

# Common and Not-So-Common Comorbidities of Psoriasis

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## ■ Abstract

Plaque psoriasis is increasingly recognized as a multisystemic disease whose most common comorbidities include psoriatic arthritis, cardiovascular disease, metabolic syndrome, overweight/obesity, inflammatory bowel disease, and depression. The presence of such comorbidities affects the therapeutic choices for clinicians. Patients often visit dermatologists more frequently than they do other clinicians, so it is incumbent upon dermatologists to recognize and address early signs of psoriatic comorbidities to prevent further deterioration and improve their patients' quality of life.

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## ■ Keywords

Cardiovascular disease; comorbidities; immune-mediated disorders; overweight/obesity; psoriasis; psoriatic arthritis; psychiatric disorders

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Scientific research continues to reveal the inflammatory process that is the basis of many chronic conditions, including psoriasis and its many associated comorbidities (**Table**).

**Psoriatic arthritis (PsA)** is among the most frequent of these comorbidities. Approximately 30% of patients with psoriasis have comorbid PsA. PsA onset typically occurs 5 to 10 years after the onset of psoriasis, ie, in the third to fifth decade of life; in children, the age of onset peaks between 11 and 12 years.<sup>1</sup>

Positioned on the frontlines for identifying PsA, dermatologists should be aware of the importance of evaluating patients for joint stiffness and pain. Physical examinations should include the fingers (dactylitis) and toes, Achilles tendon (enthesitis), sacroiliac, axial skeleton, and the large joints to identify evidence of swelling, inflammation, and nail disease (**Figure**). When examining patients who present with early onset of PsA, consider the following questions:

- Does early morning stiffness last for  $\geq 30$  minutes, eg, hands, feet, hips and other large joints, without clinical signs of PsA?
- When is a rheumatologic consultation indicated?
- PsA usually improves more dramatically than psoriasis. When does the rheumatologist refer to the dermatologist?
- Should dermatologists be ordering x-rays for suspected psoriatic joint disease?
- Can radiologists discern the early signs of PsA?

There are several self-administered screening tools for PsA:

- The *Psoriasis Epidemiology Screening Tool (PEST)* is a one-page questionnaire with a body diagram allowing patients to identify painful joints<sup>2</sup>
- The *Toronto Psoriatic Arthritis Screening Tool (TOPAS)* is meant for the general population to determine whether a person might have PsA<sup>3</sup>
- The *Psoriatic Arthritis Screening and Evaluation Tool (PASE)* can distinguish between signs and clinical symptoms of PsA and those of osteoarthritis<sup>4</sup>

## ■ TABLE Comorbidities Associated With Psoriasis

Related to systemic inflammation	<ul style="list-style-type: none"><li>• Psoriatic arthritis</li><li>• Atherosclerosis</li><li>• Diabetes and insulin resistance</li><li>• Hypertension</li><li>• Metabolic syndrome</li><li>• Myocardial infarction</li><li>• Obesity</li></ul>
Related to lifestyle risk factors or to impaired quality of life	<ul style="list-style-type: none"><li>• Alcohol abuse</li><li>• Anxiety</li><li>• Depression</li><li>• Smoking</li><li>• Suicidal ideation</li></ul>
Related to treatment (eg, systemic agents, TNF-alpha inhibitors)	<ul style="list-style-type: none"><li>• Hepatotoxicity</li><li>• Nephrotoxicity</li><li>• Nonmelanoma skin cancer</li></ul>

TNF=tumor necrosis factor. Source: Gulliver W.<sup>9</sup>

Systemic agents are effective for treating patients with comorbid PsA and plaque psoriasis because they can ameliorate cutaneous as well as joint inflammation.<sup>5</sup> Older systemic agents, such as methotrexate and cyclosporine, are used less often because of concerns about toxicity and their inability to prevent further joint destruction.<sup>5</sup> Phototherapy and topical agents address skin symptoms of psoriasis but do not relieve the disabling joint pain of PsA.<sup>5</sup>

**Cardiovascular disease** has a strong association with psoriasis. This is in part due to the fact that several of the medications commonly prescribed for psoriasis, including corticosteroids, acitretin, and cyclosporine, can further worsen dyslipidemia.<sup>6</sup> When controlled for dyslipidemia, psoriasis was found to be an independent risk factor for myocardial infarction (MI) in a prospective study comparing outcomes of patients with and without psoriasis.<sup>7</sup> This was particularly striking in the cohort of patients in their 30s with severe psoriasis vs those in their 60s.<sup>7</sup> In 30-year-old patients with mild or severe psoriasis, the adjusted relative risk (RR) of having an MI was 1.29 (95% confidence interval [CI], 1.14-1.46) and 3.10 (95% CI, 1.98-4.86), respectively. For 60-year-old patients with mild or severe psoriasis, the adjusted RR of having an MI was 1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively.<sup>7</sup> In general, patients with severe psoriasis die approximately 4 years sooner than do patients without psoriasis.<sup>8</sup>

Recent studies have explored the association between psoriasis and the immune pathogenic mechanisms in cardiovascular diseases. Cytokines such as interleukin (IL)-1–beta, IL-6, and tumor necrosis factor (TNF)-alpha are involved in the pathophysiology of many conditions, including cardiovascular disease, diabetes, obesity, Crohn disease, and dyslipidemia.<sup>9</sup> Genes that regulate some of these cytokines may be linked to psoriasis and its comorbidities.

**Metabolic syndrome** also shares a strong inflammatory association with psoriasis.<sup>10</sup> The syndrome is diagnosed when at least three of five characteristics are present: increased waist circumference, hypertension, hypertriglyceridemia, reduced high-density lipoprotein (HDL), and insulin resistance/increased serum glucose.<sup>10</sup> In a chart comparison study of 580 patients, those with moderate to severe psoriasis who were admitted for melanoma surgery were more likely to have comorbid metabolic syndrome and its components than were patients in the control group: diabetes ( $P < 0.0001$ ), hyperlipidemia ( $P < 0.01$ ), coronary heart disease ( $P < 0.01$ ), and arterial hypertension ( $P < 0.0001$ ).<sup>11</sup>

The more severe the psoriasis, the greater the likelihood of metabolic syndrome.<sup>12</sup> Furthermore, each component of metabolic syndrome is also independently associated with psoriasis.<sup>12</sup> In a study of 44,715 patients (4,065 with psoriasis and 40,650 controls) in the United Kingdom, psoriasis severity correlated with metabolic syndrome in a dose-response paradigm: The adjusted odds ratio (OR) for patients with mild psoriasis was 1.22 (95% CI, 1.11-1.35) vs 1.98 (95% CI, 1.62-2.43) for severe psoriasis.<sup>12</sup>

**Overweight and obesity**, which contribute to metabolic syndrome, also have a dose-response relationship with psoriasis: The greater the body mass index (BMI), the likelier it is that psoriasis will occur.<sup>13</sup> A Norwegian study of 8,752 men and women followed for 14 years found that individuals with a BMI of 27 kg/m<sup>2</sup> had a 32% increased risk for psoriasis; the risk increased to 43% at a BMI of 28 kg/m<sup>2</sup>, and to 71% at a BMI of  $\geq 30$  kg/m<sup>2</sup> in nonsmokers.<sup>13</sup> Independent of BMI, there was a 70% to 90% increased risk of onset of psoriasis with weight gain for both men and women.<sup>13</sup>

Adipocytes and activated inflammatory macrophages can contribute to both psoriasis and overweight/obesity.<sup>13</sup> Adipose tissue produces the hormones, adipokines, and proinflammatory cytokines responsible for psoriasis, namely IL-1, IL-6, and TNF-alpha.<sup>13</sup>

TNF-alpha was identified in 1993 as the first fat-secreted cytokine linked to insulin resistance.<sup>14</sup> Since then, research has continued to show how TNF-alpha correlates with increased BMI, percentage of

body fat, and hyperinsulinemia.<sup>14</sup> For example, TNF-alpha contributes to insulin resistance by increasing free fatty acid production, reducing adiponectin synthesis, and impairing insulin signaling.<sup>14</sup>

**Type 2 diabetes.** Likewise, there is a strong association between psoriasis and type 2 diabetes that is also correlated with disease severity.<sup>15</sup> A meta-analysis of 27 studies found that there was an overall propensity for diabetes prevalence in patients with psoriasis (OR, 1.59; 95% CI, 1.38-1.83).<sup>15</sup> The pooled OR was 1.53 (95% CI, 1.16-2.04) for mild psoriasis and 1.97 (95% CI, 1.48-2.62) for severe psoriasis.<sup>15</sup>

Mansouri and colleagues<sup>16</sup> discovered that psoriasis is an independent risk factor for the presence of coronary artery calcium (OR, 2.35; 95% CI, 1.12-4.94) in fully adjusted models. This suggests that, even after adjustment for BMI, people with psoriasis have levels of atherosclerosis comparable to those of people with type II diabetes.<sup>16</sup> The study confirmed that people with psoriasis are three to five times more likely to have moderate to severe levels of coronary calcium compared to healthy controls.<sup>16</sup>

Early treatment of psoriasis with systemic or biologic immunomodulating therapy has the potential to delay or prevent the onset of these comorbidities and decrease the risk of premature mortality.

Among the older systemic oral agents for psoriasis treatment, methotrexate was effective in reducing vascular inflammation in a study of 7,615 veterans with psoriasis and 6,707 with rheumatoid arthritis (RA).<sup>17</sup> Compared with controls, patients who received methotrexate had a significant reduction in cardiovascular disease (psoriasis: RR, 0.73; 95% CI, 0.55-0.98; RA: RR, 0.83; 95% CI, 0.71-0.96). Low-dose methotrexate was more effective than the higher dose, and concomitant folic acid administration demonstrated the highest reduction in cardiovascular disease risk.<sup>17</sup>

In a retrospective study, Wu and colleagues<sup>18</sup> found that TNF-alpha inhibitors or a combination of oral agents and phototherapy were superior to topical monotherapy for lowering the risk of MI (50% and 46%, respectively). The researchers theorized that reducing inflammation led to a decrease in the risk of MI.<sup>18</sup> When adjusted for age, TNF-alpha therapy was shown to have a greater effect in the age cohort  $> 60$  years, a difference attributed to the higher incidence of diabetes in that age group.<sup>18</sup> Clearly, biologics and methotrexate confer a cardiovascular benefit beyond ameliorating psoriasis symptoms. A Danish registry study found that the cardiovascular incidence rates per 1,000 patient-years were 6.0 (95% CI, 2.7-13.4), 17.3 (95% CI, 12.3-24.3), and 44.5 (95% CI, 34.6-57.0) for patients treated with biologic agents, methotrexate, and other therapies (retinoids, cyclosporine, and phototherapy), respectively.<sup>19,20</sup>

**Psychiatric diseases/mood disorders**—depression, anxiety, and suicidal ideation in particular—are seen at higher rates among patients with psoriasis compared with the general population.<sup>21</sup> Wu and colleagues<sup>21</sup> reported that, in a Danish registry, mental health disorders occurred in 3.1% of patients with psoriasis vs 2.2% of controls. Patients with psoriasis were more likely to be prescribed antipsychotics, anxiolytics, and antidepressants.<sup>21</sup>

A systematic review of global studies found that the prevalence of depression among patients with psoriasis ranged from 2.10% to 33.7% compared with a lower prevalence (0% to 22.7%) among healthy controls.<sup>21</sup> Similarly, among patients with PsA, there is a greater risk for depression compared with patients with plaque psoriasis (incidence rate ratio [IRR], 1.22; 95% CI, 1.16-1.29, vs 1.14; 95% CI, 1.11-1.17).<sup>21</sup> Depression and psoriasis are thought to share similar inflammatory cytokines.<sup>21</sup> Whether or not there is a definite shared underpinning for both diseases, treatment for patients with comorbid depression is often more challenging to manage.<sup>21</sup>

Although prevalence data for **anxiety** are not as robust as the depression data for patients with psoriasis, one systematic review estimated that the prevalence of anxiety ranges from 1.81% to 22.7% among patients with psoriasis, compared with 1.35% to 11.1% among patients without psoriasis.<sup>21</sup> Patients with psoriatic arthritis tend to have more severe anxiety than do those with plaque psoriasis.<sup>21</sup>



■ **FIGURE** The Many Presentations of Psoriatic Arthritis

A. Skin and joints. B. Dactylitis. C. Enthesitis. D. Arthritis mutilans.

Because joint disease usually presents 5 to 10 years after skin symptoms, dermatologists invariably see these patients first.

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The prevalence of **suicidality** among patients with psoriasis can be as high as 37.4% during a lifetime vs 1.01% to 1.94% among the general population, with two-thirds of patients attributing their suicidal ideation to their psoriasis.<sup>21,22</sup> Data are conflicting about whether there is a dose-response relationship between psoriasis severity and suicide.<sup>21</sup> Clearly, however, comorbid depression confers greater risk for suicide among patients with psoriasis than does severity of the disease alone. In one UK study, major depression contributed to a 10-fold risk for suicide among patients with psoriasis.<sup>21</sup>

Appropriate treatment of psoriasis can ameliorate comorbid depression and anxiety.<sup>21</sup> Papp and colleagues<sup>23</sup> reported significant decreases in depression and anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS), in patients treated with brodalumab 140 mg (n=219) or 210 mg (n=222) every 2 weeks, compared with patients who received placebo (n=220;  $P < 0.0001$  for brodalumab 140 or 210 mg vs placebo). Researchers also found that the TNF inhibitor adalimumab simultaneously decreased the Psoriasis Area and Severity Index (PASI) scores of >75% of patients studied and improved scores for depression ( $P < 0.001$ ).<sup>24</sup>

**Opportunistic infections** are a frequent adverse effect associated with TNF-alpha inhibitors. One study, for example, reported that the rate of serious infection was 4.02 per 100 patient-years (95% CI, 3.20-5.04).<sup>25</sup> Gastrointestinal infections were the most common, followed by tuberculosis, extrapulmonary infections, and malignancies.<sup>25</sup> Infections are also a concern with the newer biologics. In a phase 3 trial of secukinumab, a human anti-IL-17A monoclonal antibody, the most common adverse event was upper respiratory tract infection.<sup>26</sup> At minimum, clinicians ought to screen patients every 3 months for infection, at least initially.

**Malignancies.** Although the data are inconsistent, some studies have found an association between psoriasis and malignancies.<sup>9</sup> Some theorize that neoplasms share a common inflammatory

pathway, while others point to treatment-related causes, especially with high-dose methotrexate and psoralen ultraviolet A (PUVA) therapy.<sup>9</sup> A large retrospective study of 153,197 patients with psoriasis who were on systemic agents showed an increased risk of Hodgkin lymphoma (RR, 3.18; 95% CI, 1.01-9.97) and cutaneous T-cell lymphoma (RR, 10.75; 95% CI, 3.89-29.76).<sup>9</sup>

**Pain**, as assessed by patient-reported outcome (PRO) instruments, is often overlooked in dermatology practices because many dermatologists assume that pain management is under the purview of rheumatologists. Approximately 42% of patients with plaque psoriasis have reported cutaneous pain, which they described as pruritic, aching, sensitive, burning, tender, and cramping.<sup>27</sup> The cytokine IL-33 is implicated in both psoriasis and pain, but the common mechanism is not yet clear.<sup>27</sup> In a study on psoriatic pain, Patrino and colleagues<sup>27</sup> found that 43.6% of 163 patients with psoriasis had cutaneous pain, slightly more than had been reported in previous studies.

One useful tool for assessing pain is the Psoriasis Symptom Inventory (PSI), a PRO instrument that includes itch, redness, scaling, burning, cracking, stinging, flaking, and pain.<sup>28</sup> In a substudy (N=661) of the phase 3 trial AMAGINE 1, PSI results showed that the IL-17 receptor antibody brodalumab was effective in clearing moderate to severe plaque psoriasis as well as comorbid pain.<sup>28</sup>

The Dermatology Life Quality Index (DLQI) is another PRO that has been validated to assess pain in patients with moderate to severe psoriasis.<sup>29</sup> The CLEAR 52 trial demonstrated that secukinumab was more effective at relieving pain vs ustekinumab at weeks 16 and 52 ( $P < 0.05$ ) as measured by the DLQI. Moreover, secukinumab relieved itching 4 weeks faster and scaling 8 weeks faster than ustekinumab ( $P < 0.001$ ).<sup>29</sup>

**Inflammatory bowel disease (IBD)** and psoriasis are genetically linked; the risk for IBD is four times greater among patients with psoriasis than it is among healthy comparators.<sup>30</sup> For people with PsA,

the risk for IBD—especially for comorbid Crohn disease—is even greater.<sup>30</sup> Patients with comorbid psoriasis and Crohn disease tend to be younger at diagnosis than are those with psoriasis and ulcerative colitis (median, 25.8 years vs 37.3 years).<sup>30</sup> The etiology of IBD remains unclear; some hypotheses point to an immune-mediated disorder, whereas others suggest autoimmune origins.<sup>31</sup>

Treatment for comorbid psoriasis and IBD traditionally calls for the use of TNF-alpha inhibitors.<sup>30</sup> However, some studies paradoxically inculcate this class of agents as the cause of both IBD and psoriasis.<sup>30</sup> Despite this, Eppinga and colleagues<sup>30</sup> reported that most of the patients (n=385) in their IBD-psoriasis prevalence study used TNF-alpha inhibitors, followed by systemic steroids, methotrexate, and nonsteroidal anti-inflammatory drugs. Preliminary evidence also suggests that IL-17 inhibitors may precipitate IBD in up to 2 out of 1,000 patients.<sup>32,33</sup>

**Hepatic disease**, another common comorbidity associated with psoriasis, is often overlooked.<sup>34</sup> The hormone resistin and the cytokines TNF-alpha, IL-6, and IL-1-beta are associated with insulin resistance, fatty liver, and psoriasis, but their pathophysiologic mechanism of action is unclear.<sup>34</sup> Roberts and colleagues<sup>34</sup> identified the prevalence of non-alcoholic fatty liver disease (NAFLD, 47%) and non-alcoholic steatohepatitis (NASH, 22%) in a cohort of military patients with psoriasis (N=103; mean age, 52.7 years).<sup>34</sup> In patients with psoriasis, comorbid diabetes confers an even greater risk for NAFLD.<sup>34</sup>

Evidence is mounting that shows other comorbidities are also found in patients with psoriasis, including **chronic obstructive pulmonary disease (COPD), renal disease, and obstructive sleep apnea (OSA)**.<sup>35,36</sup> One British cross-sectional study of 69,000 patients revealed an association with renal disease and psoriasis (adjusted OR, 1.28; 95% CI, 1.11-1.48;  $P < 0.05$ ) and showed that the prevalence of renal disease increases with psoriasis severity.<sup>35</sup> At this time, the link between psoriasis and COPD or OSA is based on case reports; more rigorous studies are needed to clearly establish the connection.<sup>36</sup>

**Lifestyle choices** such as **tobacco and alcohol use** can exacerbate psoriasis. A UK study found a paradox in the comorbidity of smoking: While smoking was positively linked to psoriatic arthritis (Hazard Ratio [HR], 1.27; 95% CI, 1.19-1.36), it found no such association with plaque psoriasis (HR, 0.91; 95% CI, 0.84-0.99).<sup>37</sup> Another study, however, found that smoking duration and pack-years contributed to the risk of psoriasis ( $P < 0.0001$ ).<sup>38</sup> The theory behind the smoking-psoriasis link is that nicotine and dioxin activate T cells that produce cytokines IL-12, IL-17, and IL-22.<sup>38</sup>

In a study that surveyed the dietary habits of 1,206 patients with psoriasis, 13.6% of respondents said that alcohol was a main trigger for psoriasis flares, and 53.8% said that eliminating alcohol from their diet helped improve their symptoms.<sup>39</sup> Patients with psoriasis who consume alcohol have a 60% greater risk of mortality than do their healthy peers.<sup>40</sup> The top causes of alcohol-related death among patients with psoriasis were alcoholic liver disease (65.1%), fibrosis and cirrhosis of the liver (23.7%), and mental health disorders due to alcohol (7.9%).<sup>40</sup> Other commonly cited dietary triggers were sugar (13.8%), tomato (7.4%), gluten (7.2%), and dairy (6%).<sup>39</sup>

## Conclusion

Psoriasis presents a multifaceted challenge to the clinician who enjoys the medical aspects of dermatology. As an immune-mediated inflammatory disease, psoriasis is associated with numerous comorbidities. A dose-response relationship exists with psoriasis and its comorbidities: The more severe the psoriasis, the likelier an individual will have one or more comorbidities. To optimize the results of treatment for psoriasis, clinicians must look for—and address—the presence of concomitant disorders.

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