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Analysis of Factors Contributing to the Development of Cardiovascular Disorders and Atherosclerotic Changes in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease primarily characterized by symmetrical involvement of peripheral joints and a wide spectrum of extra-articular manifestations. Patients with RA exhibit significantly higher morbidity and mortality rates than those observed in the general population, with cardiovascular disease representing one of the leading causes of death. The prevalence of traditional atherosclerotic risk factors is substantially higher among individuals with RA than among those without the disease. Numerous studies have demonstrated an increased frequency of concomitant conditions, including arterial hypertension, dyslipidemia, obesity, and diabetes mellitus, in this patient population. Nevertheless, the markedly elevated incidence of cardiovascular events in RA cannot be fully explained by conventional risk factors alone. Generalized systemic inflammation, accompanied by excessive production of pro-inflammatory cytokines and elevated levels of acute-phase proteins, is considered a major contributor to the initiation and progression of premature atherosclerotic changes. This review provides a comprehensive analysis of cardiovascular risk in rheumatoid arthritis, the distinctive features of RA-associated dyslipidemia, the phenomenon known as the "lipid paradox," and the impact of chronic systemic inflammation on the development and progression of atherosclerosis in patients with RA.

Keywords: rheumatoid arthritis; atherosclerosis; cardiovascular risk; dyslipidemia.

Introduction

Rheumatoid arthritis (RA) is a chronic destructive inflammatory disease affecting the synovial membrane of joints and leading to progressive destruction of articular cartilage and bone tissue. The disease affects approximately 0.5-1% of the global population and occurs nearly three times more frequently in women than in men, affecting individuals across all age groups [1,2]. In addition to articular manifestations, RA is characterized by numerous systemic extra-articular complications, including serositides, cutaneous involvement, ocular manifestations, and other

organ-specific disorders. The pathogenesis of RA is associated with a complex interplay between genetic susceptibility and environmental triggers that activate both innate and adaptive immune responses. Activation of antigen-presenting cells initiates intensive production of inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6, together with activation of T lymphocytes. This process subsequently induces B-cell activation and stimulates the production of disease-specific autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). The migration of macrophages and activated T and B lymphocytes into the synovial membrane results in sustained secretion of pro-inflammatory cytokines and matrix metalloproteinases, ultimately leading to progressive destruction of joint structures. Despite substantial advances in pharmacological treatment and the availability of numerous disease-modifying therapies, morbidity and mortality among patients with RA remain significantly elevated. Alongside secondary infections, cardiovascular diseases constitute one of the leading causes of adverse clinical outcomes and premature mortality in this patient population. Early development of ischemic heart disease and acute cardiovascular events has been recognized as one of the principal determinants of poor prognosis in patients with RA [3,4].

Atherosclerosis, a chronic progressive inflammatory disease of the arterial wall, is closely associated with an increased risk of acute coronary syndrome and other major cardiovascular events. Disease activity and the severity of systemic inflammation (as reflected by circulating levels of TNF-α, IL-1, IL-6, and C-reactive protein) play a fundamental role in accelerating atherosclerotic vascular changes. The present review focuses on cardiovascular risk in rheumatoid arthritis, the characteristics of RA-associated dyslipidemia, the contribution of systemic inflammatory responses to vascular injury, and the importance of early therapeutic intervention for the prevention of cardiovascular complications in patients with RA [5,6,7].

Methodology

This study was conducted as a narrative literature review. A comprehensive search of peer-reviewed scientific publications was performed using major international databases, including PubMed, Scopus, Web of Science, and Google Scholar. Publications addressing rheumatoid arthritis, cardiovascular risk, atherosclerosis, dyslipidemia, systemic inflammation, and the lipid paradox were reviewed. Priority was given to recent studies, systematic reviews, meta-analyses, and clinical guidelines published in English. Relevant evidence was critically analyzed and synthesized to summarize the current understanding of the mechanisms contributing to cardiovascular disorders and atherosclerotic changes in patients with rheumatoid arthritis.

Results

Specific Features of Cardiovascular Risk Factors in Rheumatoid Arthritis

Traditional risk factors contributing to the development of atherosclerosis include dyslipidemia, arterial hypertension, obesity, metabolic syndrome, and physical inactivity. Clinical observations have consistently demonstrated that these risk factors occur significantly more frequently in patients with rheumatoid arthritis (RA) than in the general population [8]. Notably, even in the early stages of RA, treatment-naive patients without evident conventional cardiovascular risk factors may exhibit an atherogenic lipid profile, which has been shown to improve following methotrexate therapy [9]. Other studies have likewise reported a high prevalence of concomitant comorbidities among patients with RA, including arterial hypertension [10], overweight and obesity [11], physical inactivity [12], and diabetes mellitus [13].

Nevertheless, conventional cardiovascular risk factors alone cannot adequately explain the markedly increased incidence of cardiovascular events observed in RA. As previously discussed, the pathogenesis of RA is characterized by the production of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, together with the activation of lymphocytes producing disease-specific autoantibodies, thereby sustaining synovial inflammation and promoting extra-articular manifestations [14,15]. Simultaneously, systemic inflammatory mediators such as C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen are produced in increased quantities, contributing to the maintenance of chronic systemic inflammation. Several studies have

demonstrated that markers of systemic inflammation, particularly CRP, serve as independent predictors of cardiovascular mortality in patients with RA [16]. For example, an analysis investigating the association between CRP concentrations and the 10-year risk of cardiovascular events using the Expanded Risk Score in Rheumatoid Arthritis (ERS-RA) in a large cohort of patients without previous cardiovascular disease demonstrated that every 20 mg/L increase in CRP was associated with an approximately 1% increase in the estimated 10-year cardiovascular risk. These findings underscore the importance of early and intensive anti-inflammatory treatment strategies aimed at reducing systemic inflammatory burden and protecting the vascular system in patients with RA [17,18]. Furthermore, both systemic inflammation, as reflected by erythrocyte sedimentation rate (ESR), and conventional cardiovascular risk factors have been associated with accelerated progression of carotid intima-media thickness (CIMT). Treatment with methotrexate or tumor necrosis factor-α inhibitors has been shown to attenuate CIMT progression by mitigating the detrimental effects of persistent inflammation on the vascular wall [19,20].

Additional factors contributing to increased cardiovascular risk in RA include disease duration [21,22], the presence of disease-specific autoantibodies, extra-articular manifestations, and the characteristics of ongoing pharmacological therapy. In particular, treatment with cyclooxygenase-2 (COX-2) selective inhibitors (coxibs), non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids may further increase cardiovascular risk [23,24]. Both NSAIDs and coxibs may promote prothrombotic states, whereas long-term glucocorticoid therapy adversely affects body weight, blood pressure, lipid metabolism, and the development of metabolic syndrome. Consequently, glucocorticoid exposure has been associated with an increased incidence of major adverse cardiovascular events (MACE) among patients with rheumatoid arthritis [25].

Dyslipidemia in Rheumatoid Arthritis and Mechanisms Underlying Atherosclerosis Development

In the general population, dyslipidemia is typically characterized by elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). In contrast, patients with active rheumatoid arthritis (RA) often exhibit a paradoxical reduction in serum concentrations of total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C). This phenomenon, commonly referred to as the "lipid paradox," reflects the observation that cardiovascular events remain highly prevalent in patients with RA despite relatively low circulating LDL-C levels. Understanding this paradox and its contribution to accelerated atherogenesis requires consideration of the fundamental mechanisms of lipid metabolism [26,27].

Dietary lipids are absorbed in the intestine and incorporated into chylomicrons, which are subsequently hydrolyzed by lipoprotein lipase (LPL) in peripheral tissues, particularly skeletal muscle and adipose tissue, releasing free fatty acids (FFAs). Chylomicron remnants are then taken up by hepatic receptors, completing the exogenous pathway of lipid metabolism. The endogenous lipid transport pathway originates in the liver, where very-low-density lipoproteins (VLDL) are synthesized and secreted into the circulation. Following hydrolysis by LPL, VLDL particles progressively release FFAs and are converted first into intermediate-density lipoproteins (IDL) and subsequently into low-density lipoproteins (LDL). LDL particles are ultimately internalized through LDL receptors (LDL-R) and eliminated through hepatobiliary pathways into the intestine [28,29].

The HDL metabolic pathway begins with the synthesis of nascent lipid-poor HDL particles in the liver and intestine. The ATP-binding cassette transporter A1 (ABCA1) mediates the transfer of cholesterol and phospholipids from peripheral tissues to HDL particles, while lecithin-cholesterol acyltransferase (LCAT) promotes their maturation into fully functional HDL. Mature HDL particles transport cholesterol back to the liver via scavenger receptor class B type 1 (SR-B1), where it undergoes metabolism and biliary excretion. Thus, LDL primarily mediates cholesterol delivery to peripheral tissues, whereas HDL is responsible for reverse cholesterol transport and maintenance of lipid homeostasis [30,31].

Although the precise mechanisms responsible for the lipid paradox in RA have not yet been

completely elucidated, substantial evidence indicates that chronic systemic inflammation plays a central role by accelerating cholesterol catabolism and impairing the protective functions of HDL particles. Pro-inflammatory cytokines, particularly IL-6 and TNF-α, increase hepatic expression of LDL receptors and SR-B1 receptors, thereby enhancing LDL uptake and hepatic clearance. This mechanism is supported by observations that inhibition of IL-6 signaling with tocilizumab is associated with reduced LDL-R expression. Another important mechanism contributing to reduced circulating LDL concentrations is enhanced oxidative modification of LDL particles under inflammatory conditions, resulting in the formation of oxidized LDL (oxLDL) [31]. These modified lipoproteins are no longer efficiently recognized by classical LDL receptors and therefore may not be accurately reflected by conventional laboratory measurements.

Importantly, oxLDL possesses potent pro-inflammatory and immunogenic properties, inducing endothelial injury and sustaining chronic vascular inflammation. After penetrating the subendothelial space, oxLDL stimulates the expression of cellular adhesion molecules (CAMs) and monocyte chemoattractant protein-1 (MCP-1), thereby promoting monocyte recruitment into the vascular intima. These monocytes subsequently differentiate into macrophages, internalize oxidized lipoproteins, and transform into lipid-laden foam cells. This cascade is further amplified by the secretion of additional pro-inflammatory mediators, including TNF-α and IL-1, together with reactive oxygen species, resulting in progressive endothelial dysfunction and formation of atherosclerotic plaques [32].

Patients with RA have been shown to exhibit elevated circulating concentrations of oxLDL and antibodies directed against oxLDL, both of which decrease following methotrexate therapy. Under physiological conditions, HDL inhibits LDL oxidation, suppresses endothelial expression of adhesion molecules, and facilitates cholesterol efflux from macrophage-derived foam cells. However, these vasculoprotective and anti-atherogenic functions become profoundly impaired in the setting of chronic systemic inflammation associated with RA. Myeloperoxidase released during inflammatory responses oxidatively modifies HDL particles and apolipoprotein A-I (ApoA-I), resulting in decreased activity of paraoxonase-1 (PON-1), a major HDL-associated antioxidant enzyme. Treatment with TNF-α inhibitors has been shown to restore PON-1 activity and improve HDL functionality. Furthermore, the protein composition of HDL undergoes substantial remodeling during chronic inflammation. Incorporation of fibrinogen, serum amyloid A (SAA), and complement proteins transforms HDL from an anti-inflammatory lipoprotein into a pro-inflammatory particle with diminished cardioprotective properties. Tocilizumab therapy has been demonstrated to normalize the HDL proteome by reducing the relative abundance of SAA, fibrinogen, and complement components.

Collectively, the principal mechanisms underlying accelerated atherogenesis in the setting of the lipid paradox include enhanced hepatic lipid catabolism, accumulation of highly immunogenic oxidized LDL particles, and functional impairment of HDL, resulting in the loss of its anti-atherogenic properties. These processes perpetuate persistent vascular inflammation and substantially accelerate the progression of atherosclerosis in patients with rheumatoid arthritis [33].

Structural Vascular Alterations Associated with Atherosclerosis in Patients with Rheumatoid Arthritis

Chronic systemic inflammation is recognized as one of the principal drivers of early vascular injury in rheumatoid arthritis (RA). C-reactive protein (CRP) is capable of opsonizing oxidized low-density lipoproteins (oxLDL), thereby facilitating foam cell formation through enhanced macrophage uptake. In addition, CRP promotes the expression of cellular adhesion molecules (CAMs) and monocyte chemoattractant protein-1 (MCP-1) in endothelial cells, stimulating monocyte recruitment, endothelial dysfunction, and subsequent vascular injury. Consequently, virtually every stage of the atherosclerotic process is accelerated in patients with RA. Beyond generalized inflammatory alterations, RA is associated with increased arterial stiffness, progressive thickening of the carotid intima-media complex, accelerated atherosclerotic plaque formation, coronary artery calcification, and a substantially elevated incidence of major

cardiovascular events [34,35].

The earliest manifestations of vascular remodeling are typically characterized by an increase in carotid intima-media thickness (CIMT), which can be readily assessed by ultrasonographic examination. According to a meta-analysis encompassing 22 independent studies, patients with RA demonstrated a mean CIMT approximately 0.09 mm greater than that observed in healthy control subjects. Furthermore, both the prevalence and severity of coronary artery calcification and carotid plaque formation are significantly higher among individuals with RA. These findings support the concept that rheumatoid arthritis should be regarded as an independent and clinically significant cardiovascular risk factor, contributing directly to accelerated atherosclerosis and an increased burden of cardiovascular morbidity and mortality [36,37].

Discussion

Rheumatoid arthritis is associated with substantially higher morbidity and mortality rates than those observed in the general population. Long-term epidemiological studies indicate that life expectancy in patients with RA is reduced by approximately 3-10 years. More than 40% of deaths in this population are attributable to cardiovascular causes, including ischemic heart disease, cerebrovascular accidents, and peripheral vascular disease. The prevalence and burden of carotid atherosclerotic plaques are significantly greater in patients with RA than in age-matched individuals without the disease, and carotid atherosclerosis has been identified as an important predictor of acute coronary syndrome and future cardiovascular events [38,39].

Ultrasonographic assessment of carotid intima-media thickness (CIMT) together with quantification of the coronary artery calcium (CAC) score enables the detection of subclinical atherosclerosis at its earliest stages. Studies conducted by Solomon and colleagues demonstrated that rheumatoid arthritis constitutes an independent risk factor for cardiovascular disease, with the greatest relative increase in cardiovascular event rates observed among younger patients and individuals without a previous history of cardiovascular disease. Moreover, patients with RA exhibit a higher prevalence of silent (unrecognized) myocardial infarction and increased one-year mortality following the onset of heart failure compared with the general population.

Comparable patterns of accelerated atherosclerosis and increased cardiovascular mortality have also been described in other systemic autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE), systemic sclerosis, and antiphospholipid syndrome. In patients with SLE, asymptomatic coronary artery calcification and multivessel coronary involvement occur more frequently than in healthy controls, whereas in systemic sclerosis the coronary artery calcium score has been shown to correlate with the long-term incidence of major adverse cardiovascular events (MACE)[40,41].

Although conventional cardiovascular risk factors (including hypertension, smoking, dyslipidemia, and physical inactivity) are highly prevalent among patients with RA, they do not fully account for the disproportionately high incidence of cardiovascular complications. This observation strongly suggests the involvement of disease-specific mechanisms, with chronic systemic inflammation and immune dysregulation representing the principal pathogenic pathways. CRP actively contributes to atherogenesis by promoting macrophage-mediated uptake of LDL particles, inducing endothelial activation, stimulating the expression of adhesion molecules and MCP-1, activating the complement cascade, and enhancing T-cell-mediated vascular injury. Persistent systemic inflammation and elevated CRP concentrations, both of which accelerate atherosclerotic progression, are closely associated with disease-specific characteristics of RA, including seropositivity, prolonged disease duration, extra-articular manifestations, and high inflammatory disease activity.

Conclusion

The development of premature atherosclerosis and cardiovascular disease in patients with rheumatoid arthritis (RA) represents a major clinical challenge and is associated with a level of cardiovascular risk comparable to that observed in patients with diabetes mellitus. Accelerated

vascular injury in RA results from the synergistic interaction between chronic systemic inflammation and conventional cardiovascular risk factors, leading to early endothelial dysfunction, rapid progression of atherosclerosis, and an increased incidence of adverse cardiovascular events. The phenomenon of the "lipid paradox" has been consistently demonstrated in both clinical and experimental studies and constitutes one of the distinctive features of lipid metabolism in RA. Nevertheless, the precise molecular and cellular mechanisms underlying this phenomenon remain incompletely understood and warrant further investigation. A more comprehensive understanding of the complex interactions between immune-mediated inflammation, lipid metabolism, and vascular pathology may facilitate the identification of novel biomarkers and therapeutic targets for cardiovascular risk reduction in this patient population. Accumulating evidence indicates that timely initiation of intensive anti-inflammatory therapy, particularly with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), most notably methotrexate, as well as biologic disease-modifying antirheumatic drugs (bDMARDs), not only promotes sustained control of synovial inflammation and long-term clinical remission but also exerts significant vasculoprotective effects. Effective suppression of systemic inflammation has been associated with improved endothelial function, attenuation of atherosclerotic progression, and a reduction in the incidence of major cardiovascular events. Therefore, comprehensive cardiovascular risk assessment, early identification of subclinical vascular involvement, and prompt implementation of evidence-based anti-inflammatory treatment strategies should be regarded as essential components of the multidisciplinary management of patients with rheumatoid arthritis. Integration of aggressive disease control with systematic cardiovascular prevention strategies may substantially improve long-term clinical outcomes, reduce cardiovascular morbidity and mortality, and enhance both life expectancy and quality of life in this high-risk population.

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