# Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities

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Psoriasis is a chronic, inflammatory, multisystem disease that affects up to 3.2% of the US population. This guideline addresses important clinical questions that arise in psoriasis management and care, providing recommendations on the basis of available evidence. (J Am Acad Dermatol 2019;80:1073-113.)

***Key words:*** alcohol; anxiety; cancer; cardiovascular disease; chronic obstructive pulmonary disease; clinical guidelines for psoriasis; comorbidities; congestive heart failure; depression; dermatology; diabetes; erectile dysfunction; guidelines; hyperlipidemia; hypertension; inflammatory bowel disease; malignancy; metabolic syndrome; obesity; obstructive sleep apnea; psoriasis; psoriatic arthritis; relationships; renal disease; sexual health; skin disease; smoking; uveitis; work productivity.

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The following information represents the authors disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts of interest with respect to this guideline are noted with an asterisk (*). In accordance with AAD policy, a minimum 51% of work group members did not have any relevant conflicts of interest.

Participation in ≥1 of the following activities constitute a relevant conflict: service as a member of a speaker bureau, consultant,

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Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies might require revisions to the recommendations in this guideline to reflect new data.

## SCOPE

This guideline addresses the management of extracutaneous manifestations of psoriasis in adults, including comorbid conditions, mental health, psychosocial wellness, and quality of life (QoL). We emphasized the importance of a robust dialogue

or advisory board for pharmaceutical companies on psoriasis disease state, psoriasis drugs in development, or Food and Drug Administration—approved psoriasis drugs or sponsored research funding or investigator-initiated studies with partial or full funding from pharmaceutical companies on psoriasis disease state or psoriasis drugs in development or Food and Drug Administration approved psoriasis drugs. If a potential conflict was noted, the work group member recused themselves from discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline. 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*Abbreviations used:*

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| aHR: | adjusted hazard ratio |
| aOR: | adjusted odds ratio |
| BMI: | body mass index |
| BMJ: | British Medical Journal |
| BSA: | body surface area |
| CI: | confidence interval |
| CKD: | chronic kidney disease |
| COPD: | chronic obstructive pulmonary disease |
| DLQI: | Dermatology Life Quality Index |
| HR: | hazard ratio |
| IBD: | inflammatory bowel disease |
| IL: | interleukin |
| MACE: | major adverse cardiovascular events |
| MI: | myocardial infarction |
| NAFLD: | nonalcoholic fatty liver disease |
| NMSC: | nonmelanoma skin cancer |
| NPF: | National Psoriasis Foundation |
| NSAID: | nonsteroidal anti-inflammatory drug |
| OR: | odds ratio |
| OSA: | obstructive sleep apnea |
| PASI: | Psoriasis Area Severity Index |
| PsA: | psoriatic arthritis |
| QoL: | quality of life |
| RR: | relative risk |
| SIR: | standard incidence rate |
| TNF: | tumor necrosis factor |
| TNFi: | tumor necrosis factor inhibitor |

between the physician and patient to help patients understand the full breadth and depth of this disease, while empowering them to seek appropriate medical and wellness interventions as needed for each individual situation.

## METHOD

An evidence-based model was used. We obtained evidence by searching the PubMed and Medline databases for reports published during January 1, 1980-December 31, 2017, capable of addressing all of the newly identified clinical questions (Table I). Searches were limited to publications in the English language. Medical subject heading terms used in various combinations in the literature search included "psoriasis," "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "metabolic syndrome," "diabetes," "obesity," "dyslipidemia," "hypertension," "nonalcoholic fatty liver disease," "osteoporosis," "renal disease," "kidney failure," "cardiovascular disease," "coronary heart disease," "atherosclerosis," "cardiovascular events," "uveitis,"

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"psoriatic arthritis," "smoking," "tobacco," "cigarette," "smoking cessation," "environmental smoke," "cancer," "neoplasm," "lymphoma," "depression," "psychologic disorder," "anxiety," "suicide (attempt, completed)," "sexual dysfunction," "erectile dysfunction," "work productivity," "interpersonal relations," "alcoholism," and "drinking."

For a full description of the methodology used herein, please refer to the Appendix.

## DEFINITION OF PSORIASIS

See the Appendix for full definition statement.

## INTRODUCTION

Psoriasis is a common inflammatory disease of adults and children, affecting up to 3.2% of adults in the United States.[1] Affected patients are frequently undiagnosed, undertreated, or even untreated.[2] Although skin involvement is often the most

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**Table I.** Clinical questions

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| What are the available screening and/or therapeutic interventions in managing the following comorbidities in adults: |
| i. Psoriatic arthritis |
| ii. Cardiovascular disease |
| iii. Metabolic syndrome |
| iv. Mental health |
| v. Lifestyle choices |
| vi. Inflammatory bowel disease |
| vii. Malignancy |
| viii. Renal disease |
| ix. Sleep apnea |
| x. Chronic obstructive pulmonary disease |
| xi. Uveitis |
| xii. Hepatic disease |

prominent and might be the only recognized manifestation of this disease, recognition of the condition as a chronic, multisystem inflammatory disorder is imperative to optimize management. Psoriasis follows a relapsing course and can negatively impact QoL. Psoriasis is associated with inflammatory arthritis, known as psoriatic arthritis (PsA), with an incidence of 30%-33% in psoriatic patients.[3,4] Although PsA is reviewed in these guidelines, the management of PsA was also reviewed in detail in the American College of Rheumatology and National Psoriasis Foundation treatment guidelines[5,6] and the American Academy of Dermatology guidelines.[7] This section of the guidelines reviews the many potential extracutaneous manifestations of psoriasis in adults.

## PSORIATIC ARTHRITIS

Psoriasis is associated with inflammatory arthritis, known as PsA, in a significant number of patients. In addition, psoriasis can be associated with enthesitis (inflammation at the sites where tendons and ligaments insert into the bone) and dactylitis (inflammation of the small joints of the hands and feet, in association with periarticular swelling). If not adequately treated, PsA can cause significant morbidity. As such, appropriate education of patients and dermatologists about the signs and symptoms of PsA and the potential consequences of delay in diagnosis and management is imperative to optimize patient well-being and prevent permanent joint destruction. Furthermore, PsA is associated with a greater risk for clinical[8] and subclinical[9] diabetes and cardiovascular disease. The topic of PsA was reviewed in detail in the 2011 American Academy of Dermatology psoriasis guidelines[7] and in the American College of Rheumatology and the National Psoriasis Foundation treatment guidelines.[5,6]

PsA can present with various manifestations. Many patients have inflammatory arthritis of their peripheral joints (eg, small joints of the hands and feet, knees, wrists, and elbows) that in some cases can be similar to rheumatoid arthritis. Other patients have inflammatory arthritis of the spine, similar to patients with ankylosing spondylitis.

Screening patients with psoriasis for PsA is essential at each visit. In the vast majority of adult patients, cutaneous disease precedes arthritis, often by years. Uncontrolled arthritis causes radiologic signs of joint damage in >50% of patients evaluated in tertiary care rheumatology centers. Thus, a proactive approach to PsA screening is imperative.

Gisondi et al determined the prevalence of PsA in patients hospitalized for cutaneous psoriasis.[10] Using the European Spondyloarthropathy Study Group criteria, 7.7% (95% confidence interval [CI] 6.0%-9.5%) of patients received PsA diagnoses. The authors noted joint complaints (ie, arthralgia, stiffness, swelling, ankylosis, and paresthesia) were present in as many as 17% of patients. They concluded psoriatic patients experiencing joint symptoms require close clinical or radiologic follow-up to detect early changes of PsA. Similarly, Madland et al estimated the prevalence of PsA to be 1.95 (95% CI 1.80-2.10) per 1000 in the general population (population prevalence 8.6%).[11] There were no significant sex differences in rates; for both sexes, the prevalence was highest in the age group 40-59 years. Mean age was higher (50.6 years for all cases), and mean disease duration was longer (10.7 years), with increasing number of joints affected.

A large cross-sectional observational study was conducted in Europe in 2006 exploring the relationship between the duration of plaque psoriasis and the development of PsA.[12] The incidence of PsA remained constant over time at <1% (74/1000 person-years, Fig 1).[12] The prevalence of PsA increased steadily with disease duration, reaching 20.5% among patients with a 30-year history of psoriasis. Patients with a higher body surface area (BSA) involvement were more likely to acquire PsA (odds ratio [OR] for 1% increase in BSA 1.020, 95% CI 1.012-1.029, $P < .0005$). A study of the prevalence of PsA in the United States in 2005 showed that 11% of psoriasis patients had PsA, with 39% indicating it caused a significant impact on activities of daily living.[13] Thus, after reviewing the body of evidence, the prevalence of PsA among psoriasis patients is 30%-33%, with an onset time of 10-11 years.[14-17]

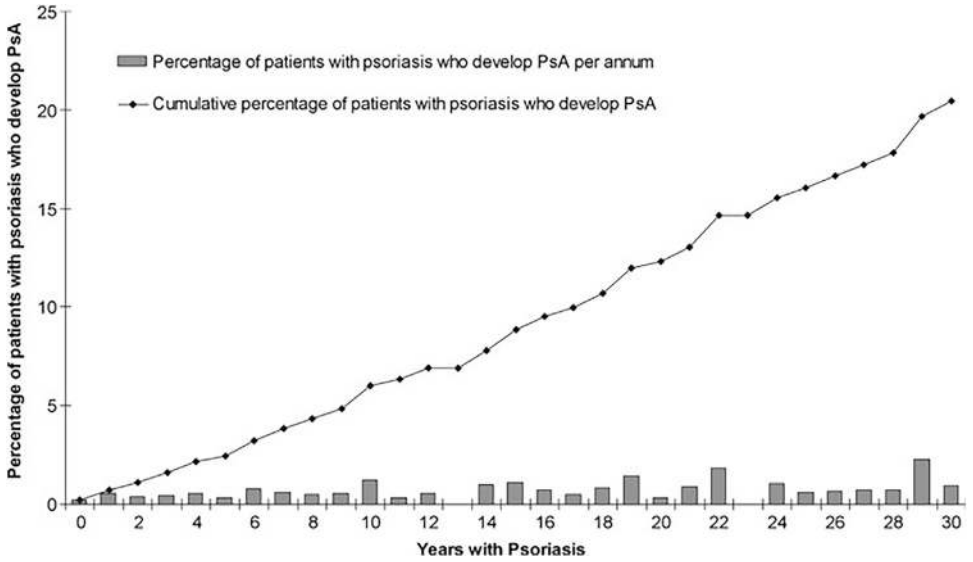


**Fig 1.** Development of PsA relative to duration of skin disease. From: Christophers E, Barker JN, Griffiths CE, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol.* 2010;24(5):548-554.[12] *PsA*, Psoriatic arthritis.

To assess the clinical manifestations and progression of skin disease relative to joint disease in psoriatic patients, Torre Alonso et al performed a prospective study of the clinical features of psoriasis and inflammatory (psoriatic) arthritis in 180 patients using the Moll and Wright classification scheme.[18,19] Skin lesions preceded arthritis in 72.7% of cases; in 9.7% of cases, skin lesions preceded joint involvement by 1 year, in 15.6% by 5 years, and in 47.4% by >5 years. In 14.9% of arthritis patients, articular pathology presented before skin lesions (Fig 2).[19] Similarly, using Moll and Wright's criteria, Scarpa et al performed a prospective study on the timing of cutaneous versus arthritic symptoms in psoriatic patients. Skin lesions preceded development of PsA in 64.5% of patients. In 19.4%, PsA symptoms developed before skin symptoms. Skin and joint symptoms developed simultaneously in 16.1%.[20]

There are several screening tools that have been developed for use among patients with psoriasis. These vary in the data used for assessment. These include the Psoriasis Epidemiology Screening Tool, the Toronto Psoriatic Arthritis Screen, the Psoriatic Arthritis Screening and Evaluation, and the Early Arthritis for Psoriatic Patients questionnaire, among others. These have been studied by several investigators and are moderately reliable and valid.[21] However, these screening tools have tended to perform less well when tested in groups of people other than those for which they were originally developed. As such, their usefulness in routine clinical practice remains controversial. Because screening and early detection of inflammatory arthritis are essential to optimize patient QoL and reduce morbidity, providers may consider using a formal screening tool of their choice.

Identifying inflammatory joint pain consistent with PsA and differentiating it from other causes of pain around the joints, such as osteoarthritis and chronic pain syndromes (eg, fibromyalgia), can be challenging. Depending on clinician time, experience, and interest, physical examination can sometimes help establish inflammatory arthritis and enthesitis if signs of inflammation are present (eg, joint swelling, redness, warmth in addition to tenderness).

Laboratory tests that can indicate systemic inflammation (eg, erythrocyte sedimentation rate, C-reactive protein) are elevated in some patients with PsA, but such testing is neither sensitive nor specific for PsA. As PsA is classically one of the seronegative arthritides, testing for rheumatoid factor or cyclic citrullinate peptide antibodies generally will be negative. Images (eg, plain X-rays) of affected joints can provide some information (eg, demonstrating erosions or other changes consistent with PsA, bony hypertrophy consistent with osteoarthritis), but they might also be normal. Signs or symptoms in or around the joints are sufficient to prompt evaluation and/or consultation.

Regarding inflammatory arthritis distribution, a cross-sectional analysis of patients with psoriasis from Italy was performed; 188 patients with PsA,

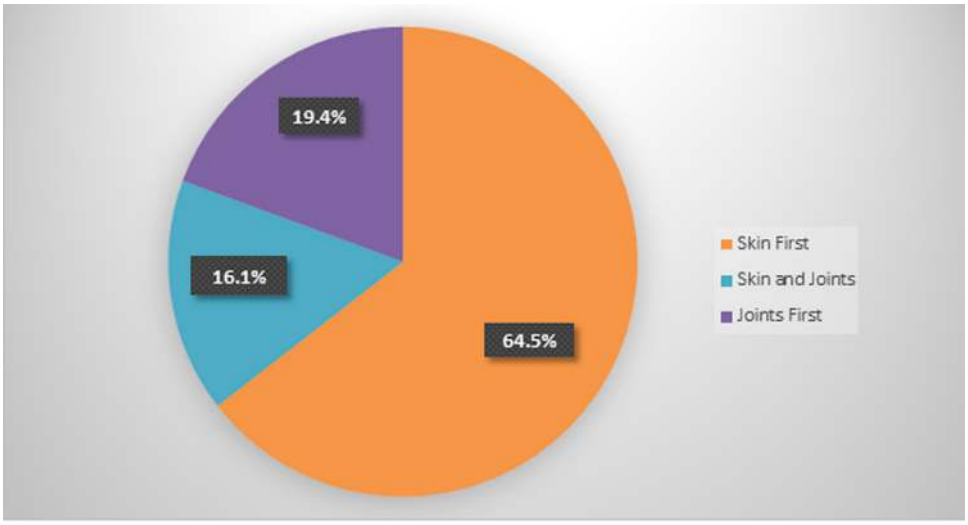


**Fig 2.** Timing of skin and joint involvement in psoriasis. Adapted from: Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM, Ballina Garcia J, Riestra Noriega JL, Lopez Larrea C. Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. Br J Rheumatol. 1991 Aug;30(4):245-50, by permission of Oxford University Press.[19]

including 85 male patients and 95 female patients (mean age 43.8 [range 10-78] years) were evaluated.[20] This study found 38.7% of patients had polyarticular disease, 16.1% mono-oligoarticular disease, 7.5% distal interphalangeal disease, 2.3% deforming or mutilans variant, and 20.9% spondylitic and/or sacroiliatic involvement.

### Role of the dermatologist

Dermatologists play an important role in screening for PsA and informing psoriasis patients about the association between psoriasis and arthritis (Tables II and III).[8-13,16,19,20,22-29] A proactive approach to patient education and a consistent approach to routine screening for signs and symptoms of PsA will facilitate the earliest possible detection. Patients should be encouraged to notify their dermatologists or primary care providers if a musculoskeletal concern (eg, morning joint stiffness, swelling) arises that cannot be explained otherwise. Consultation with a rheumatologist may be considered and pursued if available.

## CARDIOVASCULAR DISEASE

Cardiovascular disease is a common cause of morbidity and mortality in the developed world. In recent decades, there has been a growing awareness of an association between psoriasis and a number of cardiovascular risk factors (metabolic syndrome, as well as its individual components obesity, hypertension, dyslipidemia, and type 2 diabetes) and, consequently, with cardiovascular diseases (both clinical and subclinical events). While the exact mechanism of this association is unclear, it likely involves humoral and cellular inflammatory mediators, which are also important in the generation of arteriosclerosis and other cardiovascular risk factors.[30] In fact, the recent guideline on the management of blood cholesterol by the American Heart Association and American College of Cardiology has identified chronic inflammatory diseases, like psoriasis, as an enhanced risk-inducing factor for atherosclerotic cardiovascular disease.[31] Thus, an increasing awareness of the link between these disorders is both an educational opportunity and a preventive medicine strategy to optimize overall patient health and QoL.

Mansouri et al compared coronary artery calcification in 127 moderate-to-severe psoriasis patients with that in diabetic patients without psoriasis.[32] The 2 groups had equivalent calcification risk, 3 times higher than a subgroup of normal patients. The calcification risk for psoriatic patients was irrespective of body mass index (BMI), whereas BMI correlated with calcification in the diabetic subgroup. Another study recently demonstrated that coronary artery plaque prone to rupture and cause myocardial infarction (MI) was higher in psoriasis patients than in persons 10 years older with established dyslipidemia.[33] These and other studies have consistently demonstrated that patients with psoriasis have a high burden of subclinical atherosclerosis and resulting cardiovascular disease.[8]

Gelfand et al investigated the association of psoriasis and MI in a cohort study using data from the UK

**Table II.** Psoriasis and PsA comorbidity strength of recommendation

| Recommendation number | Recommendation | Strength of recommendation |
|---|---|---|
| 1.1 | Patients with psoriasis should be informed about the association between psoriasis and PsA. | B |
| 1.2 | PsA should be considered in all patients with cutaneous psoriasis. | B |
| 1.3 | Patients with signs and symptoms suspicious for PsA should be fully evaluated for PsA. Initiate appropriate PsA therapy if comfortable with the diagnosis or otherwise consult with a rheumatologist for assessment and management. | A |

*PsA*, Psoriatic arthritis.

**Table III.** Psoriasis and psoriatic arthritis comorbidity level of evidence

| Recommendation | Recommendation number | Level of evidence | Studies |
|---|---|---|---|
| Education | | | |
| Association of psoriasis and psoriatic arthritis | 1.1 | II-III | 8-13,19,20 |
| Screen | | | |
| Psoriatic arthritis | 1.2 | II-III | 10-12,16,20,22-29 |
| Positive screen for psoriatic arthritis: further evaluation and consultation with a rheumatologist | 1.3 | II-III | Expert opinion |

General Practice Research Database registered during 1987-2002.[34] There were 130,980 patients with psoriasis and 556,995 control subjects. Based on prescriptions or treatments, the psoriasis patients were further subdivided by disease severity: mild (n = 127,139) or severe (n = 3837). Overall, the rates of MI were 2.0% for controls, 1.8% for patients with mild psoriasis, and 2.9% for patients with severe psoriasis. The incidence rate per 1000 person-years was 3.58 (95% CI 3.52-3.65) for controls, 4.04 (95% CI 3.88-4.21) for patients with mild psoriasis, and 5.13 (95% CI 4.22-6.17) for patients with severe psoriasis. Furthermore, the adjusted relative risk (RR) was age dependent, with younger patients having the highest adjusted RR for MI (Fig 3).[34]

Further association between psoriasis and cardiovascular health, particularly relating to stroke, was published by Gelfand et al in 2009.[35] The electronic medical records of 132,746 psoriasis patients and 510,996 control patients treated during 1987-2002 were abstracted from the UK General Practice Research Database. The psoriasis patients were assigned to then mild (n = 129,143) or severe (n = 3603) psoriasis groups, depending on medications or treatments. After adjusting for major risk factors for stroke, both mild (adjusted hazard ratio [aHR] 1.06, 95% CI 1.0-1.1) and severe (aHR 1.43, 95% CI 1.1-1.9) psoriasis were independent risk factors for stroke. The excess risk for stroke attributable to patients with psoriasis with mild and severe disease was 1 in 4115 per year and 1 in 530 per year, respectively.

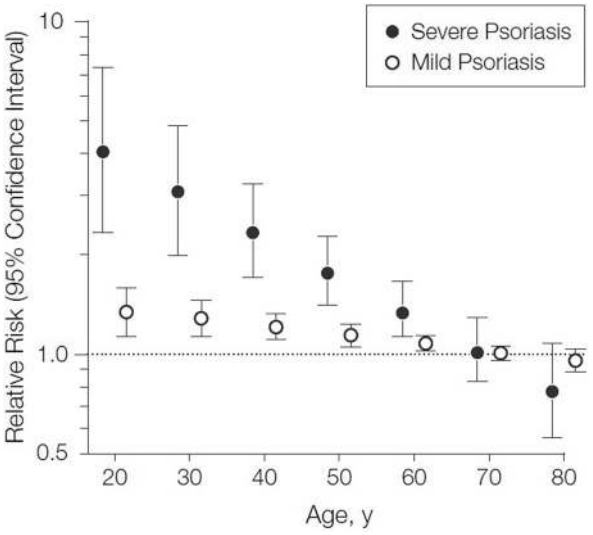


**Fig 3.** Relative risk of myocardial infarction with age for psoriasis patients. Reproduced with permission from: Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741 Copyright © 2006 American Medical Association. All rights reserved.[34]

Major adverse cardiovascular events (MACEs) is a composite of outcomes that includes MI, stroke, heart failure, and cardiovascular death. It is used in most conventional algorithms for patient population

studies and/or personal risk assessment. Examining population studies occurring during 1980-2012 via a meta-analysis, Armstrong et al determined the association between psoriasis and MACEs using data from 9 studies containing 201,239 patients with mild and 17,415 patients with severe psoriasis (severity assigned by medications or treatments).[36] The risk ratio for MACEs in mild psoriasis was 1.03 (95% CI 0.86-1.125) and for severe psoriasis was 1.39 (95% CI 1.11-1.74). The risk ratio for MI in mild psoriasis was 1.29 (95% CI 1.02-1.63) and for severe psoriasis 1.70 (95% CI 1.32-2.18). Last, the risk ratio for stroke in mild psoriasis was 1.12 (95% CI 1.08-1.16) and for severe psoriasis was 1.56 (95% CI 1.32-1.84). The authors concluded that psoriasis accounted for 11,000 additional MACEs in the United States each year and emphasized that all psoriasis patients should be educated about their increased risk for cardiovascular disease. An estimate of additional risk conferred by psoriasis is also demonstrated via a conventional risk adjustment for rheumatoid arthritis and other inflammatory disorders.[30] As such, it is suggested that risk score models should be adapted for patients with psoriasis by using a 1.5 multiplication factor when the psoriasis patient has either >10% BSA involvement or qualifies for systemic therapy or phototherapy.[8,37,38]

With the continued emergence of data establishing the relationship between psoriasis and cardiovascular health, physician scientists questioned the effect, if any, of psoriasis treatment on markers of cardiovascular disease and also subsequent cardiovascular morbidity and mortality. Wu et al performed a retrospective cohort study on 8845 psoriasis patients using data obtained from a health maintenance organization database (Table IV).[39] The study included 1637 patients who were treated with a tumor necrosis factor (TNF) $\alpha$ inhibitor (TNFi), 2097 who were TNFi naive but had received oral systemic treatments or phototherapy, and 5075 who had received only topical therapies. After adjusting for MI risk factors, the TNFi cohort had a significantly lower hazard of MI compared with the topical cohort (aHR 0.50, 95% CI 0.32-0.79). The incidence of MI in the TNFi cohort was 3.05 cases/1000 patient-years, oral and phototherapy cohort 3.85 cases/1000 patient-years, and topical cohort 6.73 cases/1000 patient-years. The authors concluded that the use of TNFi for psoriasis was associated with a significant reduction in MI risk and incidence compared with topical therapies. In addition, the use of TNFi for psoriasis was associated with a lower, but not a significantly lower, MI incidence rate compared with use of oral agents and/or phototherapy for psoriasis. Thereafter, Wu et al performed a study comparing

**Table IV.** Multivariable proportional hazards model assessing factors associated with incidence myocardial infarction in psoriasis patients

| Factor | HR (95% CI) | *P* value |
|---|---|---|
| TNF inhibitors | 0.50 (0.32-0.79) | .003 |
| Oral agents and phototherapy | 0.54 (0.38-0.77) | <.001 |
| Topical agents | Referent | |
| Female sex | 0.51 (0.39-0.67) | <.001 |
| Age ≤65 years | 0.47 (0.36-0.62) | <.001 |
| Psoriatic arthritis | 1.63 (1.15-2.32) | .006 |
| Diabetes mellitus | 2.23 (1.67-2.97) | <.001 |
| Dyslipidemia | 6.05 (3.53-10.36) | <.001 |
| Hypertension | 6.58 (3.49-12.41) | <.001 |
| $\beta$ -Blockers | 1.09 (0.83-1.43) | .56 |
| Statins | 0.31 (0.23-0.43) | <.001 |

*CI*, Confidence interval; *HR*, hazard ratio; *TNF*, tumor necrosis factor.

Reproduced with permission from: Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol.* 2012;148(11):1244-1250. Copyright © 2012 American Medical Association. All rights reserved.[39]

major cardiovascular event risk in psoriasis patients receiving methotrexate or TNFi.[40] The effect of TNFi treatment duration on major cardiovascular event risk was also assessed. Adult psoriasis patients with ≥3 TNFi or methotrexate prescriptions in the commercial health analytics database were classified as TNFi or methotrexate users. Over a 12-month observation period, TNFi users (N = 9148) had fewer cardiovascular events than methotrexate users (N = 8581) (Kaplan-Meier rates 1.5% vs 4.1%, $P < .01$). TNFi-treated patients also had overall lower cardiovascular event hazards than methotrexate users (HR 0.55; $P < .01$). Over a 24-month follow-up period, cumulative exposure to TNFi was associated with an 11% cardiovascular event risk reduction ($P = .02$) (Fig 4).[40] The authors concluded that psoriasis patients treated with TNFi had a lower MACE risk than those receiving methotrexate. Cumulative exposure to TNFi was associated with a reduced risk for MACEs. These results suggest that MACE risk reduces over time with continued therapy for psoriasis.

In a 5-year follow-up study using a Danish nationwide cohort, Ahlehoff et al assessed the rates of MACEs in patients with severe psoriasis treated with systemic anti-inflammatory drugs.[41] A total of 6902 patients with a maximum follow-up of 5 years were included in the analysis. The incidence rate per 1000 patients-years for cardiovascular events was 4.16 for patients taking biologic drugs, 6.28 for those taking methotrexate, 6.08 for those taking cyclosporine, 18.95 for those taking retinoid, and 14.63 for

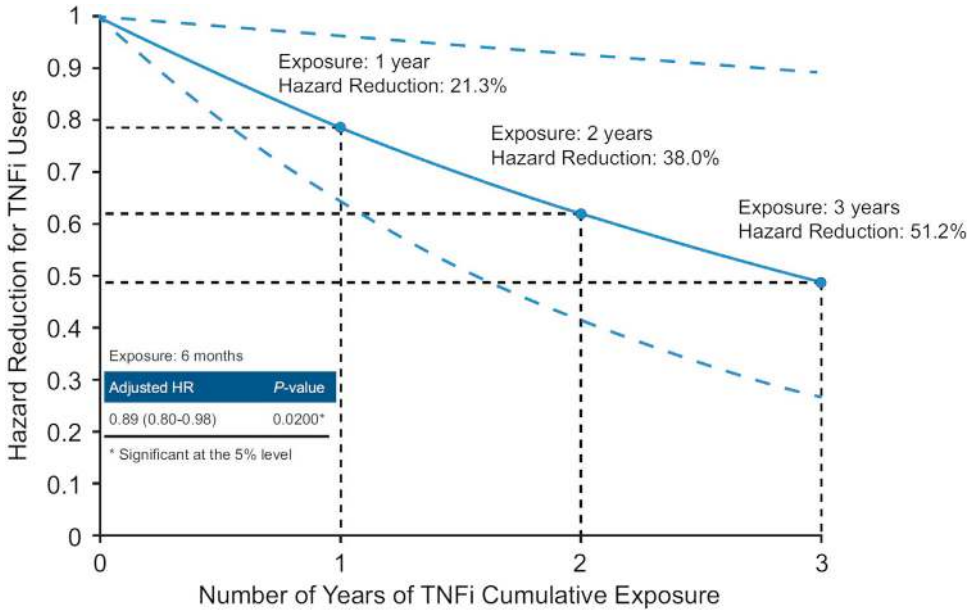


**Fig 4.** Reprinted from *Journal of the American Academy of Dermatology*, 76(1). Wu JJ, Guerin A, Sundaram M, et al. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. pages 81-90. Copyright © 2017, with permission from Elsevier.[40] *HR*, Hazard ratio; *TNFi*, tumor necrosis factor inhibitor.

those taking other therapies (topical medications, phototherapy, climate therapy). Patients treated with either TNFi (HR 0.46, 95% CI 0.22-0.98) or methotrexate (HR 0.53, 95% CI 0.34-0.83) had a reduced risk for MACEs relative to patients treated with other medications. No cardioprotective effect was noted for cyclosporine (HR 1.06, 95% CI 0.26-4.27), oral retinoids (HR 1.80; 95% CI 1.03-2.96), or the interleukin (IL) 12 and 23 inhibitor ustekinumab (HR 1.52, 95% CI 0.47-4.94).

A potential association between MACEs and the use of IL-12/23 antagonists (ustekinumab, briakinumab) was noted when examining data obtained from the placebo-controlled portions of the phase 2 and 3 registration trials.[42] In those trials, 10 MACEs were recorded among the patients receiving IL-12/23 antagonist therapy while no such events occurred in the placebo arm. Due to this imbalance, a more formal statistical analysis was performed. Ryan et al performed a meta-analysis involving 22 placebo-controlled trials containing 10,183 patients who received TNF antagonists or IL-12/23 inhibitors for psoriasis during the initial, placebo-controlled portions of the trials.[30,43] The primary outcome measure was the risk for a MACE occurring during the placebo-controlled portion of each trial. MACEs were noted in 10 of 3179 patients taking IL-12/23 antagonists. Compared with placebo (0 MACE/1474 patients), the Mantel-Haenszel risk difference was 0.012 (95% CI −0.001 to 0.026) events/person-year ($P$ = .12). During the TNFi trials, only 1 of 3858 patients had a MACE. Compared with placebo, the risk difference was −0.0005 (95% CI −0.010 to 0.009) events/person-year ($P$ = .94). The authors concluded that neither comparison was statistically significant. In addition, the study was potentially underpowered to identify a cardiovascular risk. In contrast, a meta-analysis by Tzellos et al comparing patients treated for chronic plaque psoriasis (without PsA) versus placebo but using the Peto 1-step method for statistical analysis found a statistically significant risk for MACEs in patients treated with ustekinumab and briakinumab (OR 4.23, $P$ = .04).[44]

Similarly, a study comparing topical or phototherapy, TNFi, and ustekinumab in 7550 patients with psoriasis showed that patients treated with TNFi or ustekinumab had no increased risk for a major cardiovascular event relative to patients treated with topical therapy and/or phototherapy alone.[45]

Unlike the data on TNFi and MACEs, the effects of TNF inhibition on the development or progression of congestive heart failure is less clear. No benefit was shown in randomized clinical trials involving the use of TNFi in congestive heart failure patients. In 1 trial, TNFi therapy was associated with increased mortality compared with control therapy.[46] In a population-based study involving 486 patients with congestive heart failure, Dunlay et al showed that mortality was associated with increasing TNFi use ($P$ = .016), with 1-year mortality estimates of 16%,

18%, 23%, and 32% for patients in the lowest to highest TNF-$\alpha$ quartiles, respectively.[47] Results such as these have led to the current recommendation that use of TNFi is relatively contraindicated in psoriasis patients with New York Heart Association class III or IV congestive heart failure (classification in Table V).[48]

### Role of the dermatologist

Because the risk factors for cardiovascular disease are commonly associated with psoriasis, dermatologists should inform patients regarding this association and ensure the patient is engaged with his or her primary care provider or cardiologist for appropriate screening (Tables VI-IX).[8,30,32-34,36-38,49-58] Such screening measures may include height, weight, blood pressure, blood glucose, hemoglobin A1C, lipid levels, abdominal circumference, and calculation of BMI. Efforts aimed at lifestyle modification (dietary changes to achieve and maintain a normal BMI, smoking cessation, exercise regimen) are also important. Screening intervals may vary between patients on the basis of their individual risk factors and overall health. Consultation with cardiologists and other specialists should be performed as deemed necessary by the dermatologist or primary care provider to confirm diagnoses and establish a treatment plan.

## METABOLIC SYNDROME

Metabolic syndrome is a term used to describe the presence of the collective cardiovascular risk factors of obesity, hypertension, dyslipidemia, and insulin resistance.[59] The diagnosis of metabolic syndrome is made when patients meet ≥3 of the 5 criteria listed in Table X.[60] These conditions frequently coexist in affected patients and have a significant role in overall wellness, morbidity, and mortality. Thought to be due to insulin resistance and adipose tissue dysfunction,[61] metabolic syndrome has been estimated to occur in up to 25% of the general population.[62,63]

The presence of metabolic syndrome in patients with psoriasis, women more so than men, is increasingly evident. Numerous studies confirm this association.[64] Screening for metabolic syndrome by the patient's primary care physician or dermatologist is clinically relevant because of the increased incidence of cardiovascular disease, fatty liver disease, certain forms of cancer, and death in this group of patients.[65] Physicians who care for patients with psoriasis thus have the opportunity to improve the health of their patients by informing them of this association and, if they have features of metabolic syndrome, referring them to the appropriate health care provider for treatment.

**Table V.** New York Heart Association classification of CHF

| Class | Symptoms |
|---|---|
| I | No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations (asymptomatic left ventricular dysfunction). |
| II | Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pectoris (mild CHF). |
| III | Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF). |
| IV | Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF). |

Reprinted with permission. © 1994 American Heart Association, Inc. The Criteria Committee for the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels Ninth Edition*. Boston, Massachusetts: Little Brown and Company. 1994; p 253-255.
*CHF*, Congestive heart failure.

Langan et al compared 4065 patients with psoriasis to 40,650 practice-matched control patients.[66] In total, 34% of psoriasis patients met the criteria for metabolic syndrome, compared with 26% of the controls (OR 1.50, 95% CI 1.40-1.61). Adjustments for age, sex, follow-up, smoking, and social class did not significantly alter these values. This group also examined individual components of the syndrome and found many individual disorders were significantly more common in patients with psoriasis than controls. These included obesity (38% vs 31%; OR 1.38, 95% CI 1.29-1.48), elevated triglycerides (36% vs 28%; OR 1.49, 95% CI 1.39-1.60), hypertension (31% vs 28%; OR 1.20, 95% CI 1.11-12.9), and elevated glucose levels (22% vs 16%; OR 1.44, 95% CI 1.33-1.56). The prevalence of metabolic syndrome increases with increased BSA affected by psoriasis.

Armstrong et al performed a retrospective meta-analysis on 12 observational trials having a total of 1.4 million enrolled patients, 41,853 of whom had psoriasis.[67] For the entire data set, the association of metabolic syndrome with psoriasis was significant (pooled adjusted OR 2.26, 95% CI 1.70-3.01). A study by Langan et al addressed the association between the risk for metabolic syndrome and psoriasis disease severity.[66] A total of 44,715 individuals were included: 4065 with psoriasis and 40,650 controls. Overall, 2044 participants had mild psoriasis (<2% BSA), 1377 had moderate psoriasis (3%-10% BSA), and 475 had severe psoriasis (>10% BSA). Psoriasis was associated with metabolic syndrome (adjusted OR [aOR] 1.41, 95% CI 1.31-1.51), varying in a

**Table VI.** Psoriasis and cardiovascular disease comorbidity strength of recommendation

| Recommendation number | Recommendation | Strength of recommendation |
|---|---|---|
| 2.1 | CV risk assessment (screening for hypertension, diabetes, and hyperlipidemia) with national guidelines is recommended for all patients with psoriasis. | B |
| 2.2 | Clinicians should consider early and more frequent screening for hypertension, diabetes, and hyperlipidemia in psoriasis patients who are candidates for systemic or phototherapy or who have psoriasis involving >10% of the BSA. | B |
| 2.3 | Risk score models should be adapted for patients with psoriasis by introducing a 1.5 multiplication factor when the patient with psoriasis meets either criteria: disease severity of BSA >10% or candidate for systemic or phototherapy | C |
| 2.4 | CV risk management in psoriasis for hypertension and dyslipidemia should be carried out according to national guidelines. The target for blood pressure and lipid levels are based on risk calculated for psoriasis. Antihypertensives and statins may be used as in the general population. CV risk management should be performed by either a primary care physician or other health care provider experienced in CV risk management or the dermatologist. | C |

*BSA*, Body surface area; *CV*, cardiovascular.

**Table VII.** Psoriasis and cardiovascular disease comorbidity level of evidence

| Recommendation | Recommendation number | Level of evidence | Studies |
|---|---|---|---|
| Risk assessment | | | |
| Recommended for all patients with psoriasis | 2.1 | II-III | 8,30,32-34,36,37,49-51 |
| Screening | | | |
| Early and more frequent screening for hypertension, diabetes, and hyperlipidemia in patients who are candidates for systemic or phototherapy or who have psoriasis involving >10% body surface area | 2.2 | II-III | 37,49-51 |
| Risk score models | | | |
| Should be adapted by introducing a 1.5 multiplication factor for patients with either >10% body surface area involvement or those who are candidates for systemic or phototherapy | 2.3 | II-III | 8,37,38,52 |
| Risk management | | | |
| Should be carried out according to national guidelines and performed by either primary care physician or dermatologist | 2.4 | III | 8,36,49-51,53-55 |
| Target blood pressure and lipid levels are based on risk as previously calculated | | | |
| Antihypertensives and statins may be used as in general population | | | |

**Table VIII.** Standard screening recommendations*

| Type | Criteria | Frequency |
|---|---|---|
| Hypertension[56] | Normal BP <120/80 mmHg | |
| | Age 18-39 years, no risk factors, and BP <130/85 mmHg | Every 3-5 years |
| | Age >40 years and those at increased risk for high BP (BP 130-139/85-89 mmHg, overweight/obese, black) | Yearly |
| Diabetes[57] | Adults aged 40-70 years with BMI ≥25 kg/m$^2$ | Every 3 years |
| | In those without any risk factors, testing should begin at age 45 years[58] | |
| Cardiovascular risk assessment[53] | Adults aged 20-79 years with standard risk factors (including hypercholesterolemia, obesity) | Every 4-6 years |
| | Adults aged 40-79 years: estimate 10-year risk | |

*BP*, Blood pressure.
*Based on other evidence-based guidelines.

**Table IX.** Lifestyle counseling including dietary and exercise recommendations[54,55]*

| |
|---|
| Adults age 25-80 years with type 2 diabetes mellitus |
| Adults age 25-80 years with ≥3 cardiovascular risk factors |
| Adults age 25-80 years with SBP >130 mmHg or DBP >90 mmHg |

*DBP*, Diastolic blood pressure; *SBP*, systolic blood pressure.
*Based on other evidence-based guidelines.

**Table X.** Definition of metabolic syndrome

| NCEP ATP III definition of metabolic syndrome |
|---|
| Increased waist circumference |
| M >40 inches (102 cm) |
| F >35 inches (88 cm) |
| Blood pressure >130/85 mmHg |
| Fasting triglycerides >150 mg/dL |
| Fasting HDL cholesterol levels |
| M <40 mg/dL |
| F <50 mg/dL |
| Fasting glucose ≥100 mg/mL |

*HDL*, High-density lipoprotein; *NCEP ATP*, National Cholesterol Education Program, adult treatment panel.
Adapted from: Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation.* 2005;112(17):2735-2752.[60]

severity-dependent manner, from mild (aOR 1.22, 95% CI 1.11-1.35) to severe psoriasis (aOR 1.98, 95% CI 1.62-2.43). The authors concluded that psoriasis is associated with metabolic syndrome and that the association is higher with increasing psoriatic disease severity.

These studies support the recommendation that patients with psoriasis should be informed about the risk for metabolic syndrome and be evaluated according to national guidelines by their primary care provider or dermatologists for its components by measuring blood pressure, waist circumference, fasting blood glucose and/or hemoglobin A1C, and fasting lipid levels.

Each component of metabolic syndrome will be reviewed individually below to further delineate the comorbidity of this specific condition in the psoriasis population.

## Obesity

Obesity is a complex chronic disease with a variety of genetic and environmental factors, and it affects a substantial portion of the general population. It is a significant risk factor for cardiovascular diseases, type 2 diabetes mellitus, obstructive sleep apnea (OSA), and osteoarthritis,[68] and it is a leading cause of premature and avoidable death.[59] Recent population-based studies increasingly reveal both adult and pediatric psoriasis patients are disproportionately affected compared with the general population.

The relationship between psoriasis and obesity is unclear. Increased levels of pro-inflammatory cytokines (eg, TNF-$\alpha$, IL-1$\beta$, and IL-6) and adiponectin are detected in the serum of obese patients. In addition, TNF-$\alpha$ is expressed and secreted in adipose tissue in levels correlating with the degree of adiposity. Visceral adipose tissue, also referred to as central obesity, is associated with diabetes and cardiovascular disease. The visceral adipose tissue is greater in psoriasis patients and strongly associated with subclinical vascular disease.[69]

BMI is the most commonly used metric to classify obesity in adults. Its calculation is based on the height and weight of the patient (Tables XI and XII).[70]

Obesity in adults is further classified as central or peripheral, with central obesity defined as abdominal circumferences of 40 inches (102 cm) in men and 35 inches (88 cm) in women.[71] The presence of central adiposity is associated with the presence of cardiovascular disease and/or metabolic syndrome.

Armstrong et al performed a comprehensive review and meta-analysis of 16 observational studies including 2.1 million patients.[72] Obesity was defined as BMI ≥30 kg/m$^2$ in most studies or coded directly using International Classification of Diseases codes. Of these 16 studies, 4 reported the number of patients having mild disease with obesity, and 5 reported the number with moderate-severe psoriasis with obesity. In summation, the pooled OR for all psoriatic patients with obesity was statistically significant (OR 1.66, 95% CI 1.46-1.89). A severity-dependent relationship was noted in studies where the degree of psoriasis severity was reported. The association with obesity was stronger in patients with moderate-to-severe psoriasis (OR 2.23, 95% CI 1.63-3.05) than those with mild psoriasis (OR 1.46, 95% CI 1.17-1.82).

Recently the effect of weight loss in obese psoriatic patients has been examined. A study in 2013 assessed the effect of weight reduction on psoriasis severity in overweight patients; 60 obese psoriatic patients were enrolled in a prospective randomized clinical trial and allocated to receive either a low-energy diet (800-100 kcal/day) for 8 weeks or to eat ordinary healthy foods.[73] For all patients at baseline, the median Psoriasis Area Severity Index (PASI) was 5.4 (interquartile range 3.8-7.6). At week 16, the mean body weight loss was 15.4 (95% CI 12.3-18.5)

**Table XI.** Calculation of body mass index

| Metric, $kg/m^2$ | United States, $lbs/in^2$ |
|---|---|
| Weight/(height$^2$) | Weight/(height$^2$) × 703 |

Adapted from: World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation (WHO Technical Report Series 894). 2000.[70]

**Table XII.** Classification of obesity of adult patients by body mass index

| Terminology | Body mass index, $kg/m^2$ |
|---|---|
| Underweight | <18.5 |
| Normal | 18.5-24.9 |
| Overweight | 25.0-29.9 |
| Obese class I | 30.0-34.9 |
| Obese class II | 35.0-39.9 |
| Obese class III | ≥40.0 |

Adapted from: World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation (WHO Technical Report Series 894). 2000.[70]

kg greater in the intervention group than in the control group ($P < .001$). In addition, the mean differences in PASI (−2.0, 95% CI 4.1 to −0.1, $P = .06$) and Dermatology Life Quality Index (DLQI; −2.0, 95% CI −3.6 to −0.3, $P = .02$) also favored the low-energy diet group. These results indicate a low-energy diet (with subsequent weight loss) might cause a modest reduction in PASI and improve a patient's QoL.

Egeberg et al published the effects of bariatric surgery in a population-based cohort study involving Danish patients who received gastric bypass and gastric banding; they assessed the incidence of new-onset psoriasis or progression from mild to severe psoriasis in this population.[74] Danish patients who had received gastric bypass (n = 12,364) or gastric banding (n = 1071) were identified. The adjusted HRs for new-onset psoriasis were 0.52 (95% CI 0.33-0.81) for gastric bypass and 1.23 (95% CI 0.40-3.75) for gastric banding. The adjusted HRs for progression from mild to severe psoriasis were 0.44 (95% CI 0.23-0.86) for gastric bypass and 1.18 (95% CI 0.12-11.49) for gastric banding. The authors concluded that gastric bypass was associated with a significant risk reduction for the development of psoriasis and improved the prognosis of psoriasis. Interestingly, gastric banding was not related to psoriasis risk reduction. Thus, if a psoriasis patient with a BMI >40 $kg/m^2$ fails standard weight loss measures, gastric bypass surgery should be strongly considered.

When treating a patient with psoriasis, regardless of baseline weight, the effect of treatment on weight management is an important variable to consider. With regards to weight loss, the use of apremilast was associated with weight loss in pivotal phase 3 trials.[75] In total, 1184 patients taking apremilast 30 mg twice a day were followed for 156 weeks. At that time, 21.9% of patients had lost >5% of their baseline body weight. Furthermore, anti−TNF-$\alpha$ agents are frequently used to treat a variety of inflammatory diseases including psoriasis. Because TNF-$\alpha$ is also involved in body weight homeostasis, the effect of anti−TNF-$\alpha$ therapy on weight change in psoriasis patients was explored in several studies.

Gisondi et al performed a retrospective controlled analysis of changes in body weight and BMI using 3 cohorts of patients followed for 6 months and treated with etanercept (n = 58), infliximab (n = 40), or methotrexate (n = 43).[76] During that period, a weight (mean ± standard deviation) increase of 1.5 ± 2.7 kg ($P = .0002$) in patients treated with etanercept and 2.5 ± 3.3 kg ($P = .004$) in patients treated with infliximab was noted. In contrast, methotrexate was not associated with weight change (0.6 ± 1.4 kg, $P = .4$). Similar treatment effects were noted for BMI measurements. Overall, roughly 25% of patients experienced a 4−10-kg weight gain. Differences in body weights between those treated with anti−TNF-$\alpha$ therapies and methotrexate were statistically significant ($P = .0005$). A similar study by Gisondi et al compared changes in body weight and BMI between psoriasis patients treated for 7 months with infliximab or ustekinumab. This study showed that while infliximab had a superior ≥75% reduction in PASI relative to ustekinumab (69% vs 58%), patients treated with infliximab had a statistically significant increase in BMI (2.1% ± 4.5%) and weight gain (2.5 ± 3.3 kg) compared with those who received ustekinumab (BMI 0.1% ± 3.3%; weight gain 0.6 ± 1.1 kg).[77]

Similarly, a 4-month, noninterventional, cross-sectional, multicenter study on adults with psoriasis was performed in 19 dermatologic centers in France.[78] In total, 191 psoriatic patients were included (68.6% male patients, mean age 46.9 years). After 1 year of infliximab therapy, approximately half (48.2%) had weight gain, with 9.9% experiencing a weight increase of >10%. In a multivariate analysis, patients with a hospital dietary follow-up (OR 0.36, 95% CI 0.16-0.79, $P = .01$) and patients on methotrexate (OR 0.41, 95% CI 0.18-0.93, $P = .03$) during infliximab treatment were thinner. The authors concluded that significant weight gain occurred with infliximab treatment, and it occurred more frequently in men and patients with severe psoriasis.

Patients with moderate-to-severe psoriasis should have their obesity status determined annually. This

includes measuring height, weight, waist circumference, and calculating BMI. Patients of obesity class 1 or higher (BMI >30 kg/m$^2$) and/or abdominal obesity should be referred to their primary care physician for further education and evaluation. Psoriatic patients already being monitored for obesity should be encouraged to maintain a healthy lifestyle and keep regularly scheduled follow-up visits with their primary care provider or dermatologist.

## Hypertension

Blood pressure is the measure of force of blood flow against arterial walls and is influenced by various factors, including age, vessel pliability, and vessel lumen patency. Patency can be negatively altered by plaque formation within vessel walls, as well as by inflammation and scarring from a myriad of disorders. Hypertension stages are defined by the American Heart Association (Table XIII).[53,79] Hypertension is a leading cause of death worldwide and a prominent feature of psoriasis patients. Whether psoriasis and hypertension are closely related is less clear because large, well-controlled, high-quality studies have failed to consistently demonstrate this important relationship.

Gelfand et al did not find an association between high blood pressure and psoriasis while studying MI and stroke in this patient population.[34,35] In a case-control study, Cohen et al examined 12,502 psoriasis patients >20 years of age and compared them to 24,285 age— and sex-frequency—matched controls who were enrolled in a health maintenance organization.[80] They determined that hypertension was significantly higher in psoriatic patients (38.8%) than controls (29.1%, $P < .001$). Hypertension was associated with psoriasis in a multivariate analysis when controlling for age, sex, smoking status, obesity, diabetes, nonsteroidal anti-inflammatory drugs (NSAIDs) and Cox-2 inhibitor use (OR 1.37, 95% CI 1.29-1.46).

In a review of a large health insurance database in Germany, Augustin et al identified 33,981 psoriatic patients from a data set of 1,344,071 patients.[81] The prevalence of hypertension in this cohort was higher for psoriasis patients (35.6%) than controls (20.6%) (prevalence rate 1.73, 95% CI 1.71-1.76). A similar review and meta-analysis in 2013 by Armstrong et al of 24 population-based observational studies reported on the severity of psoriasis and hypertension.[65] In total, 309,469 psoriatic patients were identified and compared with 2.7 million control patients. The OR for hypertension in all psoriatic patients versus controls was 1.58 (95% CI 1.42-1.76). In psoriatic patients with mild disease, the OR for hypertension compared with controls was 1.30 (95% CI 1.15-1.47). When comparing severe psoriasis patients with controls, the OR for hypertension increased to 1.49 (95% CI 1.20-1.86).

**Table XIII.** Blood pressure categories in adults

| Blood pressure category | Systolic, mmHg | | Diastolic, mmHg |
|---|---|---|---|
| Normal | <120 | and | <80 |
| Elevated | 120-129 | and | <80 |
| Stage 1 hypertension | 130-139 | or | 80-90 |
| Stage 2 hypertension | ≥140 | or | ≥90 |
| Hypertensive crisis* | >180 | and/or | >120 |

Use the highest category of the systolic and diastolic values.
Adapted from: Whelton PK, Carey RM. The 2017 American College of Cardiology/American Heart Association clinical practice guideline for high blood pressure in adults. *JAMA Cardiol.* 2018;3(4):352-353.[79]
*Patients needing prompt changes in medication (if there are no other indications of problems) or immediate hospitalization (if there are signs of organ damage). For more information, please see https://www.acc.org/latest-in-cardiology/articles/2017/11/08/11/47/mon-5pm-bp-guideline-aha-2017.

Takeshita et al found an association between psoriasis and inadequately controlled hypertension when using The Health Improvement Network to query the electronic medical records of 7.5 million patients in 415 UK practices.[82] This database is maintained by general practitioners and is thought to be representative of the average UK patient. A random sample of patients with psoriasis and hypertension aged 25-64 years (n = 1322) were compared with age-matched and practice-matched hypertensive controls without psoriasis (n = 11,977). The analysis revealed that with increasing skin disease severity (defined by the percentage of BSA affected), blood pressure was more difficult to control.

Queries have arisen regarding the effect of particular medications or drug classes used for hypertension and their effect, if any, on psoriasis manifestations and management. Many case reports have shown a worsening of psoriasis associated with the use of $\beta$-blockers and calcium-channel blockers. The relationship between the use of antihypertensive medications and flare of psoriasis or development of new onset psoriasis was explored in the following studies.

In the United Kingdom, a population-based case—control study examined the relationship of $\beta$-blocker use with 36,702 newly diagnosed psoriatic patients having an equal number of matched controls.[83] The cohorts were stratified for current use of $\beta$-blockers and having 1-4, 5-19, and ≥20 prescriptions for $\beta$-blockers. The study showed no association, with adjusted ORs (aORs) of 0.93 (95% CI 0.76-1.13), 1.10 (95% CI 0.97-1.24), and 1.10 (95% CI 1.01-1.20), respectively. The authors also reported risk estimates for the use of other antihypertensives at any exposure duration were all close to 1.0 (ie, no associations).

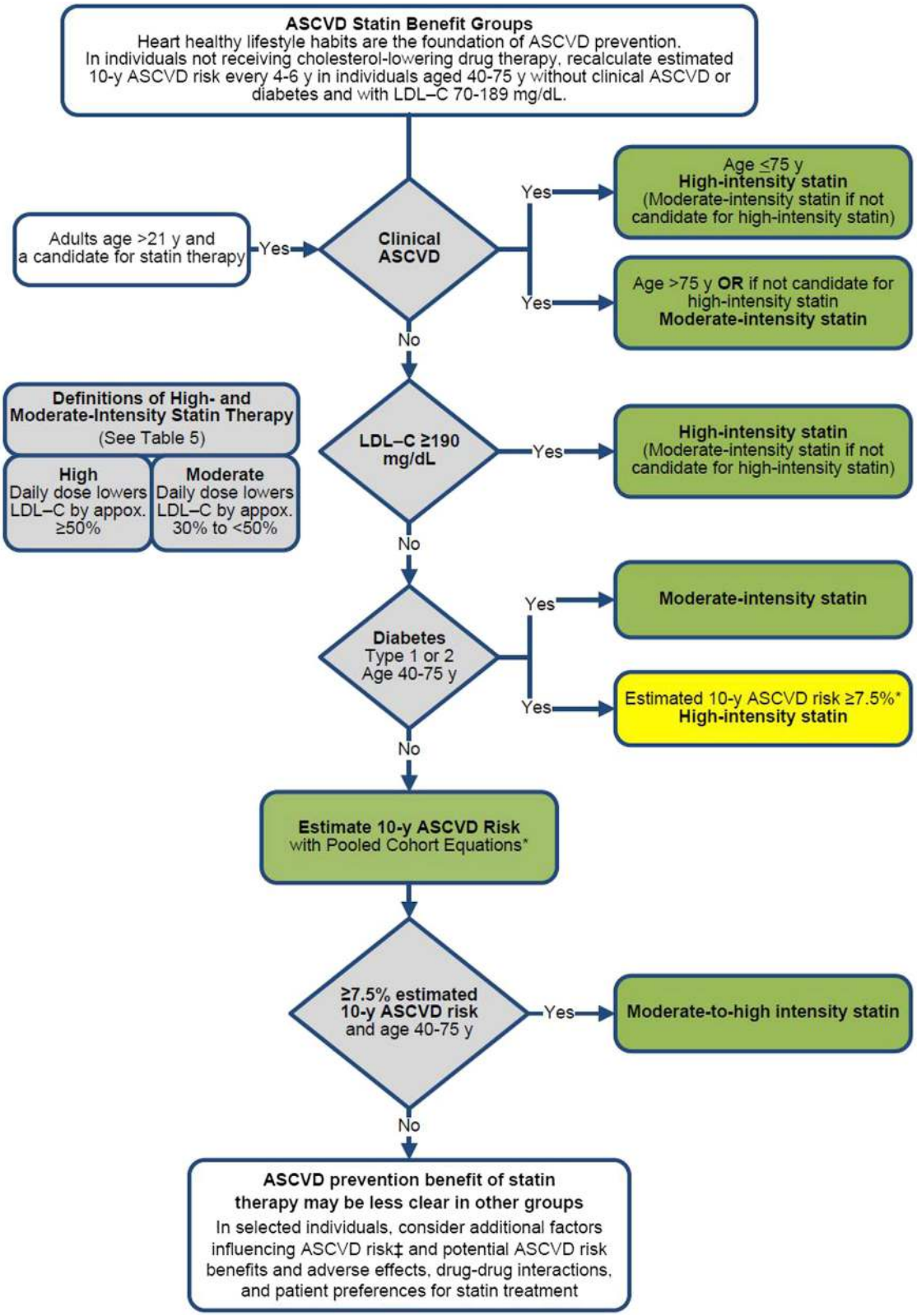


**Fig 5.** From: Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 (https://www.ahajournals.org/cms/attachment/069caaec-0338-4b71-8182-9e841cb8c509/01.cir.0000437738.63853.7av1.pdf).[87] *ASCVD*, Atherosclerotic cardiovascular disease;

Using data obtained from the Nurse's Health Study, Wu et al tested the association between β-blocker use and psoriasis with nurses who used β-blockers and control nurses who never used β-blockers.[84] No association was seen when β-blockers were used for <6 years. A statistically significant association was noted when β-blockers were used for ≥6 years (OR 1.39, 95% CI 1.11-1.73). The authors concluded long-term regular use of β-blockers was a possible risk factor for developing psoriasis.

A cohort study with nested case-controls and data obtained from the UK General Practice Research Database was reported in 2007. In total, 3994 cases of psoriasis confirmed by a general practitioner and 10,000 nonpsoriasis controls were included in the analysis.[85] No association with the use of antihypertensive agents (OR 0.9, 95% CI 0.8-1.0) was seen. In addition, there was no effect when specific groups of antihypertensives were tested as an independent risk factor (eg, β-blockers, calcium channel blockers).

These studies support the association of psoriasis and hypertension, which is strongest in patients with more severe disease. Taking this collective information into account, the preponderance of the evidence does not support the avoidance of particular antihypertensive medications (β-blockers, calcium-channel blockers, or others) in patients with psoriasis.

Conversely, it should be noted that some medications used to treat psoriasis can induce or worsen hypertension. For example, cyclosporine commonly causes new-onset hypertension or worsening of pre-existing hypertension. The calcium-channel blocker amlodipine is often found to successfully reverse the effects of cyclosporine-induced hypertension.[86]

## Dyslipidemia

Dyslipidemia refers to the persistent elevation of serum cholesterol and/or triglycerides. Elevated serum lipid levels can be due to primary (genetic) influence, secondary causes (including diseases and lifestyle factors), or both. Dyslipidemia over time leads to atherosclerosis, which is a known comorbidity for psoriasis patients, as discussed earlier in this text. The American College of Cardiology and American Heart Association published a guildeline for cholesterol management,[87] which recently was revised in context of international guidelines.[88] Although patients often presume a direct relationship between obesity and hyperlipidemia exists, the 2 conditions are not codependent. Patients of normal body weight can have dyslipidemia, and obese patients might have normal lipid levels.

In a study designed to assess the risk factors for MI occurring after the diagnosis of psoriasis, Kaye et al compared 44,164 psoriasis patients with 219,784 controls matched by age, sex, and index date.[89] The psoriasis cohort had a higher risk for hyperlipidemia than the control patients (HR 1.17, 95% CI 1.11-1.23). Al-Mutairi et al determined the prevalence of comorbidities in 1835 psoriatic patients with an equal number of controls.[90] In total, 1661 of 1835 patients were classified as having mild or moderate disease and 129 as having severe psoriasis. Adjustments were made for age, sex, and area of residence. In patients with mild or moderate disease, the aOR for dyslipidemia was 3.379 (95% CI 2.631-4.34, $P$ = .00001). For patients with severe psoriasis, the aOR for dyslipidemia was 5.55 (95% CI 3.49-8.83, $P$ = .00001). In addition to elevated cholesterol levels, the cholesterol molecule is smaller, denser, and dysfunctional in psoriatic patients relative to unaffected persons,[91] which also augments subclinical atherosclerosis.[92]

Similarly, Prodanovich et al examined cardiovascular risk factors associated with psoriasis.[93] In total, 3236 patients with a psoriasis diagnostic code were compared with 2500 control patients without a psoriasis diagnostic code. The OR for dyslipidemia in psoriasis patients was 4.35 (95% CI 3.73-5.06) versus controls. In another study, the association of

*LDL-C*, low-density lipoprotein cholesterol. *Percent reduction in LDL−C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal. ‡Primary LDL−C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, highsensitivity C-reactive protein >2 mg/L, CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity, ankle-brachial index <0.9, or elevated lifetime risk of ASCVD. For complete information on the summary of *Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults* please see link A below for 2013 guidelines and B for the updates in 2018 by the ACC/AHA. In the 2018 updated guidelines, psoriasis was deemed an ASCVD risk-enhancing condition favoring early initiation of statin therapy. A: https://www.ahajournals.org/doi/full/10.1161/01.cir.0000437738.63853.7a?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed. B: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000625 and https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf.

psoriasis with several vascular and metabolic disorders was evaluated; this case-controlled study involved 232 patients admitted for inpatient treatment of psoriasis and 1044 control patients hospitalized for surgical treatment of stage 1 melanoma.[94] The aOR for dyslipidemia between the 2 cohorts, adjusted for age and sex, was 2.09 (95% CI 1.23-3.54).

However, not all studies have shown a significant relationship between psoriasis and dyslipidemia. In a large, retrospective case-controlled study of patients in a managed care organization, Cohen et al tested the relationship of psoriasis with elements of metabolic syndrome.[95] For 6578 patients with psoriasis or PsA, the OR for elevated triglycerides was 1.0 (95% CI 1.0-1.3) and for low high-density lipoprotein cholesterol was 0.9 (95% CI 0.8-1.0) when compared with 5471 control patients.

Since dyslipidemia has a prominent role in cardiovascular disease, and some studies have found an association between psoriasis and dyslipidemia, all physicians caring for patients with moderate-to-severe psoriasis should ensure that patients have screening lipid tests performed periodically.[96] These tests include fasting total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Nonfasting laboratory tests are preferred over not obtaining test results, given the increased frequency of dyslipidemia in patients with severe psoriasis. Treatment targets for low-density lipoprotein cholesterol in patients with metabolic syndrome are recommended by the American College of Cardiology and American Heart Association (Fig 5).[87] Patients not meeting these target metrics should be referred to their primary care provider for further assessment and management.

Certain medications used to treat psoriasis have a known adverse effect on serum lipid levels, most notably acitretin and cyclosporine. Serum lipid levels should be monitored routinely upon initiation of these medications and when medication dosages are increased.

### Insulin resistance

Diabetes is a metabolic disorder characterized by hyperglycemia induced by defects in insulin production or action. Chronic hyperglycemia is associated with long-term organ damage, such as dysfunction and failure of the eyes, kidneys, peripheral nerves, and heart and blood vessels. Since many diabetes-related complications can be prevented, early diagnosis and treatment are essential. Untreated or poorly controlled diabetes can lead to a variety of acute and chronic life-threatening conditions, such as diabetic ketoacidosis and hyperosmolar syndrome. The most common cause of death in diabetics is cardiovascular disease.[61] According to the National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation, the prevalence of diabetes has been increasing over many years. As of 2017, it is estimated that 9.3% (95% CI 11.3%-13.2%) of people aged ≥18 years are diabetic.[97]

Augustin et al evaluated the prevalence of comorbidities in psoriasis using a large retrospective cross-sectional health insurance database.[81] The prevalence rates of diabetes in 33,981 psoriatic patients versus 1,344,071 controls were determined after adjusting for hypertension, obesity, and dyslipidemia. In this data set, the prevalence rate of diabetes was higher in patients with psoriasis (12.1%) than controls (6.0%) (prevalence rate ratio 2.02, 95% CI 1.96-2.08). In the study by Al-Mutairi et al described previously,[90] 1661 patients were classified as having mild or moderate psoriasis and 129 as severe psoriasis. Adjustments were made for age, sex, and area of residence. No relationship was found between type 1 diabetes and mild-to-moderate psoriasis or severe psoriasis. For type 2 diabetes, a significant association was noted among patients with mild-moderate psoriasis (37.4%) versus controls (16%; aOR 3.137, 95% CI 2.675-3.68, $P$ = .00001). The association was increased further in patients with severe psoriasis (41%) compared with controls (16%; OR 3.77, 95% CI 2.60-5.47, $P$ = .00001). In another study in 2010, an insurance-based cohort study of 3603 patients with diagnostic codes for psoriasis and 14,330 control patients matched by practice, date of registration, and psoriasis index date were analyzed.[98] When comparing patients with psoriasis versus controls, the OR for diabetes was 1.49 (95% CI 1.29-1.73).

The prevalence and incidence of type 2 diabetes in psoriasis patients and nonpsoriatic controls was determined by a systematic review and meta-analysis of 27 studies.[99] Overall, the OR of diabetes in psoriasis patients versus controls was 1.59 (95% CI 1.38-1.83). When stratified by disease severity, patients with mild psoriasis had an OR of 1.53 (95% CI 1.16-2.04) compared with controls; those with severe psoriasis had an OR of 1.97 (95% CI 1.48-2.62). These results confirm the association of diabetes with psoriasis and suggest a severity-dependent relationship exists. In a prospective, population-based cohort study in 2006, a total of 130,976 patients with psoriasis and 556,995 controls from the UK General Practice Research Database were identified[34]; 3837 patients were assigned to the severe psoriasis category on the basis of past medications and treatments. The remaining patients (n = 127,139) were assigned to the mild psoriasis category. Control patients were identified for the severe group

(n = 14,330) and the mild group (n = 496,666). The OR for diabetes in the mild psoriasis versus control group was 1.01 (95% CI 0.98-0.95). For patients with severe psoriasis, the OR was diabetes was 1.49 (95% CI 1.29-1.73). These results align with the aforementioned studies, reinforcing that an important relationship exists between the severity of psoriasis and the likelihood of diabetes.[100]

The effect of psoriasis on the development of diabetes-associated microvascular and macrovascular events was examined in a US cohort of 6164 diabetic patients with psoriasis compared with a matched diabetic cohort without psoriasis. Armstrong et al found that among diabetic patients psoriasis is generally associated with higher rates of microvascular conditions, such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications, such as cardiovascular events.[101]

These data strongly support the consistent association between psoriasis and diabetes. Furthermore, the risk for diabetes increases with increasing psoriasis severity. Thus, close communication between the dermatologist and the patient's primary health care provider is important to ensure that patients with psoriasis have a targeted health history and a fasting blood glucose and/or hemoglobin A1C if indicated (Table XIV).[102] Due to the increased risk for diabetes in psoriatic patients with moderate-to-severe disease, periodic laboratory testing for these patients should be considered. Patients with prediabetes or newly diagnosed diabetes should be referred to their primary care provider for further assessment and management and consider direct referral to a certified diabetes prevention program.[103] Because diabetes is a component of metabolic syndrome, screening for coexistent disease should be considered on the basis of each patient's individual history, risk factors, and relevant guidelines. It is important that diabetic patients with psoriasis maintain a healthy lifestyle and consistently follow-up with their primary care provider and dermatologist. Tables XIV-XVI show the health history and screening suggested for evaluating patients for diabetes.[102]

### Role of the dermatologist

Because the risk factors for metabolic syndrome and its components are tightly associated with psoriasis, it is prudent that dermatologists inform their patients regarding this association and ensure that the patient is engaged with his or her primary care provider for appropriate screening (Tables XVII and XVIII).* Such screening measures may include blood pressure, heart rate, height, weight, BMI, abdominal circumference, fasting blood glucose, hemoglobin A1C, fasting cholesterol, and triglycerides. The dermatologist should advise patients to practice a healthy lifestyle (appropriate diet, regular exercise, smoking cessation, and mental wellness) and communicate with the patient's primary care provider so that psoriatic patients are evaluated and appropriately treated for these comorbitities. Referral to the appropriate health care provider or specialist might be necessary to confirm these diagnoses and establish an appropriate treatment plan.

*34,65-67,72-76,78,80-85,89,90,93-96,99,104,105

## MENTAL HEALTH

The impact of mental health and wellness on patient QoL is increasingly recognized by the medical community and public. Addressing mental health is an essential component of comprehensive care for psoriatic patients. Patients with psoriasis might be hesitant to discuss mental health concerns due to perceived stigma or embarrassment. In addition, active mental illness often impairs a patient's ability to proactively seek intervention for their psoriasis. Also, emerging evidence suggests depression and anxiety can increase the risk for cardiovascular disease.[106] As such, dermatologists should be aware of the association of depression and anxiety with psoriasis so that appropriate patient education, resources, referrals, and treatment can be offered.

In a 2014 systematic review and meta-analysis, psoriatic patients had significantly greater symptoms of depression and were at least 1.5 times more likely to have depression than controls.[107] The use of antidepressants by psoriatic patients was also increased relative to nonpsoriatic patients. Similarly, a multicenter European cohort study from 2015 found psoriasis patients had a significantly increased risk for anxiety (OR 2.91, 2.01-4.21) and depression (OR 3.01, 1.86-4.90) relative to unaffected patients.[108]

In a cross-sectional study of 275 psoriatic patients, mild, moderate, or severe depression was observed in a significantly greater percentage of patients with psoriasis than in controls.[109]

The treatment of psoriasis and its effect on current mental illness was investigated in several studies. In a multicenter, randomized, open-label study of 352 psoriatic patients, etanercept treatment significantly improved scores for concomitant depression and anxiety.[110] In a prospective, case-controlled clinical study of patients with moderate-to-severe psoriasis, patients receiving the modified Goeckerman regimen for psoriasis showed a significant improvement in anxiety and depression

**Table XIV.** American Diabetes Association criteria for diabetes testing in asymptomatic adults, 2013

| American Diabetes Association criteria for diabetes testing in asymptomatic adults | |
|---|---|
| Body mass index ≥25 kg/m$^2$ and | • Physical inactivity<br>• First-degree relative with diabetes<br>• High-risk race/ethnicity (eg, black, Latino, Native American, Asian American, Pacific Islander)<br>• Women who delivered a baby weighing >9 lbs or with gestational diabetes mellitus diagnosis<br>• Hypertension (≥140/90 mmHg or on therapy for hypertension)<br>• HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)<br>• Women with polycystic ovary syndrome<br>• Hemoglobin A1C ≥5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing<br>• Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)<br>• History of cardiovascular disease |

*HDL*, High-density lipoprotein.
Adapted from: American Diabetes A. Standards of medical care in diabetes-2013. *Diabetes Care.* 2013;36 (Suppl 1):S11-66.[102]

**Table XV.** American Diabetes Association criteria for initiating a workup for suspected diabetes in adults

| American Diabetes Association criteria for initiating a workup for suspected diabetes in adults |
|---|
| Hemoglobin A1C ≥6.5%<br>• Fasting blood ≥126 mg/dL<br>  ○ Nonfastingblood glucose ≥200 mg/dL and polyuria, polydipsia, polyphagia, or weight loss<br>• Suspicion of prediabetes: 100 mg/dL ≥ fasting plasma glucose ≤ 125 mg/dL on 2 consecutive visits |

*HDL*, High-density lipoprotein.
Adapted from: American Diabetes A. Standards of medical care in diabetes-2013. *Diabetes Care.* 2013;36 (Suppl 1):S11-66.[102]

**Table XVI.** Targeted health history for suspected diabetes

| Targeted health history for diabetes for suspected diabetes in adults |
|---|
| • Family history of diabetes<br>• Personal history of diabetes<br>• Polydipsia<br>• Polyuria<br>• Weight Loss<br>• Taking a diabetic drug<br>• Age 40 years and over (check) or every couple of years |

*HDL*, High-density lipoprotein.
Adapted from: American Diabetes A. Standards of medical care in diabetes-2013. *Diabetes Care.* 2013;36 (Suppl 1):S11-66.[102]

scores compared with those who received conventional therapy.[111]

Kimball et al performed a double-blind, randomized, multicenter phase 2 trial of >500 psoriatic patients; this study showed a significant improvement in DLQI at 16 weeks in patients with psoriasis treated with adalimumab compared with those treated with placebo.[112] A similar study by Langley et al showed a significant improvement in DLQI at 52 weeks in patients with psoriasis treated with ustekinumab compared with those treated with placebo.[113]

In a double-blind, randomized, clinical trial of >500 psoriatic patients by Menter et al, there was a significant improvement in the Zagazig Depression Scale score at 12 weeks in patients with psoriasis treated with adalimumab compared with those treated with placebo.[114] A similar multicenter phase 3 trial of >300 psoriatic patients showed a significant improvement in the Beck Depression Inventory and Hamilton Depression Rating Scale scores at 12 weeks in patients with psoriasis treated with etanercept compared with those treated with placebo.[115] An analysis of 7490 psoriasis patients in the Psoriasis Longitudinal Assessment and Registry by Strober et al compared the rates of depression between patients receiving biologic therapy, phototherapy, and conventional systemic therapy. Biologic therapy was found to have the greatest impact on depression symptoms (incidence rate 3.01/100 patient-years), followed by conventional systemic therapy (5.7/100 patient-years) and phototherapy (5.85/100 patient-years).[116] These studies strongly suggest that when skin disease improves, patients have a concurrent improvement in their psychiatric symptoms.

**Table XVII.** Psoriasis and metabolic syndrome comorbidity strength of recommendation

| Recommendation number | Recommendation | Strength of recommendation |
|---|---|---|
| 3.1 | Patients with psoriasis should be informed about their increased risk for metabolic syndrome and have their metabolic syndrome status evaluated according to national guidelines by an appropriate health care professional. | B |
| 3.2 | Patients with moderate-to-severe psoriasis should have their obesity status determined according to national guidelines. Those patients already being monitored for obesity should be encouraged to maintain a healthy lifestyle and keep regularly scheduled follow-up visits with their primary care provider and/or dermatologist. Bariatric surgery should be considered to improve the comorbidities in psoriasis patients with a body mass index >40 kg/m$^2$ who fail standard weight loss measures. | B |
| 3.3 | Patients with mild, moderate, or severe psoriasis should have their blood pressure checked according to national guidelines. Patients with blood pressure of 140/90 mmHg or greater should be referred to their primary care provider for assessment and treatment. | A |
| 3.4 | All patients with psoriasis should have screening lipid tests performed according to national guidelines by their health care provider, with increased frequency considered for patients with severe disease. If these studies are conducted by the patient's dermatologist, those with elevated fasting triglycerides and/or high-density lipoprotein cholesterol should be referred to their primary care provider for assessment and management. | B |
| 3.5 | A fasting blood glucose and/or hemoglobin A1C should be performed by a health care provider in patients with psoriasis according to national guidelines. If these studies are conducted by the patient's dermatologist, those with prediabetes or new-onset diabetes should be referred to their primary care provider for further assessment and management. | C |

**Table XVIII.** Psoriasis and metabolic syndrome comorbidity level of evidence

| Recommendation | Recommendation number | Level of evidence | Studies |
|---|---|---|---|
| Education | | | |
| Association between psoriasis and metabolic syndrome plus screen for metabolic syndrome | 3.1 | I-III | 66,67,72,78,81,94,99,104 |
| Screening and referral | | | |
| Obesity screen and referral to primary care physician for proper follow-up and management of disease. | 3.2 | I-II | 72-76,78,81 |
| Blood pressure screen and referral to primary care physician for proper follow-up and management of disease. | 3.3 | II | 34,65,80-85 |
| Lipid status screen with referral to primary care physician for proper follow-up and management of disease. | 3.4 | II-III | 89,90,93-96,105 |
| Blood glucose screen and referral to primary care physician for proper follow-up and management of disease | 3.5 | II | 81,90,99 |

The risk for suicide ideation in patients with concomitant psoriasis and depression is unclear. In a large population-based cohort study by Kurd et al, the HR of suicidality was significantly greater for psoriasis patients than controls.[117] In a systematic review and meta-analysis of 13 studies by Singh et al, the prevalence of suicide ideation was significantly greater in psoriatic patients than in individuals without psoriasis.[118] In contrast, another systematic review and meta-analysis of

**Table XIX.** Psoriasis and mental health strength of recommendation

| Recommendation number | Recommendation | Strength of recommendation |
|---|---|---|
| 4.1 | Patients with psoriasis should be informed about the association of psoriasis and anxiety and depression. | B |
| 4.2 | Patients with psoriasis should be asked about signs and symptoms of anxiety and depression by their dermatologist or primary care provider. | B |
| 4.3 | Psoriasis patients showing signs or symptoms of anxiety, depression, or suicidal ideation should be referred to an appropriate health care professional for further assessment and management. | A |
| 4.4 | Psoriasis-specific therapy is recommended as a measure to improve psoriasis-associated anxiety and depression in individuals with psoriasis. | B |

**Table XX.** Psoriasis and mental health level of evidence

| Recommendation | Recommendation number | Level of evidence | Studies |
|---|---|---|---|
| Education | | | |
| Association with anxiety and depression | 4.1 | I-III | 106-109 |
| Screen | | | |
| Depression and anxiety | 4.2 | I-II | 106-108 |
| Referral | | | |
| Health care professional if concern about anxiety, depression, or suicidal ideation | 4.3 | I-II | Expert opinion |
| Psoriasis therapy might improve anxiety and depression | 4.4 | I-III | 110-116,120,121 |

4 low- and moderate-quality studies found the risk ratio for suicide, suicide attempt, and suicidality was not statistically different from control populations without psoriasis, regardless of disease severity.[119]

### Role of the dermatologist

Dermatologists should be aware of the association between depression, anxiety, and psoriasis and address it with their patients (Tables XIX and XX).[106-116,120,121] It is important to monitor for signs and symptoms of mental illness in psoriatic patients. The improvement in mental health of psoriatic patients treated with biologic therapies and the modified Goeckerman regimen support the use of these therapeutic agents to manage psoriasis and simultaneously improve anxiety, depression, and suicidal ideation, if present. Awareness and identification of suicidal ideation might reduce suicidality in these patients.

## LIFESTYLE CHOICES

Several comorbidities of psoriasis are influenced by personal behavior, such as diet, exercise, smoking, and alcohol ingestion. The independent association of smoking and alcohol consumption with psoriasis is discussed here.

Smoking is the most important environmental risk factor in the development of chronic obstructive pulmonary disease (COPD).[122] In addition, smoking might be associated with an increased risk of developing psoriasis. In a meta-analysis performed with 28 studies involving 146,983 psoriatic patients and 529,111 control patients without psoriasis, an association between psoriasis and smoking was identified (pooled OR 1.78, 95% CI 1.52-2.06). A similar relationship was noted in former smokers (pooled OR 1.62, 95% CI 1.33-1.99).[36]

Bo et al performed a cross-sectional study of 1144 psoriasis patients who were current or previous smokers.[123] In this study, both of these populations had a greater likelihood of having psoriasis than controls. Another cross-sectional study of 818 psoriasis patients demonstrated that the severity of psoriasis increased with increasing number of cigarettes used per day.[124] Also, individuals who smoked >15 years had more severe psoriasis than those who smoked <15 years. Individuals who stopped smoking had a progressive decline in the severity of psoriasis over time (pooled OR <1 year, 1.0; 1-9 years, 0.6, 95% CI 0.2-2.0; ≥10 years, 0.1, 95% CI 0-1.1). Further, smoking is associated with a higher severity of psoriasis.[125] Several case-controlled and cross-sectional studies demonstrate

**Table XXI.** Psoriasis and changes in quality of life strength of evidence

| Recommendation number | Recommendation | Strength of recommendation |
|---|---|---|
| 5.1 | Patients with psoriasis should be informed of the association between psoriasis and smoking, as smoking increases the risk for severe disease and the likelihood of cardiovascular comorbidities. | B |
| 5.2 | Patients with psoriasis should be counseled to limit alcohol intake, as it increases the risk for severe disease and is associated with other psoriasis comorbidities. | B |
| 5.3 | Providers should consider the amount of alcohol ingestion in their psoriasis patients when considering treatment options for their patients. | B |
| 5.4 | Patients with psoriasis who have nicotine or alcohol dependency should be referred to expert health professionals for further assistance. | A |

**Table XXII.** Psoriasis and lifestyle factors level of evidence

| Recommendation | Recommendation number | Level of evidence | Studies |
|---|---|---|---|
| Education | | | |
| Association of smoking and increased disease severity and comorbidity risk | 5.1 | II-III | 36,85,94,98,123-125 |
| Limit alcohol intake due to increased severity and comorbidity risk | 5.2 | II-III | 94,124,126-131 |
| Determine treatment path based on patient alcohol intake habits | 5.3 | II-III | 94,124,127-131 |
| Referral | | | |
| Expert health professional based on alcohol or nicotine dependency | 5.4 | II-III | Expert opinion |

psoriatic patients, especially those with palmar plantar psoriasis, are more likely to be smokers than a psoriasis-free population.[85,94,98]

Alcohol ingestion was reviewed via a case–control study by Akay et al.[126] Of 50 plaque-type psoriasis patients, the OR for alcohol consumption was 4.24 (95% CI 1.29-13.95) compared with healthy adults. In a separate cross-sectional study of 818 psoriasis patients, the OR for psoriasis severity was 2.1 (95% CI 1.4-3.1) among individuals who consumed >2 glasses of alcohol per day.[124] Similarly, a case–control study of the National Health Survey found >1 drink of alcohol daily was associated with more severe psoriasis.[127]

Not only does psoriasis tend to worsen with increasing alcohol ingestion, but the amount of alcohol ingested by psoriasis patients tends to be increased relative to controls. Poikolainen et al found that psoriatic patients had a higher likelihood of increased daily alcohol ingestion (>100 g/day, pooled OR 2.2, 95% CI 1.3-3.9) and higher rates of intoxication (at least once a week, pooled OR 1.3, 95% CI 1.1-1.5) relative to nonpsoriasis patients.[128] Three case-controlled studies found psoriasis patients consume significantly greater amounts of alcohol than control patients.[94,129,130] Parisi et al performed a case-controlled study of >55,000 patients with psoriasis. The HR of alcohol-related deaths was 1.58 (95% CI 1.31-1.91) compared with controls, including alcohol-related liver disease (65%), fibrosis and cirrhosis (24%), and mental and behavioral disorders (8%).[131] There is also evidence that severe psoriasis is a causative factor for alcohol and tobacco addiction.[132]

### Role of the dermatologist

Both smoking and excessive alcohol ingestion are associated with psoriasis and its severity. Increased usage of either substance further affects disease severity, while cessation can improve psoriasis over time. Dermatologists should strongly advise patients with psoriasis to avoid smoking and limit alcohol intake for overall health improvement and to help improve skin disease (Tables XXI and XXII).[36,85,94,98,123-131] In addition, excessive alcohol intake (and subsequent liver disease) limits some systemic treatment options available for patients and/or limits their efficacy. Because patients might need targeted counseling, therapeutics and support for successful discontinuation or moderation of alcohol and tobacco, referral to appropriate experts, and resources is warranted.

## QUALITY OF LIFE

Comprehensive care of the patient with psoriasis includes a discussion initiated by the provider, if not

raised by the patient, regarding the impact of psoriasis on the patient's QoL.

### Interpersonal relationships

Alpsoy et al in a cross-sectional study of 1485 patients investigated the relationship between psoriasis and psychosocial stressors via the Psoriasis Internalized Stigma Scale.[133] Worse outcomes on the scale were associated with greater disease severity and involvement of visible body parts and genitalia, irrespective of psoriasis subtype. Patients described feelings of alienation, perceived discrimination, and social withdrawal. In a survey of 49 female and 66 male patients with psoriasis, fear of stigmatization was greater when lesions were on the back of the hands and when lesions could not be hidden by clothing.[134] The impact was greater for women than men and greater for those who were employed than those who were unemployed. A survey by Gupta and Gupta of 215 adult psoriasis patients stratified by age found that feeling self-conscious around strangers ($P < .0001$), avoiding public places ($P = .0003$), perceptions that psoriasis is contagious ($P = .005$), and people making rude or insensitive remarks ($P = .0003$) correlated inversely with age.[135]

In a cohort study of 936 adult psoriasis patients, the most frequent problems patients experienced were shame, anger, worry, difficulties in daily activities, and an impaired social life.[136] Individuals more likely to experience these symptoms were those with more severe disease, female patients, and less educated persons. Pustular psoriasis and PsA were more likely to be associated with limitations in work and/or hobbies. In another survey of 215 adult psoriasis patients, 37% of patients felt that psoriasis affected work/school, 38% indicated it affected sex-life/intimacy, and 48% stated it made them feel like outcasts.[137] Eghlileb et al surveyed 28 relatives and 35 partners of patients with psoriasis to investigate their viewpoint of psoriasis and its psychosocial impact.[138] There was a strong relationship between the patient's QoL and that of the relative or partner (r = 0.67). The relative or partner experienced anxiety; were worried about the patient's future (70%); experienced social disruption due to lack of social confidence (55%); had limitations regarding vacation plans, sport, and leisure activities and evenings out (44%); had limitations on daily activities (37%); and experienced deterioration of close relationships (37%).

### Work productivity

In a survey of 5604 psoriasis patients, Armstrong et al found that patients with severe psoriasis were 1.7 times more likely to be unemployed than the general population.[139] Greater than 90% of patients indicated the reason for not working was due solely to psoriasis or PsA. A retrospective database analysis of 694 individuals with psoriasis indicated similar findings: there was a significantly greater reduction in work productivity in psoriasis patients relative to the general population. Persons with moderate or severe disease missed significantly more time from work than those with mild disease.[140] Fowler et al estimated that the annual cost of lost work productivity for psoriasis patients was $5508 per patient.[141] Whether treatment of psoriasis with particular medications could positively affect a patient's work abilities has been studied. In 3 randomized, double-blind, phase 3 trials, patients with psoriasis treated with ixekizumab showed significantly greater improvements in work productivity at 12 weeks than those who received placebo. The work productivity was significantly greater than etanercept at weeks 12 and 60.[142] In an open-label clinical trial of 32 psoriatic patients with moderate-to-severe chronic plaque psoriasis, there was a significant improvement in a variety of parameters that measure work productivity 32 weeks after initiating ustekinumab therapy.[143] Similarly, another randomized, double-blinded, placebo-controlled multicenter phase 3 clinical trial found a significant improvement in work productivity, reduction in work days missed, and reduction in work limitations in 820 psoriasis patients treated with ustekinumab versus those treated with placebo at weeks 12 and 24.[144]

In a randomized, double-blinded clinical trial of 557 adult psoriatic patients treated with adalimumab compared with 270 patients with psoriasis treated with placebo, significantly greater improvement in work productivity was observed at week 16 in those treated with adalimumab (15.5% vs 11.1%, $P < .001$).[120]

Reich et al compared 301 adult psoriatic patients treated with infliximab with 77 patients treated with placebo. Work productivity improved significantly at weeks 10 and 24 for those patients treated with infliximab.[145] A clinical trial of 246 psoriatic patients with moderate-to-severe disease treated with etanercept showed a significant decline in work impairment at 12 months of therapy compared with baseline productivity levels before etanercept initiation.[146]

### Sexual dysfunction

Genital psoriasis is present in up to 60% of psoriasis patients.[147] Two prospective case series of both male and female psoriasis patients with genital involvement were compared with those without. There was no difference in sexual disturbance

whether genital psoriasis was present or not, indicating sexual dysfunction applies to patients regardless of skin disease location.[148] In an observational study of 154 psoriasis patients with genital involvement and 220 patients without, the DLQI was found to be significantly worse in patients with genital disease than those without (8.5 ± 6.5 vs 4.0 ± 5.5; $P < .01$).[147]

In a cohort study, the decline in sexual activity for psoriasis patients was found to be most closely associated with depression.[149] Sexual dysfunction, while present in both sexes, is thought to be greater for female than male patients[150] and observed in both heterosexual and nonheterosexual individuals.[151,152]

Several studies have identified an association between erectile dysfunction and psoriasis. Both cardiovascular and psychologic effects of psoriasis contribute to this comorbidity.[148,153,154] In a cohort study of 12,300 male patients with psoriasis, the HR for sexual dysfunction was greater in men >60 years of age and those with PsA.[155] The risk of sexual dysfunction was not significantly elevated in patients receiving systemic treatments, such as retinoid, methotrexate, and cyclosporine.

### Role of the dermatologist

Psoriasis is a multisystem disease which might negatively affect several facets of a patient's life, including interpersonal relationships, work participation, and sexual health. The etiology of the impairment can be due to skin involvement and exacerbated by arthritis and erectile dysfunction. Concomitant mental health disorders, including anxiety and depression, might also be present and play a role. Dermatologists should sensitively raise these topics with psoriasis patients, providing validation of patient concerns and optimizing empowerment. The use of systemic therapy to address the disease appears to improve overall psychosocial wellbeing, especially pertaining to employment and sexual activity. It is important to emphasize that not all medications, both topical and systemic, as well as phototherapy have been studied in this regard. This represents a gap in our knowledge of those treatment modalities.

## INFLAMMATORY BOWEL DISEASE

Crohn's disease and ulcerative colitis are the 2 most common forms of inflammatory bowel disease (IBD), with inflammation potentially involving all of gastrointestinal tract (from mouth to anus) in Crohn's disease versus the colon and rectum only for ulcerative colitis. While the exact etiology is unknown, a maladaptive immune response in patients with genetic susceptibility is suspected.[156]

There is a known association between psoriasis and IBD. In a retrospective analysis of 33,981 patients with psoriasis compared with 1,310,090 matched controls, the likelihood of Crohn's disease was 0.92% for psoriatic patients versus 0.45% for the control group.[81] The likelihood of ulcerative colitis was also increased, with a 1.1% risk for psoriasis patients versus 0.56% for the controls (prevalence rate 1.91). In a case-controlled study in 2009, a total of 12,502 psoriasis patients were compared with 24,285 nonpsoriatic patients.[157] The prevalence ratios of both Crohn's disease (2.49) and ulcerative colitis (1.64) were increased in psoriasis patients relative to nonpsoriatic patients. Further, patients of intermediate or high socioeconomic class were more likely to develop IBD.

Li et al performed a retrospective cohort study of the Nurse's Health Study and Nurse's Health Study II in 2013.[158] Psoriasis was associated with a significantly increased risk for subsequent Crohn's disease, with a multivariate RR of 4.0 for the Nurse's Health Study cohort and 3.76 for the Nurse's Health Study II cohort. No significant risk for ulcerative colitis was found. Risk for bowel disease did increase, however with concomitant PsA (RR 6.43). Female patients had a higher overall risk than male patients. Using a case–control study design, Makredes et al investigated the association of Crohn's disease and ulcerative colitis with both psoriasis and PsA.[159] An increased association with both gastrointestinal disorders was found with psoriasis and PsA. The prevalence rate was 1.3 for psoriasis with ulcerative colitis and 2.0 for PsA with ulcerative colitis. The prevalence rate increased further to 1.6 for psoriasis and 2.1 for PsA with Crohn's disease.

Having established that psoriasis might occur before the development of IBD, Persson et al performed a case-controlled study of 152 patients with Crohn's disease, 145 patients with ulcerative colitis, and 345 controls.[160] Each IBD patient was surveyed regarding health history before IBD onset. The incidence of psoriasis among controls was 2.3%, whereas the incidence among those with ulcerative colitis was increased (4.8%, RR 2.1), and the incidence among those with Crohn's disease was further increased (6.6%, RR 2.9). A study by Yates et al from 1982 found patients with IBD had an increased risk for prior psoriasis, as well as an increased risk for affected family members.[161]

While TNFi are used as therapy for moderate-to-severe psoriasis, their use for IBD can paradoxically cause psoriasiform eruptions to emerge. A systematic review of 34 studies revealed that 69 IBD patients

developed psoriasiform eruptions while on infliximab.[162] In total, 35 discontinued infliximab treatment, with 33 showing complete resolution of the skin eruption when changed to another therapy for their bowel disease. Thirty patients continued on infliximab, receiving other treatments for the skin. Of these patients, 27 had complete skin disease resolution, while 3 patients noted a partial improvement. The authors concluded treatment should be individualized, and psoriasiform eruptions may be treated with standard psoriasis measures.

Freling et al performed a single-center, retrospective cohort study of 583 patients with IBD, assessing the incidence of dermatologic adverse events after TNFi use.[163] The incidence of psoriasiform eruptions while on TNFi therapy was 10.1%, with an increased risk with escalating TNFi dosing. An observational case-controlled study by Guerra et al found psoriasis development after TNFi initiation as well.[164] This study showed increased prevalence in patients with Crohn's disease, female patients, and current and former smokers. Discontinuation of inhibitor therapy afforded regression of skin disease in only 1 of 4 patients affected.

There are several new IL inhibitor medications that are Food and Drug Administration approved for psoriasis: 3 IL-17 inhibitors, 1 IL-12/23 inhibitor, and 1 IL-23 inhibitor. Whether these drug classes are efficacious in IBD and, thus, serve as monotherapy for patients with both psoriasis and IBD has been queried. In a study in 2012, a total of 59 Crohn's disease patients were randomized to treatment with secukinumab or placebo.[165] In this study, not only did patients receiving therapy have a reduced response and more adverse effects relative to patients receiving placebo, but some patients also had paradoxical worsening of their bowel disease. In phase 3 trials, ustekinumab was effective for the treatment of Crohn's disease, including in some patients who had failed TNF blockade.[166] Ustekinumab is now approved for the treatment of Crohn's disease.[167] On the basis of these studies, IL-17 blockade appears ineffective for IBD therapy (and might cause flares in IBD), and IL-23 blockade appears beneficial. Providers and patients should be mindful of the small risk of IBD exacerbation with the use of IL-17 inhibitors for psoriasis.

### Role of the dermatologist

There is an established association between IBD and psoriasis, and patients with IBD on TNFi therapy might develop new-onset psoriasiform eruptions. Patients should be informed of this relationship by their dermatologist; attention should be paid to signs and symptoms of bowel disease that would warrant further evaluation by the patient's primary care provider or gastroenterologist (Tables XXIII and XXIV).[81,157-166] If psoriasiform skin disease develops in patients with IBD while they are on TNFi therapy, the approach to treatment of both the bowels and skin should be individualized.

## OTHER COMORBID CONDITIONS WITHOUT RECOMMENDATIONS

### Malignancy

A correlation between psoriasis and malignancy has been noted in several studies. In a cohort study including patients with psoriasis for ≥4 years, patients with psoriasis had a higher incidence rate of lymphohematopoietic malignancies and pancreatic cancer relative to unaffected controls.[168] Malignancies of all other organs were not significantly elevated. In a separate cohort study of patients with a first-time diagnosis of psoriasis, the HR of skin cancer (3.10, 95% CI 1.24-7.71), malignancies of the oropharynx and larynx (2.16, 95% CI 1.17-3.96), digestive tract (2.02, 95% CI 1.33-3.07), and colorectum (1.70, 95% CI 1.01-2.86) were significantly elevated relative to nonpsoriatic patients.[169] Compared with unaffected patients, psoriasis patients aged 0-79 years have a greater overall risk for malignancy, which normalizes between the control and psoriasis group at age 80 years. Ultraviolet B phototherapy use was associated with reduced cancer rates for all age groups (HR 0.52, $P = .3$).

Frentz et al studied 6905 psoriasis patients who were hospitalized for their skin disease.[170] They found an increase in the standard incidence rate (SIR) for nonmelanoma skin cancer (NMSC; SIR 2.46, 95% CI 2.13-2.83) and mycosis fungoides (SIR 15.1, 95% CI 4.1-38). No such increase was found for melanoma or non-Hodgkin lymphoma. Another study of 5687 psoriatic patients noted similar results; there was no increase in the SIR for melanoma, but there was for NMSC (SIR 3.2, 95% CI 2.3-3.4) as well as Hodgkin and non-Hodgkin lymphomas.[171] Ultraviolet B treatment did not increase the RR for squamous cell carcinoma or lymphoma, nor did retinoid use increase the risk for non-Hodgkin lymphoma. No increased risk for squamous cell carcinoma was found with methotrexate use. A positive association was found between psoralen ultraviolet light A use and squamous cell carcinoma development but not non-Hodgkin lymphoma development. There were not enough patients in the cohort treated with cyclosporine to analyze the risk of its use and the development of malignancy.

In some studies, the risk for cancer and its relationship to severity of psoriatic disease was assessed. Lee et al performed a cohort study

**Table XXIII.** Psoriasis and inflammatory bowel disease strength of recommendation

| Recommendation number | Recommendation | Strength of recommendation |
|---|---|---|
| 6.1 | Patients with psoriasis should be informed about the association of psoriasis and IBD. | B |
| 6.2 | Psoriasis patients found to have concerns for IBD should be referred to their primary care provider or a gastroenterologist for further assessment and management. | A |
| 6.3 | Patients who develop psoriasiform eruptions while on TNFi therapy might respond to other medications that are used to treat psoriasis and continue on their IBD medication. If those measures do not improve the psoriasiform eruption, discontinuation of TNFi therapy might be necessary to achieve skin clearance. | B |
| 6.4 | Interleukin 17 inhibitor therapy should be avoided in patients with IBD. | C |

*IBD*, Inflammatory bowel disease; *TNFi*, tumor necrosis factor inhibitor.

**Table XXIV.** Psoriasis and inflammatory bowel disease level of evidence

| Recommendation | Recommendation number | Level of evidence | Studies |
|---|---|---|---|
| Education | | | |
| Association of IBD and psoriasis | 6.1 | I-III | 81,157-166 |
| Referral | | | |
| Primary care provider or gastroenterologist | 6.2 | I-III | Expert opinion |
| Treatment | | | |
| Patients may continue or discontinue IBD medication to achieve skin clearance | 6.3 | I-III | 162-166 |
| Interleukin 17 inhibitor therapy | | | |
| Avoid in patients with IBD | 6.4 | I | 165 |

*IBD*, Inflammatory bowel disease.

analyzing the SIR for NMSC, melanoma, and lymphoma in patients with and without psoriasis.[172] The NMSC SIR was higher among patients with severe psoriasis than among patients with mild psoriasis (SIR 3.72 vs 7.08). The SIR of melanoma in patients with severe disease was significantly increased (11.01, 95% CI 1.55-78.16), but not for those with mild disease. The SIR for lymphoma was significantly elevated in patients with both mild and severe psoriasis 2.3 (95% CI 1.15-4.60). A similar study by Margolis et al also found psoriasis patients with severe disease had a greater risk for lymphoma and NMSC development than patients with mild disease.[173] A review of 198,336 psoriasis patients and 937,716 matched controls from The Health Improvement Network UK database found a mild but significant association between psoriasis and lymphoma (aHR 1.34), NMSC (aHR 1.12), and lung cancer (aHR 1.15), and patients with severe psoriasis had a higher risk for all 3 malignancies relative to patients with mild psoriasis. No increased risk for leukemia, breast cancer, colon cancer, or prostate cancer was noted for psoriasis patients relative to the control group.[174]

In a systematic review and meta-analysis of 37 observational studies, there was an increased rate of NMSC, respiratory tract cancer, cancer of the upper aerodigestive tract, urinary tract, and non-Hodgkin lymphoma in psoriasis patients relative to controls.[175] The higher risk for squamous cell carcinoma was primarily due to prior treatment with psoralen ultraviolet light A, cyclosporine, and possibly methotrexate.

Patients with psoriasis often use systemic immunomodulators, including biologics and monoclonal antibodies, to improve their skin and joint disease. Whether such immune regulation would impact the incidence of malignancy has been queried. In a systematic review of 23,458 patients exposed to adalimumab in 71 clinical trials for psoriasis, PsA, and other inflammatory disorders to evaluate its safety, no significant increase was found in the SIR of cancers collectively (0.96, 95% CI 0.65-1.36) or in lymphomas (0.63, 95% CI 0.01-3.49).[176] However, there was a significant increase in the SIR of NMSC development (1.76, 1.26-2.39). In a meta-analysis of 20 randomized control trials of 6810 psoriatic patients treated with short-term TNFi, no increase in the OR of malignancy was found for any specific drug.[177]

Leonardi et al performed a systematic review of 13 randomized clinical trials including 3010 psoriatic patients treated with adalimumab for up to 5 years.[178]

The SIR of cancers excluding NMSC was 0.9 (95% CI 0.60-1.29) and for NMSC was 1.51 (95% CI 1.04-2.11). In a study of 1373 patients with psoriasis by Menter et al, the SIR for malignancy (excluding NMSC) was 0.39 (95% CI 0.05-1.42; 2 malignancies) in infliximab-treated patients.[121] A long-term observational study of 12,095 patients followed for 31,818 patient-years showed the use of biologic agents was not a significant predictor of malignancy compared with non-biologic therapy.[179]

With regards to ustekinumab specifically, no increased malignancy risk has been noted. An analysis of one phase 2 and three phase 3 randomized control trials by Gordon et al demonstrated that the rates of malignancy in patients treated with ustekinumab were similar to the rates of malignancies in the general US population from the Surveillance, Epidemiology, and End Results program database.[180] In a study evaluating ustekinumab safety information from 3 randomized controlled trials with 3117 patients receiving ustekinumab for up to 3 years showed a favorable safety profile.[181] A separate analysis of pooled safety data from 4 studies of ustekinumab use in 3117 psoriatic patients demonstrated the SIR for any cancer excluding NMSC (0.98, 95% CI 0.74-1.29), melanoma (1.42, 95% CI 0.52-3.09), prostate cancer (1.21, 95% CI 0.66-2.04), colorectal cancer (0.99, 95% CI 0.32-2.31), breast cancer (0.62, 95% CI 0.17-1.58), and lymphoma (0.80, 95% CI 0.10-2.91) was comparable to other biologics used to treat moderate-to-severe psoriasis.[182]

Thus, there appears to be an increased incidence of certain malignancies in patients with psoriasis, particularly lymphohematopoietic cancers (particularly cutaneous T-cell lymphoma), head and neck cancers, and digestive tract malignancies. Patients have an increased risk for NMSC, especially if they have received psoralen ultraviolet light A photochemotherapy.[175] This NMSC risk might also be elevated in patients who have used cyclosporine.[183] Some studies also suggest an increased risk for NMSC in patients receiving TNFi. Use of certain monoclonal antibody therapies, such as ustekinumab, IL-17 inhibitors, and IL-23 inhibitors, do not appear to alter malignancy risk; however, larger and longer-term studies are necessary.

**Role of the dermatologist.** Dermatologists should be aware of the increased incidence of certain malignancies in patients with psoriasis and inform their patients accordingly. A proactive approach to age-appropriate cancer screening should occur, with referral to appropriate specialists if a patient displays signs or symptoms concerning for an underlying malignancy. Dermatologists should actively assess the skin of psoriatic patients not only for psoriasis involvement, but also for the development of skin cancer, and manage them accordingly. Patients with skin findings atypical for psoriasis or whose psoriasis does not respond appropriately to therapy, should be considered for skin biopsy to rule out cutaneous T-cell lymphoma. The Centers for Disease Control and Prevention—recommended cancer screenings are listed in Table XXV.[184]

**Table XXV.** Suggested cancer screenings

Breast cancer:
- Women age 50-74 years, average risk: mammogram every 2 years
- Women age 40-50 years, above average risk: consult with provider

Cervical cancer:
- Women age 21-65 years: Papanicolaou test every 3 years

Colorectal cancer:
- Male and female patients age 50-75 years: screening
- Male and female patients age <50 years: at risk population
- Male and female patients age >75 years: consult with provider

Lung cancer:
- Male and female patients age 55-80 years: low-dose computed tomography if:
  - Smoking history of >30 pack years and
  - Currently smoke or have smoked within the past 15 years

From: Centers for Disease Control and Prevention, https://www.cdc.gov/cancer/dcpc/prevention/screening.htm.[184]

## Renal disease

While many comorbidities of psoriasis, including hypertension, vascular disease, and diabetes, can negatively affect the kidneys, psoriasis and renal disease are also independently associated. The link between chronic kidney disease (CKD) and psoriasis has been reviewed in several studies.

In a large, population-based, nested cohort study involving UK patients, Wan et al compared the rates of CKD in 136,529 psoriasis patients relative to 689,702 control patients.[185] Psoriasis severity was estimated based on treatments or medications. The aHRs for CKD in the overall, mild, and severe psoriasis groups were 1.05 (95% CI 1.02-1.07), 0.99 (95% CI 0.97-1.02), and 1.93 (95% CI 1.79-2.08), respectively. The prevalence of moderate-to-advanced CKD was also directly related to, in a dose response manner, increasing BSA affected by psoriasis. Chi et al determined the risk for CKD and

end-stage renal disease by examining a large population-based cohort involving 4633 psoriatic patients and 922,534 control patients from China.[186] The risk for incident CKD and end-stage renal disease in patients with mild psoriasis or severe psoriasis compared with controls was determined. The results showed severe psoriasis was an independent risk factor for both CKD (aHR 1.90, 95% CI 1.33-2.70) and end-stage renal disease (aHR 2.97, 95% CI 1.72-5.11) after adjustment for age, sex, comorbidities, and NSAID use. No association was noted for patients with mild psoriasis.

In a prospective study of 4344 psoriasis patients and 13,032 randomly-selected control subjects, patients were followed for up to 5 years to assess the rates of CKD and glomerulonephritis.[187] After adjustment for CKD risk factors, psoriasis was found to be associated with an increased risk for CKD (aHR 1.28, 95% CI 1.14-1.44). Psoriasis was also found to be associated with glomerulonephritis (HR 1.50, 95% CI 1.24-1.81), which might contribute to the positive association found between psoriasis and CKD. Psoriasis patients with PsA exhibited a higher risk of CKD than patients without arthritis (HR 1.62 vs 1.26). Also, NSAID use had the strongest association with CKD in psoriasis patients (aOR 1.69, 95% CI 1.14-2.49). In addition, the prevalence of urinary abnormalities in psoriasis patients versus controls was evaluated in a small observational study.[188] This study showed that routine urinalysis might not detect early kidney disease. However, the prevalence of abnormal urine albumin levels in psoriasis patients indicated subclinical glomerular dysfunction was occurring in these patients.

The concern of renal disease—associated mortality for patients with psoriasis was investigated in a Swedish registry study in 2015.[189] An association between psoriasis and 12 specific causes of death and all-cause mortality were examined. There were 39,074 patients with psoriasis and 154,775 sex-matched, age-matched, and residency-matched control patients. In patients with mild and severe psoriasis, the strongest associations for death were kidney disease (HR 2.20, $P < .01$) and liver disease (HR 4.26, $P < .001$). A review of The Health Improvement Network UK database from 1994 to 2014 by Grewal et al comparing 205,815 psoriasis patients with 1,019,140 unaffected patients found that patients with moderate-to-severe psoriasis had an increased risk for both IgA nephropathy (aHR 4.75) and glomerular disease (aHR 2.05).[190]

The presence of renal disease should be considered when over-the-counter and/or systemic medications are used in psoriatic patients. NSAIDs should be used cautiously, given known impairment in renal blood flow after their chronic use. Cyclosporine is associated with nephrotoxicity, especially in older patients, severely limiting its long-term use. Due to short-term and long-term effects on the kidney, the presence of pre-existing kidney disease is a contraindication to the use of cyclosporine in treating psoriasis. According to Feutren et al, in the absence of surveillance renal biopsies, the best predictor of cyclosporine-induced nephropathy is the percentage increase in serum creatinine above the baseline level.[191] Another study showed that the early morning blood pressure reading was a more accurate measurement for cyclosporine-induced nephropathy than serum creatinine levels.[192] Methotrexate is commonly used to treat psoriasis when topical measures fail. The primary mode of elimination for methotrexate is renal excretion, as it is filtered by the glomeruli and actively secreted across renal tubules.[193]

Renal impairment reduces the clearance of apremilast, resulting in higher peak concentrations. The Food and Drug Administration recommends a maintenance dose reduction for patients with severe renal disease.[194]

**Role of the dermatologist.** Dermatologists should be aware of the independent association of renal disease and psoriasis while also appreciating that other psoriatic comorbidities and their treatments, for example NSAIDs for arthritis, can negatively affect the kidneys. Because the association is strongest in patients with severe psoriasis, testing may be considered more frequently in such patients. In addition to blood urea nitrogen and creatinine, a urine microalbumin should be assessed to detect occult renal disease. Patients with evidence of CKD should be referred to their primary care provider or a nephrologist for further assessment and management. Providers should use caution when psoriasis patients are placed on nephrotoxic drugs, and the medications should be discontinued immediately if newly acquired renal disease is suspected. As nephrotoxicity risk from medication increases with age, and renal clearance decreases with age, renal impairment over time should be considered when psoriatic patients are placed on potentially nephrotoxic medications.

## Sleep apnea

Sleep apnea is a disorder where breathing stops and starts repeatedly during the sleep cycle. OSA is the most common type of sleep apnea, occurring when the muscles of the tongue and soft palate relax, causing obstruction of the upper airway. The resultant episodes of apnea can last 20-40 seconds, leading to reduced blood oxygen saturation. Loud

snoring is a symptom of OSA. OSA risk factors include obesity, hypertension, diabetes, chronic nasal congestion, smoking, and male sex. Because many of the OSA risk factors are shared with those of metabolic syndrome and/or psoriasis, investigators have examined the statistical association between OSA and psoriasis.

In a nationwide cohort study, Egeberg et al followed 5,459,563 Danish citizens without psoriasis, PsA, or OSA for up to 15 years.[195] Emergent psoriasis was classified as mild or severe on the basis of the prescribed medications or treatments for severe psoriasis. During the observation period, 53,290 patients were classified as having mild psoriasis, 6885 severe psoriasis, and 6348 PsA. A total of 39,908 patients were identified with new-onset OSA. Overall, the incidence rate ratio for sleep apnea was 1.30 (95% CI 1.17-1.44) for patients with mild psoriasis, 1.65 (95% CI 1.23-2.22) for those with severe psoriasis, and 1.75 (95% CI 1.35-2.26) for patients with PsA. The authors concluded a bidirectional link existed between psoriasis and OSA, speculating shared inflammatory pathways might provide a rationale.

Shalom et al performed a case-controlled study assessing 12,336 patients with psoriasis and 24,008 age-matched and sex-matched controls who were enrolled in a large community health organization.[196] The prevalence of OSA in psoriasis patients was increased compared with those in the control group (2.7% vs 1.5%, $P < .001$). In addition, a multivariate analysis revealed an association between psoriasis and OSA (OR 1.27, 95% CI 1.08-1.49, $P < .001$). The authors concluded that an association existed between psoriasis and OSA. Furthermore, physicians should realize that OSA might be present and undiagnosed in psoriatic patients.

In 2012, Yang et al investigated the risk for psoriasis or PsA in patients with OSA compared with age-matched and sex-matched unaffected individuals using a nationally representative population-based data set.[197] By using data from the Taiwan Longitudinal Health Insurance Database 2000, the cohort consisted of 2258 patients with OSA and 11,255 matched comparison patients. Of the 13,513 patients, psoriasis developed in 36 (0.27%) patients during the 3-year follow-up period; psoriasis developed in 0.49% of patients with OSA and 0.22% of patients without OSA. After adjusting for monthly income, location, urbanization level, and obesity, the HR for psoriasis during the 3-year follow-up period was 2.30 (95% CI 1.13-4.69, $P = .022$) times greater for patients with OSA than for comparison patients. The authors concluded OSA was associated with an increased risk for subsequent psoriasis or PsA.

Because independent and multifactorial associations exist between OSA and psoriasis, 2 recent studies were conducted to investigate whether treating psoriasis improves OSA. In a prospective, randomized, placebo-controlled study, Maari et al assessed the effect of adalimumab on the sleeping parameters and OSA of 10 patients with psoriasis compared with 10 controls.[198] No significant difference in change from baseline Apnea-Hypopnea Index was noted between the groups (95% CI −21.07 to 42.73, $P = .485$) at the endpoint (day 56). As part of an open-label study involving 152 psoriasis patients who had failed prior therapy (etanercept, methotrexate, or narrowband ultraviolet B), Strober et al examined the effect of psoriasis therapy on a variety of sleep disturbance parameters by employing the Medical Outcomes Study Sleep Scale.[199] The clinical endpoint was at week 16. Adalimumab treatment significantly improved sleep quality by 15% from baseline, as well as DLQI score, pain, and work productivity. No change was noted in the Medical Outcomes Study Sleep Scale item most closely mapped to apnea (ie, Do you awaken short of breath or with headache?). There are no known studies investigating whether treatment of OSA potentially improves psoriasis.

**Role of the dermatologist.** These studies demonstrate that patients with psoriasis are at increased risk for OSA. Whether this risk is correlated to BMI is unknown. Similar to other comorbidities, the risk for OSA varies according to severity of psoriasis. Psoriasis patients who have classical risk factors for OSA should be referred to the appropriate health care provider for further evaluation. Psoriasis patients with OSA should be tested for OSA-associated risk factors, such as obesity, hypertension, and diabetes.

## Chronic obstructive pulmonary disease

COPD is the result of end-organ damage to the pulmonary alveoli. Inflammation, scarring, and loss of elasticity prohibit optimal oxygen and carbon dioxide gas diffusion, with inefficient and reduced air exchange. While most cases of COPD are caused by current or former smoking (75%); other causes include asthma, chronic lung infections, and exposure to air pollutants. COPD usually develops over time, thus affecting middle age and older adults (≥40 years).[122] As a significant number of psoriasis patients smoke, the association of psoriasis as an independent risk factor for COPD development has recently been investigated.

In a large case-controlled meta-analysis, data from 7 high-quality studies involving 331,347 patients were pooled. The pooled OR of psoriatic patients with COPD versus nonpsoriatic controls was 1.45 (95% CI 1.21-1.73).[200] In a population-based, case-controlled study, Dreiher et al assessed the rate of COPD in 12,502 psoriasis patients compared with 24,287 psoriasis-free controls and adjusted for age, sex, current smoking, obesity, and socioeconomic status.[201] The adjusted OR for COPD was 1.27 (95% CI 1.13-1.42, $P < .001$). When only current smokers were examined, the OR increased dramatically to 5.56 (95% CI 4.95-8.24, $P < .001$).

A retrospective meta-analysis of 2 cohort and 2 case-controlled studies involving 42,150 psoriatic patients and 163,174 nonpsoriatic controls was performed in 2015.[202] The pooled OR for COPD was 1.90 (95% CI 1.36-2.65) for psoriasis versus controls. In a cohort study involving >10,000 patients, Chiang et al explored the relationship between psoriasis and COPD.[203] Overall, psoriasis patients were more likely to develop COPD (HR 2.35, 95% CI 1.42-3.89, $P < .01$) than controls. Yeung et al examined the prevalence of major medical comorbidities in 9035 psoriatic patients and 90,350 age-matched and practice-matched controls. The risk of having COPD was statistically significant, with an OR of 1.08 (95% CI 1.02-1.15, $P = .02$).[204] These studies demonstrate an independent association of COPD and psoriasis.

Whether the severity of psoriasis affects the risk for COPD development was also investigated in the Yeung et al study from 2013 via a subanalysis on the risk for COPD in psoriasis patients stratified by disease severity.[204] Patients with mild (0%-2% BSA), moderate (3%-10% BSA), and severe (>10% BSA) psoriasis were compared with controls, and the ORs were 1.08 (95% CI 0.99-1.18), 1.06 (95% CI 0.95-1.18) and 1.18 (95% CI 0.98-1.40), respectively ($P_{trend} = .03$). A similar subanalysis on psoriasis severity was also performed in the Li et al study of 2015.[202] This study showed the OR for mild-moderate psoriasis versus controls was 1.66 (95% CI 1.00-2.76). For severe psoriasis, the OR increased to 2.20 (95% CI 1.29-3.75). In a study from 2012, a subanalysis for disease severity was performed.[203] For patients with mild disease, the HR was 2.22 (95% CI 1.27-3.87, $P < .01$). In severe psoriasis, the HR increased to 2.81 (95% CI 1.24-6.39, $P < .05$). These results demonstrate an increase in the prevalence of COPD as psoriasis severity increases.

In a corollary subanalysis, the risk for COPD in psoriasis patients who were current smokers was significantly increased (OR 2.05, 95% CI 1.85-2.28) compared with nonsmokers.[202] The cumulative survival rates for COPD over time were investigated and adjusted for age, sex, cardiovascular disease, diabetes, chronic liver disease, chronic renal failure, autoimmune disease, cancer, monthly income, and level of urbanization.[203] The results showed psoriasis patients had significantly lower COPD-free survival rates than nonpsoriatic patients ($P < .001$).

**Role of the dermatologist.** These findings reveal that psoriatic patients are more likely to develop COPD than nonpsoriatic patients. Furthermore, patients with severe psoriasis are more likely to have COPD than those with mild disease. Dermatologists should be aware of this association and inform patients regarding the relationship. Attention to COPD risk factors should be given. Patients should be advised to discontinue smoking to reduce their risk of developing COPD.

## Uveitis

Inflammation of the middle layer of the eye (the uvea) is known as uveitis. Involvement of the anterior portion of the uveal tract (iritis) can be seen in patients with psoriasis, especially those with PsA. Anterior uveitis and iritis is one of the human leukocyte antigen B27—associated conditions (along with ankylosing spondylitis, PsA, and IBD). Because of the abundant vasculature within the uvea, inflammation can lead to significant vision problems, including permanent vision loss. The causes of uveitis are many and include systemic inflammatory disorders such as psoriasis.

In a retrospective cohort study of ~24,000 patients with mild psoriasis and 14,000 patients with severe psoriasis, the HR for uveitis was significantly greater for psoriatic patients than the unaffected control population.[205] The incidence of uveitis was greater for individuals with severe disease than mild disease. In a cohort study of 60,000 patients with mild psoriasis and >7000 patients with severe psoriasis, there was a significantly increased rate of uveitis in both populations, with a greater risk with severe disease.[206] In addition, among patients with uveitis, there was a greater likelihood of psoriasis. With regards to management of psoriasis with concomitant uveitis, a case series of 8 patients with both psoriasis and uveitis were treated with either infliximab (n = 4) or adalimumab (n = 4).[207] Of those patients, 7 achieved remission of their uveitis.

Consultation with an ophthalmologist is warranted for evaluation and management of uveitis should signs or symptoms arise.

**Role of the dermatologist.** Dermatologists should be aware of the increased incidence of uveitis in psoriatic patients. Both providers and patients should understand the signs and symptoms of uveitis

are nonspecific and that suspicious ocular signs and symptoms should be further investigated by an ophthalmologist. These symptoms include redness of the eye (with or without pain), blurred vision, and photosensitivity.[208] Early detection allows initiation of treatment to prevent ocular damage.[208] Dermatologists should consider human leukocyte antigen B27 arthritis in patients with psoriasiform skin changes and uveitis and refer them as deemed appropriate.

### Hepatic disease

Inflammation of the liver can lead to fibrosis and irreversible damage. Nonalcoholic fatty liver disease (NAFLD) is a common type of liver dysfunction, which is often found in patients with metabolic syndrome. The incidence of NAFLD in psoriasis patients relative to unaffected patients has been investigated.

Abedini et al performed liver ultrasounds on 123 psoriasis patients and 123 healthy controls that were matched for age, sex, and BMI. The psoriasis group had a significantly higher rate of NAFLD relative to healthy controls (65.6% vs 35%; $P < .01$).[209] In a case-controlled study comparing 142 patients with chronic plaque psoriasis and NAFLD versus 125 patients with NAFLD without psoriasis, patients with chronic plaque psoriasis had increased rates of metabolic syndrome ($P < .05$), obesity ($P = .043$), hypercholesterolemia ($P = .029$), and PsA ($P = .036$).[210]

The rate of severe liver damage for psoriasis patients with known NAFLD was evaluated by Pongpit et al.[211] They performed transient elastography on 165 psoriasis patients with known NAFLD, showing 18 patients (11%) had significant liver fibrosis via high liver stiffness measurement scoring. Those patients with significant fibrosis had a higher incidence of diabetes (OR 12.7, $P = .01$), elevated aspartate aminotransferase levels (OR 1.08, $P = .017$), and increased waist circumference (OR 1.24, $P = .0002$).

Hepatic damage has been noted more frequently in patients prescribed any systemic therapy for both plaque psoriasis and PsA.[212] A cohort study of The Health Improvement Network UK database found NAFLD was higher in patients with plaque psoriasis (aHR 1.97) and PsA (aHR 1.67) prescribed any systemic therapy, even compared with patients with rheumatoid arthritis prescribed any systemic therapy (aHR 0.96). In addition, the incidence of hepatic fibrosis in psoriasis patients receiving methotrexate therapy is twice that of rheumatoid arthritis patients receiving methotrexate therapy, adjusted for dosage received. Both plaque psoriasis and PsA were associated with NAFLD and cirrhosis more so than rheumatoid arthritis, even when the psoriasis patients did not receive systemic therapy.

The mechanism of hepatic damage in psoriasis patients is unclear but hypothesized to be a hepatodermal axis, where cytokine release from skin lymphocytes circulate through the liver causing damage or, conversely, that hepatic inflammatory cytokines circulate systemically and promote keratinocyte hyperproliferation.[212] Further studies are warranted.

**Role of the dermatologist.** Dermatologists should be aware of the increased prevalence of NAFLD in patients with psoriasis. While there is an independent association between psoriasis and NAFLD, patients with metabolic syndrome and/or PsA are particularly at risk. In addition, systemic medications used to treat psoriasis can be deleterious to liver function. Unidentified liver disease enables progression of liver damage, which can lead to fibrosis and cirrhosis. Early identification allows management and monitoring. The identification of liver disease might alter the treatment options chosen for the patient's psoriasis.

## PATIENT EDUCATION

Patient education and directly involving patients in their care via shared decision making is important. Discussing the etiology, potential comorbidities, treatment options, and lifestyle choices on the course and treatment of psoriasis will facilitate patient-engaged, comprehensive care and enhance QoL. Creating a therapeutic alliance with patients empowers them and might enhance their satisfaction and compliance. Educational tools include verbal discussion, pamphlets, and trusted internet resources. Patients should be made aware of psoriasis advocacy, education, and support groups, including the National Psoriasis Foundation (www.psoriasis.org) and the International Federation of Psoriasis Associations (www.IFPA-pso.org). Patients should be made aware of the risks, benefits, and alternatives of each treatment modality and be asked for their preferences regarding their treatment plan. Repetition of key concepts during follow-up visits allows consolidation and integration of knowledge.

## PEDIATRIC CONSIDERATIONS

Children can also be affected by psoriasis and its comorbidities. Considerations specific to the pediatric psoriasis population are addressed in the pediatric section of these guidelines.

## GAPS IN RESEARCH

Significant knowledge advancements regarding psoriasis comorbidities have occurred over the past 30 years. Despite this, in review of the currently available highest level of evidence, the expert work group acknowledges much has yet to be learned. The advent of new medications with unique mechanisms of action affords new opportunities for better disease control and potential reduction of comorbidities. Little is known about psoriasis and its comorbidities relative to health disparities or the correlation between genotype and phenotype and its impact on both psoriasis and its comorbidities. The interaction, independently and dependently, of psoriasis and its comorbidities is complex and yields numerous potential research avenues for better understanding of the impact of each particular entity on the others. Of fundamental importance is to determine the impact of psoriasis treatment on the ability to prevent future disease associated comorbidity. Although emerging observational data of outcomes and experimental data of important surrogate markers hold promise for bending the comorbidity curve, large randomized controlled studies are necessary to determine which treatment strategies for psoriasis will lead to benefits for patients beyond the skin.

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## SUPPLEMENTARY APPENDIX. METHODS

A multidisciplinary work group of recognized psoriasis experts consisting of dermatologists (including private practitioners), a rheumatologist, a cardiologist, and representativies from a patient advocacy organization was convened to identify important clinical questions with regards to managing the extracutaneous manifestations of psoriasis in adults, including comorbid conditions, mental health and psychosocial wellness, and quality of life (Table I). Work group members completed a disclosure of interests that was periodically updated and reviewed for potential relevant conflicts of interests throughout guideline development.

An evidence-based model was used and evidence was obtained using a search of the PubMed and Medline databases from January 1, 1980, to December 31, 2017, for all newly identified clinical questions. Searches were limited to publications in the English language. Medical subject heading terms used in various combinations in the literature search included: "psoriasis," "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "metabolic syndrome," "diabetes," "obesity," "dyslipidemia,"

"hypertension," "nonalcoholic fatty liver disease," "osteoporosis," "renal disease," "kidney failure," "cardiovascular disease," "coronary heart disease," "atherosclerosis," "cardiovascular events," "uveitis," "psoriatic arthritis," "smoking," "tobacco," "cigarette," "smoking cessation," "environmental smoke," "cancer," "neoplasm," "lymphoma," "depression," "psychological disorder," "anxiety," "suicide (attempt, completed)," "sexual dysfunction," "erectile dysfunction," "work productivity," "interpersonal relations," "alcoholism," and "drinking."

After removal of duplicate data, 516 articles were retained for final review on the basis of relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and utilized by the Work Group in developing recommendations. The Academy's prior published guidelines on psoriasis were evaluated, as were other current published guidelines on psoriasis.[5,6,7]

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of US family medicine and primary care journals (ie, American Family Physician, Family Medicine, Journal of Family Practice, and BMJ USA).[213] Evidence was graded using a 3-point scale, the quality of methodology (eg, randomized controlled trial, case–control, prospective and retrospective cohort, case series), and the overall focus of the study (ie, diagnosis, treatment-prevention-screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that are of importance to patients, such as morbidity, mortality, symptom improvement, cost reduction, and quality of life),
II. Limited-quality patient-oriented evidence, and
III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that might or might not reflect improvements in patient outcomes).

Clinical recommendations were developed on the best available evidence tabled in the guideline. These recommendations are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence,
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence, or
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

For situations in which documented evidence-based data was not available, we have utilized expert opinion to generate our clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (AAD) and AAD association administrative regulations for evidence-based clinical practice guidelines (May 2014),[214] which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors. Additionally, this guideline is developed in collaboration with the National Psoriasis Foundation and as part of the review process; the National Psoriasis Foundation medical board members provided their feedback. This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

## DEFINITION

Psoriasis vulgaris is a chronic inflammatory skin disease which classically presents with well-demarcated, red plaques with silvery scale, commonly involving the scalp, elbows, knees, and presacral region, though any area of skin might be involved, including the palms, soles, nails, and genitalia. While the severity of psoriasis is defined in part by the total body surface area (BSA) involved, with <3% BSA considered mild, 3%-10% BSA considered moderate, and >10% BSA considered severe disease, psoriasis can be severe irrespective of BSA when it has serious emotional consequences or occurs in selected locations, including but not restricted to the hands, feet, scalp, face, or genital area, or when it causes intractable pruritus. The Psoriasis Area Severity Index is a more specific means of quantifying the extent and severity of psoriasis, as it takes into account not only BSA but also intensity of redness, scaling, and plaque thickness, ultimately producing a score from 0 (no disease) to 72 (maximal disease severity). The Psoriasis Area Severity Index is used for monitoring response to treatments in clinical trials and as a research tool to judge the severity of psoriasis. It is rarely utilized by dermatologists in clinical practice to guide management.

Psoriasis has many cutaneous forms, including vulgaris (plaque), guttate, palmoplantar, inverse, and pustular, which is discussed here as a collective whole.

Psoriasis is an inflammatory, immunologically mediated condition stemming from inappropriate activation of cutaneous T cells and dendritic cells with subsequent release of a variety of cytokines and

other soluble mediators. These chemical signals are responsible for keratinocyte hyperproliferation manifesting as characteristic psoriasis morphology. In addition, they contribute to the rampant inflammation underlying a number of systemic disease associations, including arthritis and cardiometabolic diseases, such as dyslipidemia, metabolic syndrome, and heart disease. To combat the local and systemic inflammation inherent to psoriasis, a number of topical and systemic medications have been developed and utilized with varying degrees of success.