

Fatigue in psoriasis: a phenomenon to be explored*

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Summary

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Fatigue is a prevalent and substantial phenomenon in many patients with chronic inflammatory diseases, often rated by patients as the most troublesome symptom and aspect of their disease. It frequently interferes with physical and social functions and may lead to social withdrawal, long-standing sick leave and disability. Although psychological and somatic factors such as depression, sleep disorders, pain and anaemia influence fatigue, the underlying pathophysiological mechanisms by which fatigue is generated and regulated are largely unknown. Increasing evidence points towards a genetic and molecular basis for fatigue as part of the innate immune system and cellular stress responses. Few studies have focused on fatigue in dermatological diseases. Most of these studies describe fatigue as a phenomenon related to psoriatic arthritis and describe the beneficial effects of biological agents on fatigue observed in clinical studies. It is therefore possible that this problem has been underestimated and deserves more attention in the dermatological community. In this review, we provide a definition and explanation for chronic fatigue, describe some commonly used instruments for measuring fatigue, and present hypothetical biological mechanisms with an emphasis on activation of the innate immune system and oxidative stress. An overview of relevant clinical studies covering the theme 'psoriasis and fatigue' is given.

What's already known about this topic?

- Fatigue is prevalent in patients with chronic inflammatory diseases, cancer and some neurological diseases.
- Depression, sleep disorders and pain influence fatigue.
- Genes and molecular signalling pathways are increasingly recognized as important contributors to fatigue.

What does this study add?

- The relationship of fatigue with psoriasis disease activity is unclear.
- Biological drugs have a beneficial effect on fatigue in patients with psoriasis.
- More knowledge regarding the prevalence, severity and impact of fatigue in patients with psoriasis is needed.
- Future therapeutic studies should include fatigue as an outcome variable.

Chronic fatigue is a frequent and often disabling phenomenon that occurs in patients with chronic inflammatory and autoimmune diseases, cancer, neurological diseases and a number of other conditions in which inflammation and/or cellular stress occurs. Fatigue may be defined as 'an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion'.¹ For the

individual, as well as for society, it is important to gain knowledge of the mechanisms through which fatigue is generated, and to develop effective treatment strategies.

Chronic fatigue syndrome (CFS)/myalgia encephalomyelitis (ME) is a condition characterized by chronic fatigue and in which no underlying disease or condition can be identified.

However, in contrast to popular media reports and beliefs, most people with chronic fatigue have an underlying primary disease other than CFS/ME, with the latter reported in 0.2–0.4% of subjects in community-based studies, and 2.6% of patients in primary care.^{2,3}

There is a complex inter-relationship between mental depression, pain and fatigue. Also, sleep disorders in general, and disrupted sleep in dermatological disorders such as atopic dermatitis, have been linked to daytime sleepiness.⁴ However, it is outside the scope of this review to cover these important psychosocial aspects of fatigue in depth.

Fatigue varies in intensity between patients, and may be so profound that it severely interferes with activities of daily living, leading to long-standing sick leave and disability. Many patients with chronic diseases consider fatigue their most troublesome challenge.⁵

The frequently reported lack of an association between fatigue and disease activity in many studies is a paradox, and apparently goes against common beliefs and conceptions.⁶ It is clear that social and psychological factors play a role, but the paradox may have a foundation in genetic and molecular mechanisms that are crucial for the generation and regulation of fatigue.⁷ Emerging evidence points to the innate immune system as an important 'fatigue generator', brought on by invading pathogens, autoimmune diseases, cancer or other 'danger-signals', as well as cellular stress responses.⁸

Many dermatological diseases and conditions demonstrate inflammatory or autoimmune features, suggesting that fatigue would be an accompanying phenomenon in a number of chronic skin diseases. Also, psoriasis shares common pathways of immune signalling with other inflammatory diseases including psoriatic arthritis and rheumatoid arthritis (RA), such as the interleukin (IL)-23/T helper cell (Th)17 axis.^{9–12} The proinflammatory cytokine IL-23 orchestrates T-cell-dependent pathways of inflammation, and of special importance is activation of the T-cell subtype Th17, which produces IL-17 and other proinflammatory cytokines.^{13,14}

From this perspective, one would expect fatigue to be common in dermatological diseases, but the literature on this matter is sparse and deals mainly with the effect of biological agents on fatigue reported as quality-of-life measures. It is therefore both important and challenging to explore the extent of this problem and identify how – and if – this phenomenon interferes with the lives of patients with such diseases.

What is fatigue?

Fatigue is a poorly understood phenomenon. It is abstract in nature and has been described as 'like water it slips away and cannot be grasped'.¹⁵ Although everyone seems to recognize it, fatigue is often less focused on, overlooked or underestimated by clinicians,^{5,16} which may reflect there being no specific treatment for chronic fatigue.¹⁷

While fatigue is difficult to define and treat, it is also a challenge to measure. Making it even more complex, there is

conceptual disagreement about whether chronic fatigue can be considered a unidimensional phenomenon, or whether several dimensions or subscales of fatigue exist, such as physical fatigue, muscular fatigue, mental fatigue, cognitive fatigue etc. Arguments for the first view are that fatigue is a universal and global experience that to varying degrees interferes with – or has an impact on – different aspects of human life, including traits or attributes associated with the disease. Arguments for the latter comprehension of fatigue are that fatigue is a phenomenon that more or less specifically influences the muscles, brain, mood, initiative, physical activity etc., and should therefore be considered a separate feature.¹⁸

Fatigue interferes with several aspects of life including emotional, physical and social functioning. The burden of chronic fatigue on society is high, primarily due to medical expenses, sick leave and loss of work.^{19,20} In a qualitative study of patients with primary Sjögren syndrome (pSS) where the effects of medications on fatigue were examined, two themes emerged after individual interviews.²¹ Patients clearly differentiated fatigue from normal tiredness and described 'a heavy resistant body and ever present lack of vitality' and 'an unpredictable, uncontrollable fluctuation in fatigue'. This differs from the normal tiredness everyone feels after being exposed to mental and physical stress, and fatigue does not respond to rest as in a healthy individual. Chronic fatigue is therefore not to be confused with tiredness.

Biological mechanisms of fatigue

A highly relevant model for fatigue may be sought in the so-called 'sickness behaviour', which represents an adaptive and complex response in humans and animals during the course of an infection.^{22–24} Sick individuals demonstrate loss of appetite, initiative, grooming and interest in other individuals. They develop sleepiness and withdraw from normal social activities.²⁵ Fatigue is a prominent and dominant feature of this response. Sickness behaviour seems to be deeply conserved throughout evolution and, as such, it is not a maladaptive response but a subconscious strategy for the survival of the individual and the species (the genome) during viral and bacterial infections.

Activation of the innate immune system, which is found in all plant and animal life and which provides the immediate host immune response to infection and other immunological 'danger', may be a key regulator of fatigue in both acute and chronic conditions. A number of studies show that sickness behaviour is associated with proinflammatory cytokines such as IL-1 β , IL-6 and tumour necrosis factor (TNF)- α .^{23,26} Among these cytokines, IL-1 β seems to have a pivotal role.²⁷ IL-1 β possesses an early and strong proinflammatory effect and is secreted mainly by activated monocytes, macrophages and dendritic cells.^{28–30} IL-1 β also reaches neuronal cells in the brain where it binds to specific IL-1 receptors not causing inflammation, but instead triggering the behavioural response.^{22,31}

There is substantial experimental evidence from animal models for an essential role of IL-1 β in promoting sickness

behaviour. IL-1 β is rapidly transported through the blood–brain barrier in injected animals, followed by rapid upregulation of both IL-1 receptor antagonist and IL-1RI in the brain.^{32–35} Also, injection of lipopolysaccharide into the abdominal cavity activates lipopolysaccharide receptors on the vagal nerve. Through neuronal signalling, this leads to production of IL-1 β in the brain, which is followed by the animal exhibiting sickness behaviour.³⁶ IL-1RI knockout mice are resistant to the sickness-inducing effects of IL-1 β .³¹ All these observations point strongly to IL-1 β as a key factor for sickness behaviour and fatigue.

In humans, blockade of IL-1 in both RA and pSS results in reduced fatigue.³⁷ Also, a number of studies in different diseases have demonstrated beneficial effects on fatigue by all biologics given (i.e. anti-TNF- α , anti-IL-6, anti-CD20 and the cytotoxic T-lymphocyte-associated protein 4 Ig fusion protein, abatacept).^{38–41}

Oxidative stress is observed in acute and chronic inflammatory diseases, and an association between chronic fatigue and measures of oxidative stress has been demonstrated in CFS/ME and systemic lupus erythematosus (SLE).^{42,43} There are no such studies in dermatological disorders. Oxidative stress results from an imbalance in which reactive oxygen species (ROS) dominate over antioxidant defences.^{44–46} ROS are important in the first line of defence against infections, as they kill pathogens engulfed in cellular phagolysosomes.⁴⁷ Chronic inflammation causes a prolonged state of increased oxidative stress, as reported in several diseases including psoriasis.^{48–51}

Oxidative stress is part of the innate immune response and is triggered by activation of pattern-recognition receptors on innate immune cells such as macrophages and granulocytes. To protect against the harmful effects of free radicals, cells have developed a highly efficient system for combating the cellular stress imposed by these reactive intermediates.⁸ The exact mechanism for how oxidative stress is associated with fatigue is unknown, but could involve activation of genes important for cellular viability and protection. These genes might also be responsible for development of fatigue across different disease groups such as chronic inflammatory, neurodegenerative and neoplastic diseases.⁷

How to measure fatigue

Objective markers of fatigue do not exist, and all fatigue instruments are based on self-reporting. Some tests attempt to measure multiple aspects of fatigue, whereas others use a single unidimensional approach.⁵² Also, some fatigue instruments are designed to be used in specific diseases and thus include disease-specific variables, for example the Parkinson Fatigue Scale,⁵³ Fatigue Impact Scale for multiple sclerosis⁵⁴ and Profile of Fatigue for pSS.⁵⁵ Other instruments are generic and may be used across different disease entities, for example the Fatigue Severity Scale (FSS)⁵⁶ and the Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F).⁵⁷ An overview of selected fatigue instruments is given in Table 1.

In patients with psoriasis, studies of fatigue have been assessed mainly by the use of the medical outcomes study short form 36-item (SF-36) health survey.⁵⁸ Only three studies have used FACIT-F.^{59–61} The SF-36 health survey is a 36-item general health status instrument. It contains subscales for eight domains, where the Vitality subscale is supposed to cover energy and fatigue.⁵⁸ A change of 3 or more points in the SF-36 Vitality subscale score is considered clinically meaningful.⁶² The FACIT-F self-administered questionnaire, originally developed to assess fatigue associated with anaemia in patients with cancer, includes 13 questions regarding the impact of fatigue on patients' activities over the past 7 days.⁵⁷ The FACIT-F scores ranges from 0 to 52, with lower scores indicating more fatigue. A change in score of at least 3 points is considered to be a minimally clinically important difference.⁶³

Fatigue in chronic diseases

Fatigue is the defining feature of CFS/ME. The syndrome is diagnosed when no other disease or underlying condition can be identified.⁶⁴ No main causes of the syndrome have been agreed upon, but a dominant hypothesis is that CFS is a condition caused by the interaction between a common viral infection and individual susceptibility factors such as genetic and immune system dysfunction.⁶⁵

Table 1 Selected generic self-reported fatigue instruments

Name of scale	Dimension	What is assessed	No. of scale items	No. of subscales	Scale type
Fatigue Severity Scale ⁵⁶	Unidimensional	Impact and functional outcomes	9	1	7-point Likert
Fatigue Visual Analogue Scale ¹¹⁰	Unidimensional	Severity	1	1	Visual analogue
Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) ⁵⁷	Unidimensional	Severity and impact	13	1	5-point Likert
Medical Outcomes Study Short Form 36-item scale (SF-36) ⁵⁸	Multidimensional	Severity	36	8	3–6-point Likert, yes/no
Multidimensional Fatigue Inventory (MFI-20) scale ¹¹¹	Multidimensional	Severity and impact	20	5	7-point Likert
Multidimensional Assessment of Fatigue (MAF) ¹¹²	Multidimensional	Severity and impact	16	4	4–10-point Likert

Fatigue accompanies inflammation and is frequently reported among patients with a wide range of chronic inflammatory conditions. The prevalence of fatigue in patients with RA, defined as a score of > 20 on the fatigue visual analogue scale, was reported to be 41% in one study,⁶⁶ and fatigue is among the most commonly reported phenomena in multiple sclerosis, pSS and SLE.^{67–70} In inflammatory diseases, as well as in cancer-related fatigue, the fatigue has sometimes been related to altered or increased proinflammatory cytokine production.^{71,72} However, in general there seems to be a poor correlation between disease activity and the severity of fatigue.^{6,73–75} Lee *et al.*⁷⁶ postulated that among patients with RA there is a large subgroup with low levels of systemic inflammation and low disease activity, yet high levels of fatigue and pain. This could be consistent with a chronic noninflammatory central pain syndrome as seen in fibromyalgia, which is a condition also associated with high levels of fatigue, pain and sleep problems.⁷⁷ The underlying pathogenic mechanism, as compared with those with high disease activity inflammatory burden and high fatigue scores, could therefore be somewhat different.

Cancer-related fatigue affects both patients with cancer and cancer survivors.⁷⁸ There are no major differences in fatigue depending on cancer type, origin and disease stage.⁷⁹ Interestingly, cancer-related fatigue worsens during treatment with cytostatic agents and radiation therapy, and may persist for years in some cancer survivors after the cancer has been eradicated.⁸⁰

Parkinson disease and cerebral stroke are examples of neurological conditions with no clear inflammatory component, and in which fatigue is common and may be debilitating.⁸¹ In cerebral stroke, it is possible that there is a disturbance of neuronal circuits within the basal ganglia, thalamus and cerebral cortex, while the fatigue mechanisms in neurodegenerative diseases are less clear, but might well be due to cellular stress responses.^{82,83}

Confounding factors

Depression, sleep disorders and pain are confounding factors to fatigue. Fatigue is strongly associated with depression and

vice versa.^{84–86} There is an overlap in symptomatology between fatigue and depression, but fatigue also appears without depression.⁶⁸ Both depression and fatigue in chronic inflammatory disorders, as well as in depressive diseases, have been associated with proinflammatory cytokines.⁸⁷ Intriguingly, patients with chronic fatigue are less responsive to antidepressant drugs than depressed patients.⁸⁸ Notably, several biological agents used in chronic inflammatory disorders have shown improvement in both depression and fatigue scores.^{89–91} Some evidence indicates that IL-1 and TNF- α may play a role in the regulation of sleep.⁹² The clinically interesting question is why these behavioural alterations present more easily and are more severe in some individuals than in others.

Fatigue in psoriasis

Psoriasis vulgaris (plaque psoriasis) is an immune-mediated chronic inflammatory disease affecting about 2% of the world's population.⁹³ The inflammation is thought to be a consequence of a T-cell-mediated immune response to an as-yet unidentified autoantigen. Several lines of evidence suggest an important role for IL-17 in the pathogenesis of psoriasis, as well as in psoriatic arthritis and other chronic inflammatory disorders.⁹⁴ Psoriasis may have a major impact on a patient's life, especially when the disease is moderate to severe.⁹⁵

While psychosocial aspects have been widely studied in dermatological diseases, less is known about fatigue.⁹⁶ For an overview of genuine studies of fatigue in psoriasis, see Table 2. The majority of data regarding this phenomenon are derived from the Vitality subscale of the SF-36, a general measure of health-related quality of life. This subscale consists of only four questions, providing some indications of fatigue (Table 1). One study using the SF-36 in dermatological outpatient clinics in Norway reported significantly lower scores than the general norms on eight subscales of the SF-36, and higher levels of psoriasis-specific symptoms (itching, burning, scaling, suppuration, stinging and joint pain) were significantly related to all of the SF-36 subscales.⁹⁷ It was not stated whether some patients also had psoriatic arthritis.

Table 2 Genuine studies on fatigue in psoriasis

Study	Design	Fatigue instrument	Outcome (mean)
Rapp (1999) ¹¹³	Postal questionnaire study where scores of 317 patients with psoriasis were compared with those from 10 different health conditions	SF-36 VS	Vitality subscale 45.4
Wahl (2000) ⁹⁷	283 patients with psoriasis were included and scores compared with general populations norms	SF-36 VS	Vitality subscale 48.2
Evers (2005) ⁹⁶	Questionnaires administered to 128 outpatients with psoriasis	VAS-Fatigue	VAS-Fatigue 3.8
Verhoeven (2007) ¹¹⁴	Postal questionnaire study where scores of 112 patients with psoriasis registered in general practice were compared with those from nine other skin conditions	VAS-Fatigue	VAS-Fatigue 3.2, 28% reported severe fatigue (VAS > 5)
Jankovic (2011) ¹¹⁵	Questionnaires administered to 110 outpatients with psoriasis	SF-36 VS	Vitality subscale 48.9

SF-36 VS, Medical Outcomes Study Short Form 36-item scale (SF-36) Vitality subscale; VAS, visual analogue scale.

Table 3 Effect of biological agents on fatigue in patients with psoriasis

Study	Design	Study duration (weeks)	No. of patients	Concomitant arthritis (%)	Drug	Fatigue instrument	Improvement (scores)
Krueger (2005) ¹⁰¹	R, DB, PC, MC,OL	24	583	26–28	ETN	SF-36 VS	($P < 0.001$) ^a
Reich (2006) ¹⁰²	R, DB, PC, MC	50	378	NA	IFX	SF-36 VS	4.7
Krishnan (2007) ⁵⁹	OL, MC	84	591	33–35	ETN	FACIT- F	> 5
Shikiar (2007) ¹⁰³	R, DB, PC, MC	12	147	NA	ADA	SF-36 VS	12.5
Revicki (2007) ¹⁰⁴	R, DB, PC, MC	52	1212	28	ADA	SF-36 VS	6.7
Feldman (2008) ¹⁰⁵	R, DB, PC, MC	50	835	26–28	IFX	SF-36 VS	4.2
Revicki (2008) ¹⁰⁶	R, DB, PC, MC	52	1205	28	ADA	SF-36 VS	3.3
Dauden (2009) ¹⁰⁷	R, OL, MC	54	711	NA	ETN	SF-36 VS	5.8
Reich (2009) ⁶⁰	R, DB, PC, MC	24	142	11–16	ETN	FACIT- F	3.7
Lebwohl (2010) ¹⁰⁸	R, DB, PC, MC	76	766	29–37	UST	SF-36 VS	2.6
Papp (2011) ⁶¹	R, OL, C, MC	308	1468	26	ADA	FACIT- F	3.2
Nakagawa (2012) ¹⁰⁹	R, DB, PC, MC	64	158	9	UST	SF-36 VS	> 5
Kalb (2013) ³⁸	OL, P, MC	26	215	NA	IFX	SF-36 VS	5.4

R, randomized; DB, double blind; PC, placebo controlled; MC, multicentre; OL, open label; C, continuation study; P, prospective study; NA, not applicable; ETN, etanercept; IFX, infliximab; ADA, adalimumab; UST, ustekinumab; SF-36 VS, Short Form-36 Vitality subscale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue subscale. ^aScores not given.

The prevalence of psoriatic arthritis in patients with psoriasis is estimated to be as high as 30%.⁹⁸ Few comparative studies of health-related quality-of-life measures between patients with psoriasis with and without arthritis have been performed. In one study, patients with psoriasis without arthritis were found to have less fatigue, as measured by the FSS and the Vitality subscale of the SF-36, compared with patients with arthritis.⁹⁹ In this study, the mean Dermatology Life Quality Index of patients with psoriasis was 7.7, indicating a moderate effect on patients' lives. These findings are in contrast to the 2005 Spring US National Psoriasis Foundation Quality of Life study, where no differences were found in overall health-related quality of life between these groups.¹⁰⁰ This study was conducted by telephone interviews, which might affect the quality of the data collected. To what degree arthritis influences fatigue in patients with psoriasis is therefore difficult to assess.

The majority of data on fatigue in patients with psoriasis arises from therapeutic clinical trials in which patients with arthritis have frequently been included, and these studies often lack information on the number of subjects with arthritis (for an overview see Table 3).^{38,59–61,101–109} Patients who were included generally had moderate-to-severe psoriasis with a mean Psoriasis Area and Severity Index (PASI) > 14. All therapeutic studies in psoriasis employing biological agents have demonstrated a beneficial effect on the Vitality subscale of the SF-36. Only three studies used the FACIT-F, but revealed a clinically meaningful reduction of fatigue with the TNF- α inhibitors adalimumab or etanercept.^{59–61} Tying *et al.* reported less fatigue as measured with the FACIT-F, which was associated with improvements in joint and skin pain with the use of etanercept. In this study, up to 35% of the patients included had arthritis, and it was debated whether the effect of etanercept on fatigue could be attributed to an effect on psoriatic arthritis.⁹¹

To the best of our knowledge, no studies have investigated fatigue in relation to disease activity in patients with psoriasis who did not have arthritis. Also, because most patients with psoriasis have low C-reactive protein or erythrocyte sedimentation rate, it is difficult to evaluate the influence that psoriatic inflammation might have on fatigue. Finally, the prevalence and the degree of fatigue in a general population with psoriasis compared with a healthy control group remains to be studied.

Conclusions

Fatigue is an important feature of all inflammatory diseases. In psoriasis and other dermatological diseases, knowledge of fatigue is sparse and could represent a major but hidden problem in a considerable number of patients with psoriasis. Moreover, is it not known whether fatigue in patients with psoriasis is related to the extent of the disease (PASI scores) or other disease characteristics. It is therefore important to determine the prevalence, severity and impact of fatigue because this will add to the clinician's understanding and management of patients with psoriasis. Also, future therapeutic studies should include fatigue as an outcome variable.

The psychological and social factors that influence fatigue are outside the scope of this review. These issues need to be reviewed and synthesized as part of future research projects.

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