Review Article

# Cardiovascular Risk and Systemic Inflammation in Rheumatoid Arthritis: Comparative Insights with Psoriatic Arthritis

**Mateusz Kęska[1], Wiktoria Suchy[1]***

[1]SSG of Clinical Pharmacology, Jagiellonian University Medical College, Cracow, Poland.

## Abstract

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Both conditions are characterized by systemic inflammation that contributes to an increased risk of CVD, yet the underlying mechanisms and associated risk factors differ. This review investigates the immunological responses, inflammatory pathways, and genetic predispositions that influence the risk of cardiovascular disease (CV) in people with RA and PsA. Endothelial dysfunction and atherosclerosis in RA are primarily caused by pro-inflammatory cytokines, specifically interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), as well as the existence of autoantibodies such as anti-citrullinated protein antibodies (ACPA). Additionally, RA displays a "lipid paradox," in which a decreased risk of CVD is paradoxically correlated with a higher risk of cholesterol, most likely as a result of ongoing systemic inflammation. Different paths of CV impact are indicated by unique lipid profile changes and less prominent autoantibody participation in PsA, despite the fact that the risk of CVD is also enhanced. Genetic factors like HLA-DRB1 are more prominent in RA, while PsA has a unique association with metabolic syndrome and obesity-related inflammation. Despite the well-established CV risk in both RA and PsA, current risk calculators do not include PsA, and only two models account for RA. This review highlights the need for better risk assessment tools that incorporate disease-specific factors. Recognizing the overlapping and divergent mechanisms in RA and PsA can enhance the development of more targeted strategies for managing CV health and guide personalized treatment approaches.

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

## Introduction

Rheumatoid arthritis (RA) is a chronic, multifactorial autoimmune disease primarily involving the synovial joints but also, less frequently, extra-articular organs. Its prevalence is higher than that of PsA, ranging from 0.16% to 1.3% worldwide [1, 2], and seems to be rising [3], affecting women two to three times more often than men [1, 2]. Clinically, it is characterized by symmetrical pain and swelling of the joints, especially metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints, as well as the wrists, usually accompanied by morning joint stiffness. Other manifestations of the disease include vasculitis, pleural effusions, interstitial lung disease, atherosclerosis, keratoconjunctivitis, pericarditis, or anemia [1, 4]. Studies indicate that about 40% of patients with RA will develop an extra-articular involvement during the course of the disease [5], which potentially might result in the incorporation of the cardiovascular (CV) system and its damage. Common laboratory findings include increased erythrocyte sedimentation rate (ESR) and elevated levels of C-reactive protein (CRP) [1, 2]. Numerous autoantibodies, particularly rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), are caused by dysregulation in the immune response [2, 4, 6]. PsA and RA differential diagnosis is displayed in **(Table 1)**.

**Address for correspondence:** Wiktoria Suchy, SSG of Clinical Pharmacology, Jagiellonian University Medical College, Cracow, Poland.
wiktoria.suchy@student.uj.edu.pl



**How to cite this article:** Kęska M, Suchy W. Cardiovascular Risk and Systemic Inflammation in Rheumatoid Arthritis: Comparative Insights with Psoriatic Arthritis. Arch Pharm Pract. 2024;15(3):58-65. https://doi.org/10.51847/EjiHWNs210

**Table 1.** Differential diagnosis of RA and PsA based on [7-9].

| 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, discovertebral junction, entheses) |
| **DIP joint involvement** | - | +++ |
| **Spine involvement** | Cervical | Axial |
| **Productivity of bone changes** | Destructive changes (e.g. erosions, juxtaarticular 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, TNF – tumor necrosis factor.

Although the exact cause of the disease remains unknown, environmental and genetic factors seem to play a significant role in its development. The heritability of RA is estimated to be about 65% [2, 6]. One of the strongest genetic risk factors is HLA-DRB1 alleles, especially DR4 and DR1. Since the precise region of the HLA molecule that is in charge of antigen presentation is known as the "shared epitope," they are both composed of a certain sequence of five amino acids [6]. Furthermore, research has shown a substantial correlation between the aforementioned alleles and ACPA-positive RA, suggesting that a "shared epitope" may be in charge of presenting the citrullinated peptides [10, 11]. As for the environmental risk factors, smoking cigarettes is the best-established and most consistent one among studies, but researchers also mention obesity, infections, periodontitis, exposure to UV light, and changes in microbiome as possible contributors [1, 2, 4]. Some of them should also be considered as the factors predisposing to CV disease (CVD) itself, therefore compounding enhanced CV risk already carried by RA.

## CV Risk in RA

Similarly to PsA, RA is also associated with a higher risk of CVD, comparable to that in patients with diabetes mellitus [12]. Patients with RA have a 50% greater risk of developing cardiovascular disease, with a corresponding 50-60% increase in cardiovascular mortality compared to the general population [13, 14]. Several studies revealed an association between higher disease activity and the occurrence of CV events [12, 14]. Moreover, patients who are ACPA-positive are at even greater risk of developing CVD [15], which is also true for patients without RA [16]. This might be due to the occurrence of citrullinated proteins in atherosclerotic plaques so that ACPA may bind to them and accelerate endothelial dysfunction [17]. Avina-Zubieta *et al.*'s meta-analysis indicates that individuals with RA have a 68%, 41%, and 87% increased risk of myocardial infarction (MI), cerebrovascular accident, and heart failure, respectively [13]. On the other hand, a more recent study with a larger patient cohort discovered that RA patients had a 20% and 50% increased risk of stroke and MI, respectively [18]. This could be explained by the fact that, in contrast to historical statistics, cases of RA today frequently exhibit less severe disease activity [19]. Furthermore, individuals with RA are at greater risk of developing silent MI and experiencing sudden cardiac death [20]. Greater risk cannot be fully explained only by traditional risk factors like smoking, obesity, diabetes, hypertension, or dyslipidemia [4, 13, 14], which indicates that some other factors play a significant role in that phenomenon. Therefore, the CV risk of patients with RA calculated using traditional risk scores leads to its underestimation [21], and that is why experts suggest multiplying the calculated risk by 1.5 to obtain a reliable result [14, 22].

## The Role of Cytokines

As mentioned above, atherosclerosis as well as its initial step - endothelial dysfunction, are both driven by inflammation, a state characteristic for the development and the course of not

only RA but also PsA. Several cytokines, which are significantly increased in both of these conditions, accelerate the vascular damage. Elevated levels of IL-6 and TNF-α result in increased production of acute phase proteins by the liver, such as CRP or fibrinogen, enhanced expression of the adhesion molecules and increased permeability of EC, as well as the attraction of inflammatory cells, therefore enabling their trafficking across the vessel wall [23, 24]. In addition, they contribute to insulin resistance – another CVD risk factor [25]. TNF-α is also responsible for downregulating eNOS and upregulating iNOS expression, which results in disrupted NO production [26]. Another molecule that is closely associated with the IL-6 family is called leptin, an adipokine that is primarily used as a regulator of energy intake and body weight. Patients who are obese tend to have higher amounts of this substance since adipose tissue secretes it most of the time. But as it found out, its function is far more extensive and involves immune response modulation as well. It stimulates the proliferation, activation, and maturation of different immune cells, as well as increases the production of IL-6 and TNF-α. This might elucidate the basis of low-grade inflammation present in obese individuals, which makes them more prone to developing CVD [27, 28]. Furthermore, leptin might accelerate atherosclerosis by altering lipid profile, in particular lowering HDL levels and increasing the accumulation of cholesterol in monocytes, as well as facilitating their entry into the vessel wall and transformation of macrophages into foam cells [29, 30]. Patients with RA exhibit elevated levels of leptin as compared to controls and its concentration was found to be correlated with disease activity, therefore suggesting its possible part in the pathogenesis of the disease [27, 31]. IL-1β is another contributor to more pronounced CV risk in RA by its role in increasing nitrooxidative stress, altering lipid metabolism, and in the formation as well as destabilization of atherosclerotic plaques. Apart from this, IL-1β is also crucial in the process of adverse heart muscle remodeling following myocardial infarction [32], which is associated with a greater risk of post-infarction one-year mortality [33]. A study conducted by Ikonomidis *et al*. compared two groups of RA patients – with and without coronary artery disease (CAD). It revealed that patients with CAD had 3 times higher IL-1β concentrations than those without, which suggests the possible contribution of this cytokine to the development of this comorbidity. Moreover, the administration of anakinra - an IL-1 receptor antagonist, resulted in improvement in vascular and myocardial functions in both groups, but it was significantly more prominent in the CAD group [34].

## *Endothelial Progenitor Cells*

A different issue worth discussing is endothelial progenitor cells (EPCs), whose role in endothelial homeostasis has been discussed above. Likewise in PsA, several studies indicated that RA patients have decreased levels of EPCs [35, 36]. Interestingly, a study conducted by Rodríguez-Carrio *et al*. depicted an intriguing association between IFN-α levels and EPCs – patients with elevated levels of IFN-α had also higher EPC count, in contrast to patients with lower levels of IFN-α, who exhibited depletion of EPCs [37]. It is a surprising outcome because IFN-α was found to accelerate ED, which suggests that it should have a negative impact on EPC count [38]. However, the investigators point to premature differentiation of EPCs caused by IFN-α as a possible mechanism for disabling their regenerative properties and therefore increasing CV risk in patients [37]. The role of IFN-α in inflammatory arthritis is complex as the treatment of viral diseases like hepatitis C or neoplasms like melanoma with this cytokine can induce the onset of RA or PsA [39-41]. Moreover, it seems to be remarkable in the course of a number of autoimmune disorders – especially in systemic lupus erythematous [42], but it might also be important in RA since elevated levels of IFN-α have been observed among these patients as compared to controls and they were related to increased disease activity [37]. However, the significance of IFN-α in the pathogenesis of RA remains poorly understood and thus this issue requires further research. In other studies, reduced EPC count in RA patients was found to be associated with vitamin D deficiency, higher bone erosion scores, and elevated levels of ADMA, an inhibitor of eNOS [43-45]. Nevertheless, not all studies are consistent in terms of decreased EPCs levels in RA patients, since some of the researchers noted increased or unchanged EPC counts in these individuals as compared to controls [46-48]. Also, the correlation between EPCs levels and disease activity remains controversial, as studies revealed contradictory results [46, 49]. Furthermore, there is evidence that EPCs accumulate in the synovial tissue, resulting in vasculogenesis and therefore increased immune cell influx, which might accelerate inflammation and joint damage [50, 51]. There is also another subset of cells that plays a pivotal role in endothelial repair by cooperating with EPCs – angiogenic T cells (Tang). Their decreased levels have also been noted among RA patients and they were associated with disease activity, seropositivity, and levels of IFN-α. A significant correlation of a number of cells crucial for vascular homeostasis with disease-specific features, but not with traditional CV risk factors, implies that CV burden in RA should be assessed considering disease-related markers [52]. Another important factor accounting for ED is oxidative stress. It can be defined as an imbalance between the generation of reactive oxygen species (ROS) and the amount of their scavengers – antioxidants. ROS can be detrimental to organism homeostasis as they can damage numerous biomolecules such as proteins, lipids, or DNA. They also play a significant role in ED by promoting LDL oxidation, enhancing inflammation, or decreasing NO bioavailability [53]. A study conducted by Mateen *et al*. revealed significantly increased levels of not only ROS but also markers of their harmful activity, as well as decreased amounts of antioxidants in RA patients as compared to controls. Factors that were found to affect the burden of oxidative stress were serological status (RF positivity/negativity), disease activity, and its duration, implying that oxidative stress might play a significant role in the pathogenesis of RA [54].

## *Genetic Factors*

Although numerous mechanisms of endothelial dysfunction are similar in PsA and RA, there are some significant differences. First, patients with RA who are HLA-DRB1 positive have a greater risk of death due to CVD [55, 56]. This may suggest that "shared epitope" plays a role in endothelial dysfunction in RA and therefore results in a more severe presentation of the disease and poorer outcome [56, 57]. A study conducted by Gonzalez-Gay *et al*. indicated over 4-fold increased risk of CV mortality in patients with HLA–DRB1*04 and almost 7-fold for those HLA–DRB1*0404 positive as compared to the general population [56]. A different study that included 1,022 patients with inflammatory polyarthritis, out of which 74% met the criteria for RA diagnosis, revealed that the CV risk of mortality was increased over 3-fold for patients carrying the HLA–DRB1*01/*04 combination as compared to those with 0 or 1 shared epitope allele [55]. However, this association remains unclear and further research is highly recommended.

Contrary to RA, an antigen linked with PsA is HLA-B27. Its prevalence among patients with PsA is estimated to be about 20% [58]. However, there is a different condition that has an even stronger connection to this region, which is ankylosing spondylitis (AS). It is present in more than 80% of patients with AS [58], which makes it one of the strongest known associations between MHC antigen and a disease [59]. There have been many studies that tried to evaluate the impact of HLA-B27 on the CV system. Most of them focused on the influence of that antigen on the heart, especially the conducting system and valves. In a group of 83 patients with total heart block and no indications of HLA-B27-associated rheumatic disease, 14 patients (17%) tested positive for HLA-B27, compared to 6% in the control group, according to a study by Bergfeldt *et al*. [60]. However, a more recent piece of research depicted that conduction disturbances in patients with AS were not associated with HLA-B27 status [61]. Another study revealed that patients with AS who were HLA-B27 positive had significantly increased aortic root index as compared to HLA-B27 negative patients. Although the prevalence of aortic valve regurgitation did not seem to differ between these two groups, an elevated aortic root index reflects a higher risk of developing this condition, therefore patients with this genetic variant might require regular echocardiographic screening [62]. Nevertheless, it needs to be emphasized that the majority of these studies have been conducted on patients with AS as its relationship with HLA-B27 antigen is well-established and more prominent than with PsA.

### *"Lipid Paradox"*

Another issue is a surprising lipid pattern present in patients with RA. Several studies have indicated that in these individuals, contrary to the general population, low levels of total cholesterol and LDL cholesterol are associated with a higher risk of CVD. This phenomenon is known as the "lipid paradox" [63]. However, lipid alterations in RA are not only quantitative but also functional. They include the presence of pro-inflammatory HDL with impaired function [64]. It might be due to a decreased level of paraoxonase 1 [65] – an enzyme responsible for the antioxidant properties of HDL [66]. Another disturbance is a high concentration of glycated lipoproteins and oxidated LDL (ox-LDL) in individuals with RA [67]. Furthermore, cholesterol transport is disturbed in RA due to the downregulation of proteins responsible for cholesterol efflux and the upregulation of scavenger receptors. Therefore, it is more difficult for macrophages to maintain lipid homeostasis, which results in increased foam cell formation [68].

The presence of lipid paradox in PsA is controversial. However, some structural disturbances in lipoproteins have been noted. First is the occurrence of neoepitopes on HDL that triggers the formation of autoantibodies (anti-aHDL). They were detected in patients with psoriasis and were associated with increased disease severity. Moreover, their presence might be linked to enhanced development of atherosclerosis in these individuals [69]. Other abnormalities include alterations in HDL-associated proteins – increased levels of acute phase proteins and reduced levels of apolipoproteins like apoA-1 and apo-M. What is more, differences in lipid content in HDL were noted - a decrease in cholesterol and phospholipids levels, thus resulting in impaired cholesterol efflux [70]. Oxidative stress is also an important contributor to lipid disturbances in PsA, resulting in the formation of ox-LDL. Higher concentrations of this modified lipoprotein have been observed in patients with PsA than in healthy controls [71, 72]. Moreover, a study conducted by Profumo *et al*. revealed that ox-LDL levels were higher in patients with IMT>1 than with IMT<1, suggesting that it might be an accelerator of atherogenesis [72].

### *Immune Responses and Autoantibodies*

Different matter specific to RA is the post-translational modification of proteins that results in the occurrence of several autoantibodies. ACPA, the most well-known among them, is in fact a group of autoantibodies that are directed against numerous citrullinated proteins [73], and its numerous variants may be to blame for a number of abnormalities in the cardiovascular system. For example, one study found that higher levels of anti-citrullinated vimentin and fibrinogen antibodies correlated with increased left ventricle mass, and another study found that higher concentrations of anti-citrullinated histone 2B antibodies were associated with greater coronary artery calcification [74, 75]. Moreover, research suggests that ACPA might also be responsible for platelet activation in RA [76]. Another type of protein modification is carbamylation, which also seems to be an important contributor to elevated CV risk in RA. An Italian study showed an association of anti-CarP antibodies with parameters of subclinical atherosclerosis – flow-mediated dilation (FMD), cardio-ankle vascular index (CAVI), and carotid intima-media thickness (cIMT) [77].

However, PsA has also been proven to be driven by autoimmune reactions, therefore resulting in the formation of

numerous autoantibodies. While some patients with PsA present with autoantibodies typical for RA – RF (2-15%) [78], ACPA (0.9-17.5%, its occurrence may be linked to increased disease activity and polyarthritis) [79] and anti-CarP (its higher levels in patients with PsA than in controls have been observed in a single study, thus evidence on this is limited) [80], there are also some novel biomarkers that seem to be more specific for PsA. They are directed against cathelicidin (LL-37) and a disintegrin and metalloprotease domain containing thrombospondin type 1 motif-like 5 (ADAMTS-L5). These autoantigens are present abundantly in psoriatic lesions [81], as well as, in the case of LL-37, in the synovium [82]. LL-37 is an antimicrobial peptide produced by keratinocytes that plays a significant role in activating dendritic cells [78, 81] and ADAMTS-L5 is a protein responsible for modulating microfibril function [83]. A study conducted by Yuan *et al*. revealed that levels of anti-LL-37 and anti-ADAMTS-L5 are significantly increased in patients with PsA as compared to controls but also to patients with psoriasis without PsA, which may suggest their contribution to disease development [84]. Nevertheless, their pathogenic relevance as well as their impact on the CV system requires further research.

### *"Obesity Paradox"*

Another surprising finding in patients with RA that stands in opposition to what can be observed in the general population is the so-called "obesity paradox". It is a situation when a high BMI acts as a protective factor and a low BMI is associated with a higher risk of mortality [85, 86]. What is more, two studies conducted on US veterans have revealed that weight loss is also associated with increased risk of all-cause [85] and CV mortality [87]. However, researchers do not suggest that weight loss itself is the cause of death, but it reflects the process of systemic inflammation. A high concentration of cytokines results in increased proteolysis and reduced muscle mass [88]. Thus, patients might lose weight but still have high levels of adipose tissue - this phenomenon is called rheumatoid cachexia [89, 90]. This might lead to changes in body composition and the development of central obesity, an established CV risk factor [90].

This intriguing relationship seems not to be accurate in PsA, where obesity is even more prevalent than in RA [91]. There is evidence that short-term weight loss in obese PsA patients is associated with improvement in disease activity and this correlation is characterized by a dose-response manner [92]. Long-term weight loss sustained this outcome and was also found to improve blood levels of glucose, urate, and lipids [93]. Moreover, reduction of body weight was related to a better response to anti-TNF treatment and a greater chance of achieving minimal disease activity [94]. Therefore, dietary advice and subsequent weight loss should be an inherent part of treatment in PsA patients with comorbid obesity.

### *Therapy*

There are also some similarities as well as differences between PsA and RA in terms of treatment. In both cases, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate, leflunomide, cyclosporine, and sulfasalazine, are recommended as a first-line therapy, especially methotrexate is widely used [95, 96]. Other therapy options include TNF inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol) in both PsA and RA, IL-17A inhibitors (secukinumab, ixekizumab) and IL-12/23 inhibitors (ustekinumab; guselkumab is an IL-23 inhibitor) in PsA and IL-6 receptor antagonists (tocilizumab, sarilumab) and IL-1 receptor antagonist (anakinra) in RA. Moreover, non-steroidal anti-inflammatory drugs and corticosteroids are commonly used in both conditions to alleviate symptoms [8, 9].

This review provides a comprehensive comparison of CV risk and systemic inflammation in RA and PsA. Our analysis highlights that both RA and PsA are associated with an increased risk of CVD due to systemic inflammation. However, the mechanisms and implications of this risk differ between the two conditions. RA shows a higher incidence of CVD, potentially exacerbated by genetic factors such as the HLA-DRB1 "shared epitope," and the presence of autoantibodies like ACPA. PsA, while also linked with elevated CV risk, demonstrates distinct lipid and inflammatory profiles.

The findings underscore the need for tailored CV risk assessment and management strategies in RA and PsA patients. Despite the increased risk associated with both conditions, PsA is notably excluded from most CV risk calculators, and RA is considered in only a limited number of these tools [97, 98]. This lack of inclusion in standardized risk assessment frameworks highlights a significant gap in CV health management for patients with PsA and RA. For RA, the strong association between ACPA positivity and CV events suggests that integrating ACPA testing into routine evaluations could enhance risk stratification [17]. When creating customised therapy regimens, systemic inflammation and autoantibodies should be taken into account. Particular monitoring and therapeutic strategies are required for PsA because to its unique lipid changes and lessened correlation with standard CV risk factors. Mechanistically, both conditions reveal how systemic inflammation accelerates endothelial dysfunction and atherosclerosis. Elevated levels of inflammatory cytokines, such as IL-6 and TNF-α, contribute to vascular damage and increased cardiovascular risk in both RA and PsA. Notably, while IL-6 is a key driver of inflammation in RA, the inflammatory response in PsA is primarily mediated by TNF-α [99]. This distinction underscores the need for different therapeutic approaches targeting these cytokines to effectively reduce inflammation and mitigate cardiovascular risk in each condition.

Our review supports existing literature on the increased CV risk in RA and PsA, while also presenting new insights into disease-specific mechanisms. Previous studies have established the link between systemic inflammation and CV

risk, but our review adds depth by comparing the relative contributions of different inflammatory mediators and genetic factors in RA and PsA.

Future research should focus on longitudinal studies to better understand the temporal relationship between systemic inflammation and CV events in RA and PsA. Investigating the impact of targeted therapies on CV outcomes in these patients could provide valuable insights into effective management strategies. Additionally, more research is needed to explore the role of specific autoantibodies and genetic markers in predicting CV risk and guiding treatment decisions. Investigating the interplay between genetic predispositions, systemic inflammation, and lifestyle factors could further clarify their combined effect on CV risk.

## Conclusion

In summary, this review highlights the complex interplay between systemic inflammation and CV risk in RA and PsA. While both conditions are associated with increased CV risk, the mechanisms and specific risk factors vary. The lack of inclusion of PsA in most CV risk calculators, coupled with the limited incorporation of RA in only a few such tools, underscores the need for improved risk assessment models. Understanding these differences is crucial for developing targeted strategies to mitigate CV risk in patients with RA and PsA. Continued research is essential to refine risk assessment tools and therapeutic approaches, ultimately improving patient outcomes.

ACKNOWLEDGMENTS: The authors are deeply grateful to PhD Barbara Lorkowska-Zawicka and PhD Beata Bujak-Giżycka from the Department of Pharmacology for their invaluable guidance and support throughout the development of this research.
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

## References

1. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020;9(4):880.
2. Jahid M, Khan KU, Rehan-Ul-Haq, Ahmed RS. Overview of rheumatoid arthritis and scientific understanding of the disease. Mediterr J Rheumatol. 2023;34(3):284-91.
3. Scott IC, Whittle R, Bailey J, Twohig H, Hider SL, Mallen CD, et al. Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis epidemiology in England from 2004 to 2020: An observational study using primary care electronic health record data. Lancet Reg Health Eur. 2022;23:100519.
4. Sparks JA. Rheumatoid arthritis. Ann Intern Med. 2019;170(1):ITC1-16.
5. Chirila RM, Berianu F, Abril A, Butendieck RR. Extra-articular involvement of rheumatoid arthritis in three seropositive patients in the absence of initial joint involvement. Immun Inflamm Dis. 2021;9(4):1613-7.
6. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. J Autoimmun. 2020;110:102400.
7. Jevtic V, Lingg G. Differential diagnosis of rheumatoid and psoriatic arthritis at an early stage in the small hand and foot joints using magnetic resonance imaging. Handchir Mikrochir Plast Chir. 2012;44(3):163-70.
8. Saalfeld W, Mixon AM, Zelie J, Lydon EJ. Differentiating psoriatic arthritis from osteoarthritis and rheumatoid arthritis: A narrative review and guide for advanced practice providers. Rheumatol Ther. 2021;8(4):1493-517.
9. Merola JF, Espinoza LR, Fleischmann R. Distinguishing rheumatoid arthritis from psoriatic arthritis. RMD Open. 2018;4(2):1-13.
10. Roudier J, Balandraud N, Auger I. How RA associated HLA-DR molecules contribute to the development of antibodies to citrullinated proteins: The hapten carrier model. Front Immunol. 2022;13:930112.
11. Jung SM, Park YJ, Park KS, Kim KJ. Clinical implications of shared epitope and anti-citrullinated peptide antibody in patients with rheumatoid arthritis. J Rheum Dis. 2022;29(3):171-80.
12. Johri N, Varshney S, Gandha S, Maurya A, Mittal P, Jangra S, et al. Association of cardiovascular risks in rheumatoid arthritis patients: Management, treatment and future perspectives. Health Sci Rev. 2023;8:100108.
13. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: A meta-analysis of observational studies. Ann Rheum Dis. 2012;71(9):1524-9.
14. Dijkshoorn B, Raadsen R, Nurmohamed MT. Cardiovascular disease risk in rheumatoid arthritis anno 2022. J Clin Med. 2022;11(10):2704.
15. Westerlind H, Id O, Id O, Holmdahl R, Id O, Length F. Anti-citrullinated protein antibody specificities, rheumatoid factor isotypes and incident cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheumatol. 2020;72(10):1658-67.
16. van Boheemen L, van Beers-Tas MH, Kroese JM, van de Stadt LA, van Schaardenburg D, Nurmohamed MT. Cardiovascular risk in persons at risk of developing rheumatoid arthritis. PLoS One. 2020;15(8):e0237072.
17. Sokolove J, Brennan MJ, Sharpe O, Lahey LJ, Kao AH, Krishnan E, et al. Citrullination within the atherosclerotic plaque: A potential target for the anti-citrullinated protein antibody response in rheumatoid arthritis. Arthritis Rheum. 2013;65(7):1719-24.
18. Kang S, Han K, Jung JH, Eun Y, Kim IY, Hwang J, et al. Associations between cardiovascular outcomes and rheumatoid arthritis: A nationwide population-based cohort study. J Clin Med. 2022;11(22):6812.
19. Finckh A, Gilbert B, Hodkinson B, Bae SC, Thomas R, Deane KD, et al. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol. 2022;18(10):591-602.
20. Ali A, Ali A, Kumar D, Kumar R, Elahi K, Suman F, et al. Comparison of incidence of myocardial infarction in patients with rheumatoid arthritis and diabetes mellitus. Cureus. 2021;13(6):e15716.
21. Argnani L, Zanetti A, Carrara G, Silvagni E, Guerrini G, Zambon A, et al. Rheumatoid arthritis and cardiovascular risk: Retrospective matched-cohort analysis based on the RECORD study of the Italian society for rheumatology. Front Med. 2021;8:745601.
22. Rawla P. Cardiac and vascular complications in rheumatoid arthritis. Reumatologia. 2019;57(1):27-36.
23. Pandolfi F, Franza L, Carusi V, Altamura S, Andriollo G, Nucera E. Interleukin-6 in rheumatoid arthritis. Int J Mol Sci. 2020;21(15):5238.
24. Blum A, Adawi M. Rheumatoid arthritis (RA) and cardiovascular disease. Autoimmun Rev. 2019;18(7):679-90.
25. Carbone F, Bonaventura A, Liberale L, Paolino S, Torre F, Dallegri F, et al. Atherosclerosis in Rheumatoid Arthritis: Promoters and Opponents. Clin Rev Allergy Immunol. 2020;58(1):1-14.
26. Zhang H, Park Y, Wu J, Chen XP, Lee S, Yang J, et al. Role of TNF-α in vascular dysfunction. Clin Sci (Lond). 2009;116(3):219-30.
27. Lee YH, Bae SC. Circulating leptin level in rheumatoid arthritis and its correlation with disease activity: A meta-analysis. Z Rheumatol. 2016;75(10):1021-7.
28. Poetsch MS, Strano A, Guan K. Role of leptin in cardiovascular diseases. Front Endocrinol. 2020;11:354.
29. Kang KW, Ok M, Lee SK. Leptin as a Key between obesity and cardiovascular disease. J Obes Metab Syndr. 2020;29(4):248-59.
30. Wang C, Chang L, Wang J, Xia L, Cao L, Wang W, et al. Leptin and risk factors for atherosclerosis: A review. Medicine (Baltimore). 2023;102(46):e36076.

31. Lee YH, Song GG. Circulating leptin and its correlation with rheumatoid arthritis activity: A meta-analysis. J Rheum Dis. 2023;30(2):116-25.
32. Lugrin J, Parapanov R, Milano G, Cavin S, Debonneville A, Krueger T, et al. The systemic deletion of interleukin-1α reduces myocardial inflammation and attenuates ventricular remodeling in murine myocardial infarction. Sci Rep. 2023;13(1):4006.
33. Berezin AE, Berezin AA. Adverse cardiac remodelling after acute myocardial infarction: Old and new biomarkers. Dis Markers. 2020;2020:1215802.
34. Ikonomidis I, Tzortzis S, Andreadou I, Paraskevaidis I, Katseli C, Katsimbri P, et al. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. Circ Cardiovasc Imaging. 2014;7(4):619-28.
35. Verma I, Syngle A, Krishan P. Predictors of endothelial dysfunction and atherosclerosis in rheumatoid arthritis in Indian population. Indian Heart J. 2017;69(2):200-6.
36. Herbrig K, Haensel S, Oelschlaegel U, Pistrosch F, Foerster S, Passauer J. Endothelial dysfunction in patients with rheumatoid arthritis is associated with a reduced number and impaired function of endothelial progenitor cells. Ann Rheum Dis. 2006;65(2):157-63.
37. Rodríguez-Carrio J, de Paz B, López P, Prado C, Alperi-López M, Javier Ballina-García F, et al. IFNα serum levels are associated with endothelial progenitor cells imbalance and disease features in rheumatoid arthritis patients. PLoS One. 2014;9(1):e86069.
38. Jones Buie JN, Oates JC. Role of interferon alpha in endothelial dysfunction: Insights into endothelial nitric oxide synthase-related mechanisms. Am J Med Sci. 2014;348(2):168-75.
39. Cacopardo B, Benanti F, Pinzone MR, Nunnari G. Rheumatoid arthritis following PEG-interferon-alfa-2a plus ribavirin treatment for chronic hepatitis C: A case report and review of the literature. BMC Res Notes. 2013:6:437.
40. Oliveira TL, Caetano AZ, Belem JM, Klemz BC, Pinheiro MM. Interferon-a induced psoriatic arthritis and autoimmune hemolytic anemia during chronic hepatitis C treatment. Acta Reumatol Port. 2014;39(4):327-30.
41. Yasmine M, Ajlani H, Boussaud S, Jammali S, Sehli H, Choeur E, et al. THU0606 Rheumatoid arthritis induced by alpha-interferon therapy: A rare case presentation. Ann Rheum Dis. 2020;79:544-45.
42. Tanaka Y, Kusuda M, Yamaguchi Y. Interferons and systemic lupus erythematosus: Pathogenesis, clinical features, and treatments in interferon-driven disease. Mod Rheumatol. 2023;33(5):857-67.
43. Lo Gullo A, Mandraffino G, Bagnato G, Aragona CO, Imbalzano E, D'Ascola A, et al. Vitamin D status in rheumatoid arthritis: Inflammation, arterial stiffness and circulating progenitor cell number. PLoS One. 2015;10(8):e0134602.
44. Park YJ, Kim JY, Park J, Choi JJ, Kim WU, Cho CS. Bone erosion is associated with reduction of circulating endothelial progenitor cells and endothelial dysfunction in rheumatoid arthritis. Arthritis Rheumatol. 2014;66(6):1450-60.
45. Surdacki A, Martens-Lobenhoffer J, Wloch A, Marewicz E, Rakowski T, Wieczorek-Surdacka E, et al. Elevated plasma asymmetric dimethyl-L-arginine levels are linked to endothelial progenitor cell depletion and carotid atherosclerosis in rheumatoid arthritis. Arthritis Rheum. 2007;56(3):809-19.
46. Komici K, Perna A, Rocca A, Bencivenga L, Rengo G, Guerra G. Endothelial progenitor cells and rheumatoid arthritis: Response to endothelial dysfunction and clinical evidences. Int J Mol Sci. 2021;22(24):13675.
47. Rodríguez-Carrio J, Prado C, de paz B, López P, Gómez J, Alperi-López M, et al. Circulating endothelial cells and their progenitors in systemic lupus erythematosus and early rheumatoid arthritis patients. Rheumatology (Oxford). 2012;51(10):1775-84.
48. Egan CG, Caporali F, Garcia-Gonzalez E, Galeazzi M, Sorrentino V. Endothelial progenitor cells and colony-forming units in rheumatoid arthritis: Association with clinical characteristics. Rheumatology. 2008;47(10):1484-8.
49. Grisar J, Aletaha D, Steiner CW, Kapral T, Steiner S, Seidinger D, et al. Depletion of endothelial progenitor cells in the peripheral blood of patients with rheumatoid arthritis. Circulation. 2005;111(2):204-11.
50. Rüger B, Giurea A, Wanivenhaus AH, Zehetgruber H, Hollemann D, Yanagida G, et al. Endothelial precursor cells in the synovial tissue of patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 2004;50(7):2157-66.
51. Grisar JC, Haddad F, Gomari FA, Wu JC. Endothelial progenitor cells in cardiovascular disease and chronic inflammation: From biomarker to therapeutic agent. Biomark Med. 2011;5(6):731-44.
52. Rodríguez-Carrio J, Alperi-López M, López P, Alonso-Castro S, Ballina-García FJ, Suárez A. Angiogenic T cells are decreased in rheumatoid arthritis patients. Ann Rheum Dis. 2015;74(5):921-7.
53. Shaito A, Aramouni K, Assaf R, Parenti A, Orekhov A, Yazbi A el, et al. Oxidative stress-induced endothelial dysfunction in cardiovascular diseases. Front Biosci (Landmark Ed). 2022;27(3):105.
54. Mateen S, Moin S, Khan AQ, Zafar A, Fatima N. Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis. PLoS One. 2016;1(4):e0152925.
55. Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum. 2008;58(2):359-69.
56. Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, Garcia-Porrua C, Miranda-Filloy JA, Ollier WER, et al. HLA – DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Rheum. 2007;57(1):125-32.
57. Sharma S, Plant D, Bowes J, Macgregor A, Verstappen S, Barton A, et al. HLA-DRB1 haplotypes predict cardiovascular mortality in inflammatory polyarthritis independent of CRP and anti-CCP status. Arthritis Res Ther. 2022;24(1):90.
58. Feld J, Chandran V, Haroon N, Inman R, Gladman D. Axial disease in psoriatic arthritis and ankylosing spondylitis: A critical comparison. Nat Rev Rheumatol. 2018;14(6):363-71.
59. Braun J, Sieper J. Fifty years after the discovery of the association of HLA B27 with ankylosing spondylitis. RMD Open. 2023;9(3):e003102.
60. Bergfeldt L, Möller E. Complete heart block — another HLA B27 associated disease manifestation. Tissue Antigens. 1983;21(5):385-90.
61. Forsblad-D'Elia H, Wallberg H, Klingberg E, Carlsten H, Bergfeldt L. Cardiac conduction system abnormalities in ankylosing spondylitis: A cross-sectional study. BMC Musculoskelet Disord. 2013;14:237.
62. Baniaamam M, Heslinga SC, Konings TC, Handoko ML, Kamp O, van Halm VP, et al. Aortic root diameter is associated with HLA-B27: Identifying the patient with ankylosing spondylitis at risk for aortic valve regurgitation. Rheumatol Int. 2022;42(4):683-8.
63. Yan J, Yang S, Han L, Ba X, Shen P, Lin W, et al. Dyslipidemia in rheumatoid arthritis: The possible mechanisms. Front Immunol. 2023;14:1254753.
64. Charles-Schoeman C, Wang J, Shahbazian A, Wilhalme H, Brook J, Kaeley GS, et al. Power doppler ultrasound signal predicts abnormal HDL function in patients with rheumatoid arthritis. Rheumatol Int. 2023;43(6):1041-53.
65. Rodriguez-Carrio J, Lopez-Mejıas R, Alperi-Lopez M, Lopez P, Ballina-Garcia FJ, Gonzalez-Gay MA, et al. Paraoxonase 1 activity is modulated by the rs662 Polymorphism and IgG anti-high-density lipoprotein antibodies in patients with rheumatoid arthritis potential implications for cardiovascular disease. Arthritis Rheumatol. 2016;68(6):1367-76.
66. Jakubowski H. Proteomic exploration of paraoxonase 1 function in health and disease. Int J Mol Sci. 2023;24(9):7764.
67. Kim JY, Lee EY, Park JK, Song YW, Kim JR, Cho KH. Patients with rheumatoid arthritis show altered lipoprotein profiles with dysfunctional high-density lipoproteins that can exacerbate inflammatory and atherogenic process. PLoS One. 2016;11(10):1-17.
68. Voloshyna I, Modayil S, Littlefield MJ, Belilos E, Belostocki K, Bonetti L, et al. Plasma from rheumatoid arthritis patients promotes pro-atherogenic cholesterol transport gene expression in THP-1 human macrophages. Exp Biol Med. 2013;238(10):1192-7.
69. Paiva-Lopes MJ, Batuca JR, Gouveia S, Alves M, Papoila AL, Alves JD. Antibodies towards high-density lipoprotein components in patients with psoriasis. Arch Dermatol Res. 2020;312(2):93-102.

70. Paiva-Lopes MJ, Delgado Alves J. Psoriasis-associated vascular disease: The role of HDL. J Biomed Sci. 2017;24(1):1-6.
71. Pietrzak A, Chabros P, Grywalska E, Kiciński P, Franciszkiewicz-Pietrzak K, Krasowska D, et al. Serum lipid metabolism in psoriasis and psoriatic arthritis – An update. Arch Med Sci. 2019;15(2):369-75.
72. Profumo E, di Franco M, Buttari B, Masella R, Filesi C, Tosti ME, et al. Biomarkers of subclinical atherosclerosis in patients with autoimmune disorders. Mediators Inflamm. 2012;2012:503942.
73. Liu J, Gao J, Wu Z, Mi L, Li N, Wang Y, et al. Anti-citrullinated protein antibody generation, pathogenesis, clinical application, and prospects. Front Med. 2022;8:802934.
74. Geraldino-Pardilla L, Giles JT, Sokolove J, Zartoshti A, Robinson WH, Budoff M, et al. Association of anti–citrullinated peptide antibodies with coronary artery calcification in rheumatoid arthritis. Arthritis Care Res. 2017;69(8):1276-81.
75. Geraldino-Pardilla L, Russo C, Sokolove J, Robinson WH, Zartoshti A, van Eyk J, et al. Association of anti-citrullinated protein or peptide antibodies with left ventricular structure and function in rheumatoid arthritis. Rheumatology. 2017;56(4):534-40.
76. Xu M, Du R, Xing W, Chen X, Wan J, Wang S, et al. Platelets derived citrullinated proteins and microparticles are potential autoantibodies ACPA targets in RA patients. Front Immunol. 2023;14:1084283.
77. Spinelli FR, Pecani A, Ciciarello F, Colasanti T, di Franco M, Miranda F, et al. Association between antibodies to carbamylated proteins and subclinical atherosclerosis in rheumatoid arthritis patients. BMC Musculoskelet Disord. 2017;18(1):1-9.
78. Koussiouris J, Chandran V. Autoantibodies in psoriatic disease. J Appl Lab Med. 2022;7(1):281-93.
79. Emmungil H, İlgen U, Direskeneli RH. Autoimmunity in psoriatic arthritis: Pathophysiological and clinical aspects. Turk J Med Sci. 2021;51(4):1601-14.
80. Chimenti MS, Triggianese P, Nuccetelli M, Terracciano C, Crisanti A, Guarino MD, et al. Auto-reactions, autoimmunity and psoriatic arthritis. Autoimmun Rev. 2015;14(12):1142-6.
81. Fuentes-Duculan J, Bonifacio KM, Kunjravia N, Jason E, Cueto I, Li X, et al. Autoantigens ADAMTSL5 and LL-37 are significantly upregulated in active psoriasis and associated with dendritic cells and macrophages. Exp Dermatol. 2019;26(11):1075-82.
82. Frasca L, Palazzo R, Chimenti MS, Alivernini S, Tolusso B, Bui L, et al. Anti-LL37 antibodies are present in psoriatic arthritis (PsA) patients: New biomarkers in PsA. Front Immunol. 2018;9(1936):1-16.
83. Zhu J, Shi XF, Chu CQ. Autoantibodies in psoriatic arthritis: Are they of pathogenic relevance? Chin Med J (Engl). 2020;133(24):2899-901.
84. Yuan Y, Qiu J, Lin ZT, Li W, Haley C, Mui UN, et al. Identification of novel autoantibodies associated with psoriatic arthritis. Arthritis Rheumatol. 2019;71(6):941-51.
85. Baker JF, Billig E, Michaud K, Ibrahim S, Caplan L, Cannon GW, et al. Weight loss, the obesity paradox, and the risk of death in rheumatoid arthritis. Arthritis Rheumatol. 2015;67(7):1711-7.
86. Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(10):1471-9.
87. England BR, Baker JF, Sayles H, Michaud K, Caplan L, Davis LA, et al. Body mass index, weight loss, and cause-specific mortality in rheumatoid arthritis. Arthritis Care Res. 2018;70(1):11-8.
88. Malla J, Zahra A, Venugopal S, Selvamani TY, Shoukrie SI, Selvaraj R, et al. What role do inflammatory cytokines play in cancer cachexia? Cureus. 2022;14(7):e26798.
89. Lemmey AB. Rheumatoid cachexia: The undiagnosed, untreated key to restoring physical function in rheumatoid arthritis patients? Rheumatology. 2016;55(7):1149-50.
90. Efthymiou E, Grammatikopoulou MG, Gkiouras K, Efthymiou G, Zafiriou E, Goulis DG, et al. Time to deal with rheumatoid cachexia: Prevalence, diagnostic criteria, treatment effects and evidence for management. Mediterr J Rheumatol. 2022;33(3):271-90.
91. Kumthekar A, Ogdie A. Obesity and psoriatic arthritis: A narrative review. Rheumatol Ther. 2020;7(3):447-56.
92. Klingberg E, Bilberg A, Björkman S, Hedberg M, Jacobsson L, Forsblad-D'Elia H, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: An interventional study. Arthritis Res Ther. 2019;21(1):17.
93. Klingberg E, Björkman S, Eliasson B, Larsson I, Bilberg A. Weight loss is associated with sustained improvement of disease activity and cardiovascular risk factors in patients with psoriatic arthritis and obesity: A prospective intervention study with two years of follow-up. Arthritis Res Ther. 2020;22(1):254.
94. di Minno MND, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor α blockers. Ann Rheum Dis. 2014;73(6):1157-62.
95. Coates LC, Merola JF, Grieb SM, Mease PJ, Duffin KC. Methotrexate in psoriasis and psoriatic arthritis. J Rheumatol. 2020;96:31-5.
96. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology. 2021;59(Suppl 1):I37-46.
97. Assign-Score.com [Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network; 2014 [updated March 2014; cited 2024 Sep 8]. Available from: https://www.assign-score.com/estimate-the-risk/.
98. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: Prospective cohort study. BMJ. 2017;357:j2099.
99. Ogata A, Kumanogoh A, Tanaka T. Pathological role of interleukin-6 in psoriatic arthritis. Arthritis. 2012;2012(1):713618.