

Psoriasis-Associated Fatigue: Pathogenesis, Metrics, and Treatment

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PRACTICE POINTS

- Psoriasis-associated fatigue results from the impact of the inflammatory cascade on the central nervous system and from the negative influences of disease on patients.
- Although psoriasis-associated fatigue is common, there is a lack of validated systems to quantify its severity and guide therapy.
- Given the overlapping pathophysiology of psoriasis and fatigue, biologic agents may be beneficial for treating psoriasis-associated fatigue.

Fatigue, a substantial symptom of psoriasis, is triggered by complex interactions of inflammation in psoriatic disease, both directly via inflammatory cytokines and indirectly via psychological and physiological factors. We provide data and observations that highlight the importance of qualifying and quantifying fatigue among patients with psoriasis and psoriatic arthritis and underscore the need to develop novel therapeutics to target this debilitating element of a multi-system disease.

Cutis. 2016;97:125-132.

Fatigue is defined as “an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work,”¹ and it is experienced by most patients with chronic disease. There are 2 types of fatigue: acute and chronic.²

Acute fatigue typically is caused by an identified insult (ie, injury), is self-limited, and is relieved by rest. Chronic fatigue, which may have multiple unknown causes, may accompany chronic illness and lasts longer than 6 months.² In chronic disease, fatigue can originate peripherally (neuromuscular dysfunction outside of the central nervous system) or centrally (neurotransmitter activity within the central nervous system). Generally, central fatigue is more relevant in patients with chronic disease; however, both central and peripheral fatigue frequently coexist.

Fatigue, even with its accepted definition, is a nonspecific symptom, making it difficult to measure. Because of its subjective nature and the lack of effective therapies, clinicians often ignore fatigue. Still, patients with chronic disease continue to cite fatigue as one of the most challenging aspects of their disease that frequently decreases their quality of life (QOL).²

Fatigue has been well recognized in a number of chronic inflammatory diseases such as rheumatoid arthritis,^{3,4} systemic lupus erythematosus,⁵ fibromyalgia,⁶ and primary Sjögren syndrome.⁷ Similarly, fatigue is a frequent concern among patients with psoriasis and psoriatic arthritis.⁸ Given the prevalence and significance of psoriasis-associated fatigue,⁹ new efforts are needed to understand its

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The authors report no conflict of interest.

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pathophysiology, to develop new metrics for its evaluation, and to investigate therapeutic strategies to target it clinically. The following discussion provides an overview of the association between fatigue and psoriatic disease as well as the commonly used metrics for evaluating fatigue. Possible therapeutic agents with which to manage fatigue in this patient population also are provided.

Pathogenesis of Psoriasis-Associated Fatigue

Immunologic/Molecular Basis for Psoriasis-Associated Fatigue—Several theories aim to explain the pathophysiology of fatigue in patients with psoriatic disease. Psoriasis is a chronic inflammatory disease characterized by sharply demarcated erythematous plaques with adherent scale (Figure 1). Many in vitro studies have demonstrated the complex cytokine network that underlies the histopathologic alterations we observe in psoriatic lesions.^{10,11} Until recently, psoriasis was considered a type I autoimmune disease with strong T_H1 signaling, influenced by IFN- γ , IL-2, and IL-12.¹² T_H1-producing proinflammatory cytokines, tumor necrosis factor α (TNF- α), and IFN- γ are elevated in psoriatic lesions.¹³ Studies on the efficacy of ustekinumab, a monoclonal antibody targeting IL-12 and IL-23, demonstrate the integral role of the immune system in psoriasis pathogenesis as the production of IL-12 polarizes T cells into T_H1 cells.^{14,15} However, in recent years, T_H17 cells have been linked to autoimmune inflammation¹⁶ and have been localized to the dermis in psoriatic lesions.¹⁷

Among a milieu of inflammatory cytokines, IL-1 is crucial for the early differentiation of T_H17 cells.¹⁸ The IL-1 family of cytokines serve as primary mediators of inflammation with members including the IL-1 agonists (IL-1 α , IL-1 β),¹⁹

IL-1 receptor antagonist (IL-1RA),²⁰ and IL-1 receptor type II (IL-1RII).²⁰ The latter two inhibit IL-1 agonists from binding to their receptor (IL-1RI).^{19,20} A study by Yoshinaga et al²¹ investigated the level of inflammatory cytokines within lesional and non-lesional psoriatic skin, finding elevated levels of IL-1 β in lesional skin. Another study found that IL-1 β expression was increased 357% within biopsied psoriasiform lesions from flaky-skin mice, a useful model to examine the hyperproliferative alterations in the skin. This same study revealed that in vivo IL-1 β neutralization alleviated the psoriasiform features in these same mice, suggesting IL-1 β is integral to psoriasis pathogenesis.²²

Evidence indicates that the aforementioned inflammatory mediators may contribute to psoriasis-associated fatigue. When the peripheral immune system is continuously activated, such as in psoriasis, the peripherally produced proinflammatory cytokines and subsequent immune signaling are monitored by the brain via afferent nerves, cytokine transporters at the blood-brain barrier, and IL-1 receptors on macrophages and endothelial cells of brain venules.²³ For example, subseptic doses of lipopolysaccharide injected into rats induced messenger RNA expression of IL-1 β in the choroid plexus, circumventricular organs, and the meninges,²⁴ sites where cytokines can enter the blood-brain barrier via diffusion or cytokine transporters.²³ These results may suggest a pathway that relays the peripheral immune signals that underlie psoriatic disease to the brain, resulting in activation of brain circuitry that mediates various negative behavioral responses, including fatigue.²³ Following a central IL-1 β infusion in mice, investigators found a significant decrease in the running performance ($P < .01$)²⁵; the same infusion increased lethargy, malaise, and fatigue in rats.²⁶ Interestingly,



Figure 1. Broad, pink, well-demarcated plaque with retention hyperkeratosis consistent with plaque psoriasis.

administration of IL-1RA significantly increased run time to fatigue ($P < .05$), supporting the hypothesis that IL-1 β plays an important role in fatigue.²⁵ Other investigators found that administration of many cytokines (IL-1 β , IL-6, TNF- α) into rats induced depressivelike behaviors²⁷ and suppressed locomotor activity.²⁸ Lastly, another investigation found that IL-1RI knockout mice were resistant to symptoms of sickness, such as social exploration, anorexia, immobility, and weight loss, following IL-1 β injections.²⁹ Although the translatability of these studies to humans is not entirely clear, one study found that the proinflammatory cytokines IL-1 and TNF- α were elevated in patients with chronic fatigue syndrome.³⁰ Furthermore, a 2013 systematic review found that several serum inflammatory markers including IL-6 and TNF- α were elevated in patients with severe plaque psoriasis compared to healthy controls.³¹ Therefore, these shared inflammatory cytokines may contribute to and explain the pathogenesis of both fatigue and psoriasis.

Confounding Factors—Although fatigue may be partially explained by the joint effect of inflammatory mediators on both the skin and the brain, there is evidence to suggest that other confounding factors may modify this association and affect its clinical presentation. The pathophysiology of fatigue in psoriasis may not be strictly immunologic; the environmental, psychological, and physical effects of psoriasis may all contribute to and perpetuate fatigue.^{9,32,33} Interestingly, the pathophysiology of psoriasis involves many cytokines also known to contribute to features of the metabolic syndrome.³⁴ For example, elevated levels of free fatty acids,

TNF- α , and IL-6 act in concert to promote inflammation, alter glucose metabolism, and dysregulate endothelial cell function, contributing to dyslipidemia, insulin resistance, and cardiovascular disease.³⁵ A systematic review found a high prevalence of metabolic syndrome in patients with psoriasis and have found that those with more severe disease have an even greater risk for developing metabolic syndrome.³⁴

Numerous studies have documented that upward of 80% of patients consider psoriasis to have a major impact on their QOL.³⁶⁻³⁸ The National Psoriasis Foundation assessed patients' perspectives on the social, physical, and psychological aspects of their disease, finding that health-related QOL is impaired in patients with psoriatic disease.^{36,39} Patients reported their disease interfered with overall emotional well-being and life enjoyment and cited feelings of anger, frustration, helplessness, embarrassment, and self-consciousness, all of which can influence fatigue.^{36,39} Pain and pruritus (Figure 2) can interrupt sleep and thus may also contribute to symptoms of fatigue.⁴⁰ Patients with psoriatic disease have a higher incidence of both depression and anxiety compared with the general population. Another study found that patient-reported factors of disability, pain, and fatigue were associated with clinical depression and anxiety; however, these factors are commonly observed in this cohort of patients and thus it is unclear whether they are predictors of or the result of depression.³⁸

Furthermore, psoriatic disease leads to considerable economic burdens; one study (N=5604) found that among respondents who were not employed,



Figure 2. Confluent, erythematous, excoriated psoriasiform plaques on the lower legs.

Selected Studies of Fatigue in Patients With Psoriasis

Reference (Year)	Findings
SF-36	
Krueger et al ⁴² (2005)	Etanercept reduced fatigue to a greater extent than placebo
Reich et al ⁴³ (2006)	Infliximab reduced fatigue to a greater extent than placebo
Daudén et al ⁴⁴ (2009)	Significant reductions in fatigue with continuous etanercept versus paused therapy ($P < .01$)
Kalb et al ⁴⁵ (2013)	Nonresponders to etanercept experienced a reduction in fatigue after switching to infliximab
FACIT-F	
Tyring et al ⁹ (2006)	Statistically significant improvement in fatigue in patients treated with etanercept ($P < .0001$)
Chandran et al ⁴⁶ (2007)	Validated FACIT-F for use in patients with psoriatic arthritis
Krishnan et al ⁴⁷ (2007)	Etanercept sustained reduction in fatigue for up to 96 weeks
Reich et al ⁴⁸ (2009)	Fatigue was higher than the population average in patients with psoriasis and approached the population norm after 24 weeks of etanercept treatment
Papp et al ⁴⁹ (2011)	Patients who relapsed after withdrawal of adalimumab treatment experienced significantly less fatigue with re-treatment
Thaci et al ⁴⁰ (2014)	Fatigue decreased significantly following treatment with etanercept ($P < .001$)
FSS	
McDonough et al ³⁸ (2014)	Fatigue is highly correlated with an increased risk for depression and anxiety in patients with psoriasis
VAS	
Evers et al ⁵⁰ (2005)	Levels of psychological distress correlated with symptoms of fatigue
Verhoeven et al ⁵¹ (2007)	Patients with skin diseases, including psoriasis, experienced greater than average levels of fatigue
Modified-FSS and SF-36	
Husted et al ⁵² (2009)	Fatigue should be considered as a primary outcome measure in psoriatic disease, as its resolution does not correlate with resolution of other outcomes
Modified-FSS	
Rosen et al ⁵³ (2012)	Patients with psoriatic arthritis have a higher fatigue level than patients with cutaneous psoriasis alone

Abbreviations: SF-36, 36-item short-form health survey; FACIT-F, functional assessment of chronic illness therapy-fatigue survey; FSS, fatigue severity scale; VAS, visual analog scale.

92% reported they were unemployed solely due to their psoriatic disease.³⁶ One study explored the relationship between fatigue, work disability, and psoriatic arthritis, finding that the association between fatigue and work productivity loss persisted after controlling for cutaneous/musculoskeletal activity.⁴¹ However, another investigation revealed contradicting results, finding that improvements in fatigue correlated with improvements in joint and skin pain.⁹

Therefore, we can conclude that the pathogenesis of psoriasis-associated fatigue is the result of a multifactorial immunologic, psychologic, and physiologic pathway that triggers symptoms of exhaustion and lethargy. Fatigue is a complex multidimensional symptom activated by psoriatic disease, directly by shared inflammatory cytokines and indirectly by factors of disease activity and psychiatric distress that inherently influence somatic manifestations of fatigue. Regardless of its pathogenesis, these data and observations highlight the importance of fatigue symptoms and the need for new therapeutics to target this debilitating disease.

Measurement of Fatigue in Psoriasis

A patient's level of fatigue is not objectively quantifiable. For this reason, clinicians and investigators have relied on self-report instruments to gauge fatigue (Table).^{9,38,40,42-53} These survey instruments each have distinct advantages and disadvantages, though all are subject to common difficulties. Many rely on the literacy of patients and their interpretation of each item, which can make completing the survey difficult and yield variability between subjects. Patients are inaccurate in self-reporting even measurable characteristics such as height and weight,⁵⁴ which introduces an element of uncertainty in the reporting of subjective symptoms (ie, fatigue). Lastly, there are several biases implicit in self-reporting including recall bias, selective recall, and digit preference.⁵⁵

When analyzing fatigue due to a chronic disease, several symptoms may be misconstrued or interfere with the interpretation of fatigue. For instance, patients with multiple sclerosis may confuse neuropathy-associated muscle weakness with fatigue. These interactions can be controlled for in self-report instruments and validated through careful study of many patients. Disease-specific questionnaires have been validated for use in several diseases,⁵⁶⁻⁵⁸ though none have been validated for cutaneous psoriasis in the absence of psoriatic arthritis. The need for validated instruments in psoriasis is great, as symptoms such as sleep disturbance and arthralgia may confound metrics of fatigue.

Thus far, 4 self-report instruments have been used to study fatigue in psoriasis: the medical outcomes 36-item short-form health survey (SF-36), the functional assessment of chronic illness therapy-fatigue, the fatigue severity scale (FSS), and the visual analog scale (VAS) for fatigue.

The SF-36 is a 36-item survey designed to measure 8 dimensions of health status in patients with chronic disease.⁵⁹ Items are answered using a 3- to 6-point Likert scale, or in a yes/no format. Although the SF-36 is typically administered by a trained interviewer, it relies on a patient's interpretation of language that must be used to describe their level of fatigue, which may not capture the full range of symptoms. Also, the length of the survey makes it impractical for use in clinical practice.

The functional assessment of chronic illness therapy-fatigue survey is validated for use in psoriatic arthritis. It is similar to the SF-36 in its use of a 5-point Likert scale to answer each of 13 items. It improves on the SF-36 model by including questions about associated symptoms (ie, pain, medication side effects) that may interfere with the measurement of fatigue. It also investigates the impact of fatigue on several areas of functioning. However, it is subject to the same pitfalls of interpretation and a rigid scale with which to answer questions.

The FSS is another Likert scale-based instrument that gauges both level of fatigue and its impact using 9 items and a 7-point scale. Investigators used the FSS to uncover an association between increasing fatigue scores and depression in patients with psoriatic disease.³⁸

The VAS overcomes many of the language and interpretation issues inherent in Likert scale-based instruments. Patients are presented with a single item in which they are asked to plot their level of fatigue on a continuous line, with one end representing no fatigue and the other end the worst possible fatigue. Although VAS adds simplicity of response and removes some ambiguity from surveying, it provides no information about the functional impact of fatigue on patients. It also does not provide a method to control for other symptoms.

Treatment of Psoriasis-Associated Fatigue

Much of our understanding of psoriasis-associated fatigue arises from therapeutic clinical trials. Because increased concentrations of proinflammatory cytokines are associated with fatigue, it has been suggested that blocking these cytokines with biologic agents may relieve fatigue symptoms. For example, investigators found that patients treated with etanercept, a soluble TNF- α receptor fusion protein, had clinically meaningful improvement in fatigue

compared to those receiving placebo, with sustained improvements at 96 weeks.^{9,47} We must note, however, that the decrease in fatigue correlated with improvements in cutaneous/arthritis pain. Nevertheless, another study found that treatment with the same drug decreased fatigue in patients with psoriasis, even after controlling for improvements in the psoriasis area severity index score.⁴⁰ Adalimumab is another monoclonal antibody for TNF- α that has caused a notable decline in fatigue symptoms.⁴⁹

These data suggest that biologic agents are useful in the treatment of fatigue. Biologic agents are frequently administered to patients with moderate to severe psoriasis in whom more conservative treatments previously failed. However, cutaneous/arthritis disease severity is not always correlated with fatigue, so these data may urge clinicians to lower their threshold for treatment with biologics in patients with substantial fatigue symptoms. Although further investigations are necessary, we may even consider using a biologic therapy for severe fatigue in those without severe psoriatic disease.

Conclusion

Fatigue is a multidimensional symptom, impacted both directly and indirectly by psoriasis pathophysiology. The prevalence of fatigue within this patient population suggests that clinicians need to recognize the symptom as a core domain in psoriasis evaluation. Although a host of metrics have been used to quantify/qualify fatigue, there remains a need for a validated instrument for assessing fatigue in patients with psoriatic disease.

Biologic agents have proven useful in the treatment of psoriasis-associated fatigue. The central role of proinflammatory cytokines to both fatigue and psoriasis pathogenesis provide insight into potential treatment targets. Understanding the overlapping pathophysiology of psoriasis and fatigue provides an avenue for developing innovative strategies to target molecules implicated in the activation of the immune system. In the future, it may be possible to predict the severity of fatigue by measuring the levels of serum inflammatory cytokines; in fact, a new study aims to identify a panel of soluble biomarkers that can predict joint damage in psoriatic arthritis.⁶⁰ Taken together, the findings described suggest that further study is needed to characterize, measure, and treat psoriasis-associated fatigue.

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