

Adhesion Molecules in Psoriatic Arthritis: Linking Inflammation, Endothelial Dysfunction, and Cardiovascular Disease

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Abstract

Psoriatic arthritis (PsA) is associated with increased cardiovascular morbidity and mortality that cannot be fully explained by traditional cardiovascular risk factors. Adhesion molecules, particularly intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), have emerged as important mediators linking chronic

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inflammation with endothelial dysfunction and atherosclerosis. To review current evidence regarding the role of adhesion molecules in endothelial dysfunction and cardiovascular disease in patients with psoriatic arthritis. A narrative literature review was conducted using PubMed, Scopus, and Web of Science databases. Studies evaluating ICAM-1, VCAM-1, endothelial dysfunction, subclinical atherosclerosis, and cardiovascular risk in PsA were identified and analyzed. Available evidence demonstrates that elevated adhesion molecule levels are associated with endothelial dysfunction, increased carotid intima-media thickness, inflammatory activity, and cardiovascular risk in PsA. Histopathological studies further support their involvement in synovial and vascular inflammation. Recent data suggest that VCAM-1 may be more closely associated with inflammatory burden and endothelial activation than ICAM-1. Emerging evidence also indicates that modern biologic and targeted therapies may influence adhesion molecule expression. Adhesion molecules play an important role in the pathogenesis of endothelial dysfunction and atherosclerosis in PsA. VCAM-1 appears to be a promising candidate biomarker of endothelial activation, although its prognostic value remains to be established.

Keywords: psoriatic arthritis, adhesion molecules, ICAM-1, VCAM-1, endothelial dysfunction, atherosclerosis.

1. Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease associated with an increased risk of cardiovascular morbidity and mortality. Numerous studies have demonstrated that patients with PsA exhibit accelerated atherosclerosis and increased prevalence of subclinical vascular damage compared with the general population [1–3]. Although traditional cardiovascular risk factors contribute substantially to this increased burden, chronic systemic inflammation is now recognized as an independent driver of endothelial dysfunction and atherogenesis.

Endothelial dysfunction represents one of the earliest stages of vascular injury and precedes the development of clinically overt atherosclerosis. Persistent inflammatory activation promotes leukocyte recruitment, oxidative stress, lipid oxidation, and vascular remodeling, creating a proatherogenic environment. Among the molecular mediators involved in these processes, adhesion molecules have emerged as key regulators of endothelial activation and leukocyte trafficking. In particular, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1

(VCAM-1) have attracted considerable attention because of their central role in linking chronic inflammation with cardiovascular damage [4,5].

The aim of this review is to summarize current evidence regarding the role of adhesion molecules in endothelial dysfunction, atherosclerosis, and cardiovascular risk in patients with psoriatic arthritis.

2. Materials and Methods

A narrative literature review was conducted to summarize current evidence regarding the role of adhesion molecules in endothelial dysfunction, atherosclerosis, and cardiovascular disease in patients with psoriatic arthritis. Relevant publications were identified through searches of PubMed, Scopus, and Web of Science from database inception to June 2026. Search terms included combinations of “psoriatic arthritis”, “adhesion molecules”, “ICAM-1”, “VCAM-1”, “endothelial dysfunction”, “atherosclerosis”, “cardiovascular disease”, “subclinical atherosclerosis”, and “vascular inflammation”.

Original studies involving patients with PsA were prioritized, particularly those evaluating circulating or tissue expression of adhesion molecules in relation to disease activity, endothelial dysfunction, vascular imaging, cardiovascular risk, or treatment exposure. Systematic reviews, meta-analyses, experimental studies, and studies conducted in other inflammatory diseases or the general cardiovascular population were included when relevant to the biological or pathophysiological context. Non-English publications, conference abstracts with insufficient methodological information, and studies without relevance to adhesion molecules or vascular involvement were excluded. Reference lists of selected articles were additionally screened to identify relevant publications.

Given the narrative design and the limited and heterogeneous PsA-specific literature, no formal risk-of-bias assessment or quantitative evidence synthesis was performed. Evidence derived directly from PsA populations was distinguished from mechanistic or contextual evidence extrapolated from other inflammatory diseases and the general cardiovascular literature.

3. Adhesion Molecules and Endothelial Dysfunction

The presence of accelerated atherosclerosis has been well documented in several chronic inflammatory rheumatic diseases, including rheumatoid

arthritis and systemic lupus erythematosus [6–10]. One of the earliest pathophysiological events associated with atherosclerotic development is endothelial dysfunction [11–13], which represents the response of the vascular endothelium to traditional cardiovascular risk factors and precedes clinically apparent atherosclerosis (Figure 1).

Endothelial dysfunction contributes to atherosclerotic lesion formation through multiple mechanisms, including increased expression of adhesion molecules, secretion of chemokines, enhanced leukocyte adhesion to the vascular wall, increased endothelial permeability, oxidation of low-density lipoproteins, platelet activation, production of pro-inflammatory cytokines, and migration and proliferation of vascular smooth muscle cells [14]. A central component of this process is the impairment of nitric oxide (NO) production and bioavailability, leading to the loss of endothelium-dependent vasodilation and the development of a proatherogenic vascular environment [15,16].

Inflammatory cytokines further amplify endothelial injury, with tumor necrosis factor- α (TNF- α) playing a particularly important role through activation of signaling pathways involved in vascular inflammation, oxidative stress, and atherogenesis [17–19].

In addition to disturbances in endothelial vasoactive mediators, several molecular mechanisms may contribute to endothelial injury and atherogenesis during chronic inflammation. One such mechanism involves cholesterol 27-hydroxylase, an enzyme expressed by endothelial cells and macrophages that participates in cholesterol homeostasis by converting cholesterol into the more soluble metabolite 27-hydroxycholesterol. Experimental studies have demonstrated that circulating immune complexes containing C1q suppress the expression of cholesterol 27-hydroxylase, thereby potentially impairing cholesterol efflux from the arterial wall [20]. Reduced enzyme activity may favor lipid retention within vascular tissues and contribute to the development of a proatherogenic environment.

Interferon-gamma (IFN- γ) exerts a similar inhibitory effect on cholesterol 27-hydroxylase, further linking immune activation with disturbances in vascular lipid metabolism [20]. At the same time, pro-inflammatory cytokines including interleukin-1 (IL-1), TNF- α , and IFN- γ induce profound changes in endothelial cell function [21]. These mediators suppress the expression of endothelial anticoagulant receptors such as the endothelial protein C receptor (EPCR) while simultaneously promoting the expression

of adhesion molecules and chemokines, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) [22]. The resulting endothelial phenotype is characterized by enhanced leukocyte recruitment, increased vascular inflammation, and a greater propensity for atherosclerotic lesion development.

Atherosclerosis is currently regarded as a chronic inflammatory disease characterized by a complex cascade of cellular and molecular events. One of the earliest stages of atherogenesis involves increased endothelial permeability and disruption of endothelial integrity, facilitating the migration of inflammatory cells from the circulation into the subendothelial space [23,24]. This process depends on activation of cell adhesion molecules expressed on both endothelial cells and circulating leukocytes [25,26].

Selectins (P-selectin, E-selectin, and L-selectin) initiate leukocyte rolling and transient adhesion to activated endothelium [27–29]. These early interactions are subsequently stabilized by ICAM-1 and VCAM-1, together with leukocyte integrins, resulting in firm adhesion to the endothelial surface. Platelet endothelial cell adhesion molecule-1 (PECAM-1) facilitates transendothelial migration of leukocytes into the vascular intima [30]. ICAM-1 and VCAM-1 exist in both membrane-bound and soluble forms. Whereas membrane-bound molecules mediate leukocyte adhesion and transendothelial migration, circulating sICAM-1 and sVCAM-1 are commonly assessed as indirect markers of endothelial and inflammatory activation.

Oxidized low-density lipoproteins (OxLDL) further amplify these mechanisms by stimulating endothelial expression of adhesion molecules and chemokines such as MCP-1 [31]. This promotes monocyte recruitment into the arterial wall, where they differentiate into macrophages and internalize OxLDL, forming foam cells that represent a hallmark of early atherosclerotic lesions [32].

Activated foam cells release cytokines, chemokines, growth factors, and matrix metalloproteinases, promoting vascular inflammation, extracellular matrix remodeling, and smooth muscle cell proliferation. Additional recruitment of monocytes, T lymphocytes, and B lymphocytes further amplifies local inflammation through enhanced production of TNF- α and IL-1 β , contributing to plaque progression and instability [33]. Mast cells located within the vascular adventitia also participate in these processes

through secretion of IL-8 and MCP-1, facilitating recruitment of additional inflammatory cells [34].

Beyond their pathogenic role, adhesion molecules possess important diagnostic and prognostic value. Increased expression of VCAM-1, ICAM-1, and L-selectin has been identified within atherosclerotic plaques, while elevated circulating concentrations of soluble VCAM-1 and soluble ICAM-1 have been associated with increased cardiovascular risk [35–38]. Elevated sICAM-1 levels have been reported in asymptomatic individuals, whereas sVCAM-1 appears to be more closely associated with clinically manifest coronary artery disease [39,40].

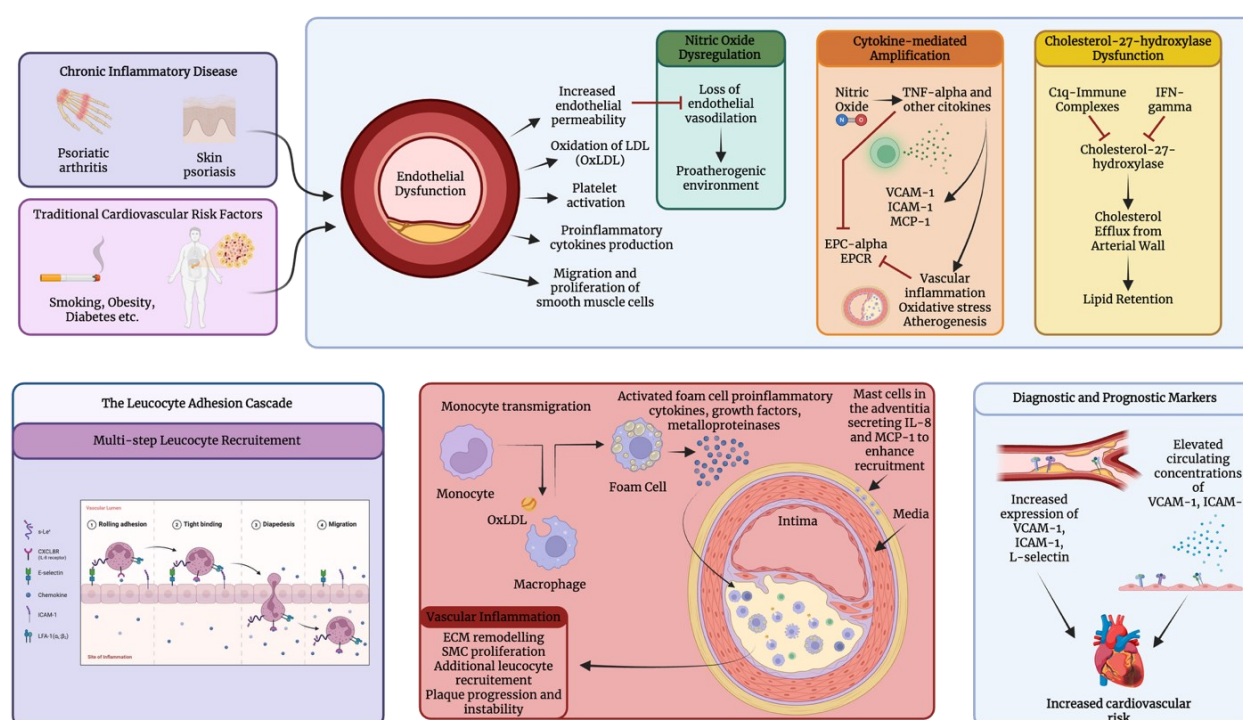


Figure 1. Integrated pathophysiological pathways linking chronic inflammation to endothelial dysfunction, leukocyte recruitment, and atherogenesis. This diagram integrates the cellular and molecular pathways linking chronic inflammation and traditional cardiovascular risk factors to endothelial dysfunction. Pro-inflammatory cytokines trigger a cascade involving altered nitric oxide bioavailability, reduced cholesterol efflux, and the multi-step recruitment of leukocytes via adhesion molecules, ultimately leading to foam cell formation, plaque progression, and instability. Abbreviations: C1q, complement component 1q; ECM, extracellular matrix; EPCR, endothelial protein C receptor; ICAM-1, intercellular adhesion molecule-1; IFN-gamma, interferon-gamma; IL-8, interleukin-8; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; OxLDL, oxidized low-density lipoprotein; SMC, smooth muscle cell; TNF-alpha, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1. Created in BioRender. Dimitrov, S. [2026] <https://BioRender.com/nb17sty>.

4. Adhesion Molecules, Lipid Abnormalities and Cardiovascular Risk

In addition to promoting leukocyte recruitment, oxidized low-density lipoproteins (OxLDL) establish an important mechanistic link between inflammation, endothelial activation, and atherosclerosis. OxLDL activates endothelial cells through nuclear factor-kappa B (NF- κ B)-dependent signaling pathways, resulting in increased expression of adhesion molecules, including VCAM-1 and ICAM-1, as well as pro-inflammatory chemokines such as monocyte chemoattractant protein-1 (MCP-1). These changes facilitate monocyte adhesion to the vascular endothelium and subsequent migration into the arterial wall, thereby accelerating the development of atherosclerotic lesions [25,31,41].

Beyond the effects of modified LDL particles, chronic inflammation may profoundly alter the structure and function of high-density lipoprotein cholesterol (HDL-C). Under physiological conditions, HDL exerts anti-inflammatory, antioxidant, antithrombotic, and endothelial-protective effects through promotion of reverse cholesterol transport and inhibition of LDL oxidation. However, persistent inflammatory activity can transform HDL into a dysfunctional particle with reduced atheroprotective capacity. Dysfunctional HDL exhibits impaired cholesterol efflux capacity, diminished antioxidant activity, and a reduced ability to suppress endothelial activation and adhesion molecule expression, thereby contributing to sustained vascular inflammation and endothelial dysfunction [42,43].

Inflammatory cytokines that play a central role in psoriatic arthritis, particularly TNF- α , IL-6, and IL-17, further influence lipid metabolism and lipoprotein composition. Consequently, patients may develop a proatherogenic vascular phenotype despite apparently normal conventional lipid parameters. This phenomenon, often referred to as the “lipid paradox” of chronic inflammatory diseases, suggests that qualitative changes in lipoprotein function may be more important than absolute cholesterol concentrations alone. In parallel, ongoing endothelial activation promotes persistent expression of VCAM-1 and ICAM-1, creating a self-perpetuating cycle linking inflammation, dyslipidemia, and atherosclerosis [41,44,45].

Collectively, these findings indicate that adhesion molecules occupy a central position at the intersection of inflammatory and metabolic pathways involved in atherogenesis. Through their interactions with modified lipoproteins, activated endothelial cells, and circulating

leukocytes, ICAM-1 and VCAM-1 may represent important mechanistic mediators linking chronic inflammation with accelerated cardiovascular disease in patients with psoriatic arthritis.

5. VCAM-1 versus ICAM-1: Are all adhesion molecules equally informative?

Although most studies have evaluated ICAM-1 and VCAM-1 simultaneously, accumulating evidence suggests that these molecules may not provide equivalent information regarding cardiovascular risk in PsA. Elevated concentrations of both adhesion molecules have been reported in association with endothelial dysfunction and subclinical atherosclerosis [46–48]. However, VCAM-1 appears to demonstrate a more consistent relationship with inflammatory activity and vascular involvement. In the study by Gündüz et al., both ICAM-1 and VCAM-1 correlated with CIMT, whereas recent data from Markov et al. showed that only VCAM-1 remained associated with CRP, ESR, disease activity, and treatment exposure [48,49]. Similar observations have been reported in cardiovascular populations, where circulating VCAM-1 concentrations correlate more closely with atherosclerotic burden than ICAM-1 [35,36]. These findings suggest that VCAM-1 may more closely reflect persistent endothelial activation and inflammatory activity in PsA, although its independent prognostic value remains to be established.

6. Heterogeneity of Published Findings

Despite the overall consistency of evidence linking adhesion molecules with cardiovascular involvement in PsA, considerable heterogeneity exists across studies. Earlier investigations consistently reported significantly elevated ICAM-1 and VCAM-1 concentrations compared with healthy controls [46–48]. In contrast, Markov et al. observed comparable adhesion molecule concentrations among PsA patients, ankylosing spondylitis patients, and controls despite significant associations between VCAM-1 and inflammatory activity [49]. Several factors may account for these discrepancies, including differences in disease duration, sample size, cardiovascular risk profile, laboratory methodology, and treatment exposure. The increasing use of biologic and targeted synthetic therapies in contemporary cohorts may attenuate endothelial activation and partially normalize circulating adhesion molecule levels, thereby reducing differences between patients and healthy individuals.

Additional methodological factors may also contribute to the observed variability. Studies have employed different laboratory assays, evaluated heterogeneous patient populations, and used varying definitions of disease activity and cardiovascular risk. Moreover, disease duration differed substantially across cohorts, ranging from recent-onset PsA to long-standing disease. Such differences may influence circulating adhesion molecule concentrations and complicate direct comparisons between studies. Therefore, the absence of significant between-group differences should not necessarily be interpreted as evidence against endothelial involvement but rather as a reflection of the complex interaction between inflammation, treatment, and vascular biology.

7. Therapeutic Implications

The association between adhesion molecule concentrations and treatment exposure raises the possibility that these biomarkers may reflect changes related to inflammatory control. Markov et al. reported higher VCAM-1 concentrations among biologic-naïve patients, whereas lower levels were observed in patients receiving biologic therapies and particularly in those treated with JAK inhibitors [49]. However, the cross-sectional design does not allow these differences to be attributed directly to treatment effects. Longitudinal studies are needed to determine whether changes in ICAM-1 and VCAM-1 parallel treatment response and whether they are accompanied by measurable improvement in vascular function or cardiovascular outcomes.

8. Limitations and Future Directions

Several limitations of the current evidence should be acknowledged. Direct evidence on adhesion molecules in PsA remains limited, and much of the current understanding of their role in vascular inflammation is derived from studies in other inflammatory diseases and the broader atherosclerosis literature. These data provide a useful mechanistic framework but should be interpreted separately from findings obtained directly in PsA populations. Most available studies are cross-sectional and involve relatively small patient populations, limiting the ability to establish causal relationships between adhesion molecules and cardiovascular outcomes. Furthermore, the majority of investigations rely on surrogate markers such as CIMT, FMD, or circulating biomarker concentrations rather than hard cardiovascular endpoints. Future prospective longitudinal studies are required to determine whether ICAM-1 and VCAM-1 independently predict cardiovascular events and whether therapeutic

modulation of endothelial activation translates into meaningful cardiovascular benefit.

The available literature supports a model in which adhesion molecules occupy a central position at the interface between chronic inflammation, endothelial dysfunction, and atherosclerosis. While significant progress has been made in understanding their biological and clinical relevance, further studies are required to clarify their prognostic value and potential role as therapeutic targets in psoriatic arthritis.

9. Conclusions

Adhesion molecules represent an important mechanistic link between chronic inflammation, endothelial dysfunction, and accelerated atherosclerosis in psoriatic arthritis. Experimental and clinical studies consistently demonstrate that ICAM-1 and VCAM-1 participate in leukocyte recruitment, vascular inflammation, and early atherogenic processes. Available evidence further suggests that elevated adhesion molecule levels are associated with markers of endothelial dysfunction and subclinical vascular involvement in patients with PsA.

Among the investigated biomarkers, VCAM-1 appears to show a more consistent relationship with inflammatory activity and vascular abnormalities, suggesting that it may better reflect ongoing endothelial activation. Although recent therapeutic advances may influence adhesion molecule expression, their precise role in cardiovascular risk stratification remains incompletely defined. Further longitudinal studies are required to determine whether adhesion molecules can identify patients at increased cardiovascular risk and whether changes in their circulating concentrations translate into improved vascular outcomes.

Declarations

Author Contributions

M.M.: Conceptualization, literature search, data interpretation, writing – original draft preparation. S.B.: Literature review, data interpretation, writing – review and editing. S.D.: Visualization, figure preparation, writing – review and editing. T.G. & M.D.: Supervision, critical revision of the manuscript, writing – review and editing. All authors have read and approved the final version of the manuscript. Generative AI (Claude, Opus 5, Anthropic Inc.) was used as a language-editing and formatting assistant

during manuscript preparation. It helped refine English phrasing, improve clarity, and align the structure with Rheumatology (Bulgaria) formatting requirements. No AI tools were used for data generation, analysis, interpretation, or reference fabrication. All scientific content, interpretation, and conclusions are entirely the authors' own. The authors take full responsibility for the accuracy and integrity of the submitted work.

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Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Адхезионни молекули при псориатичен артрит: връзка между възпалението, ендотелната дисфункция и сърдечно-съдовите заболявания

Резюме

Псориатичният артрит (PsA) е свързан с повишена сърдечно-съдова заболеваемост и смъртност, които не могат да бъдат напълно обяснени с традиционните сърдечно-съдови рискови фактори. Адхезионните молекули, особено междуклетъчната адхезионна молекула-1 (ICAM-1) и съдовата клетъчна адхезионна молекула-1 (VCAM-1), се утвърждават като важни медиатори, свързващи хроничното възпаление с ендотелната дисфункция и атеросклерозата. Да се направи обзор на наличните доказателства относно ролята на адхезионните молекули в развитието на ендотелна дисфункция и сърдечно-съдови заболявания при пациенти с псориатичен артрит. Проведен е наративен литературен обзор чрез търсене в базите данни PubMed, Scopus и Web of Science. Анализирани са проучвания, оценяващи ICAM-1, VCAM-1, ендотелната дисфункция, субклиничната атеросклероза и сърдечно-съдовия риск при пациенти с PsA. Наличните данни показват, че повишените нива на адхезионните молекули са свързани с ендотелна дисфункция, увеличена дебелина на комплекса интима-медия на каротидните артерии, по-висока възпалителна активност и повишен сърдечно-съдов риск при PsA. Хистопатологичните изследвания допълнително потвърждават тяхното участие в синовиалното и съдовото възпаление. Последните данни предполагат, че VCAM-1 е по-тясно свързана с възпалителната активност и ендотелната активация в сравнение с ICAM-1. Натрупват се и доказателства, че съвременните биологични и таргетни терапии могат да повлияят експресията на адхезионните молекули. Адхезионните молекули играят важна роля в патогенезата на ендотелната дисфункция и атеросклерозата при псориатичен артрит. VCAM-1 се очертава като особено обещаващ биомаркер на съдовото възпаление. Необходими са допълнителни проспективни проучвания, за да се изяснят прогностичната и терапевтичната стойност на адхезионните молекули при оценката на сърдечно-съдовия риск.

Ключови думи: псориатичен артрит, адхезионни молекули, ICAM-1, VCAM-1, ендотелна дисфункция, атеросклероза.