# Systemic Inflammation in Psoriasis: A Guide for Dermatology Care Providers

Practical guidance for dermatology care providers on the importance of screening patients with psoriasis for associated comorbidities.

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Psoriasis is a chronic autoimmune disease affecting more than seven million adults in the United States, commonly presenting as epidermal plaques with skin erythema, induration, and adherent silvery-white scales.[1] Psoriatic plaques can be pruritic, and visibility of the disease can cause embarrassment, shame, and stress, which can have a significant negative impact on emotional health and productivity.[2]

Psoriasis was originally considered a benign skin condition with minimal serious complications. However, numerous recent studies have unequivocally shown that psoriasis is a systemic inflammatory disease, and many of the key drivers of psoriasis are also implicated in the pathogenesis of other common chronic inflammatory diseases.[3] Thus, patients with psoriasis are at increased risk for inflammatory comorbidities.[4]

This review discusses sources of systemic inflammation in psoriasis and how cytokines involved in psoriasis pathogenesis cause inflammation in other organ systems. Practical guidance is provided for dermatology care providers on the importance of screening patients with psoriasis for associated comorbidities.

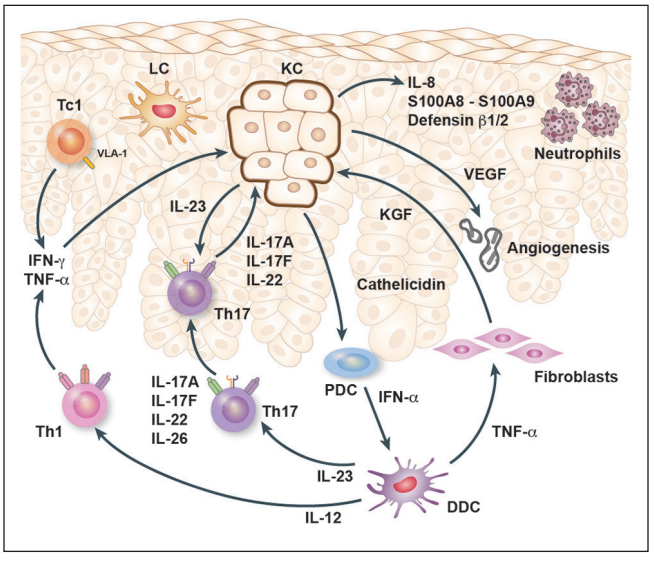


**Figure 1. Immunopathogenesis of Psoriasis[5]**

Adapted from Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol. 2009;129(6):1339-1350, with permission from Elsevier.

Abbreviations: DDC, dermal dendritic cells; IFN, interferon; IL, interleukin; KC, keratinocytes; KGF, keratinocyte growth factor; LC, lymphocytes; PDC, plasmacytoid dendritic cells; Tc, cytotoxic T cell; Th, T helper cell; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VLA, very late antigen.

## SYSTEMIC INFLAMMATORY BURDEN OF PSORIASIS

Immunopathogenic pathways that stimulate inflammation and abnormal/excessive growth of skin cells in psoriasis are illustrated in Figure 1.[5] Psoriasis can be triggered by environmental, infectious, and genetic factors, which place stress on keratinocytes. These triggers initiate a cascade of events, including activation of dendritic cells and differentiation of naïve T cells into T helper 1 and T helper 17 cells, which mediate immune responses characterized by release of pro-inflammatory cytokines. Key cytokines in these pathways include tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-22, IL-23, IL-6, IL-1β, and interferon-γ.[6]

In uncontrolled psoriasis, levels of inflammatory cytokines are increased in skin lesions and blood plasma.[7] Such a sys-

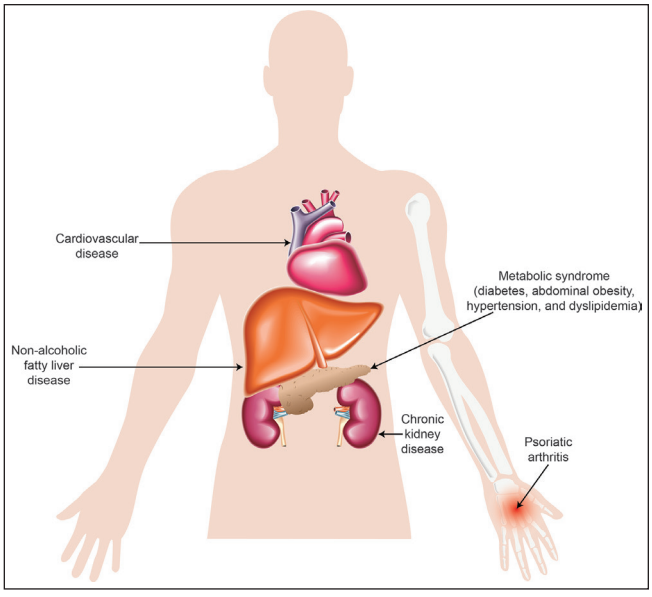


**Figure 2. Comorbidities Associated With Psoriasis**

temic increase results in chronic inflammation throughout the body, including in the heart, liver, kidneys, intestines, muscles, and tendons.[3,8,9] Systemic inflammation is present most frequently in moderate-to-severe psoriasis; however, recent studies have shown that subclinical vascular and hepatic inflammation is also present in mild psoriasis.[10,11]

This systemic inflammation, driven by a common set of cytokines, increases risk for comorbidities, including cardiovascular disease, psoriatic arthritis, chronic kidney disease, metabolic syndrome, and non-alcoholic fatty liver disease (Figure 2).[4,12,13] For example, patients with psoriasis are at significantly higher risk than individuals without psoriasis for comorbid cardiovascular disease, and comorbid metabolic syndrome and each of its components (Table 1).[14-18] Furthermore, psoriasis is associated with an estimated 10-year increased risk for major adverse cardiac events of 6.2 percent, including significantly higher risk for death compared with the general population.[19] Imaging studies suggest that increased cardiovascular risks in psoriasis may be associated with increased aortic wall inflam-

**TABLE 1. CHARACTERISTICS OF COMORBIDITIES ASSOCIATED WITH PSORIASIS[4,12,14-18,25,27]**

| Comorbidity | Increased Risk With Psoriasis | Roles of Pro-inflammatory Cytokines |
|---|---|---|
| Cardiovascular disease | 1.7-fold increased risk of MI<br>1.6-fold increased risk of stroke<br>Shortens average lifespan by ~6 years | Promote coronary artery inflammation<br>Increase atherosclerotic plaque instability |
| Metabolic syndrome (overall) | 2.3-fold increased risk | Exert systemic effects on insulin regulation and lipid metabolism in skin and plasma |
| Metabolic syndrome components | | |
| Abdominal obesity | 1.7-fold increased risk | Promote chronic subclinical adipose tissue inflammation, angiogenesis, and endothelial dysfunction |
| Insulin resistance | 1.6-fold increased risk of diabetes | Work synergistically with adipokines to induce insulin resistance in endothelial cells |
| Hypertension | 1.6-fold increased risk | Promote aortic stiffening and inflammation that cause vascular damage<br>Similar inflammatory profiles seen in psoriasis and in hypertensive changes to the renin-angiotensin-aldosterone system |
| Dyslipidemia | 1.0- to 5.6-fold increased risk | Contribute to dysregulation and elevation of serum lipids<br>Alter lipoprotein composition<br>Increase lipid deposition on arterial walls |
| Kidney disease | 1.9- to 3-fold increased risk | Stimulate chemoattractants that promote inflammation<br>Increases sodium reabsorption and renal fibrosis<br>Promote renal artery stiffening |
| Non-alcoholic fatty liver disease | >2-fold increased risk | Promote metabolic dysfunction and hepatic fibrosis/steatosis |
| Psoriatic arthritis | Affects ~30% of patients with psoriasis vs ~1% of the general population | Promote synovitis, osteoclastogenesis, and bone resorption |

Abbreviation: MI indicates myocardial infarction.

| TABLE 2. SUGGESTED COMORBIDITY SCREENINGS FOR PATIENTS WITH PSORIASIS[33,34] | |
|---|---|
| **Comorbidity** | **Recommendations** |
| Cardiovascular disease | Aged 20-79 y: Every 4-6 y, check for risk factors of age, sex, total and HDL cholesterol levels, SBP, use of antihypertensive therapy, diabetes mellitus, and smoking<br>Aged 40-79 y: Every 4-6 y, estimate 10-y risk for nonfatal MI, CHD death, and nonfatal and fatal stroke using pooled cohort equations<br>Refer patients with CHD or other serious cardiovascular comorbidities to a cardiologist |
| Hypertension | Perform screenings every 3-5 y for patients aged 18-39 y with BP <130/85 mmHg without risk factors of overweight or obese, and African American race<br>Perform screenings annually for patients aged ≥40 y and for all patients with risk factors |
| Diabetes | Screen asymptomatic patients every 3 y if they are aged 40-70 y and are overweight or obese<br>Refer patients with diabetes to a primary care physician or endocrinologist |
| Obesity | Monitor body weight, BMI, and waist circumference at each visit<br>Ensure that overweight/obese patients are not underdosed with fixed-dose biologics or cyclosporine<br>Counsel patients on the importance of maintaining a healthy weight, eating a healthy diet, and obtaining sufficient physical activity |
| Liver disease | In addition to routine liver function bloodwork, screen patients for excessive alcohol use, and counsel regarding the associated risks<br>Refer patients to a hepatologist if they have signs of hepatitis (eg, appetite loss, fatigue, nausea, pruritus, jaundice) |
| Chronic kidney disease | Monitor patients with psoriasis BSA ≥3% for renal insufficiency by checking serum creatinine, BUN, and urinalysis for microalbuminuria |
| Psoriatic arthritis | At each visit, ask patients about joint symptoms (eg, swelling, tenderness, morning stiffness) and signs of nail changes<br>Refer patients with suspected psoriatic arthritis to a rheumatologist |
| Abbreviations: BMI indicates body mass index; BP, blood pressure; BSA, body surface area; BUN, blood urea nitrogen; CHD, coronary heart disease; HDL, high-density lipoprotein; MI, myocardial infarction; SBP, systolic blood pressure; y, years. | |

mation, subcutaneous adipose tissue inflammation, and atherosclerosis.[20,21]

The systemic increase in pro-inflammatory cytokine levels (eg, TNF-α, IL-6, and IL-17) promotes insulin resistance and metabolic abnormalities, which increase the risk for obesity, diabetes mellitus, and non-alcoholic fatty liver disease.[22-24] Increased plasma levels of these cytokines cause increased renal inflammation and immune-mediated kidney damage in psoriasis, providing a possible explanation for a 1.9-fold to 3-fold increased risk for kidney disease and up to 4-fold increased risk for death from kidney disease in severe psoriasis.[12,25]

Another common comorbidity, affecting 30 percent of patients with psoriasis, is psoriatic arthritis, a form of inflammatory arthritis that commonly presents with asymmetrical joint pain, swelling, and stiffness.[26] Psoriatic arthritis pathogenesis is linked with upregulation of IL-17, IL-23, IL-8, and other pro-inflammatory chemokines and cytokines.[27]

## SCREENING PATIENTS WITH PSORIASIS FOR ASSOCIATED COMORBIDITIES

In the field of dermatology, guidance is lacking regarding how and when to screen patients with psoriasis for common cardiometabolic comorbidities. In the authors' opinions, dermatologists, nurse practitioners, and physician assistants can play an important role in ensuring that such screenings are performed,

| TABLE 3. CRITERIA FOR DIAGNOSIS OF METABOLIC SYNDROME | |
|---|---|
| **Risk factor** | **Defining level** |
| Abdominal obesity<br>Men<br>Women | Waist circumference<br>>102 cm (>40 in)<br>>88 cm (>35 in) |
| Triglycerides | ≥150 mg/dL |
| HDL cholesterol<br>Men<br>Women | <br><40 mg/dL<br><50 mg/dL |
| Blood pressure | ≥130/≥85 mm Hg |
| Fasting glucose | ≥110 mg/dL |
| Patients meeting ≥3 of the 5 criteria have metabolic syndrome.<br>Abbreviation: HDL indicates high-density lipoprotein. | |

| TABLE 4. RISK FOR COMORBIDITIES INCREASES WITH PSORIASIS SEVERITY[29] | | | | |
|---|---|---|---|---|
| | OR by Disease Severity (95% CI) | | | |
| **Comorbidity** | **Mild** | **Moderate** | **Severe** | **Adjusted P for Trend** |
| Cerebrovascular disease | 0.98 (0.71–1.35) | 1.14 (0.80–1.64) | 2.50 (1.46–4.26) | .03 |
| Chronic pulmonary disease | 1.08 (0.99–1.18) | 1.06 (0.95–1.18) | 1.18 (0.98–1.40) | .03 |
| Diabetes mellitus | 1.14 (0.99–1.32) | 1.22 (1.03–1.46) | 1.32 (1.00–1.74) | .004 |
| Diabetes with complications | 1.17 (0.89–1.54) | 1.36 (0.97–1.89) | 1.87 (1.16–2.99) | .003 |
| Mild liver disease | 1.29 (0.93–1.79) | 1.46 (0.97–2.18) | 1.69 (0.96–2.97) | .007 |
| Peripheral vascular disease | 1.05 (0.71–1.55) | 1.92 (1.29–2.85) | 1.85 (0.95–3.61) | .003 |
| Renal disease | 0.97 (0.77–1.21) | 1.41 (1.11–1.79) | 1.83 (1.26–2.68) | <.001 |
| Rheumatologic disease | 2.01 (1.56–2.58) | 1.85 (1.36–2.50) | 2.89 (1.84–4.53) | <.001 |
| Atherosclerotic outcomes | 1.14 (0.93–1.39) | 1.39 (1.11–1.76) | 1.81 (1.25–2.63) | <.001 |

Abbreviations: CI indicates confidence interval; OR, odds ratio.
Reproduced with permission from *JAMA Dermatol*. 2013;149(10):1173-1179. Copyright© 2013 American Medical Association.Table 5. Possible Side Effects of Conventional Systemic Psoriasis Treatments That Can Contribute to Comorbidity Burden33,34

along with well-established screenings (eg, tuberculosis prior to biologic initiation and monitoring for infections or malignancies). Comorbidity screenings for patients with psoriasis should include taking a complete medical history, thorough physical examination, blood pressure measurement, and a comprehensive metabolic panel, including liver and kidney function, and measurements of glucose, triglyceride, and cholesterol levels (Table 2). Patients meeting three or more of the criteria from Table 3 have metabolic syndrome.

Dermatology care providers knowledgeable about psoriasis and associated comorbidities can provide proper referral to a primary care physician or specialist. Interdisciplinary collaboration between dermatologists, primary care, and other specialists is important to ensure that care is coordinated and patients receive appropriate follow-up for optimal management of comorbidities

Dermatology care providers can also help by encouraging patients to make healthy lifestyle choices, including following a healthy diet, obtaining adequate physical activity, and avoiding smoking and excessive alcohol consumption. Patients should also be advised to see their primary care physicians for screenings or preventive services that are not part of routine dermatologic care. Additionally, by providing patient education related to psoriasis being a systemic disease, dermatology care providers can encourage patients to become more involved in their disease management and self-care.

## TREATMENT OF PSORIASIS AS A SYSTEMIC DISEASE

Choice of psoriasis treatment is generally based on severity of skin disease and impact on quality of life, although clinicians should also consider the effects of different treatments on systemic inflammation and associated comorbidities. Of particular concern for patients with moderate-to-severe psoriasis is the observation that comorbid cardiovascular disease shortens the average lifespan by five to six years compared with patients with mild psoriasis.[25,28] However, it is not yet known if reducing psoriasis severity can lengthen patient lifespan. Table 4 summarizes a population-based study evaluating differences in risks for associated comorbidities by psoriasis severity.[29] Risk for many inflammatory comorbidities increases significantly with increasing psoriasis severity.

| TABLE 5. | |
|---|---|
| **Treatment** | **Effects on Common Inflammatory Comorbidities** |
| Methotrexate | • Overweight/obese patients at increased risk for hepatic fibrosis associated with methotrexate<br>• Use with caution in patients with liver disease |
| Cyclosporine | • Increased risk for hypertension<br>• Increased risk for hyperlipidemia<br>• May reduce renal function or cause nephrotoxicity |
| Acitretin | • Increased risk for dyslipidemia<br>• Can cause joint pain and nail changes<br>• Associated with elevations in liver enzyme levels |

Because topical therapies and ultraviolet B phototherapy are applied locally to psoriatic lesions, these treatments may

primarily have local effects. In contrast, some conventional oral systemic therapies, especially methotrexate, are associated with reductions in cardiovascular risk in patients with psoriasis and inflammatory arthritis.[30,31] Possible effects of methotrexate on inflammation are being tested in an ongoing study (the Cardiovascular Inflammation Reduction Trial [CIRT]; NCT01594333), evaluating the effects of low-dose methotrexate on major adverse cardiac events incidence in approximately 7,000 patients with type 2 diabetes or metabolic syndrome with history of coronary artery disease.[32]

While conventional systemic treatments may improve skin symptoms and methotrexate may reduce cardiovascular risk, these therapies are associated with systemic side effects, which can negatively impact other organ systems and increase risks for comorbidities (Table 5).[33,34]

Since 2003, eight new biologics have been approved for treatment of moderate-to-severe psoriasis. These therapies target key inflammatory cytokines (ie, TNF-α, IL-17A, IL-12/23, and IL-23) associated with psoriasis pathogenesis. The newest biologics have minimal screening requirements and no requirements for ongoing safety monitoring. Thus, in our opinion, providers must be diligent in screening for comorbidities associated with psoriasis and not become complacent in screening for comorbidities due to the safety profiles of newer biologics. To holistically care for and manage patients with moderate-to-severe psoriasis, providers must fully recognize the systemic nature of the disease.

Retrospective studies have shown that TNF-α inhibitors (eg, adalimumab, etanercept, and infliximab) are associated with cardiometabolic benefits in psoriasis, including reduced incidence of myocardial infarction, improved insulin sensitivity, and prevention of progression of liver injury.[35,36] However, a recent randomized, placebo-controlled trial of adalimumab in psoriasis showed that after 16 weeks of treatment, vascular inflammation levels as measured by 18fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography were not statistically different with TNF-α therapy compared with placebo.[37] The ongoing Vascular Inflammation in Psoriasis (VIP) study of adalimumab (NCT01553058) and the VIP extension study (NCT01866592) will provide further insight into the effects of TNF-α inhibition on vascular inflammation, lipid metabolism, and inflammatory biomarker levels.

The effects of IL-12/23 inhibition on inflammation and risk for cardiovascular events are poorly understood.[28] In a study of 10 patients with moderate-to-severe psoriasis receiving ustekinumab who achieved 75 percent improvement in baseline Psoriasis Area and Severity Index, inflammation of the liver, spleen, and aorta as measured by 18fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography were significantly decreased compared with age, gender, and body mass index-matched controls.[38] The ongoing VIP-Ustekinumab (VIP-U; NCT02187172) study will provide additional data from patients with psoriasis on the effects of IL-12/23 inhibition on cardiometabolic risk.

> "Until the spectrum of disease severity and inflammation is better understood, clinicians should focus their efforts on being alert and sensitive to the myriad inflammatory effects known to occur in patients with psoriasis and to consider these issues as part of the appropriate treatment of patients with psoriasis."

Because IL-17 promotes vascular inflammation, endothelial dysfunction, and arterial hypertension in experimental models of psoriasis,[39,40] it is hypothesized that monoclonal antibodies neutralizing IL-17A (eg, secukinumab and ixekizumab) could reduce inflammation associated with liver and kidney diseases, obesity, hypertension, and atherosclerosis. The ongoing VIP-Secukinumab (VIP-S; NCT02690701) study will evaluate the effects of secukinumab treatment compared with placebo on aortic vascular inflammation in poorly controlled moderate-to-severe plaque psoriasis. Additionally, another study of secukinumab (NCT03055494) is underway, which will evaluate the effect of secukinumab treatment compared with placebo on adipose tissue in moderate-to-severe plaque psoriasis.

## CONCLUSION

Psoriasis is a systemic, inflammatory disease with associated comorbidities, in which the role of important cytokines, such as TNF-α, IL-17, and IL-23, have not been well understood until recently. Dermatology care providers need to consider this association when screening patients for psoriasis and when determining optimal strategies to maximize treatment benefits while balancing known risks. Until the spectrum of disease severity and inflammation is better understood, clinicians should focus their efforts on being alert and sensitive to the myriad inflammatory effects known to occur in patients with psoriasis and to consider these issues as part of the appropriate treatment of patients with psoriasis.

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**Conflicts of Interest**

**Wendy Cantrell** served as an investigator for Eli Lilly, Pfizer, Novartis, Janssen, Merck, AbbVie, and Amgen; and a consultant for Eli Lilly, Pfizer, and Novartis.

**Joe Gorelick** served as a speaker for AbbVie, Allergan, Aqua, Eli Lilly, Novartis, Galderma, Bayer, Cipher, Dusa, Leo, Medimetriks, Promius, PuraCap, Ranbaxy, and Taro; a consultant for Allergan; and an advisory board member for Allergan, Novartis, Galderma, Celgene, Exceltis, Leo, and Regeneron.

**Kristine Kucera** served as a speaker or adviser for AbbVie, Bayer, Janssen, Novartis, Promius, Celgene, Encore, Anacor, GenRX, Regeneron, and Valeant; and a consultant for Eli Lilly.

**Scott Freeman** served as an investigator for DUSA; a speaker for Galderma, Leo, Bayer, Aqua, Promius, and GenRx; and an advisory board member for LeoPharma, Celgene, Novartis, and Genentech. ■

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