiovascular risk reduction in rheumatoid arthritis patients. In this review, we outline scientific developments that have shed light on the processes that link rheumatoid arthritis and cardiovascular disease, the cardiovascular risks connected to certain rheumatoid arthritis medications, and pertinent therapeutic therapy.

Burden of cardiovascular disease in patients with rheumatoid arthritis

In an analysis of 50 studies, which included 91 618 patients and 33 250 fatalities, cardiovascular disease accounted for 39.6% of deaths, making it the leading cause of excess mortality in rheumatoid arthritis [2]. Rheumatoid arthritis was linked to a 48% higher risk of cardiovascular events (relative risk 1.48, 95% confidence interval 1.36 to 1.62) and a 50% higher incidence of cardiovascular disease-related mortality (standardised mortality ratio 1.50, 95% confidence interval 1.39 to 1.61) compared with the general population, according to two large meta-analyses that included more than 150 000 patients in total [3, 4]. The focus of this analysis reflects the fact that atherosclerosis and congestive heart failure (CHF) are the most prevalent cardiovascular disease presentations.

Mechanisms involving cardiovascular disease and rheumatoid arthritis

- **Cardiovascular risk factors**

Although the focus of this study is on variables specific to rheumatoid arthritis that increase cardiovascular risk, it is important to recognise the role that traditional cardiovascular risk factors play in people with rheumatoid arthritis. In a prospective cohort study, it was discovered that inflammatory markers in rheumatoid arthritis were less closely related to hypertension, dyslipidemia, and insulin resistance than were surrogate markers of cardiovascular

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disease, such as microvascular function, endothelial function, and carotid intima media thickness [5]. The frequency and development of coronary artery calcium scores over a long period of time were similar in rheumatoid arthritis patients and controls, with conventional risk factors being more predictive than the disease's symptoms [6]. Although these findings have not been consistently repeated, it appears that traditional cardiovascular risk factors such as obesity, diabetes, smoking, and hypertension are overrepresented in rheumatoid arthritis [7, 8, 9, 10]. Contrarily, smoking has repeatedly been found to be a significant and common risk factor for the onset of rheumatoid arthritis and cardiovascular disease [11].

- **Inflammation and disease activity**

The immune system may play a major role in the aetiology of cardiovascular disease, according to growing data, and pro-inflammatory cytokines linked to rheumatoid arthritis may potentially promote atherogenesis [12]. So, in order to enhance cardiovascular risk assessment, "risk calculators" that effectively account for disease activity must be developed, as standard risk variables do not entirely explain the extra burden of cardiovascular disease in rheumatoid arthritis [13]. Multiple observational studies have found links between worse cardiovascular outcomes and rheumatoid arthritis disease activity, substantiating this claim. Higher disease activity was linked to higher odds of acute coronary syndrome (ACS) in a Swedish nested case-control study of incident rheumatoid arthritis, according to acute phase response as well as various composite measures of disease activity (odds ratio 1.32 per unit increase in 28 joint disease activity score (DAS28); odds ratio 1.61 for moderate and 2.59 for high European Union League Against Rheumatism (EULAR) disease activity score compared with to low disease activity) [14]. Similar findings were found in a US cohort study where, independent of conventional cardiovascular risk factors and rheumatoid arthritis treatments, time averaged disease activity in the remission range was associated with a 53% lower risk of cardiovascular events than in high disease activity [15]. In the Nijmegen early rheumatoid arthritis cohort, these findings were further supported by the finding that a 1 unit rise in time averaged DAS28, but not illness duration, was linked to a 33% increased risk of cardiovascular disease [16]. Similar results were found for higher levels of C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in two sizable US investigations as well as a Spanish cohort of people with rheumatoid arthritis [17, 18, 19]. Each six-week flare was linked to a 7% increase in the risk of cardiovascular disease, according to a population-based cohort study of incident rheumatoid arthritis, but patients in remission had a risk equivalent to that of non-rheumatoid arthritis controls [20].

- **Cardiac function and disease activity**

The presence of the rheumatoid arthritis illness is not only a powerful predictor of cardiovascular events but also of cardiac function. Greater left ventricular strain was found using speckle-tracking echocardiography in rheumatoid arthritis patients compared to controls, and this strain was linked to disease activity [21]. The global longitudinal strain of the left ventricle and the thickness of the left ventricle are both positively correlated with increased rheumatoid arthritis disease activity [22, 23]. Additionally overrepresented in rheumatoid arthritis patients, diastolic dysfunction is linked to greater levels of interleukin (IL)-6 in the blood [24]. Given the correlations between disease activity and the factors discussed above, rheumatoid arthritis therapies that focus on remission may be required to best protect heart function. Patients with rheumatoid arthritis who were in remission (Simplified Disease Activity Index < 3.3) demonstrated improved left ventricular function when compared to those who had low, moderate, or high disease activity, as measured by stress-corrected mid-wall shortening and global longitudinal strain [25]. Traditional cardiovascular risk variables had no effect on variations in left ventricular function [25]. Furthermore, there were no variations in left ventricular performance between rheumatoid arthritis patients in remission and healthy controls.

- **Surrogate markers and disease activity**

Several observational studies have looked at the relationship between the activity of the rheumatoid arthritis illness and the indicators of cardiovascular disease in order to better understand the contributions of inflammation. Rheumatoid arthritis patients had a higher burden of coronary artery plaque than controls in a cross-sectional study using computed tomography-angiography, and higher disease activity was associated with the presence of unstable plaque [26], suggesting that disease-related inflammation contributes not only to plaque development but also to their

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vulnerability and rupture. The advancement of the carotid plaque in rheumatoid arthritis was linked to both swollen joint counts and CRP [27], and the calcification of the coronary arteries was linked to both circulating IL-6 and tumour necrosis factor α (TNF-α) concentrations [28]. The link between rheumatoid arthritis and coronary artery calcification was also decreased by multivariable analyses that took IL-6 and CRP concentrations into account, indicating that inflammation modulates the pathophysiologic mechanisms of both stable and unstable plaque [29]. A cohort study of rheumatoid arthritis patients who underwent repeated carotid ultrasonography over a period of three years revealed that systemic inflammation and traditional risk factors both predicted the progression of atherosclerosis [30], which explored how traditional and non-traditional risk factors together contribute to risk of cardiovascular disease. Importantly, the likelihood of systemic inflammation appeared to rely on the presence of certain conventional risk factors. Only those with two or more conventional risk factors for rheumatoid arthritis had ESR levels that indicated the development of atherosclerosis, showing an interaction between conventional and rheumatoid arthritis-related cardiovascular risk factors.

- **Cellular mechanisms**

Studies conducted ex vivo and in vitro have started to clarify the molecular pathways by which the inflammation associated with rheumatoid arthritis causes cardiovascular disease. TNF-α and IL-18 expression were higher in the aorta adventitia of rheumatoid arthritis patients having coronary artery bypass grafting than in controls, and endothelial cells in the aortic adventitia vasa vasora also expressed higher levels of IL-33 and IL-33 ligand [31]. These results point to a distinct pro-inflammatory adventitial milieu in rheumatoid arthritis that promotes atherogenesis by integrating innate and adaptive immune responses, with IL-18 and IL-33 playing important roles. Recently, cell subsets substantially related with coronary artery calcification were found in circulating peripheral blood mononuclear cells obtained from rheumatoid arthritis patients [32]. Unique effector memory CD4 T cell and monocyte subsets were linked to coronary artery calcification independently of conventional cardiovascular risk factors and other aspects of rheumatoid arthritis, indicating a potential intrinsic relationship between immune subsets that are typical of rheumatoid arthritis and cardiovascular disease. Endothelial cells were incited to become pro-inflammatory, pro-thrombotic, and pro-coagulant in vitro when IL-17 and TNF-α were added [33]. The endothelium-specific adhesion molecule VE-cadherin [34], which is crucial for maintaining endothelial tight junctions, is likewise broken down by TNF-α. In vivo haemorrhage, interstitial edoema, and enhanced permeability might ensue from the cleavage of this molecule. The pro-inflammatory networks between rheumatoid arthritis and cardiovascular disease still need to be clarified despite these exciting discoveries.

- **Oxidative stress**

Another potential common link between the illnesses is oxidative stress, which is an imbalance of reactive oxygen species (ROS) and antioxidants. Oxidative stress is often elevated in the setting of inflammation and contributes to the development of cardiovascular disease and rheumatoid arthritis [35, 36]. Malondialdehyde and nitrotyrosine concentrations, two markers of nitro-oxidative stress, are linked to higher myocardial strain in rheumatoid arthritis [37]. In comparison to controls, the serum of people with rheumatoid arthritis has higher levels of myeloperoxidase, a source of oxidants. Additionally, high density lipoproteins (HDL) appear to be targeted by and compromised by oxidants produced by myeloperoxidase [38]. Rheumatoid arthritis patients had higher levels of advanced glycosylation end products than controls, which are negatively related to endothelial function and produced in the presence of hyperglycemia and oxidative stress [39].

A greater quantity of oxidative stress-related aldehyde was found in the serum and left ventricular tissues of rats with adjuvant-induced arthritis (AIA), an animal model of rheumatoid arthritis, compared to controls [40]. In left ventricular tissues of AIA rats, NADPH and glutathione pools were 30% smaller than those of controls, indicating possible depletion of important antioxidant system reserves connected to inflammatory arthritis. Renin-angiotensin activation in the AIA mouse increased vascular hypertrophy and oxidative stress, whereas angiotensin II type-1 receptor blockade decreased NADPH oxidase activity and oxidative stress in aortic tissues and enhanced endothelial function, demonstrating the complexity and interconnectedness of systems [41].

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- **Endothelial dysfunction**

Vascular tone and homeostasis are regulated by the endothelium, and its dysregulation is essential to atherogenesis. Endothelial dysfunction has been linked to rheumatoid arthritis and appears to change during the course of the disease. A longitudinal research found no variations in endothelial function between newly diagnosed cases of rheumatoid arthritis and controls, despite the fact that the patients' carotid intima media thickness increased with time [42]. In early rheumatoid arthritis, asymmetric dimethylarginine, an inhibitor of endogenous nitric oxide synthase (eNOS), which is crucial for controlling vascular tone, leukocyte adhesion, and platelet aggregation, was found to be negatively associated with impaired coronary flow reserve. There have been conflicting reports regarding how disease activity affects endothelial function. Circulating IL-1β, TNF-α, and MIP-1α concentrations were found to be inversely correlated with endothelial function in the AIA model, and effective disease-modifying anti-rheumatic medications (DMARDs) can enhance microvascular endothelial function [44, 45]. In contrast, endothelial function was linked to composite cardiovascular risk scores rather than rheumatoid arthritis disease activity in at least one cross-sectional investigation [46]. Endothelial progenitor cells (EPCs) and newly found angiogenic T cells (Tang) are essential for endothelial function, repair, and neovascularization. EPCs and Tang are decreased in rheumatoid arthritis compared to controls, with patients who also have concomitant cardiovascular disease having the lowest Tang numbers [47, 48]. Inverse correlations with disease activity and increased EPC numbers following TNF inhibitor therapy [47, 48] further support their link with rheumatoid arthritis. The fact that oxidative stress also affects endothelial function emphasises the intricate interaction of processes even more. Endogenous ligands and products of phospholipid oxidation activate endothelial cells through NFkB pathways via toll-like receptor 4 signalling, according to in vitro studies utilising endothelial cells from individuals with rheumatoid arthritis [49]. By demonstrating that dysregulation of NADPH oxidases and eNOS occurred and led to increased lipid peroxidation, the production of vascular ROS, and impairment of aortic endothelial function, the AIA model was used to characterise the downstream effects of systemic inflammation in rheumatoid arthritis [50].

- **Post-translational modifications and autoantibodies**

The enzymatic conversion of the amino acid arginine to citrulline, or citrullination, is one example of a post-translational protein modification that may have a role in the development of rheumatoid arthritis. The majority of rheumatoid arthritis patients have anti-citrullinated protein antibodies (ACPA), which are extremely disease-specific, and which foretell more severe arthritis. Epidemiologic investigations on the correlations between autoantibody and cardiovascular disease have produced conflicting findings. An higher risk of ischemic heart disease and incident CHF has been associated with anti-cyclic citrullinated peptide (CCP; a commercial ACPA assay) and rheumatoid factor positive [17, 51, 52]. However, seropositivity was not linked to an increased risk of ACS or cardiovascular disease-related morbidity or death in independent nested case-control and cohort investigations [14, 53]. In the Multi-Ethnic Study of Atherosclerosis (rheumatoid factor and anti-CCP) and Northwick Park Heart Study (anti-CCP), seropositivity was linked to an increased risk of cardiovascular disease even in the absence of rheumatoid arthritis, providing evidence for a potential pathogenic role for these autoantibodies [54, 55]. Autoantibodies and heart function have been associated in a number of observational studies. In rheumatoid arthritis, cardiac magnetic resonance imaging has shown an association between anti-CCP antibody and left ventricular global longitudinal strain, poorer left ventricular relaxation, and reduced left ventricular mass, stroke volume, and end diastolic volume [22, 56, 57]. These results triggered a search for citrullinated antigens that would serve as potential targets for pathogenic autoantibodies in the myocardium. Left ventricular tissues from rheumatoid arthritis patients stained more strongly for citrullinated proteins and peptidyl arginine deiminases (enzymes catalysing citrullination) compared to control specimens [58].

❖ **Mechanisms of RA Pertinent to Cardiovascular Disease**

T cells appear to have a critical pathogenic role in both RA and cardiac disease, according to emerging findings (58,59). HLA-DRB1, the key RA risk gene, predisposes to illness by enhancing the selection and survival of autoreactive CD4+ T cells. HLA-DRB1 alleles are also linked to an elevated risk of MI and other non-RA-related heart disease(60,61). T cells isolated from the joints of

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RA patients exhibit increased production of interferon- and interleukin-17, which apparently mediate chronic inflammation (62,63). Perhaps the most persuasive evidence that T cells are harmful in RA is the efficiency of antagonising T-cell co-stimulation (64). Similarly, in CAD, percutaneous stents that elute T-cell suppressing medications (e.g., sirolimus) reduce in-stent restenosis and recurrent re-vascularization (65). CD4+ T cells in people with RA or heart disease typically lose expression of the co-stimulatory molecule, CD28, which normally provides the'second signal' essential for T-cell activation. T cells that are 'CD28null' are thought to have undergone reprogramming, resulting in premature senescence (66). Expansion of senescent T cells in RA patients is linked to extra-articular inflammatory symptoms such as vasculitis and lung illness, as well as CAD (67,68). CD28null T cells have been found in atherosclerotic plaque in the presence of heart disease, where they are thought to contribute to the inflammatory process by generating cytokines and killing vascular smooth muscle cells (69). Interestingly, the RA-risk gene HLA-DRB1 also predisposes to the development of CD28null T cells in RA and CAD (61,70). T cell senescence appears to be mediated by underlying haematological system abnormalities in RA. Telomere erosion in CD34+ hematopoietic progenitor cells has increased, indicating senescence (71). Naive T cells in RA patients also age prematurely, with increased fragility and DNA damage due to low activity of basic DNA repair enzymes (72,73). Telomere shortening in hematopoietic progenitor cells also associated with cardiac dysfunction in CAD patients (74). The development of RA and heart disease correlates with the loss of thymic emigration of naive T cells in the fifth decade, indicating that T-cell senescence may play a role in the pathophysiology of both of these age-related illnesses. In the near future, rejuvenation of senescent T lymphocytes by the use of novel medicines that restore genomic repair and integrity might be a successful method for the prevention and treatment of cardiovascular disease (75).

II. CONCLUSION

Heart disease is still a big issue for RA sufferers. Systemic inflammation has a significant impact on the vasculature, both directly and indirectly. More research is needed to identify disease pathways and to create and test risk assessment tools, biomarkers, preventative methods, and therapies tailored to RA. The CV risk in RA patients is not well recognised by practising physicians, and improved detection and management of conventional risk factors in RA patients is critical. Coordination of treatment among rheumatologists, cardiologists, and primary care physicians will be required for appropriate CV risk management in RA patients. Tight management of systemic inflammation in RA patients may help lower CV risk. Patients with RA who exhibit symptoms indicative of CAD should be assessed immediately, and early referral to a CV expert for proper diagnosis and therapy gives the best chance of optimising results. It is difficult to disentangle the link between RA inflammation, immune modifying therapy, and CV risk. Specific disease-modifying medicines (for example, methotrexate and TNF-inhibitors) efficiently regulate inflammation in RA while simultaneously lowering CV risk. Glucocorticoids, on the other hand, appear to raise CV risk due to their negative metabolic effects, which appear to exceed their anti-inflammatory advantages. Common CV risk-reduction therapies (e.g., statins) are expected to be helpful in RA patients, although there is limited empirical proof for this. Trials that are now recruiting patients, such as one that is delivering methotrexate (a first-line therapy for RA) to post-MI patients without RA, should give insight into whether lowering inflammation alone is linked with lower CV risk (76). Finally, T-cell-directed or anti-cytokine treatments (IL-1, IL-6, etc.) may be investigated as therapeutic targets in RA and cardiac disease (77,78). Indeed, an anti-IL-1 monoclonal antibody (canakinumab) is being tested for the treatment of cardiac disease (79). These research are expected to shed new light on the pathogenesis and therapy of cardiac disease.

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