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REVIEW

Cardiovascular Considerations and Implications for Treatment in Psoriasis: An Updated Review

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Abstract: Psoriasis, a prevalent chronic inflammatory skin disorder affecting 2–3% of the global population, has transcended its dermatological confines, revealing a profound association with cardiovascular diseases (CVD). This comprehensive review explores the intricate interplay between psoriasis and cardiovascular system, delving into genetic links, immune pathways, and adipose tissue dysfunction beyond conventional CVD risk factors. The pathophysiological connections unveil unique signatures, distinct from other inflammatory skin conditions, in particular psoriasis-specific genetic polymorphisms in IL-23 and TNF-α have consistently been linked to CVD. The review navigates the complex landscape of psoriasis treatments, addressing challenges and future directions in particular relevance to CVDs in psoriasis. Therapeutic interventions, including TNF inhibitors (TNFi), present promise in reducing cardiovascular risks, and methotrexate could constitute a favourable choice. Conversely, the relationship between IL-12/23 inhibitors and cardiovascular risk remains uncertain, while recent evidence indicates that Janus kinase inhibitors may not carry CVD risks. Emerging evidence supports the safety and efficacy of IL-17 and IL-23 inhibitors in patients with CVDs, hinting at evolving therapeutic paradigms. Lifestyle modifications, statins, and emerging therapies offer preventive strategies. Dedicated screening guidelines for CVD risk assessment in psoriasis are however lacking. Further, the impact of different disease phenotypes and treatment hierarchies in cardiovascular outcomes remains elusive, demanding ongoing research at the intersection of dermatology, rheumatology, and cardiology. In conclusion, unraveling the intricate connections between psoriasis and CVD provides a foundation for a holistic approach to patient care. Collaboration between specialties, advancements in screening methodologies, and a nuanced understanding of treatment impacts are essential for comprehensive cardiovascular risk management in individuals with psoriasis.

Plain Language Summary: Psoriasis is a skin condition that not only affects the skin but is also linked to issues in the body's fat tissue, which can lead to inflammation and heart problems. The fat tissue in people with psoriasis contains various immune cells, contributing to obesity and insulin resistance. Research has found a strong connection between inflammation in fat tissues and cardiovascular problems in people with psoriasis. Specific substances released by fat tissue, like leptin, resistin, and adiponectin, can impact inflammation and cardiovascular health. Psoriasis patients often show increased levels of these substances.

Treatment for psoriasis may influence cardiovascular health. Some studies suggest that certain medications, like methotrexate or TNF inhibitors, may lower the risk of heart events. However, there are also concerns about potential adverse effects, and further research is needed to fully understand how psoriasis treatments affect cardiovascular outcomes.

To manage the cardiovascular risks associated with psoriasis, regular screening for heart-related issues is recommended. Lifestyle changes, such as a healthy diet, stress management, and smoking cessation, are also essential. Additionally, specific medications, like statins and metformin, may be beneficial in controlling cardiovascular risk factors in people with psoriasis.

Despite advancements in understanding the relationship between psoriasis and cardiovascular health, there are still challenges. Research is ongoing to develop better screening guidelines and treatment strategies. Collaboration between dermatologists, rheumatologists, and cardiologists is crucial to address the complex nature of this condition and its impact on the heart.

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Introduction

Psoriasis is a chronic inflammatory skin disorder affecting approximately 2–3% of the global population.[1] Our comprehension is expanding to recognize that psoriatic disease encompasses three primary domains: the skin, joints, and vascular system.[2] The intricate interplay between psoriasis and cardiovascular implications has evolved into a focal point of research, reshaping clinical paradigms and emphasizing the need for integrated approaches spanning dermatology, rheumatology, and cardiology. Beyond the conventional risk factors shared with cardiovascular diseases (CVD), such as hypertension and hyperlipidemia, psoriasis introduces unique genetic links, immune pathways, and adipose tissue dysfunction that contribute to an independent cardiovascular risk profile.

Despite the well-established association, the assessment of cardiovascular risk in psoriasis patients frequently lacks comprehensiveness.[3] Multiple questionnaire-based studies have revealed that surveyed physicians, including dermatologists, rheumatologists, cardiologists and primary care physicians, often fail to conduct comprehensive screenings for hypertension, dyslipidemia, smoking, and diabetes mellitus, with more than half of primary care physicians unaware of the connection between psoriasis and cardiovascular disease.[4,5] A recent Delphi consensus has affirmed the significance of cardiovascular disease as a crucial comorbidity in patients with psoriatic disease.[6] It emphasized the need for evaluation in clinical trials, marking this as an area warranting further investigation. Several recent randomized controlled trials (RCTs), like the Vascular Inflammation in Psoriasis Trials, have utilized cardiovascular disease surrogate endpoints. These include assessments of vascular inflammation through 18F-2-fluorodeoxyglucose-positron emission tomography/computed tomography imaging and blood-based cardiometabolic parameters.[7,8]

This narrative review navigates through the complex pathophysiological connections, exploring the genetic underpinnings, immune mechanisms, and adipose tissue involvement that form the foundation of the psoriasis-CVD relationship. Furthermore, it delves into the impact of various psoriasis treatments on cardiovascular health, providing insights into their potential benefits and risks. The manuscript not only highlights the challenges in the current understanding of cardiovascular implications in psoriasis but also outlines crucial future directions, emphasizing the necessity for tailored risk assessment models and evidence-based hierarchies of treatments.

Cardiovascular Risk Profile of Psoriasis Patients

Psoriasis is an Independent Risk Factor for Cardiovascular Diseases

In 2006, Gelfand et al conducted a pioneering investigation that identified psoriasis as an independent risk factor for MI, utilizing prospective data sourced from the United Kingdom General Practice Research Database.[9] The analysis, adjusting for major cardiovascular risk factors, revealed an increased adjusted relative risk (RR) for MI in patients with psoriasis, with the greatest RR observed in young patients with severe psoriasis. This suggests that psoriasis may independently contribute to the risk of MI, particularly in younger individuals with severe forms of the condition. Aligning with these insights, Samarasekera et al and Armstrong et al delved into the risk of CVDs considering psoriasis severity, revealing an elevated risk of major cardiovascular events (MACE), including MI and stroke, as well as cardiovascular mortality in severe psoriasis patients.[10,11] Additionally, Egeberg et al established a stronger association between longer disease duration and the risk of MACE.[12]

Numerous studies have shown that conventional cardiovascular risk scores often underestimate the risk in individuals with psoriasis and PsA.[13–15] Bolstered by compelling evidence, psoriasis has garnered recognition in both European and American Guidelines on cardiovascular disease prevention.[16,17] It is acknowledged as a risk factor multiplier for cardiovascular risk.[18] In adults aged 40 to 75 without diabetes mellitus and falling within a CV intermediate risk category, psoriasis is recognized as a risk-enhancing factor, supporting the initiation of statin therapy.[19] Furthermore, the collaborative guidelines from the Joint American Academy of Dermatology (JAAD) and National Psoriasis Foundation (NPF) underscore the importance of advising psoriasis patients about their heightened cardiovascular risk. The guidelines recommend referral to primary care physicians or cardiologists for further management.[20] This collective body of

research underscores the pivotal role psoriasis plays as an independent risk factor for CVDs, influencing risk assessments and treatment considerations in clinical guidelines.

Common Risk Factors Between Psoriasis and Cardiovascular Diseases

Individuals with psoriasis exhibit an increased occurrence of conventional (and modifiable) CVD risk elements, including arterial hypertension, diabetes mellitus, hyperlipidemia, obesity, and metabolic dysfunction-associated steatotic liver disease (MASLD).[21] A systematic review and meta-analysis of 24 observational studies, encompassing approximately 2.7 million participants, revealed that individuals with psoriasis, particularly severe cases, have a higher prevalence of hypertension, with an odds ratio of 1.58 compared to controls. Additionally, PsA patients exhibited an even greater prevalence of hypertension with an odds ratio of 2.07.[22] Another systematic review and meta-analysis of 63 studies involving 15,939 psoriasis patients and 103,984 controls found a significantly increased prevalence of metabolic syndrome (MetS) among psoriasis patients (30.29%) compared to the control group (21.70%), with an odds ratio of 2.077 [95% CI, 1.84–2.34], emphasizing the need for regular monitoring of psoriasis patients for associated MetS complications and related risk factors.[23]

In the context of the risk of MASLD in psoriasis, a comprehensive systematic review and meta-analysis incorporating data from 15 observational studies with 249,933 psoriasis patients and 1,491,402 controls revealed a noteworthy correlation between psoriasis and the prevalence of MASLD.[24] The pooled random-effects odds ratio of 1.96 (95% CI 1.70–2.26) suggests that the risk of MASLD in psoriasis patients is linked to the severity of their disease. An observational study found that psoriasis patients with MASLD exhibited a higher rate of subclinical atherosclerosis compared to psoriasis patients without liver disease and to controls with liver disease, highlighting the cardiovascular implications of associated MASLD in psoriasis.[25]

Pathophysiological Connections

The pathophysiology of CVD in psoriasis involves various mechanisms, extending beyond traditional risk factors. Psoriasis patients exhibit a higher prevalence of modifiable CVD risk factors, such as hypertension, diabetes, hyperlipidemia, obesity, and smoking. While these factors contribute to CVD, epidemiological studies suggest that psoriasis may have additional pathophysiological driving properties.

Genetic Link Between Psoriasis and Cardiovascular Diseases

Genetic investigations reveal no reported association between IL-12 or IL-17 gene polymorphism and CVDs;[26,27] instead, IL-23 gene polymorphisms, particularly IL-23R rs6682925T/C, are linked to the occurrence and progression of coronary artery disease.[28,29] A functional single-nucleotide polymorphism, rs11209026 G/A in IL-23R, exhibits protective effects against atherosclerosis progression.[30] Furthermore, the IL-23 gene rs2066808 polymorphism, associated with susceptibility to psoriasis and psoriatic arthritis (PsA), increases the genetic risk of premature coronary artery disease (CAD).[31–34] Large-scale genome-wide association studies confirm that variants of IL-23R are significantly associated with psoriasis susceptibility.[35] Further, a TNF- 238 G/A polymorphism is inversely associated with psoriasis risk but significantly associated with coronary artery disease susceptibility in Europeans and North Asians, indicating complex genetic interactions in these conditions.[36–38]

In a meta-analysis and Mendelian randomization, psoriasis showed a significant association with increased CAD and myocardial infarction (MI) risk in European and East Asian populations.[39] Mendelian randomization revealed a positive genetic link between psoriasis and CAD in both groups, suggesting a shared genetic basis. These findings propose targeted psoriasis treatment as a potential avenue to enhance cardiovascular outcomes, presenting a novel approach to prevent CVD.

Immune Pathways Bridge the Pathogenesis Between Psoriasis and Cardiovascular Diseases

Atherosclerosis is not merely a passive metabolic condition; inflammation plays a crucial role in its development.[40] The interconnection between psoriasis and atherosclerosis lies in the shared involvement of immune cells, particularly T cells, dendritic cells, monocytes, macrophages, and neutrophils. Psoriasis, recognized as a T-cell-mediated disorder, engages both Th1 and Th17 cells in its pathogenesis.[41,42] Th1 cells, activated in the inflammatory cascade of psoriasis, play a pivotal role in psoriatic inflammation by inducing the release of pro-inflammatory cytokines.[41] Interestingly, Th1 cells are also implicated in atherosclerosis, where their elevated presence is noted in patients with unstable angina and acute coronary syndrome.[43,44]

Th17 cells, another subset involved in psoriasis, release cytokines such as IL-17 and are associated with increased angiogenic inflammatory mediators.[45,46] The role of Th17 cells in atherosclerosis, however, presents conflicting data.[47,48] Regulatory T cells (Treg cells), which inhibit inflammation, show impaired function in psoriasis, contributing to chronic auto-inflammation.[49] Similarly, reduced levels of circulating Treg cells are observed in acute coronary syndrome patients.[50,51] TNF-α emerges as a potent proatherogenic cytokine, influencing LDL transcytosis, macrophage activity, and cardiac functions.[52,53] Elevated serum TNF-α in psoriasis patients aligns with its role in endothelial dysfunction.[54,55] While IL-12/23p40 and IL-17 show skin-specific impacts in psoriatic plaques, IL-12 links to atherosclerosis progression, and IL-17 exhibits both proatherogenic and protective effects.[56,57] Human data indicates elevated IL-17 levels in coronary artery disease, suggesting a potential cause-and-effect relationship.[58] The complex interplay of these cytokines underscores the proatherogenic role of IL-17, contributing to cardiovascular events in severe psoriasis patients.

Role of Myeloid Origin Cells

Other immune cells, including dendritic cells, monocytes, macrophages, and neutrophils, contribute to both psoriasis and atherosclerosis, indicating a complex interplay.[59–64] Neutrophils, despite their abundant presence, have received less attention but are implicated in the IL-17-driven mechanisms of both conditions.[59,60] Notably, novel findings on low-density granulocytes (LDGs) and neutrophil extracellular traps (NETs) underscore their potential roles in psoriasis and atherosclerosis, linking these immune processes at a molecular level.[65,66]

A cross-sectional study investigated the relationship between circulating monocyte subsets and non-calcified coronary plaque (NCB) in psoriasis patients using coronary computed tomography angiography (CCTA).[67] Classical monocytes positively correlated with psoriasis severity and NCB, while non-classical monocytes showed a negative association with NCB. Moreover, the cumulative count of myeloid cells, encompassing low-density neutrophils, platelets, and classical monocytes, demonstrated associations with both psoriasis severity and bone marrow FDG uptake, suggesting a potential role in partially mediating the link between psoriasis severity and non-calcified coronary plaque.

In two exploratory studies, untreated severe psoriatic patients were compared with healthy subjects to investigate potential markers of cardiovascular risk. The first study focused on the non-canonical WNT/Wnt5a pathway in circulating monocytes, revealing a higher frequency of WNT5a+ cells in psoriatic patients along with elevated levels of inflammatory cytokines, chemokine receptors, and the pro-atherogenic marker ADAMTS7.[68] The second study examined monocyte phenotype, ADAMTS7, and mTOR activity, finding higher levels of inflammatory cytokines in M1 and M2 monocytes of psoriatic patients, along with increased serum ADAMTS7 and mTORC activation markers, suggesting potential pathways for predicting and detecting cardiovascular risk in psoriasis.[69]

Role of Complement System

Local complement activation within psoriatic lesions has long been recognized, characterized by the presence of complement activation products such as C3a, C3b, and C5a.[70] While systemic complement activation is not as apparent, circulating levels of complement components and split products have been observed to be elevated in psoriasis patients.[71] Furthermore, complement activation has been identified as a major alteration in early atherosclerotic plaques, with increased levels of complement C5 protein observed in the intima of fibrolipidic plaques.[72] Elevated plasma levels of C5 have been associated with the presence of generalized subclinical atherosclerosis.[72] An observational study investigated the association between the complement system and subclinical atherosclerosis in psoriasis patients.[73] Proteomic analysis revealed dysregulation of complement-related proteins in patients with psoriasis and atherosclerosis, suggesting a role for complement cascades in the development of atherosclerotic plaques.

Adipose Tissue Dysfunction in Psoriasis

Adipose tissue dysfunction in psoriasis contributes to systemic inflammation and cardiovascular complications. Adipose tissue in psoriasis patients, housing various immune cells such as T cells, B cells, dendritic cells, neutrophils, mast cells, and adipose tissue macrophages, plays a role in obesity and insulin resistance.[74] The distinction between visceral and subcutaneous adiposity is crucial, with visceral adiposity linked to subclinical cardiovascular disease and vascular inflammation in PsA and psoriasis.[75,76] The unique subset of adipose tissue macrophages in psoriasis lean towards pro-

inflammatory cytokine expression and adipose tissue dysfunction.[77] Additionally, perivascular adipose tissue surrounding blood vessels may contribute to cardiometabolic disease, promoting atherosclerosis through adipokine and chemokine production.[78,79] Leptin, a peptide hormone released by the adipose tissue is elevated in psoriasis and correlates with disease severity and subclinical atherosclerosis, while resistin and adiponectin contribute to innate immune activation.[80,81] Peri- and epicardial fat tissues, elevated in psoriasis patients, are additional sources of inflammatory cytokines associated with coronary heart disease.[82,83]

Kaiser et al examined the correlation between vascular inflammation and inflammation in diverse adipose tissues, spleen, and bone marrow in psoriasis patients, employing 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) and carotid ultrasound imaging.[84] Their findings revealed a substantial inflammatory connection among these compartments, irrespective of the presence of cardiovascular disease. Overall, psoriasis patients are considered at increased cardiovascular risk due to the complex interplay of inflammatory responses, immune cell involvement, and systemic effects on metabolic and vascular processes. The pathophysiology of cardiovascular adverse effects in psoriasis has been depicted in Figure 1.

Impact of Psoriasis Treatments on Cardiovascular Health

Multiple investigations delve into the influence of psoriasis treatments on cardiovascular outcomes. Within conventional systemic therapies, certain studies propose that methotrexate is linked to a reduced risk of MACEs, while acitretin or cyclosporine shows no discernible impact on MACEs.[85,86] Apremilast exhibited a neutral association with aortic vascular inflammation but generally beneficial effects on specific cardiometabolic biomarkers and consistent reductions in visceral and subcutaneous adiposity in a nonrandomized clinical trial involving patients with moderate to severe psoriasis.[7]

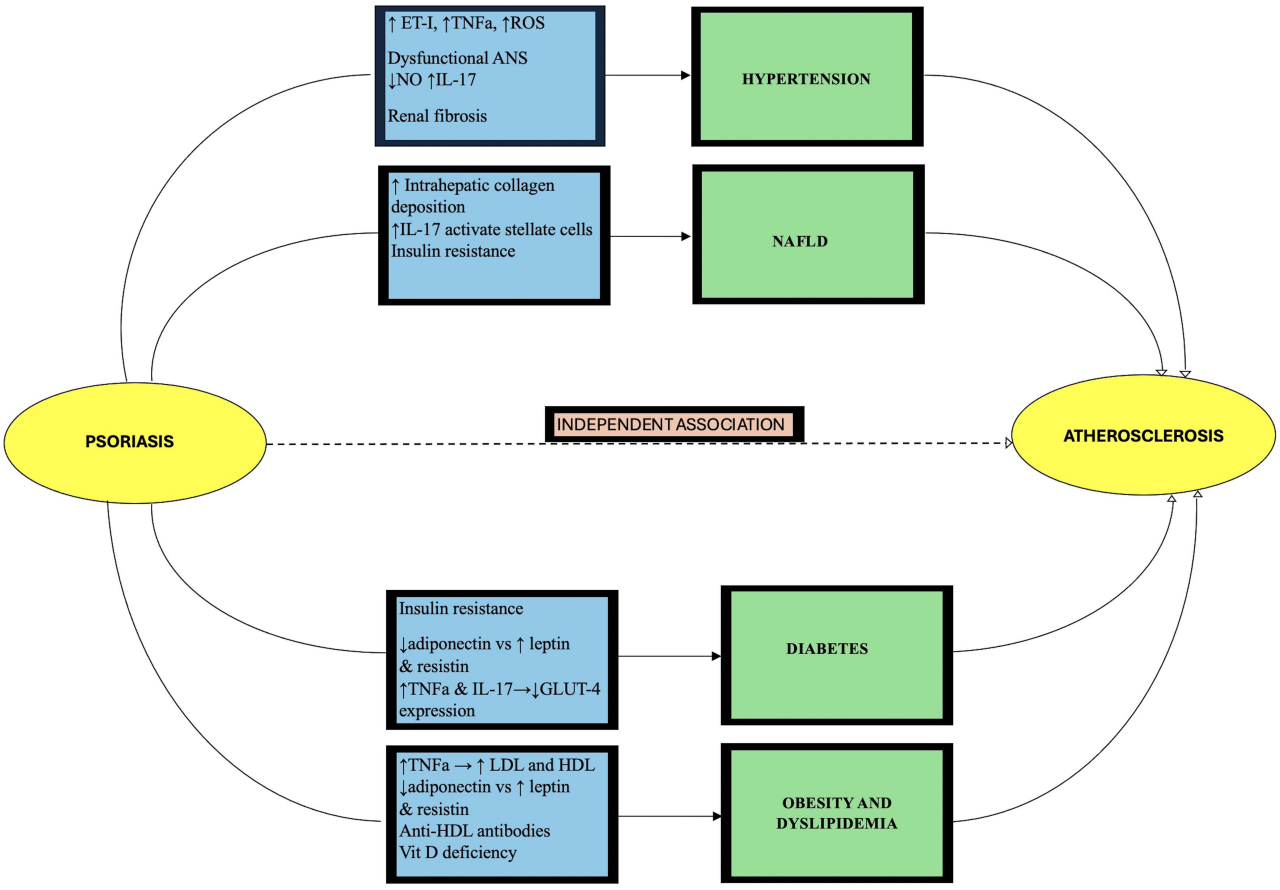

Figure 1 Pathophysiological pathways leading on to adverse cardiac effects in psoriasis.
Abbreviations: ET, endothelin; TNFa, tumor necrosis factor alpha; NO, nitric oxide; ROS, reactive oxygen species; ANS, autonomic nervous system; IL, interleukin; GLUT, insulin related glucose transfer; LDL, low density lipoprotein; HDL, high density lipoprotein; NAFLD, non-alcoholic fatty liver disease.

A retrospective cohort study by Wu et al, involving 8845 psoriasis patients, found that those treated with tumor necrosis factor (TNF) inhibitors (TNFi) had a significantly lower hazard of MI compared to those using topical therapies.[87] Another study by Wu et al compared MACEs in psoriasis patients treated with methotrexate or TNFi, revealing fewer cardiovascular events in TNFi users over a 12-month period. A cumulative exposure to TNFi was associated with an 11% reduction in cardiovascular event risk over 24 months.[88] Ahlehoff et al's Danish nationwide cohort study demonstrated that patients treated with TNFi or methotrexate had a reduced risk for MACEs compared to those on other medications.[89] While TNFi treatment's impact on congestive heart failure (CHF) is less clear, some studies suggest increased mortality with higher TNFi use, leading to recommendations against TNFi use in such settings.[90]

The effect of IL-12/23 inhibitors (ustekinumab and briakinumab) on CVD is controversial, showing potential predisposing associations with MACEs in some analyses.[91,92] A study by Poizeau et al suggested that ustekinumab may increase the risk of severe cardiovascular events such as acute coronary syndrome or stroke in patients with high baseline cardiovascular risk shortly after treatment initiation.[93] However, limitations in the study design, such as the non-transient nature of ustekinumab exposure and arbitrary risk windows, along with conflicting evidence from other studies, indicate that more research is needed to establish a clear relationship.[94] Further, a Phase IV, randomized, double-blind, placebo-controlled crossover study of patients with moderate-to-severe psoriasis, ustekinumab treatment led to a transient 18.65% reduction in aortic vascular inflammation (AVI) at 12 weeks, though AVI levels returned to baseline after a year of treatment.[95] Simultaneously, ustekinumab significantly decreased inflammatory cytokines TNF-α, IL-1β, IL-17α, and IL-6, along with a notable reduction in VCAM-1, demonstrating sustained impacts on biomarkers linked to atherosclerotic cardiovascular diseases.

The IL-23/Th17 pathway, integral to psoriasis pathogenesis, is also implicated in cardiometabolic comorbidities. A study by Elnabawi et al on biologic-naïve psoriasis patients showed a 12% reduction in non-calcified plaque burden after one year of anti-IL-17 treatment, outperforming anti-IL-12/23 and non-biologic therapies.[96] Another study revealed a significant reduction in lipid-rich necrotic core (LRNC) only in the biologic group, including anti-IL-17 therapy.[97] Elnabawi et al's investigation using the perivascular fat attenuation index (FAI) showed a significant decrease in coronary inflammation after one year in patients treated with biologics, with the greatest improvement in the anti-IL-17 group.[78] The CARIMA study demonstrated improved endothelial function with secukinumab,[98] and Makavos et al found anti-IL-17 treatment led to greater improvement in myocardial and vascular function compared to conventional treatments.[99] However, Marovt et al's study and the VIP-S trial failed to show significant improvement in selected parameters of subclinical atherosclerosis in psoriasis patients receiving biologic therapies, indicating mixed impact of such treatments on cardiovascular outcomes.[8,100] Observational studies hint at subclinical cardiovascular improvement via diverse imaging biomarkers, but RCTs, primarily focused on vascular inflammation, yield inconsistent results. Further trials with varied imaging biomarkers and extended follow-up are needed to ascertain potential reductions in cardiovascular disease risk.[101]

Nevertheless, there is not exclusively positive evidence, as these treatments may have adverse effects on cardiovascular health. In a retrospective pharmacovigilance study analyzing over 25 million adverse events in the FDA Adverse Event Reporting System, cardiac adverse events associated with newly approved therapeutic agents for psoriasis were reported in 3852 cases.[102] Notably, secukinumab had the highest number of reported adverse events.[102] There was a notable association between risankizumab and adverse cardiac events in particular coronary artery disease and atrial fibrillation, Similarly, tildrakizumab and ixekizumab have been linked to initiation and progression of atrial fibrillation.[102]

Cardiovascular Risk Assessment in Psoriasis

Screening for cardiovascular comorbidities in psoriasis patients is crucial but is often overlooked in clinical practice.[3] As the nexus between psoriasis and CVDs becomes more apparent, dermatologists, rheumatologists, and primary care physicians find themselves taking on the additional role of preventive cardiologists. The imperative to promptly refer patients to cardiologists when necessary underscores the gravity of recognizing and managing cardiovascular risks in psoriasis patients (Figure 2). Given the current lack of comparative data on their suitability for assessing CVD risk in psoriasis, endorsing one score over another is challenging; therefore, it is advisable to utilize cardiovascular risk scores according to regional guidelines and conduct assessments as outlined therein.

Traditional cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, assume heightened significance in the context of psoriasis. Often underestimated, the risk of CVD in the psoriasis population is not adequately

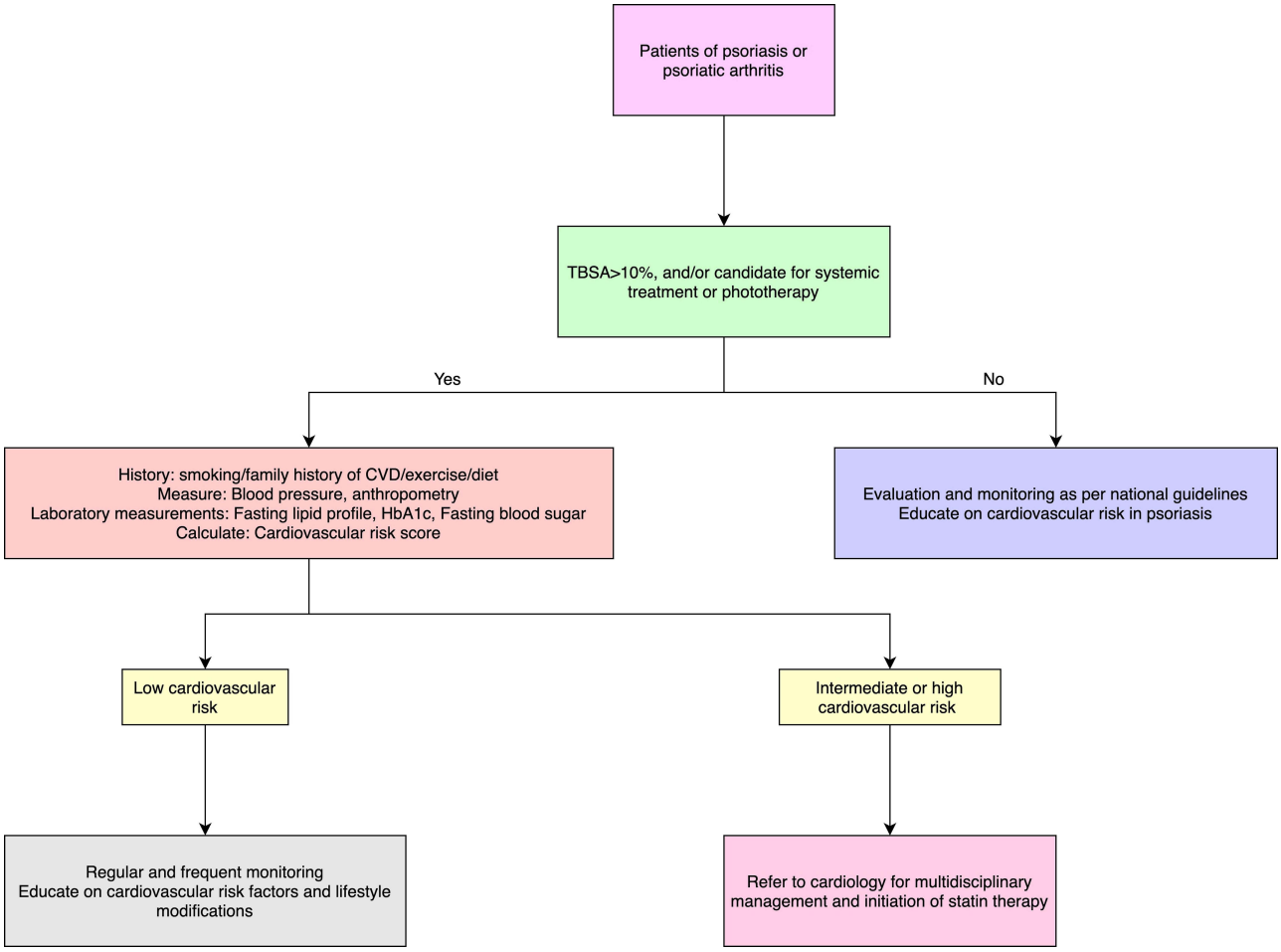

Figure 2 Flowchart illustrating the management approach for patients with psoriasis and psoriatic arthritis concerning their association with cardiovascular risk.
Abbreviations: CVD, cardiovascular disease; TBSA, total body surface area.

captured by current scoring criteria designed for the general population, failing to recognize the independent risk posed by underlying inflammation. Incorporating risk score models tailored for psoriasis patients is an evolving aspect of cardiovascular risk assessment. The recommendation, as per the 2019 American College of Cardiology/American Heart Association guidelines and the 2019 European Society of Cardiology guidelines, is to consider psoriasis as a cardiovascular risk enhancer.[16,17] Joint AAD-NPF guidelines propose introducing a 1.5 multiplication factor in patients with moderate to severe psoriasis, acknowledging the heightened risk profile in this subgroup.[20] However, observational studies have shown that traditional risk scores, including both short-term and lifetime assessments, fail to adequately identify CVD risk in psoriasis patients, even when modified by this multiplication factor, indicating an underestimation of actual CVD risk.[103] Further considerations should include the impact of ongoing treatments on the cardiovascular comorbidities and risk factors.

A recent study indicated the potential use of nail fold capillaroscopy (NFC) in detecting cardiovascular risk in psoriasis; psoriasis patients showed microvascular abnormalities, increased inflammation and increased intima-media-thickness in comparison to matched controls suggesting a direct link between psoriasis and CVD attributable to the microangiopathy associated with psoriasis. There is need for further prospective studies on NFC's predictive value for cardiovascular risk in psoriasis.[104]

In recent years, research has increasingly focused on the utility of various widely accessible peripheral blood biomarkers in evaluating cardiovascular risk among individuals with psoriasis. Studies have shown that elevated neutrophil-to-lymphocyte ratio levels are associated with increased NCB in psoriasis patients, independent of high-sensitivity C-reactive protein (hs-CRP)

levels.[105] Similarly, the triglyceride-to-glucose ratio, a surrogate marker for insulin resistance, has been linked to cardiometabolic risk factors and subclinical atherosclerosis in psoriasis patients.[106] Furthermore, the monocyte-to-high-density lipoprotein ratio has been found to correlate with insulin resistance, hs-CRP levels, and 18F-fluorodeoxyglucose uptake in various tissues, indicating its potential as a comprehensive biomarker of cardiovascular risk.[107] However, the reliability of these biomarkers in accurately capturing the true cardiovascular risk of psoriasis patients remains a topic of debate.

There is no universal consensus regarding the optimal frequency of monitoring cardiovascular risk factors in psoriasis patients. The NPF suggests adhering to regional guidelines for screening, emphasizing early and frequent monitoring for individuals with moderate to severe psoriasis.[20] The European Academy of Dermatology and Venerology (EADV) recommends cardiovascular risk factor assessment every six and twelve months during systemic and local psoriasis treatments, respectively.[108] These recommendations collectively emphasize the dynamic nature of cardiovascular risk assessment in psoriasis, stressing the need for tailored, patient-centric approaches to mitigate the risks associated with this intricate interplay. Table 1 summarizes the screening recommendations for cardiovascular comorbidities and risk factors in psoriasis patients.

Preventive Strategies and Management Approaches

Primary Prevention

Implementing optimal lifestyle changes in psoriasis, particularly through a hypocaloric diet in overweight or obese patients, is a fundamental strategy recommended by the NPF to reduce CVD risk.[109] Supported by a meta-analysis of seven RCTs involving over 900 overweight or obese psoriasis patients, caloric restriction leading to weight loss has shown notable improvement in psoriasis skin severity, including a threefold higher skin clearance rate when combined with psoriasis treatment compared to treatment alone.[110] Additionally, the NPF weakly recommends a Mediterranean

Table 1 Screening for Cardiovascular Comorbidities and Risk Factors in Psoriasis Patients. Moderate to Severe Psoriasis is Defined as Total Body Surface Area Exceeding 10%, and/or Requiring Systemic Treatment or Phototherapy

Comorbidities	Frequency of Screening	Mode of Screening
Cardiovascular disease	• Risk assessment as per national guidelines using validated tools • Early and frequent monitoring for patients with moderate to severe psoriasis • Risk score models should be adapted by introducing a 1.5 multiplication factor in patients with moderate to severe psoriasis	• Blood pressure • Fasting blood glucose or HBA1c • Fasting lipid profile • Body mass index • 10-year cardiovascular disease risk score
Hypertension	• Annual screening in patients >18 years of age • At every visit in patients receiving cyclosporine A	• Office blood pressure monitoring • Consider ambulatory blood pressure monitoring if indicated
Heart rate	• At least every two years (in view of increased risk of atrial fibrillation)	• Heart rate • Cardiology consult and Holter monitoring for patients with tachycardia or symptomatic palpitations
Type 2 diabetes mellitus	• Periodic screening as per the national guidelines, consider higher frequency of monitoring in patients with moderate to severe psoriasis	• Fasting blood glucose, or • HBA1c
Dyslipidemia	• Periodic screening as per the national guidelines, consider higher frequency of monitoring in patients with moderate to severe psoriasis • Regular monitoring if the patient is on acitretin or cyclosporine (every 3 to 6 months)	• Fasting total cholesterol • Low-density lipoprotein cholesterol • High-density lipoprotein cholesterol • Triglycerides
Obesity	• Every two years for patients with normal initial body mass index • Annual monitoring in patients with moderate to severe psoriasis	• Height • Weight • Waist circumference • Body mass index

diet, noting that adherence is associated with improved psoriasis skin condition, reduced fat mass, and lower levels of hs-CRP.[109] Encouraging smoking cessation is also advised, not only for its CVD risk reduction but also for potential improvements in psoriasis skin severity.[111]

Effectively managing stress is crucial in the intricate relationship between stress, psoriasis, and cardiovascular disease. Stress exacerbates both conditions, creating a cycle that underscores the importance of stress reduction.[112,113] Limited studies highlight the potential benefits of lifestyle modifications, including yoga, relaxation techniques, and exercise, as accessible interventions.[114] In regions with limited access to advanced treatments like biologics, prioritizing stress management and lifestyle changes becomes integral for comprehensive patient care.

Statin Therapy

Although limited trials address CVD risk factor management in psoriasis, the attendant dyslipidemia and increased coronary risk merit appropriate lipid control. A study with 9000 psoriasis patients showed statin therapy significantly reduced MI risk (hazard ratio: 0.31).[87] High-intensity statins in psoriasis patients matched efficacy with non-psoriasis counterparts in lowering lipids and cardiovascular events.[115] A randomized trial showed that 2 weeks of atorvastatin significantly reduced LDL cholesterol and hs-CRP, indicating potential vascular health benefits in young psoriasis patients without traditional indications for statins.[116] Psoriasis task force of EADV recommends that psoriasis patients with low to moderate cardiovascular risk maintain LDL-c levels below 100 mg/dL, those with high risk keep levels below 70 mg/dL with a ≥50% reduction vs baseline, and those with very high risk aim for levels below 55 mg/dL with the same reduction.[117] High-intensity statin treatment, such as atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily, is suggested for achieving a ≥50% LDL-C reduction, while moderate-intensity treatment, including atorvastatin 10–20 mg daily or rosuvastatin 5–10 mg daily, is recommended for a 30% to 49% reduction. The potential anti-inflammatory benefits of statins in psoriasis are unclear, but elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in psoriasis, linked to vascular inflammation, suggest added benefits of lipid-lowering. Genetically proxied inhibition of PCSK9, a target of lipid-lowering drugs, is consistently associated with a lower risk of psoriasis, suggesting PCSK9's implication in psoriasis pathogenesis and proposing the use of existing PCSK9 inhibitors for preventive measures.[118]

Metformin for Psoriasis and Associated Metabolic Syndrome

Metformin, commonly prescribed for type 2 diabetes, exhibits additional benefits for psoriasis patients by preventing MetS progression, curbing weight gain, and enhancing treatment effectiveness.[119] Numerous RCTs indicate significant improvement in Psoriasis Area Severity Index (PASI) with metformin use.[120–122] Apart from its hypoglycemic effects, metformin's anti-inflammatory properties, mediated through adenosine monophosphate-activated protein kinase, contribute to enhanced treatment efficacy by suppressing dendritic cell and T-cell activation and proliferation.[123] While a meta-analysis of three RCTs involving 148 psoriasis patients affirms metformin's positive impact on both metabolic parameters and inflammatory markers, the limited number of studies and data availability necessitate further evidence before recommending routine metformin use in psoriasis with MetS.[124]

Emerging Therapies

Semaglutide therapy demonstrated notable reductions in epicardial fat inflammation, improvements in psoriasis severity, and beneficial effects on glycemic control and abdominal fat levels in a patient with abdominal obesity, type-2 diabetes, and severe psoriasis, suggesting its potential as a treatment option for individuals resistant to biologic therapies.[125] Probiotics, along with prebiotics and symbiotics, hold promise in mitigating cardiovascular disease risk in psoriasis patients by potentially decreasing cholesterol levels through the synthesis of bile salts and bile acid deconjugation.[126,127] Simultaneously, these formulations may contribute to managing psoriasis by modulating skin inflammation and differentiation, as suggested by experimental studies in cell lines and animal models.[128,129] Ongoing research, including clinical studies, aims to further elucidate the dual benefits of these interventions in the context of both cardiovascular health and psoriasis management.

Choice of Systemic Therapy in Psoriasis Patients

Given the potential of TNFi in mitigating the risk of MACEs, these agents have been endorsed as an optimal therapeutic choice for patients with cardiovascular risk factors.[88] However, prudence is advised, particularly in individuals with severe CHF, as the use of TNFi may be relatively contraindicated in this subgroup. Among conventional treatments, methotrexate exhibits similar efficacy and stands out as a favorable therapeutic option.[85] Cyclosporine and acitretin are best avoided in individuals with established cardiovascular risk factors due to well-documented adverse effects such as hypertension and hyperlipidemia. Conversely, the relationship between IL-12/23 inhibitors and cardiovascular risk remains uncertain, while recent evidence indicates that Janus kinase inhibitors (JAKi) may not carry CVD risks.[92,130,131] Conversely, emerging evidence lends support to the safety and effectiveness of IL-17 and IL-23 inhibitors in patients with CVD, hinting at the potential for these therapies to become the primary approach in managing psoriasis in the future.[132]

Care-Coordination Models

The screening for CVD risk factors among psoriasis patients is often inadequate, leading to suboptimal management.[133] This issue is compounded by dermatologists and rheumatologists' hesitance to prescribe statins,[4] highlighting the need for better coordination and clear delineation of responsibilities among healthcare providers. A survey-based study by Barbieri et al reported optimistic views from both dermatologists and patients regarding the adoption of a care model led by dermatologists or rheumatologists for CVD prevention.[134]

Song et al proposed a clinical care model where dermatologists or rheumatologists screen patients for CVD risks and refer them to a care coordinator at the NPF.[135] The coordinator assesses the patient's 10-year risk of developing atherosclerotic CVD and formulates a comprehensive plan covering diet, exercise, and smoking cessation, in collaboration with the patient's primary care provider, including statin therapy if warranted. However, despite recommendations, statin initiation remains low, with only two out of 23 patients starting treatment, though these patients showed significant improvements in their CV risk parameters. Without specific care coordination, CV risk screening could be integrated into regular dermatological evaluations. Management of identified CV risks should be handled by the patient's primary care provider. Moreover, collaboration with preventive cardiologists is recommended, similar to the interdisciplinary approach taken with rheumatologists when managing psoriatic arthritis.

Challenges and Future Directions

As our understanding of immune mediators and systemic inflammation in psoriasis advances, the introduction of biological agents has raised the prospect of early systemic intervention to modify the disease course and lower long-term risks. However, evidence supporting this notion is limited, and there are even contrary indications that early systemic treatment might have adverse effects, potentially increasing overall comorbidity. Prospective randomized controlled trials are crucial to assess the impact of systemic therapies on the "psoriatic march". Yet, the absence of definitive biomarkers for determining cardiovascular progression poses a significant challenge, underscoring the need for further research in this area.

Further, the absence of dedicated screening guidelines and risk assessment models tailored specifically to individuals with psoriasis impedes early identification and intervention for cardiovascular risk factors in this population. The long-term impact of medications used in psoriasis and PsA on cardiovascular system requires comprehensive investigation. Additionally, the influence of different disease phenotypes on cardiovascular health has not been fully elucidated. There is a pressing need for ongoing research focused on developing and evaluating therapies that not only target psoriasis symptoms but also address the associated cardiovascular comorbidities. Furthermore, the hierarchy of treatments in patients with existing cardiovascular risk factors or established CHF remains unclear and lacks a robust evidence base, underscoring the necessity for further exploration in this complex disease involving dermatology, rheumatology and cardiology.

Conclusion

In conclusion, the intricate relationship between psoriasis and CVD has been extensively explored, revealing a multifaceted interplay between genetics, immune pathways, and traditional cardiovascular risk factors. Psoriasis, recognized as an independent risk factor for CVD, demands heightened vigilance from healthcare providers to accurately assess and manage cardiovascular risks in affected individuals. The shared immune pathways, involving T cells, cytokines, and adipose tissue

dysfunction, provide a molecular basis for the observed connection between psoriasis and atherosclerosis. Psoriasis treatments, particularly TNFi, show promise in mitigating cardiovascular risks, but challenges persist, including the need for tailored screening guidelines, understanding the long-term impact of medications, and elucidating the influence of disease phenotypes on cardiovascular health. While advancements in therapeutic options, including emerging biologics and lifestyle interventions hold promise for managing both psoriasis and its cardiovascular comorbidities, ongoing research and collaboration between dermatologists, rheumatologists, and cardiologists is the need of the hour.

Disclosure

The authors report no conflicts of interest in this work.

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