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Cardiovascular Risk and Systemic Inflammation in Rheumatoid Arthritis: A Comparative Analysis with Psoriatic Arthritis

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Abstract

Cardiovascular diseases (CVD) represent a major cause of morbidity and mortality in people with rheumatoid arthritis (RA) and psoriatic arthritis (PsA), both of which are characterized by systemic inflammation that increases the risk of CVD. Although these two conditions share this common inflammatory component, the specific pathways and associated factors that elevate cardiovascular risk differ. This article delves into the immune system's response, inflammatory processes, and genetic factors that contribute to cardiovascular complications in RA and PsA. In RA, endothelial dysfunction and the development of atherosclerosis are primarily driven by inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), along with the presence of certain autoantibodies, such as anti-citrullinated protein antibodies (ACPA). An interesting feature of RA is the "lipid paradox," where the presence of elevated cholesterol levels paradoxically correlates with a lower incidence of cardiovascular events, possibly due to ongoing inflammation. PsA, while also increasing cardiovascular risk, shows a different mechanism, with variations in the lipid profiles and reduced autoantibody involvement. In this case, factors such as metabolic syndrome and obesity-related inflammation play a more substantial role. Genetic factors, particularly the HLA-DRB1 gene, are strongly associated with RA, while PsA has more significant associations with obesity-driven inflammation. Although the cardiovascular risk in RA and PsA is well-documented, existing risk calculators fail to include PsA and only a limited number of models factor in RA. This review emphasizes the importance of developing more disease-specific tools for cardiovascular risk assessment. By understanding the overlapping and distinct pathways between RA and PsA, clinicians can work toward more individualized and effective strategies for cardiovascular care.

Keywords: Systemic inflammation, Rheumatoid arthritis, Cardiovascular risk, Psoriatic arthritis

Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily targets the synovial joints, though it can occasionally affect other organs outside of the joints. The global prevalence of RA is greater than that of Psoriatic arthritis (PsA), ranging between 0.16% and 1.3% [1, 2], with an increasing trend [3], and it is more common in women, occurring 2 to 3 times more frequently than in men [1, 2].

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Clinically, rheumatoid arthritis (RA) presents with joint pain and swelling that is symmetrical, predominantly affecting the metatarsophalangeal, metacarpophalangeal, and proximal interphalangeal joints, as well as the wrists, often with associated morning stiffness. Additional symptoms can include pleural effusions, vasculitis, atherosclerosis, interstitial lung disease, keratoconjunctivitis, pericarditis, and anemia [1, 4].

Research suggests that approximately 40% of individuals with RA will experience extra-articular involvement as the disease progresses [5], which could potentially lead to cardiovascular system involvement and associated damage. Routine lab results typically show an elevated erythrocyte sedimentation rate (ESR) and heightened C-reactive protein (CRP) levels [1, 2]. A variety of autoantibodies, particularly rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), emerge due to an immune response dysregulation [2, 4, 6]. The

differential diagnosis between PsA and RA is presented in **(Table 1)**.

Table 1. Differential diagnosis of RA and PsA based on Jevtic and Lingg [7], Jevtic *et al.* [8], and Merola *et al.* [9].

Characteristic	Rheumatoid arthritis	Psoriatic arthritis
Joint involvement	Symmetric	Asymmetric
Number of affected joints	Polyarthritis	Mono-/oligoarthritis
Main manifestation	Synovitis	Enthesitis
Type of affected joints	Synovial (MCP, MTP, PIP joints, wrists)	Fibrocartilaginous (sacroiliac joints, disco-vertebral junction, entheses)
DIP joint involvement	-	+++
Spine involvement	Cervical	Axial
Productivity of bone changes	Destructive changes (e.g. erosions, juxta-articular demineralization)	Productive changes (e.g. osteosclerosis, periostosis, bone ankylosis)
Dactylitis	+	+++
Skin lesions	-	+++
Nail dystrophy	-	+++
RF, ACPA	+++	-
Inflammatory markers (CRP, ESR)	+++	++
Main cytokines	TNF-α, IL-6, IL-1	IL-17A, IL-12/23, TNF-α
Genetics	HLA-DRB1	HLA-B27

Number of symbols (+) reflects the frequency of the characteristic. The dash (–) indicates that the characteristic is not frequent.
ACPA: anti-citrullinated protein antibody, CRP: C-reactive protein, DIP: distal interphalangeal, ESR: erythrocyte sedimentation rate, HLA: human leukocyte antigen, IL: interleukin, MCP: metacarpophalangeal, MTP: metatarsophalangeal, PIP: proximal interphalangeal, RF: rheumatoid factor, and TNF: tumor necrosis factor.

While the exact etiology of rheumatoid arthritis (RA) is not fully understood, both genetic and environmental factors appear to significantly influence its onset. The heritability of RA is estimated to be approximately 65% [2, 6]. A major genetic risk factor is the presence of HLA-DRB1 alleles, particularly DR4 and DR1. These alleles are linked to the "shared epitope," a specific sequence of five amino acids within the HLA molecule responsible for antigen presentation [6]. Additionally, studies have shown a strong association between these alleles and ACPA-positive RA, suggesting that the shared epitope plays a critical role in presenting citrullinated peptides [10, 11]. Among environmental factors, smoking has been consistently identified as a major risk factor, but other contributors such as obesity, infections, periodontitis, UV exposure, and changes in the microbiome have also been implicated [1, 2, 4]. Several of these environmental factors may also predispose individuals to cardiovascular disease (CVD), further exacerbating the increased cardiovascular risk associated with RA.

This article delves into the immune system's response, inflammatory processes, and genetic factors that contribute to cardiovascular complications in RA and PsA.

Results and Discussion

CV risk in RA

Rheumatoid arthritis (RA) has been linked to an increased cardiovascular disease (CVD) risk, a risk level similar to that observed in individuals with diabetes mellitus [12]. Patients with RA are found to have a 50% greater likelihood of developing cardiovascular issues and a 50-60% rise in cardiovascular mortality compared to the general population [13, 14]. Numerous studies have shown that more active disease states in RA correlate with a higher frequency of cardiovascular incidents [12, 14]. In particular, RA patients who test positive for anti-citrullinated protein antibodies (ACPA) face an even higher risk of cardiovascular problems [15], a trend that extends to individuals outside of the RA population as well [16]. This may be due to the accumulation of citrullinated proteins within atherosclerotic plaques, which allow ACPA to bind and contribute to endothelial dysfunction [17]. A meta-analysis by Avina-Zubieta *et al.* [13] found that RA patients have a significantly higher risk—68%, 41%, and 87%—of experiencing myocardial infarction (MI), cerebrovascular events, and heart failure, respectively. However, more recent studies with larger participant groups have shown that the risk for RA patients in terms of stroke and MI is 20% and 50% higher, respectively [18]. These differences could be attributed to the fact that RA patients today often exhibit milder disease activity than those in earlier studies [19]. Furthermore, those with RA are at an increased risk for silent myocardial infarctions and sudden cardiac death [20]. The elevated risk in RA patients cannot solely be attributed to traditional cardiovascular risk factors such as smoking,

obesity, or diabetes [4, 13, 14], suggesting that other significant factors are at play. Consequently, conventional cardiovascular risk calculators tend to underestimate the actual risk for RA patients [21], which has led experts to recommend multiplying the calculated risk by a factor of 1.5 to obtain a more accurate estimate [14, 22].

The role of cytokines

Endothelial dysfunction, the initial step of atherosclerosis, is a condition driven by inflammation, a hallmark feature in the development and progression of both rheumatoid arthritis (RA) and psoriatic arthritis (PsA). In these diseases, several cytokines, which are notably elevated, contribute to vascular damage. The increased levels of IL-6 and TNF-α lead to higher production of acute-phase proteins like C-reactive protein (CRP) and fibrinogen in the liver, promote the expression of adhesion molecules, enhance endothelial cell permeability, and attract inflammatory cells, enabling their movement across the blood vessel wall [23, 24]. These cytokines also play a role in insulin resistance, which is another risk factor for cardiovascular disease (CVD) [25]. Additionally, TNF-α contributes to the suppression of endothelial nitric oxide synthase (eNOS) and the upregulation of inducible nitric oxide synthase (iNOS), impairing nitric oxide (NO) production [26]. A closely related molecule to IL-6 is leptin, an adipokine primarily involved in regulating energy balance and body weight. Leptin levels tend to be higher in obese individuals due to its secretion by adipose tissue. Beyond its metabolic functions, leptin has a broader impact on immune system regulation by stimulating the activation, proliferation, and maturation of immune cells, while also increasing IL-6 and TNF-α production. This mechanism may explain the persistent low-grade inflammation observed in obesity, which predisposes individuals to an elevated risk of CVD [27, 28]. Moreover, leptin may accelerate atherosclerosis by altering lipid metabolism, lowering HDL cholesterol, increasing cholesterol accumulation in monocytes, and facilitating the migration of these cells into the vessel walls, where they transform into foam cells [29, 30]. In RA patients, leptin levels are higher compared to healthy controls, and its concentration correlates with disease activity, suggesting its involvement in disease pathogenesis [27, 31]. IL-1β is another cytokine contributing to increased cardiovascular risk in RA through its effects on oxidative stress, lipid metabolism, and the destabilization of atherosclerotic plaques. Additionally, IL-1β plays a crucial role in adverse remodeling of the heart muscle following a myocardial infarction (MI), a process linked to higher one-year post-infarction mortality rates [32, 33]. A study by Ikonomidis *et al*. examined RA patients with and without coronary artery disease (CAD), revealing that IL-1β levels were three times higher in those with CAD compared to those without. This finding suggests that IL-1β may contribute to the development of CAD in RA. Furthermore, treatment with anakinra, an IL-1 receptor antagonist, improved vascular and myocardial functions in both groups, with a more significant benefit observed in the CAD group [34].

Endothelial progenitor cells

Endothelial progenitor cells (EPCs) are critical for endothelial homeostasis, as previously discussed, and their role in rheumatoid arthritis (RA) has been the subject of various studies. Similar to psoriatic arthritis (PsA), RA patients generally exhibit lower EPC levels [35, 36]. However, an intriguing study by Rodríguez-Carrio *et al*. highlighted an interesting link between EPCs and interferon-alpha (IFN-α) levels. Patients with elevated IFN-α levels had higher EPC counts, while those with reduced IFN-α levels showed a depletion of EPCs [37]. This finding was unexpected since IFN-α is known to promote endothelial dysfunction (ED), suggesting that it should decrease EPC numbers [38]. The researchers hypothesized that IFN-α might cause premature differentiation of EPCs, thus impairing their regenerative capacity and potentially increasing cardiovascular (CV) risk [37]. IFN-α's role in inflammatory diseases is complex. Its use in treating viral infections like hepatitis C or cancers like melanoma has been associated with the onset of RA and PsA [39-41]. In addition, elevated IFN-α levels are often observed in other autoimmune disorders, particularly systemic lupus erythematosus [42], and have also been linked to heightened disease activity in RA [37]. Despite this, the precise role of IFN-α in RA pathogenesis remains unclear, requiring further investigation.

In other research, lower EPC levels in RA patients were correlated with vitamin D deficiency, increased bone erosion scores, and higher levels of asymmetric dimethylarginine (ADMA), a known eNOS inhibitor [43-45]. However, not all studies align on the issue of EPC depletion in RA, as some have reported stable or even increased EPC counts in these patients compared to

controls [46-48]. The relationship between EPC levels and disease activity is also debated, with conflicting findings across studies [46, 49]. Furthermore, evidence suggests that EPCs accumulate in the synovial tissue, where they contribute to vasculogenesis, leading to increased immune cell infiltration and potentially exacerbating inflammation and joint damage [50, 51]. Another important player in endothelial repair is angiogenic T cells (Tang), which collaborate with EPCs. These cells are found to be reduced in RA patients and have been linked to disease activity, seropositivity, and IFN-α levels. This strong association between specific cell types vital for vascular health and disease-related markers, rather than traditional CV risk factors, underscores the importance of evaluating CV burden in RA based on disease-specific markers [52].

Oxidative stress also plays a key role in endothelial dysfunction. It refers to the imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them with antioxidants. ROS are harmful to cellular integrity, damaging proteins, lipids, and DNA, and they contribute significantly to ED by promoting LDL oxidation, enhancing inflammation, and reducing nitric oxide (NO) availability [53]. A study by Mateen *et al.* [54] found significantly elevated ROS levels and markers of oxidative damage in RA patients, along with decreased antioxidant levels, compared to healthy controls. Factors such as serological status (e.g., RF positivity), disease activity, and disease duration influenced the extent of oxidative stress, suggesting its prominent role in the pathogenesis of RA.

Genetic factors

Although the mechanisms underlying endothelial dysfunction are largely shared between PsA and RA, there are important differences between the two. In RA, individuals who test positive for the HLA-DRB1 gene seem to face a higher risk of death from cardiovascular disease (CVD) [55, 56]. This suggests that the "shared epitope" found within HLA-DRB1 may contribute to endothelial damage, leading to a more severe form of RA and worse overall outcomes [56, 57]. Gonzalez-Gay *et al*. [56] observed that individuals with the HLA-DRB104 allele experienced a more than fourfold increased risk of cardiovascular mortality, and those carrying HLA-DRB10404 had nearly seven times the risk compared to the general population. Furthermore, in a study of 1,022 patients with inflammatory polyarthritis (74% of whom were diagnosed with RA), those who carried both the HLA-DRB1*01 and *04 alleles had over three times the cardiovascular mortality risk compared to those with fewer or no shared epitope alleles [55]. The connection between HLA-DRB1 and cardiovascular mortality in RA remains uncertain, necessitating further research.

On the other hand, PsA is associated with the HLA-B27 antigen, present in roughly 20% of those affected by the disease [58]. However, this antigen is more strongly linked with ankylosing spondylitis (AS), where it is found in over 80% of patients [58], making it one of the most robust MHC antigen-disease associations known [59]. Several studies have explored how HLA-B27 influences cardiovascular health, particularly focusing on its effects on the heart's conduction system and valves. For instance, in a group of 83 patients with total heart block but no evidence of HLA-B27-related rheumatic disease, 17% tested positive for HLA-B27, compared to 6% in a control group, as noted by Bergfeldt *et al.* [60]. More recent research, however, has shown no significant connection between HLA-B27 and conduction abnormalities in AS patients [61]. Another investigation found that AS patients who were HLA-B27 positive had a significantly higher aortic root index than those who were HLA-B27 negative. Although aortic valve regurgitation rates were similar between the two groups, an increased aortic root index suggests a higher risk of developing cardiovascular issues, highlighting the need for routine echocardiographic screening for HLA-B27-positive individuals [62]. Nonetheless, it is important to note that the majority of studies focus on AS, as its association with HLA-B27 is more strongly established compared to PsA.

"Lipid paradox"

In patients with RA, an unusual lipid pattern has been observed, which contradicts the general population's lipid profile. Specifically, low levels of total and LDL cholesterol in these individuals correlate with an increased risk of cardiovascular disease (CVD), a phenomenon referred to as the "lipid paradox" [63]. However, these lipid alterations are not limited to mere quantitative changes; they also involve functional abnormalities. One such issue is the presence of pro-inflammatory HDL, which exhibits impaired functionality [64]. This dysfunction may stem from decreased levels of paraoxonase 1, an enzyme crucial for HDL's antioxidant actions [65, 66]. Additionally, patients with RA show elevated concentrations of glycated lipoproteins and oxidized LDL (ox-LDL) [67].

Cholesterol transport is also disrupted due to the downregulation of key proteins that mediate cholesterol efflux and the upregulation of scavenger receptors. This impairs macrophages' ability to maintain lipid balance, promoting foam cell formation [68].

While the lipid paradox in PsA remains a subject of debate, certain lipoprotein disturbances have been documented. Specifically, neoepitopes on HDL, which provoke the production of anti-aHDL autoantibodies, have been found in individuals with psoriasis. These autoantibodies are linked to greater disease severity and may contribute to accelerated atherosclerosis in these patients [69]. Further disruptions in HDL include an increase in acute phase proteins and a decrease in key apolipoproteins like apoA-1 and apo-M. There is also a reduction in cholesterol and phospholipid content in HDL, impairing its cholesterol efflux capacity [70]. Oxidative stress plays a key role in lipid abnormalities in PsA, leading to higher levels of ox-LDL in these patients compared to healthy individuals [71, 72]. A study by Profumo *et al.* [72] showed that patients with greater intima-media thickness (IMT > 1) had significantly higher ox-LDL levels, suggesting that this modified lipoprotein could accelerate atherogenesis.

Immune responses and autoantibodies

A significant factor in RA is the modification of proteins after translation, which gives rise to various autoantibodies. Among these, ACPA stands out, consisting of autoantibodies directed against citrullinated proteins [73], and its different variants may contribute to various cardiovascular issues. For example, research indicates a correlation between higher levels of anti-citrullinated vimentin and fibrinogen antibodies with increased left ventricle mass, and anti-citrullinated histone 2B antibodies have been associated with more severe coronary artery calcification [74, 75]. Additionally, ACPA might play a role in activating platelets in RA patients [76]. Another important modification is carbamylation, which appears to exacerbate cardiovascular risk in RA. A study from Italy found that anti-CarP antibodies were linked to indicators of subclinical atherosclerosis, such as flow-mediated dilation (FMD), carotid intima-media thickness (cIMT), and cardio-ankle vascular index (CAVI) [77].

In PsA, similar autoimmune reactions lead to the production of various autoantibodies. Some individuals with PsA have autoantibodies seen in RA, such as RF (present in 2-15% of patients) [78], ACPA (observed in 0.9-17.5% of PsA cases, with higher levels linked to polyarthritis and disease severity) [79], and anti-CarP (which has been found at higher levels in PsA patients compared to healthy controls, though further studies are required) [80]. However, PsA is also associated with distinct autoantibodies. For example, autoantibodies targeting cathelicidin (LL-37) and ADAMTS-L5 have been found to be more specific to this condition. These autoantigens are prominently present in psoriatic lesions [81] and, in the case of LL-37, within the synovium [82]. LL-37 is a peptide produced by keratinocytes that plays a vital role in dendritic cell activation [78, 81], while ADAMTS-L5 regulates the function of microfibrils [83]. Research by Yuan *et al.* [84] highlighted significantly higher levels of anti-LL-37 and anti-ADAMTS-L5 in PsA patients compared to controls and psoriasis patients without PsA, suggesting these autoantibodies may contribute to the disease process. However, further investigation is needed to clarify their pathogenic significance and how they may affect cardiovascular health in PsA.

"Obesity paradox"

In patients with RA, there is a surprising phenomenon known as the "obesity paradox," which contradicts what is typically observed in the general population. In this paradox, individuals with a higher BMI may have a reduced risk of mortality, whereas those with a lower BMI have an increased likelihood of dying [85, 86]. Research involving US veterans has indicated that weight loss in these patients correlates with an elevated risk of both overall and cardiovascular mortality [85, 87]. However, experts argue that weight loss itself is not the direct cause of death, but rather it reflects an underlying state of systemic inflammation. Elevated levels of pro-inflammatory cytokines can lead to muscle breakdown and a reduction in lean body mass [88]. As a result, individuals may lose weight while still retaining excess fat, a condition known as rheumatoid cachexia [89, 90]. This shift in body composition may promote the development of central obesity, which is a well-documented cardiovascular risk factor [90].

This paradoxical relationship does not seem to apply to PsA, where obesity is more common than in RA patients [91]. Studies suggest that short-term weight loss in obese PsA patients leads to improvements in disease activity, with a dose-response effect observed [92]. Furthermore, long-term weight reduction has been shown to positively influence metabolic parameters, such as glucose, urate,

and lipid levels [93]. Additionally, weight loss is linked to better outcomes with anti-TNF therapy and increases the chances of achieving minimal disease activity [94]. Therefore, managing body weight through dietary intervention should be an essential component of treatment for PsA patients with obesity-related comorbidities.

Therapy

While PsA and RA share some therapeutic strategies, there are also notable distinctions in their treatment approaches. In both disorders, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), including methotrexate, leflunomide, cyclosporine, and sulfasalazine, are commonly employed as initial therapy, with methotrexate remaining the most frequently utilized agent [95, 96]. Beyond csDMARDs, both conditions benefit from the use of TNF inhibitors such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. However, their targeted biological treatments diverge in some aspects. PsA is treated with IL-17A inhibitors (secukinumab, ixekizumab) and IL-12/23 pathway blockers like ustekinumab, along with IL-23-specific inhibition using guselkumab. In contrast, RA management incorporates IL-6 receptor blockers, including tocilizumab and sarilumab, as well as the IL-1 receptor antagonist anakinra. Additionally, both diseases utilize non-steroidal anti-inflammatory drugs and corticosteroids to control symptomatic inflammation [8, 9].

This analysis presents an in-depth evaluation of cardiovascular (CV) risk profiles and systemic inflammation in RA and PsA, emphasizing both shared and unique pathological features. It is evident that systemic inflammation in both diseases significantly contributes to the heightened cardiovascular disease risk. Nevertheless, the underlying mechanisms differ; RA patients often experience a higher rate of CVD, potentially linked to genetic predispositions such as the HLA-DRB1 “shared epitope” and the presence of autoantibodies like ACPA. Conversely, PsA is also tied to increased cardiovascular complications but is characterized by distinct inflammatory and lipid alterations.

These observations indicate the importance of disease-specific CV risk evaluations and personalized care strategies. A significant gap remains in CV risk stratification, as PsA is typically omitted from major risk prediction models, while RA is considered in only a small subset of them [97, 98]. This underrepresentation calls for improvements in CV health monitoring, especially in PsA. In RA, the strong link between ACPA and cardiovascular events suggests that integrating ACPA screening into standard assessments could enhance risk prediction accuracy [17]. Effective therapeutic planning should incorporate systemic inflammatory activity and autoantibody profiles. PsA, due to its atypical lipid profiles and a weaker association with traditional cardiovascular risk indicators, necessitates a different monitoring framework and treatment approach. On a mechanistic level, both disorders demonstrate how chronic systemic inflammation promotes endothelial damage and atherosclerotic progression. Elevated pro-inflammatory mediators, particularly TNF-α and IL-6, contribute to vascular injury in both conditions. However, IL-6 has a dominant role in RA’s inflammatory cascade, whereas TNF-α is more central in PsA pathophysiology [99]. This cytokine-driven divergence underscores the necessity for tailored biological interventions that specifically target these molecules to effectively control inflammation and reduce cardiovascular complications.

The findings from this review align with previous research indicating increased cardiovascular risk in RA and PsA but also offer novel perspectives by dissecting disease-specific pathways. While earlier investigations established the inflammation-CVD link, this review enhances current understanding by delineating the distinct roles played by inflammatory markers and genetic traits in each disease context.

To advance the field, future studies should prioritize long-term cohort investigations that explore how systemic inflammation correlates with the timing and incidence of cardiovascular events in RA and PsA. Evaluating how specific targeted treatments affect CV outcomes will be essential for optimizing therapeutic decisions. Additionally, further investigation into the predictive value of autoantibodies and genetic factors in cardiovascular risk could improve individualized treatment planning. Research into how genetic predisposition, inflammatory processes, and environmental or lifestyle variables interact may also shed light on their combined influence on cardiovascular vulnerability.

Conclusion

This review underscores the intricate relationship between systemic inflammation and elevated cardiovascular (CV) risk in both RA and PsA while drawing attention to the unique contributing factors and underlying mechanisms specific to each disease. Despite the clear association with increased CV complications, PsA remains largely excluded from existing CV risk prediction models, and RA is represented only in a select few, highlighting a significant shortfall in current risk evaluation frameworks. Recognizing these distinctions is essential for crafting more precise and individualized strategies to address CV risk in these patient populations. Ongoing investigation is imperative to advance the accuracy of risk stratification methods and to optimize therapeutic interventions, with the ultimate goal of enhancing long-term clinical outcomes.

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