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Review Article

Pathophysiology of Atherosclerosis in Psoriatic Arthritis: New Insights into Inflammation and Lipid Metabolism

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Abstract

Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with heightened cardiovascular morbidity, primarily due to accelerated atherosclerosis. Despite increasing evidence linking PsA to endothelial dysfunction, dyslipidemia, and chronic inflammation, cardiovascular risk assessment in PsA remains underdeveloped. This literature review synthesizes current evidence on the shared pathophysiological mechanisms between PsA and atherosclerosis. *Materials and methods*: A systematic search of PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus was conducted to identify studies published between 1990 and 2025. Studies were selected based on relevance to inflammatory pathways, lipid metabolism, and immune-mediated endothelial dysfunction in PsA-related atherosclerosis. *Results*: PsA contributes to atherosclerosis through persistent systemic inflammation, driven by key cytokines such as IL-17, IL-23, TNF-α, and IL-22. These mediators promote endothelial dysfunction, increased leukocyte adhesion, and plaque formation. Altered lipid metabolism in PsA patients, particularly dysfunctional HDL characterized by impaired cholesterol efflux and pro-inflammatory modifications, further exacerbates cardiovascular risk. Additionally, a disrupted Th17/Treg balance perpetuates vascular inflammation and atherogenesis. The interplay between immune dysregulation and metabolic alterations underscores the systemic nature of PsA and its cardiovascular complications. *Conclusion*: PsA-associated systemic inflammation accelerates atherosclerosis through immune-mediated endothelial dysfunction and lipid metabolism disturbances. Current cardiovascular risk assessment models fail to capture this increased burden. Targeting IL-17, IL-23, and TNF-α, alongside restoring HDL functionality, may offer novel therapeutic strategies. Future research should focus on longitudinal studies to better characterize cardiovascular outcomes in PsA patients and guide tailored interventions to mitigate atherosclerotic risk.

Keywords

Psoriatic Arthritis, Atherosclerosis, Cardiovascular Risk, Endothelial Dysfunction

1. Introduction

Psoriatic arthritis (PsA) is a chronic, immuno-inflammatory, seronegative arthritis associated with psoriasis. It affects approximately 0.5% of the general population and 25% of psoriasis patients, making it a significant disease [1]. PsA is linked to various comorbidities, with cardiovascular disease (CVD) being the leading cause of death. Studies show an

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increased risk of coronary artery disease (CAD), heart failure (HF), and cerebrovascular events in PsA patients. However, unlike rheumatoid arthritis (RA), no specific cardiovascular risk assessment modifications exist, despite shared chronic inflammation pathways. Markers of subclinical atherosclerosis, including increased carotid intima-media thickness and impaired flow-mediated dilation, suggest heightened cardiovascular risk. Systemic inflammation via IL-17 and Th1/Th17-mediated cytokines, along with an atherogenic lipid profile (low HDL, high TC, TG, and LDL), may contribute to this risk, underscoring the need for further pathophysiological investigation [2].

PsA pathogenesis involves genetic and environmental factors, such as biomechanical stress, obesity, and dysbiosis, interacting with predispositions like HLA-C*06:02 and HLA-B alleles. Mutations in TNFAIP3 and TNIP1 genes impair NF-kB inhibition, promoting inflammation. Antigen-presenting cells (APCs), including dendritic cells and macrophages, drive cytokine release (IL-1β, IL-6, IL-17A, IL-23, TNF-α), activating T lymphocytes, furthermore Th17 cells, stimulated by IL-6, IL-23, and TGF-β, secrete IL-17, IL-22, IL-23, and IL-21 - key mediators of systemic inflammation and its cardiovascular consequences [3-5].

As chronic inflammation is central to atherosclerosis, PsA-associated immune dysregulation likely accelerates cardiovascular pathology. This review aims to explore the pathophysiological links between PsA inflammation and atherosclerosis, identifying potential molecular targets and gaps in knowledge to inform future research and therapeutic strategies.

2. Materials and Methods

This review was conducted following rigorous standards to ensure a comprehensive and unbiased overview of existing literature regarding the pathophysiological mechanisms linking PsA with atherosclerosis.

2.1. Search Strategy and Selection Criteria

We performed a systematic literature search in major electronic databases, including PubMed, MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus, using a combination of MeSH terms and keywords related to "psoriatic arthritis", "psoriasis", "atherosclerosis", "cardiovascular disease", "inflammation", "cytokines", "lipid metabolism", and "immune mechanisms". The search covered literature published from January 1990 to January 2025, restricted to studies published in English. Relevant cross-references and citations from selected articles were also reviewed to ensure comprehensiveness.

2.2. Inclusion and Exclusion Criteria

We included peer-reviewed original research articles, reviews, meta-analyses, and systematic reviews discussing pathophysiological aspects of cardiovascular involvement, specifically atherosclerosis, in patients with PsA or psoriasis. Emphasis was placed on studies exploring cytokine-mediated pathways, endothelial dysfunction, alterations in lipid metabolism, and immunological factors associated with atherogenesis in the context of PsA.

We excluded case reports, conference abstracts, editorials, commentaries, letters, and articles without full-text availability or lacking sufficient data on mechanisms linking PsA and atherosclerosis. Studies focusing exclusively on clinical outcomes without discussion of underlying pathophysiological mechanisms were also excluded.

2.3. Data Extraction and Synthesis

Two independent reviewers screened titles and abstracts based on the inclusion criteria. Disagreements were resolved by discussion or consultation with a third reviewer. Full-text articles meeting initial criteria were retrieved and evaluated for eligibility. Relevant data on study design, population characteristics, pathophysiological mechanisms, key cytokines, immune cell involvement, genetic factors, lipid profiles, and findings on atherosclerosis markers were systematically extracted into standardized data forms.

Extracted information was qualitatively synthesized to present a coherent overview of current understanding regarding shared inflammatory pathways and metabolic disturbances underpinning atherosclerosis in PsA. Particular attention was paid to identifying cytokines such as IL-17, IL-23, TNF-alpha, IFN-gamma, and IL-22, and their roles in endothelial dysfunction, lipid metabolism alteration, and plaque formation.

2.4. Quality Assessment

Quality and risk of bias in individual studies were assessed using relevant tools tailored to study type, including the Newcastle-Ottawa Scale for observational studies, AMSTAR 2 for systematic reviews/meta-analyses, and relevant guidelines from PRISMA for comprehensive assessment of review articles.

2.5. Analytical Approach

Given the narrative nature of this review, findings were summarized and synthesized qualitatively. Pathophysiological links were structured following a logical progression: initiation of atherosclerosis, progression mechanisms, and complications, further connected to immunopathological insights specific to PsA. Mechanistic insights were complemented with schematic figures adapted from authoritative sources to enhance clarity and understanding of complex interactions.

This structured methodology ensured a comprehensive and critical analysis, providing clinically relevant insights into

potential therapeutic targets and highlighting areas needing further research.

3. Results

3.1. Pathogenetic Basis of Atherosclerosis

Atherosclerosis progresses through three main phases: initiation, progression, and complications. The initiation phase involves endothelial dysfunction, lipoprotein metabolism alterations, and inflammation. The endothelium, which regulates vascular homeostasis, is disrupted by turbulent blood flow, reducing protective shear stress and downregulating anti-atherogenic genes like eNOS while increasing pro-inflammatory mediators such as MCP-1, PDGFs, and VCAM-1. Kruppel-like factor 2 (KLF2) normally supports eNOS expression and limits endothelial activation, but chronic inflammation (TNF-α, IL-1, IL-6) suppresses eNOS, reducing nitric oxide (NO) production, impairing vasodilation, and promoting leukocyte adhesion and platelet activation [6]. Additionally, inflammatory cytokines (IL-17, TNF-α) trigger NF-κB signaling, enhancing adhesion molecule and pro-thrombotic factor expression, further driving atherogenesis [7].

Lipoprotein metabolism alterations, primarily involving LDL cholesterol, contribute to atherosclerosis. Endothelial dysfunction, combined with inflammatory and metabolic factors, facilitates subendothelial retention of atherogenic apolipoprotein B (apoB)-containing lipoproteins (LDL, VLDL, chylomicron remnants) [7]. These accumulate via scavenger receptors (SR-B1, ALK1, LDLR) and undergo oxidation due to reactive oxygen species and lack of antioxidants, leading to defective LDL-LDLR interactions and increased uptake by macrophage scavenger receptors. This promotes macrophage activation and pro-inflammatory cytokine release [7].

Monocyte recruitment follows LDL deposition and endothelial activation. Endothelial cells secrete adhesion molecules (P-selectin, VCAM-1, ICAM-1) and chemokines (MCP-1, CCL3, CCL4), guiding monocytes into the intima, where they differentiate into pro-inflammatory macrophages (M1). These macrophages engulf oxidized LDL via scavenger receptors (CD36, SRA-1, LOX-1), forming foam cells. Reverse cholesterol transport (RCT), typically mediated by HDL and apoA1, is impaired by systemic inflammation, further driving foam cell accumulation. Dendritic cells exposed to oxidized LDL recruit T cells, sustaining local inflammation [8].

During the progression phase, foam cells, macrophages, and smooth muscle cells (SMCs) accumulate lipids and synthesize extracellular matrix components (collagen, elastin, proteoglycans), forming the atherosclerotic plaque [9]. Antigenic plaque components stimulate T and B cell responses in local lymph nodes, with IFN-γ impairing fibrous cap integrity. Matrix metalloproteinases (MMPs) degrade collagen, increasing the risk of plaque rupture. Macrophage apoptosis and cholesterol crystal deposition contribute to the necrotic core [10].

The complication phase begins when plaque rupture exposes subendothelial collagen, triggering thrombosis. The resulting thrombus can enlarge, occluding the vessel, or dislodge, causing distal embolism. Both processes disrupt blood flow, leading to ischemia, organ dysfunction, and potential infarction. These mechanisms will be explored in the context of psoriatic arthritis and psoriatic disease [11].

3.2. Common Inflammatory Pathways in Psoriatic Arthritis and Atherosclerosis

The potential links between psoriatic arthritis and atherosclerosis are complex, involving the impact of systemic inflammation associated with psoriatic arthritis on endothelial activation and alterations in cell-mediated immunity, as well as metabolic disturbances such as dyslipidemia, metabolic syndrome, and insulin resistance, which are commonly observed in psoriatic arthritis patients. Psoriasis is a disease mediated by immune cells from both the innate system, and the adaptive system, that is Th1 cells, Th17 cells, regulatory T cells (Treg), dendritic cells, monocytes/macrophages and neutrophils. All of these cells contribute to the pathogenesis of atherosclerosis.

3.2.1. Triggers of Psoriasis and Immune Response Initiation

It is generally known that psoriasis can be induced by different triggers in genetically susceptible people, such as trauma, injury, infection etc. (Koebner effect) [12] which induces the production of LL37, a peptide derived from cathelicidin (also known as cathelicidin antimicrobial peptide or CAMP) that binds to the extracellular self-DNA from dying keratinocytes converting it in a potential stimulating antigen for plasmacytoid dendritic cells (pDCs) [13]. These activated pDCs produce IFN-alpha/beta, as well as IL-12 and IL-23 which serve as the substrate for further immune cells activation [14, 15].

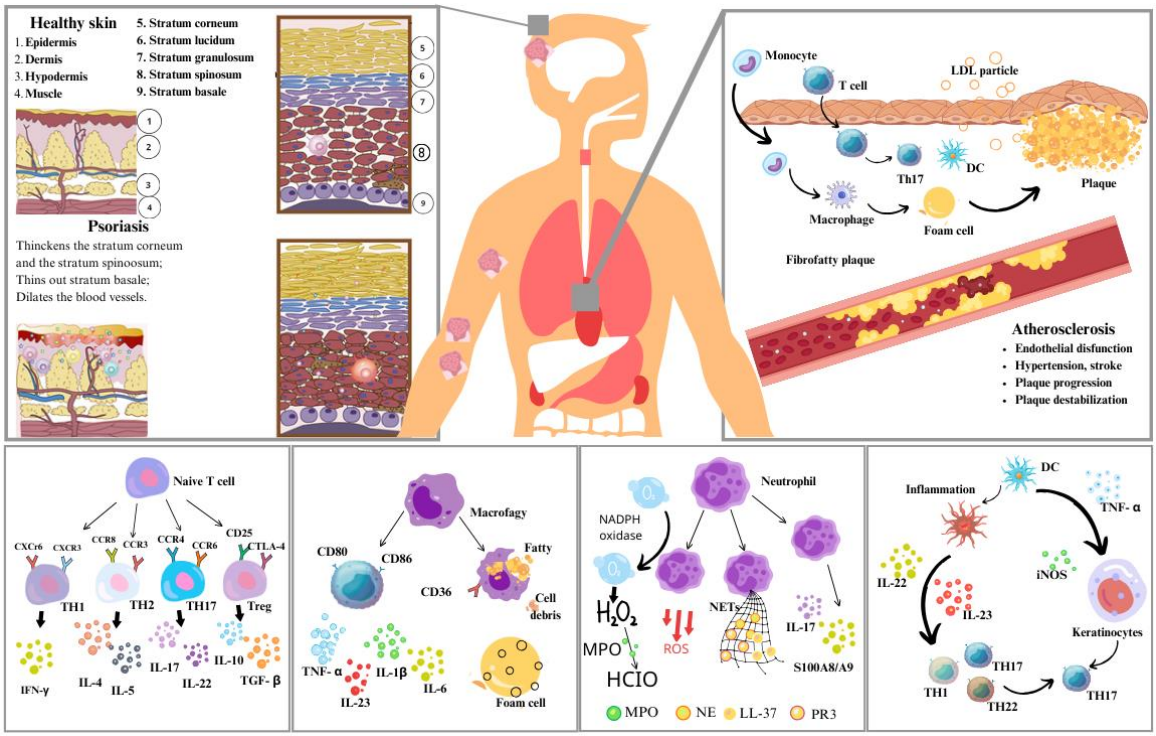

Figure 1. *Pathophysiological links between psoriasis, psoriatic arthritis and atherosclerosis. This schematic representation illustrates the interconnected mechanisms underlying psoriasis, psoriatic arthritis and atherosclerosis, emphasizing shared inflammatory pathways. Healthy skin vs Psoriasis: on the left, a comparison between normal skin and psoriatic lesions is depicted. Psoriasis is characterized by thickening of the stratum corneum and stratum spinosum, basal layer thinning, and increased vascular dilation, leading to epidermal hyperproliferation and chronic inflammation. Inflammatory cell activation: naive T lymphocytes differentiate into Th1, Th2, Th17, and regulatory T cells (Tregs) under the influence of various cytokines. In psoriatic disease, Th17 cells are upregulated, producing IL-17, IL-22, and IL-23, which sustain chronic inflammation. Atherosclerosis progression: the top right panel depicts immune mediated mechanisms leading to endothelial dysfunction and plaque formation in atherosclerosis. Low-density lipoprotein (LDL) oxidation and macrophage activation result in foam cell accumulation, further driven by Th17 cells and dendritic cell (DC)-mediated inflammation. Neutrophil and macrophage contributions: neutrophils, through neutrophil extracellular traps (NETs) and oxidative stress (reactive oxygen species [ROS]), enhance IL-17-driven inflammation. Macrophages, via CD36 and lipid uptake, contribute to foam cell formation, further exacerbating systemic inflammation in both PsA and atherosclerosis. Shared inflammatory pathways: cytokines such as IL-17, TNF-α, and IL-23 drive chronic inflammation in PsA and contribute to endothelial activation, vascular remodeling, and plaque destabilization in atherosclerosis. The lower right panel highlights the role of DCs, keratinocytes, and pro-inflammatory cytokines in maintaining systemic immune dysregulation. This figure underscores the common immunopathological mechanisms linking PsA and cardiovascular disease, supporting the hypothesis of a systemic inflammatory burden contributing to increased cardiovascular risk in psoriatic patients.*

3.2.2. Role of IL-12 in Immune Cell Differentiation

IL-12, an interleukin from the interleukin 12 family, which work as a connection deck between innate and adaptive immune systems by activating CD4+ naive T cells, induces T cell differentiation into Th1 (and other subsets) [16] that produce IFN-gamma, TNF-alpha which in turn activate neutrophils, macrophages and cytotoxic T lymphocytes (CD8+ T cells) that contribute to the inflammatory pathways of the disease [17].

IL-12 works through JAK-STAT pathway, by binding to the IL-12 receptor (IL-12R), formed by IL-12Rbeta1 and IL-12Rbeta2, that further provide binding sites for kinases such as Tyk2 and Jak2 that activate transcription factor proteins such as STAT4 [18].

3.2.3. Role of IFN-Gamma in Atherosclerosis

In atherosclerosis, IFN-gamma promotes expression of MHC class II genes, costimulatory CD40 and CD40L, CD80 and CD86 in macrophages, induces expression of VCAM-1 in SMC and ICAM-1 in macrophages and decreases collagen synthesis of SMC, therefore worsening plaque stability. IFN-gamma is a strong inducer of reactive nitrogen and oxygen radicals in macrophages at local vascular inflammation sites [19]. Moreover, IFN-gamma has been shown to downregulate ABCA1 expression in foam cells, through interference with liver X receptor alpha (LXRalpha), which is one of the main molecules that regulate RCT by inducing ABCA1 expression, therefore IFN-gamma reduces the capacity of cholesterol efflux in the subendothelial space [20]. These mechanisms are supported by the significant reduction in

atherogenesis in studies with IL-12 blockade [21].

3.2.4. Role of IL-23 in Th17 Cell Differentiation

IL-23, another interleukin from the interleukin 12 family, commonly found along with IL-23 receptor expressing cells such as gamma-delta T cells, and Th17 cells in carotid and aortic atherosclerotic plaques [22-24], as well as in serum of psoriatic arthritis patients [22], activates the differentiation of naive CD4 T cells into Th17 cells, which are the main producers of IL-17 and IL-17F and also synthesize IL-6 and TNF-alpha [25]. This differentiation occurs via interaction of IL-23 with a receptor consisting of IL-12R-beta 1 subunit and IL-23R subunit, which activates the STAT3, that in turn bind to promoters of Th17 specific genes such as IL-17a, IL21, IL17F and also retinoic acid orphan receptor C2 (ROR gamma-t), therefore regulating key Th17 differentiation stages [26, 27].

Additionally, there have been multiple types of T cells secreting IL-17 in psoriasis patients, such as CD8+ T cells (cytotoxic T cells), which among the TNF-alpha and IFN-gamma as the main cytokines secreted, they also produce IL-17, IL-21 and IL-22 [28]. The importance of IL-23 on differentiation of naive CD4+ cells into IL-17 producing cells is proven in studies of cellular cultures, that indicate increased IL-17, IL-17F and IL-6 RNA levels, among with reduced IFN-gamma RNA upon IL-23 driven cultures, as opposed to IL-12 for example [29].

3.2.5. Role of Th17 Cells in Psoriatic Arthritis

Numerous studies point to Th17 as the main immunologic driving force in psoriasis [30-32]. The differentiation of Th17 requires IL-23 as described above for maintenance of cytokine secretion, but a stronger induction signal is from IL-6 and TGF beta [30]. Psoriatic arthritis provides a perfect environment with the conditions required for Th17 proliferation and activation, with increased serum concentrations of TGF beta mainly from macrophages, dendritic cells and natural killer (NK) cells from synovial tissue inflammation and skin plaques, reaching serum levels higher than other autoimmune diseases like rheumatoid arthritis, osteoarthritis or ankylosing spondylitis [33]. IL-6, although probably not with a critical role in PsA if compared to RA for example, has proved to have consistently increased serum levels in PsA patients [34], arising from other activated immune cells, act synergically with TGF beta for inducing Th17 differentiation. It is generally believed that IL-6 and TGF-beta lead to upregulation of IL23R expression in Th17, therefore providing a clutch for further IL-23 signaling [35]. Th17 effector cytokines with function in psoriatic arthritis as well as atherosclerosis are IL-17 family, IL-22 and IL-21 [36].

3.2.6. Role of IL-17A in Psoriasis and Atherosclerosis

IL-17A is an interleukin from the IL-17 family that shares similar genomic sequencing with IL-17B, IL-17C, IL-17D, IL-17E (or IL-25) and IL-17F. The shared features include the classic cystine knot structural motif [37], which represents a ring formed by two disulfide bonds, connected to the backbone structure with a third disulfide bond, which allows for an efficient and stable structure [38]. These interleukins act on a specific family of receptors, named the IL-17R family, formed by five different homologous subunits: IL-17RA to IL-17RE, with each having specific bonding strength with the interleukins, that is for example IL-17A and IL-17F bind to an IL-17R formed by IL-17RA and IL-17RC subunits [39]. An important feature of the IL-17R, which makes it unique in the receptor world, is the presence of a protein sequence in the cytoplasmic region of the receptor, named SEFIR (similar expression of fibroblast growth factor genes and IL-17Rs) [40] which binds to a cytoplasmic protein named Act1 (also containing SEFIR), that further docks to TNF receptor associated factors (TRAFs) allowing nuclear translocation of NFkappa-beta and the activation of its targeted genes [41]. Therefore it is to be concluded that IL-17A acts synergistically with TNF, helping to stabilize mRNA of the TNF activated genes, leading to amplification of TNF effects.

IL-17A contributes to psoriasis disease pathogenesis in several different ways: first of all, it acts on keratinocytes via IL-17RA inducing expression of regenerating islet-derived protein 3-alpha (REG3A), which binds subsequently to exostosin-like 3 (EXTL3) inhibiting differentiation genes such as keratin-10, filaggrin, loricrin etc, while also stimulating hyperproliferation [42]. Furthermore, IL-17A stimulates the inflammatory system by increasing proinflammatory cytokines/chemokines expression, as well as promoting antimicrobial peptide expression such as beta-defensin 2 [43], that can potentially bind to extracellular DNA, and therefore serve as antigen for APCs. The cytokines and chemokines induced by IL-17A are: IL-8, that is a strong neutrophil chemoattractant, granulocyte-colony stimulating factor (G-CSF) which stimulates proliferation and overall function of neutrophils, chemokine C-C motif ligand 20 (CCL20) which is a strong Th17 cell recruiter, IL-6 and IL-1beta [44]. It is also important to remind the synergy of IL-17A and TNF alpha as described above, that was proven in studies with reverse transcriptase-PCR techniques, identifying hundreds of genes that are upregulated by both IL-17 and TNF-alpha and are the key drivers of inflammation in psoriatic keratinocytes and synoviocytes [45]. This theory is sustained by several studies that have detected increased Th17 cells, and higher IL-17RA expression in synovial fibroblasts from PsA patients, as compared with osteoarthritis patients [46, 47]. These studies have also suggested increased production of IL-6, CXCL-8 and MMP3s in response to IL-17A stimulation.

The role of IL-17 on atherosclerosis has not been completely defined, however there are multiple studies suggesting a pro-atherogenic role. Firstly, there have been multiple reports on the presence of IL-17 molecules, as well as IL-17R expressing cells, such as plaque cells, macrophages, neutro-

phils and T cells in coronary atherosclerotic lesions [48, 49]. Secondly, morphological studies of atherosclerotic prone mice have indicated a 40% reduction in atherosclerotic plaque formation when these mice have been introduced to IL-17R deficient bone marrow, suggesting a pro-atherogenic profile of IL-17 [50]. Furthermore, inhibition of IL-17 via IL-17A antibodies suggested decreased pathogenesis of atherosclerosis at several levels including cell adhesion, infiltration by macrophages in plaque lesions, T cell activation and decreased Ag presentation [51]. The mechanisms by which IL-17 promotes atherosclerosis include multiple stages. On endothelial cells, IL-17A stimulation lead to expression of CXCL8, IL-1beta, ICAM1, VCAM1, E-selectin, MCP-1 and IL-6 [51] suggesting increased chemotaxis and adhesion on activated endothelium for inflammatory circulating cells. The same study has reported similar findings on IL-17A stimulation of macrophages and VSMCs, with the addition of increased secretion of MMPs such as MMP1 and MMP9 [51], suggesting an increased risk of plaque rupture and destabilization. Furthermore, studies [52] reported increased costimulatory molecules such as CD80 and CD43 in IL-17A stimulated dendritic cells. In addition to that, it has been proven that IL-17 in combination with TNF-alpha inhibit CD39/ATPDase expression, which is a strong inhibitor of platelet activation, and also stimulate tissue factor production, leading to a prothrombotic state therefore worsening plaque lesions [53].

3.2.7. Role of IL-22 in Psoriatic Arthritis and Atherosclerosis

IL-22, an interleukin from the IL-10 cytokine family, highly increased in serum of patients with PsA [54], plays an important role in the development of atherosclerosis and cardiovascular disease. Derived from Th1, Th17 and Th22 cells, IL-22 binds to the IL-22 receptor (IL-22R), activating JAK1, and inducing STAT3 phosphorylation [55]. Moreover, IL-22 also works via protein kinase B (Akt), mitogen-activated protein kinase (MAPK), c-Jun-N-terminal kinase (JNK) and others [56]. Some of the positive regulators of IL-22 in atherosclerosis are IL-23 and IL-1beta, which are also increased in psoriatic arthritis patients [57, 58].

In psoriatic arthritis, IL-22 role seems to be important, as increased levels of IL-22 have been reported in psoriatic patients serum and in PsA synovial fluid [59, 60]. Moreover, IL-22 has been proven to act on IL-22Ralpha1 on fibroblast-like synoviocytes (FLS) in PsA, leading to activation and proliferation [61]. IL-22 together with TNF-alpha lead to increased secretion of antimicrobial peptides and chemokines by phosphorylating MAPK specifically p38 in keratinocytes and synovial T cells [62].

In atherosclerosis, IL-22 acts at multifactorial levels, first of all it regulates adhesion molecules such as ICAM-1, VCAM-1 therefore promoting adhesion of monocytes and leukocytes at sites of activated endothelium [63]. Moreover, it stimulates CXC chemokine ligands, CCL2, CCL5, CXCL5 and others through STAT1 and STAT5 pathways [64]. In addition to that, the widely expressed IL22R1 in macrophages, which upon binding with IL-22 activates STAT1, STAT5, MAPK lead to proinflammatory macrophage phenotypes, by triggering inflammatory cascades such as NF-kb, toll-like receptor 4 pathway, and MAPK [65]. Another mechanism through which IL-22 promotes atherosclerosis is by inhibiting ABCG1 expression and therefore impairing macrophage cholesterol efflux, probably through inhibiting LXR [66, 67]. Studies that inhibited STAT1 and STAT5 pathways have reported reduced accumulation of oxLDL and therefore reduced foam cell formation [68, 69], thus supporting the IL-22 effect on lipid metabolism. IL-22 is also thought to act on IL-22R1 in VSMC, leading to VSMC proliferation and migration in atherosclerotic lesions [70] probably through pathways described above.

3.2.8. Treg/Th17 Imbalance in Psoriatic Arthritis

The balance between regulatory T cells (Tregs) and Th17 cells is critical for maintaining immune homeostasis, as Tregs synthesize IL-10 and TGF-beta, with strong anti inflammatory properties [71]. In psoriatic arthritis, this balance is disrupted, contributing to chronic inflammation and disease progression. Treg dysfunction, marked by downregulation of Foxp3, plays a pivotal role in this imbalance, with IL-6 being a key regulatory cytokine. IL-6 inhibits Treg functionality by reducing Foxp3 expression, a process mediated by increased phosphorylation of Stat3. Stat3, a downstream molecule of the IL-6 receptor (IL-6R), binds to a silencing element within the Foxp3 locus, effectively suppressing Treg development [72]. This phenomenon was demonstrated in vitro, where human Treg-mediated suppression of responder T cells was reversed by recombinant human IL-6 (rhIL-6) or IL-6-producing dendritic cells (DCs) [73]. There is demonstrated a positive correlation between the ratio of Th17 cells to Treg cells in serum and psoriatic disease activity scores [74].

3.3. Lipid Metabolism Alteration in Psoriatic Arthritis

3.3.1. HDL Metabolism and Its Alteration in Psoriatic Arthritis

It is generally known that HDL possesses a potent anti-atherogenic and anti-inflammatory function, through its reverse cholesterol transport (RCT) capacity, which includes cholesterol efflux capacity and specific apoprotein modifications, both of which are affected in systemic inflammation. The subtypes of HDL define its function, therefore HDL particles pass through a maturation process: pre-beta-HDL, HDL-3, and HDL-2, with the latter having the most anti-atherosclerotic potential [75]. Furthermore, studies [76] have proved that particularly HDL-2 and HDL-3 particles are decreased in RA patients, therefore indicating that the lack of HDL-2 and HDL-3 might be correlated to atherogenesis in PsA patients. The metabolism of HDL consists first of the

synthesis in the liver of the main structural apolipoprotein, apoA-I, which being fat free allows itself to receive cholesterol from enterocytes, hepatocytes and macrophages (foam cells) through ATP-binding-cassette-transporter-A1 (ABCA1), forming pre-beta HDL, process known as cholesterol efflux. Pre-beta-HDL later on suffers a maturation process through lecithin cholesterol acyltransferase (LCAT), enzyme characterized by being dependent of Apo-AI, which assures esterification of the free cholesterol from the first step, with the additional lipidation by interaction with ATP-binding-cassette-transporter-G1 (ABCG1), resulting in the formation of alpha-HDL (or HDL-3 and HDL-2). In the end, these matured HDL particles transfer their cholesterol to the liver through scavenger-receptor-B1 (SR-B1) or to lipoproteins that contain apo-B, such as VLDL or LDL through cholesteryl-ester transfer protein (CETP) for further hepatic clearance [77].

3.3.2. Impact of Systemic Inflammation on HDL Function

The process through which PsA systemic inflammation might affect HDL metabolism includes the ABCA1 pathway, in which the proatherogenic cytokine IL-1 beta, significantly increased in PsA [78] has proved to inhibit the expression of ABCA1, along with TNF-alpha which suppresses ABCA1 activity, therefore leading to decreased anti-atherogenic HDL maturation [79].

Studies [80] suggest that chronic systemic inflammatory diseases (including PsA) might affect apoA-1 stimulation of LCAT via the excess polymorphonuclear cells' derived myeloperoxidase (MPO), which can modify apoA-1, causing HDL particles to not fully undergo maturation. Other studies [81] reported that TNF-alpha and TGF-beta directly inhibit LCAT activity, therefore suppressing the esterification process. Furthermore, the overall levels of HDL in rheumatoid arthritis decrease, probably because of reduced synthesis of apoA-I, being a negative acute phase reactant (APR) protein, which resembles the most important structural part of HDL. The decreased synthesis of apoA-I is a consequence of increased circulatory levels of TNF-alpha and IL-1beta, which represses apoA-I production and increases the synthesis of serum amyloid A (SAA) which replaces apoA-I in the structure of HDL, thus leading to an increased turnover of HDL particles [82]. In addition to that, RA is characterized by increased levels of phospholipase A2 (sPLA2) [83] which produce hydrolysis of phospholipids in HDL, resulting in flawed cholesterol-efflux capacity and decreased levels of total HDL [84].

3.3.3. Qualitative Changes in HDL Structure and Function in PsA

Besides, chronic inflammation does not only affect quantitative changes of HDL as described above, but induce qualitative alterations as well, such as changes in protein components and structure of the HDL particle, therefore impairing its anti-inflammatory, anti-atherogenic and antioxidant function, and changing its profile into a pro-inflammatory lipoprotein. Some of the most important protein components of anti-atherogenic and anti-inflammatory HDL are apoA-1, apoE, apoC, LCAT, CETP, platelet-activating-factor-acetyl-hydrolase (PAF-AH), paraoxonase1 (PON-1), glutathione phospholipid peroxidase (GPP) etc. [85]. The anti-atherogenic property of HDL is assured by reverse cholesterol transport from peripheral tissues and macrophages to the liver for clearance into the bile, process which is accomplished mainly by: apoA-1, which is the main functional and structural protein of HDL, regulating LCAT activity and providing a framework for binding with different proteins; LCAT, which activates the esterification of cholesterol in HDL; CETP, which participates in the relocation of cholesterol esters from HDL to LDL and VLDL, for further clearance of cholesterol in the liver through bile excretion etc. [86]. The anti-inflammatory property, which also helps in preventing atherosclerosis induced by systemic inflammation through progressive buildup of macrophages and immune cells in the arterial intima, is mainly due to apoA-1 and sphingosine-1-phosphate (S1P) [87, 88]. These compounds from the HDL structure are thought to inhibit the expression of adhesion molecules including vascular-cell-adhesion-molecule-1 (VCAM-1), intercellular-adhesion-molecule-1 (ICAM-1) and E-selectin, through which the monocyte adhere to the deteriorated endothelium [85]. The mechanism for this inhibition process is thought to include the suppression of endothelial sphingosine kinase activity by apoA-1 and S1P. This enzyme is involved in the activation and nuclear translocation of nuclear-factor-kb (NF-kb) by TNF-alpha [88].

3.3.4. Mechanisms Altering HDL Anti-Inflammatory and Antioxidant Properties in PsA

The antioxidant property of HDL is due to enzymes that destroy the lipid hydroperoxides that further oxidize LDL phospholipids and contribute to atherosclerosis. These enzymes are PON-1, PON-3, GPP, PAF-AH which in combination with apoA-1 lead to the transport mechanism that binds and carries away oxidant molecules [89]. Therefore, the increased levels of TNF-alpha, IL-6, IL-1, TGF-beta, caused by chronic inflammation of PsA lead to the alteration of the anti-atherogenic and anti-inflammatory properties of HDL mentioned above, and even transforming its function into a proinflammatory-HDL. Studies have shown that TNF-alpha decreases the production of apoA-1, possibly through the kinase c-jun-N-terminal kinase (JNK) signaling pathway and stimulates the activity of sPLA2, which degrades apoA-1 during the inflammatory acute phase response (APR), therefore leading to decreased cholesterol efflux, and increased deposition of these defectuous HDL molecules in the arterial intima [90].

3.3.5. Alteration of HDL Proteins During Acute Phase Response in PsA

Negative APR proteins from HDL such as apoA-1, are replaced by positive APR proteins, mainly serum-amyloid-A (SAA) [91], clusterin (apoJ) and lipopolysaccharide-binding protein (LBP) probably through the activating effect of IL-6, highly increased in PsA, on the JAK-STAT3 activation pathway in hepatocytes [92]. SAA is known for inhibiting HDL's ability to affect cholesterol efflux and therefore maintaining cholesterol content in the peripheral tissues [93]. Moreover, SAA has the capacity of binding to vascular proteoglycans, and therefore when HDL particles are high in concentration of SAA, the latter might restrain HDL particles in the vascular matrix [94]. Clusterin (apoJ) may wield its effect by decreasing apoA-1 expression and increased de novo lipogenesis in the liver through less known mechanisms, therefore contributing to a weakened cholesterol efflux function of HDL. [95]. LBP is a secretory APR protein, which functions through the binding to CD14 receptors on macrophages, activating certain signal transduction pathways and the production of pro-inflammatory cytokines [96].

3.3.6. Enzyme Alterations Affecting HDL Function in PsA

The level of PAF-AH in PsA patients is decreased [97], thus leading to decreased hydrolysis of platelet-activating-factor (PAF) which is a potent mediator of inflammation by activating neutrophils, increasing vascular permeability etc. [98]. Serum concentrations of LCAT in PsA patients are substantially decreased, probably through the action of TNF-alpha and TGF-beta, and the lack of apoA-1 described above, therefore causing inhibition of HDL maturation and depleted RCT function of HDL [99].

3.3.7. Altered Ceruloplasmin/Transferrin ratio in PsA and Its Implications

Chronic inflammation associated with increased levels of IL-1beta and IL-6 such as PsA, lead to elevated synthesis of ceruloplasmin (Cp) and reduced levels of transferrin (Tf). Increased ratio of Cp to Tf may play a crucial role in atherosclerosis because of increased oxidation of LDL in endothelial cells [100].

4. Discussion

PsA is increasingly recognized as a systemic disease, not merely confined to joint and skin involvement but intricately linked with heightened cardiovascular morbidity and mortality, notably through accelerated atherosclerosis. This comprehensive review elucidates the complex pathophysiological interconnections between PsA and atherosclerosis, emphasizing inflammatory mechanisms and lipid metabolic alterations as key drivers of cardiovascular risk.

Our findings underscore the critical role of systemic inflammation driven by cytokines, predominantly IL-17, IL-23, TNF-α, and IL-22, in promoting endothelial dysfunction, a pivotal early event in atherogenesis. Endothelial dysfunction, marked by decreased nitric oxide (NO) availability and enhanced adhesion molecule expression, was prominently noted in PsA, mediated largely by persistent cytokine-induced activation of nuclear factor-kappa B (NF-κB). These cytokines, particularly IL-17, not only perpetuate synovitis and psoriasis but also synergize with TNF-α to amplify vascular inflammation. Importantly, such cytokine synergy exacerbates endothelial activation, promoting leukocyte adhesion, transmigration, and foam cell formation, hallmark features of atherosclerotic plaque initiation [7, 17].

Additionally, this review emphasizes that the altered lipoprotein metabolism characteristic of PsA further exacerbates atherogenesis. A consistent pattern emerges: systemic inflammation in PsA adversely modifies HDL functionality, transitioning it from an anti-atherogenic to a pro-inflammatory state [22, 30]. Reductions in HDL subtypes (HDL-2, HDL-3) crucial for reverse cholesterol transport (RCT) have been demonstrated, paralleling findings from other chronic inflammatory conditions such as rheumatoid arthritis. Cytokine-mediated downregulation of crucial cholesterol transporters like ABCA1, and modifications in HDL structural proteins via acute phase reactants (e.g., serum amyloid A replacing apoA-I), lead to impaired HDL maturation and functionality [30, 77-79, 85]. This aberrant HDL loses its anti-inflammatory, antioxidative, and cholesterol efflux capacities, thus promoting lipid retention in the arterial intima, central to plaque formation.

Furthermore, the disruption of the Th17/Treg balance in PsA plays a pivotal role in sustaining chronic inflammation and consequently, atherosclerosis. Our analysis highlights the centrality of IL-23 in sustaining Th17-mediated inflammation, a crucial pathway in PsA pathogenesis [25, 26]. Elevated IL-17 and IL-22 levels, closely linked to Th17 activity, have been consistently associated with both disease severity in PsA and enhanced atherosclerotic plaque instability, promoting mechanisms including macrophage activation, endothelial dysfunction, and enhanced vascular smooth muscle cell proliferation. Conversely, the suppressive effects on regulatory T cells (Tregs) mediated by IL-6 further exacerbate the inflammatory milieu, underscoring a fundamental immunological imbalance contributing to cardiovascular risk [34].

Our synthesis of existing literature also identifies significant gaps warranting future research. While the pro-atherogenic roles of IL-17 and IL-23 are well-documented, their precise mechanistic contributions to plaque instability and rupture in PsA remain underexplored. Clinical evidence correlating cytokine levels with cardiovascular outcomes in PsA patients is also scarce, limiting the translation of these insights into targeted therapeutic interventions. Further longitudinal studies elucidating these cytokine-pathway contributions are imperative.

From a clinical perspective, this review reinforces the necessity for routine cardiovascular risk assessment in PsA patients, emphasizing that traditional risk stratification tools inadequately capture the heightened risk conferred by systemic inflammation inherent to PsA. Tailored interventions targeting inflammatory cytokines (IL-17, IL-23, TNF-α) have the potential to mitigate cardiovascular risk, beyond their established efficacy in joint and skin manifestations. Moreover, recognizing the pro-inflammatory transformation of HDL in PsA may guide novel therapeutic strategies focusing on restoring HDL functionality rather than merely elevating HDL levels.

5. Conclusions

This review underscores the critical role of systemic inflammation in psoriatic arthritis (PsA) as a major driver of accelerated atherosclerosis, highlighting cytokines IL-17, IL-23, TNF-α, and IL-22 as key mediators. These cytokines induce endothelial dysfunction, promote leukocyte adhesion, and accelerate foam cell formation, central events in early atherogenesis. Additionally, lipid metabolism disturbances in PsA, particularly the transition of HDL from an anti-inflammatory to a pro-inflammatory state due to cytokine-driven alterations, significantly contribute to cardiovascular risk.

The Th17/Treg imbalance, driven by elevated IL-23 and IL-6, perpetuates chronic inflammation, further enhancing cardiovascular vulnerability in PsA patients. Current cardiovascular risk assessment tools inadequately reflect this heightened risk, highlighting the urgent need for PsA-specific cardiovascular screening and management protocols.

Targeting inflammatory cytokines (IL-17, IL-23, TNF-α) and restoring HDL functionality emerge as promising therapeutic strategies to mitigate cardiovascular morbidity and mortality in PsA. Further research is required to translate these insights into effective clinical interventions, ultimately improving cardiovascular outcomes in PsA patients.

Abbreviations

ABCA1	ATP-Binding Cassette Transporter A1
ABCG1	ATP-Binding Cassette Transporter G1
AMSTAR	A Measurement Tool to Assess Systematic Reviews
APC	Antigen-Presenting Cell
apoA-I	Apolipoprotein A-I
apoB	Apolipoprotein B
apoC	Apolipoprotein C
apoE	Apolipoprotein E
apoJ	Apolipoprotein J (Clusterin)
ATPDase	Adenosine Triphosphate Diphosphohydrolase
CAD	Coronary Artery Disease
CCL20	C-C Motif Chemokine Ligand 20
CD36	Cluster of Differentiation 36
CETP	Cholesteryl Ester Transfer Protein
Cp	Ceruloplasmin
CVD	Cardiovascular Disease
CXCL8	C-X-C Motif Chemokine Ligand 8
DC	Dendritic Cell
eNOS	Endothelial Nitric Oxide Synthase
Foxp3	Forkhead Box P3
GPP	Glutathione Phospholipid Peroxidase
HDL	High-Density Lipoprotein
HF	Heart Failure
HLA	Human Leukocyte Antigen
ICAM-1	Intercellular Adhesion Molecule-1
IFN-γ	Interferon Gamma
IL	Interleukin
JAK	Janus Kinase
JNK	c-Jun N-terminal Kinase
LBP	Lipopolysaccharide Binding Protein
LCAT	Lecithin-Cholesterol Acyltransferase
LDL	Low-Density Lipoprotein
LOX-1	Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1
MAPK	Mitogen-Activated Protein Kinase
MCP-1	Monocyte Chemoattractant Protein-1
MHC	Major Histocompatibility Complex
MMP	Matrix Metalloproteinase
MPO	Myeloperoxidase
NETs	Neutrophil Extracellular Traps
NF-kB	Nuclear Factor Kappa B
NK	Natural Killer
NO	Nitric Oxide
PAF-AH	Platelet-Activating Factor Acetylhydrolase
PDGF	Platelet-Derived Growth Factor
PON-1	Paraoxonase 1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
RCT	Reverse Cholesterol Transport
ROS	Reactive Oxygen Species
S1P	Sphingosine-1-Phosphate
SAA	Serum Amyloid A
SMC	Smooth Muscle Cell
sPLA2	Secretory Phospholipase A2
SRA-1	Scavenger Receptor A-1
STAT	Signal Transducer and Activator of Transcription
TC	Total Cholesterol
Tf	Transferrin
TG	Triglycerides
TGF-β	Transforming Growth Factor Beta
Th	T-helper cell
TNF-α	Tumor Necrosis Factor Alpha
TRAF	TNF Receptor-Associated Factor
VCAM-1	Vascular Cell Adhesion Molecule-1

VSMC Vascular Smooth Muscle Cell

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Conflicts of Interest

The authors declare no conflicts of interest.

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