Fatigue in psoriasis: prevalence and biological mechanisms

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Scientific environment

The present work was performed in the Clinical Immunology Research group in cooperation with the Department of Dermatology at Stavanger University Hospital. The Clinical Immunology Research Group, headed by professor Roald Omdal focuses largely on the neurological aspects of chronic inflammatory autoimmune diseases, and especially the biological mechanisms of chronic fatigue. The group has resources to organize studies, and to collect and store data and biological samples, and has access to a well-equipped, staffed research laboratory with Luminex and electrochemi-luminescence platform (MSD) for cytokine analyses that was used in the current project. The group has a number of international partners. The present work started in 2012, financed by a grant from the Stavanger Health Research. The majority of the work in this thesis was mainly conducted in the period from 2016 to 2019 when I received financial support as a doctoral research fellow from the Western Norway Regional Health Authority.

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Inger Marie Skoie

Abstract

Background

Fatigue is prevalent in patients with chronic inflammatory diseases and often rated as the most troublesome aspect of their disease. Clinical experience indicates that fatigue is common also in patients with psoriasis, but studies are sparse.

A model for understanding fatigue is the "*sickness behavior model*" in animals. Following the onset of an infection a coordinated set of behavioral changes occurs in the sick animal, commonly recognized as lethargy, depression, loss of thirst, hunger, and reduction in grooming. Fatigue is a prominent and dominant feature of this response. This behavior is signaled by interleukin (IL)-1β in the brain, and has many similarities with chronic fatigue in humans. Chronic inflammatory disease resembles a "chronic infection". Thus, fatigue is continuously induced through "danger signals" triggering the innate immune system and leading to a "*sickness behavior response*".

Although activation of the innate immune system and IL-1β play pivotal roles in generation of fatigue, other immune regulatory mechanisms have been suggested as potential mediators. The frequent reported lack of association between disease activity and fatigue in chronic inflammatory diseases is a paradox that could be explained by involvement of down-regulatory immune mechanisms and responses involved in protection against cellular stress. However, the entire biological mechanisms of fatigue are yet poorly understood.

Fatigue can be challenging for the patients to live with and for the clinicians to treat. There is a lack of management guidelines. Evidence suggest that biological drugs could be effective, however this effect has not been systematically evaluated.

Main objectives

- Write a review article with focus on current knowledge, biological mechanisms and identifying research gaps on fatigue in psoriasis

- Investigate and describe fatigue in chronic plaque-type psoriasis patients and compare with age- and gender matched healthy subjects to obtain a better understanding of the extent and severity of this phenomenon
- Estimate the efficacy of biological drugs on fatigue in psoriasis
- Uncover biological processes and signaling pathways that cause fatigue in psoriasis.
    - Investigate plasma levels of markers of oxidative stress in psoriasis patients compared to healthy subjects, and explore the associations with fatigue
    - Investigate plasma levels of selected cytokines in psoriasis patients compared to healthy subjects, and explore the association with fatigue
    - Compare gene expression of selected heat shock protein genes in psoriasis patients with high and low fatigue levels

Subject and methods

Fatigue was measured in 84 patients with chronic plaque-type and 84 age- and gender-matched healthy subjects. The patients were recruited from the Department of Dermatology, Stavanger University Hospital and the healthy subjects were predominantly recruited form acquaintances of the patients. Fatigue severity was assessed using three different generic fatigue instruments: the fatigue Visual Analog Scale (fVAS), the Fatigue Severity Scale (FSS), and the Short Form 36 (SF-36) vitality scale. Cut-off scores were defined as ≥50 for fVAS, ≥4 for FSS, and ≤35 for SF-36 vitality scale. Disease activity was evaluated using the Psoriasis Area and Severity Index (PASI), and the impact on quality of life (QoL) with the Dermatology Life Quality Index (DLQI).

To investigate oxidative stress, we measured plasma levels of advanced oxidation protein products (AOPP) and malondialdehyde (MDA) in plasma using UV-spectrophotometry and high performance liquid chromatography connected to a fluorescence detector.

Plasma levels of IL-1β, IL-1Rα, IL-6, and IL-10 were measured by electrochemiluminescence based Meso Scale Discovery assay, IL-1RII by sandwich enzyme-linked immunosorbent assay.

Peripheral blood transcriptional profiles of HSP genes from 10 patients with high fatigue and 10 patents with low fatigue were compared. The expression levels of four of these genes (*HSPB11*, *HSPA14, HSP90B1*, *HSP90AB1*) were re-evaluated by reverse transcription quantitative real-time polymerase reaction in 20 patients with high and 20 patients with low fatigue.

Results

We found that:

- Fatigue is overlooked and an under-researched phenomenon in psoriasis.
- Nearly 50% of psoriasis patients suffer from clinically important fatigue. Fatigue severity is associated with pain, depression and smoking, but not with psoriasis disease severity
- Biological drugs have a small to moderate effect on fatigue in psoriasis
- Plasma concentrations of AOPP and MDA are not associated with fatigue in psoriasis patients. These biomarkers of oxidative stress are not increased in psoriasis patients compared to healthy subjects. Plasma AOPP and MDA are strongly dependent on gender and other non-disease related factors. Several physiological and methodological factors influence concentrations of AOPP and MDA
- Plasma concentrations of IL-1β, IL-1Rα, IL-1RII, IL-6, and IL-10 are not associated with fatigue. Plasma concentrations of IL-1Ra and IL-6 were influenced by BMI, not disease severity in psoriasis patients
- Fatigue is associated with altered expression of some HSPs. A tendency to higher expression levels of *HSPB11* and lower expression of *HSP90B1* is

demonstrated in patients with high fatigue scores compared to those with low fatigue scores.

Conclusions

Fatigue is common and severe in psoriasis patients. Fatigue is strongly associated with pain and depression, but not with disease activity. There is a modest positive effect of biological drugs. Fatigue is not related to plasma markers of oxidative stress or selected cytokines, but associations to gene expression levels of selected HSPs are evident.

List of Publications

I. **Skoie IM**, Ternowitz T, Jonsson G, Norheim K, Omdal R.
Fatigue in psoriasis: a phenomenon to be explored.
Br J Dermatol. 2015;172(5):1196-203.

II. **Skoie IM**, Dalen I, Ternowitz T, Jonsson G, Kvivik I, Norheim K, Omdal R.
Fatigue in psoriasis: a controlled study.
Br J Dermatol. 2017 Aug;177(2):505-512.

III. **Skoie IM**, Dalen I, Omdal R, Jonsson G. Malondialdehyde and advanced oxidation
protein products are not increased in psoriasis: a controlled study.
Arch Dermatol Res. 2019 May;311(4):299-308.

IV. **Skoie IM**, Dalen I, Omdal R.
Effect of Biological Treatment on Fatigue in Psoriasis: A Systematic Review and Meta-Analysis.
Am J Clin Dermatol. 2019 Aug;20(4):493-502.

V. **Skoie IM**, Dalen I, Kvivik I, Bårdsen K, Omdal R.
Fatigue in patients with plaque-type psoriasis: lack of an association with plasma cytokines. Eur J Dermatol. 2020 Feb 1;30(1):16-23.

VI. **Skoie IM**, Bårdsen K, Nilsen M, Eidem L, Dalen I, Omdal R
Heat shock genes in peripheral blood mononuclear cells are differently expressed in psoriasis patients with high and low fatigue.

Contents

Abbreviations

AOPP	Advanced oxidation protein products
BBB	Blood brain barrier
CD	Crohn´s disease
cDNA	Complementary DNA
CI	Confidence interval
CLR	C-type lectin receptor
CNS	Central nervous system
CVD	Cardiovascular disease
CV	Coefficient of variation
DAMP	Damage-associated molecular pattern
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FPKM	Fragments per kilobase of gene per million mapped reads
FSS	Fatigue Severity Scale
fVAS	Fatigue Visual Analog Scale
GWAS	Genome-wide associations study
HADS	Hospital Anxiety and Depression Scale
HLA	Human leukocyte antigen
HPLC	High-performance liquid chromatography
HSP	Heat shock protein
IFN	Interferon
IQR	Interquartile range
IL	Interleukin
IL-1RI	IL-1 receptor type 1
IL-1RAcPb	IL-1R accessory protein brain
JAK	Janus kinase
LLOD	Lower limit of detection
LPS	Lipopolysaccharide
MDA	Malondialdehyde
MSD	Meso Scale Discovery
NF-κB	Nuclear factor kappa B
NOD	Nucleotide-binding oligomerization domain-like receptors
OR	Odds ratio
PAMP	Pathogen associated molecular pattern
PASI	Psoriasis Area Severity Index
PBMC	Peripheral blood mononuclear cells
PCA	Principal component analysis
PCR	Polymerase chain reaction
PMC	PubMed Central
PRR	Pattern recognition receptor
PSOR1	Psoriasis susceptibility locus 1

pSS	Primary Sjögren's syndrome
PsA	Psoriatic arthritis
QoL	Quality of life
RLR	Retinoic acid inducible gene-I-like receptor
RT-qPCR	Reverse-transcription real-time quantitative polymerase chain reaction
RNA	Ribonucleic acid
RNA-seq	RNA-sequencing
ROS	Reactive oxygen species
SD	Standard deviation
SF-36 VS	Short Form 36 Health Survey Vitality Subscale
SMD	Standardised mean difference
SNP	Single nucleotide polymorphism
STAT	Signal transducer and activator of transcription
TBA	Thiobarituric acid
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNFAIP3	Tumor necrosis factor alpha induced protein 3
TRAF3IP2	Tumor necrosis factor receptor associated factor interactive protein 2

1. Background

1.1 Psoriasis

1.1.1 Epidemiology and clinical presentation

Robert Willan (1757-1812), a British dermatologist, is considered to have given the first detailed clinical description of psoriasis in his publication “On cutaneous diseases” in 1808, and thereby distinguished psoriasis from other similar skin conditions (1).

Psoriasis is an immune-mediated chronic inflammatory skin disorder affecting about 2% of the Western population. The prevalence varies according to geographical regions of the world (2), and in Scandinavian countries a large span ranging from 2% to 11% has been reported (3, 4).

The most common clinical variant is plaque-type psoriasis (also known as psoriasis vulgaris) representing about 85% to 90% of patients. This variant is characterized by sharply demarcated, occasionally painful and itchy, erythrosquamous plaques with predilection to extremities and the lower back. The severity of the disease can be highly variable ranging from minor signs to overt clinical manifestations. Other less prevalent clinical variants of psoriasis include guttate (droplet) or eruptive psoriasis in which there are usually numerous very small teardrop shaped plaques; pustular psoriasis which can be grouped into generalized pustular psoriasis and localised forms including palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau. Erythrodermic psoriasis is a term used when more than 80% of the skin is involved. This condition is sometimes life-threatening, and can develop in any type of psoriasis (5). The different clinical variants may be overlapping, or one type may transform into another clinical type. They can be further divided into sub-phenotypes according to distribution, anatomical localisation, size and thickness of plaques, onset and disease activity (6).

The histopathological features of the psoriatic plaque show keratinocyte hyperproliferation (epidermal hyperplasia) with dysfunctional differentiation overlying dermal inflammatory cell infiltrates consisting of dermal dendritic cells, macrophages, T-cells and neutrophils. The presence of neutrophils into the epidermis is one of the hallmark histological features of psoriasis (5).

1.1.2 Genetics

A genetic basis has long been acknowledged in psoriasis. There is a higher incidence of psoriasis among relatives of psoriasis patients than in the general population, and about 30% of patients have an affected first degree relative (6). If a co-twin has psoriasis, monozygotic twins are more likely to have psoriasis than bizygotic twins (7).

Psoriasis is an autoimmune disease (8). An autoimmune disease is a condition in which the immune system is autoreactive, i.e. T-cells or B-cells or both, recognize bodily molecular structures (epitopes) as foreign (non-self). Psoriasis is considered a mainly T-cell driven disease, although B-cells and other parts of the complex immune system such as the innate immune system involving macrophages, dendritic cells and cytokines, are more or less involved in the attack on skin elements (9).

The majority of autoimmune diseases are linked with the human leukocyte antigen (HLA) system (10). “HLA” is the designation used for the human version of the major histocompatibility complex, a set of genes that code for cell surface proteins essential for the acquired immune system to recognize foreign structures in vertebrates (11). The HLA complex in humans consists of more than 200 genes located close together on the short arm of chromosome number 6 (6p21). The gene complex can be categorized into three different classes. Proteins produced from HLA class I genes are expressed on the surface of nearly all nucleated cells, while proteins produced from HLA class II genes are typically present on the surface of antigen-presenting cells (monocytes, macrophages and dendritic cells), B-cells and activated

T-lymphocytes. HLA class III contains genes coding for immune responses like the complement system, cytokines and heat shock proteins (HSPs). Classically, HLA class I and II proteins present peptides for T-cells. Genetic variants/polymorphisms in the HLA complex locus have been shown to influence susceptibility to most autoimmune diseases. Educating the immune system to distinguish between self and non-self is a vital step in preventing autoimmunity. However, self-reactive T-cells may escape the negative selection in thymus and be activated by complexes of certain HLA molecules and self-peptides (12).

The most common genetic loci linked to psoriatic susceptibility are found within the HLA gene complex. HLA-Cw6 is the major risk allele, also known as the psoriasis susceptibility locus 1 (*PSORS1*) (13). HLA-Cw6 is present in more than 60% of psoriasis patients, and increases the relative risk for psoriasis from 9 to 23 fold depending on heterozygosity or homozygosity (14).

Notably, the majority of autoimmune diseases are multigenic, i.e. an unfortunate set of variants of immune response genes are necessary for disease development. Genome wide associations studies (GWAS) have identified several loci outside the HLA region that increase the risk for psoriasis, but with much lower strength of association than the *PSORS1* gene (15). The *PSORS2* is another chromosomal locus with linkage to psoriasis. Recent studies have shown that this is due to mutations in the *CARD14* gene on chromosome 17q25 (16). *CARD14* mutations influence psoriasis susceptibility by activation of NF-κB and upregulation of a subset of psoriasis-associated genes in keratinocytes (16).

Single nucleotide polymorphisms (SNP)s are substitutions of one base pair with another. The majority of the SNPs are found in non-coding regions of the genome and only some of the substitutions influence biological functions (17). Various SNPs located close to genes involved in immune regulation as well as in skin barrier function have been associated with increased risk of psoriasis (18). Multiple gene loci involving the interleukin (IL)-23 pathway are also associated with increased risk of

psoriasis e.g. IL-12B, IL-23A, IL-23R, tumor necrosis factor alpha induced protein 3 (TNFAIP3), TNF receptor associated factor interactive protein 2 (TRAF3IP2), and signal transducer and activator of transcription (STAT) 3.

The variety of clinical manifestations seen in psoriasis reflects differences in genetic setup. HLA-Cw6 is strongly linked to early and acute onset psoriasis, but is not associated with pustular psoriasis (19, 20). Loss of function mutations in *IL36RN* which encodes an antagonist to the IL-36 receptor, have been linked to pustular psoriasis, but not plaque-type psoriasis (21). IL-36 belong to the IL-1 pro-inflammatory cytokine family (22).

Overall, no single genetic variant seems to be sufficient to account on its own for the development of disease, and a complex interplay between many genetic loci is required. Also, several SNPs associated with psoriasis are overlapping with other immune mediated conditions like Crohn´s disease, celiac disease and ankylosing spondylitis, and illustrates that there is a genetically predisposed tendency to develop autoimmune disease in general, and that the distinct diseases are not inherited per se (14).

1.1.3 Epigenetics

However, the lack of a clear and strong inheritance pattern indicates that genetic predisposition might not be the only factor contributing to disease. Environmental factors are thought to be contributors or triggers for development of autoimmune diseases. Exposure to certain drugs and viral infections are examples of factors that influence how genes are read or translated. DNA is wrapped around histone protein complexes. Histone proteins can be modified by several processes that influences accessibility of chromatin to the transcriptional complex. Such epigenetic modifications influence gene expressions without changing the genomic sequence, and may add to the disease risk. Important epigenetic mechanisms include DNA methylation, histone modifications, and microRNA (miRNA).

DNA methylation is a biochemical process in which a methyl group (CH_3) is added from the carbon-5 position of cytosine in a cytosine base to create a 5-methylcytosine. DNA methylations commonly occur at sites in the promoter and enhancer regions of genes, and prevent transcription of a gene. This results in suppressed expression (silencing) of that gene.
DNA hypomethylation (demethylation) means removal of one or more methyl groups from cytosine bases and has the opposite effect of methylation. This process can activate or increase the expression of a gene that was previously silenced or reduced in activity (23).

The consequences of histone modifications for transcription depend on the specific combinations of modifications, i.e. what type of histone protein, specific amino acid and type of modifications involved. Some modifications are associated with active transcription while others are associated with silencing (23).

miRNAs are small evolutionarily conserved, noncoding RNAs. They base pair with complementary sequences within mRNA molecules and regulate gene expression at the posttranscriptional level. This will usually lead to downregulation of the gene expression.

Epigenetics changes have been observed in psoriatic skin cells as well as in peripheral blood cells of psoriasis patients (24). A decrease in number of methylation sites in genes involved in epidermal function and differentiation has been demonstrated in lesional psoriatic skin tissue which mapped to genes highly upregulated in psoriasis (25). Multiple miRNAs have been found to be aberrantly expressed in psoriatic skin of which some are likely to influence key processes in psoriasis pathogenesis including epidermal differentiation and inflammation (26). These findings support an epigenetic contribution in gene regulation relevant to the psoriasis pathophysiology

1.1.4 Immunopathophysiology

The IL-23/Th17 axis along with TNF-α is considered to play a dominating role in the disease pathophysiology of the chronic phase of psoriasis (27). IL-23 drives the expansion and activation of Th17 T cells that produce IL-17, and therapeutic agents targeting IL-17 and IL-23 signalling are highly effective and result in rapid and substantial improvement in about 90% of patients (28).

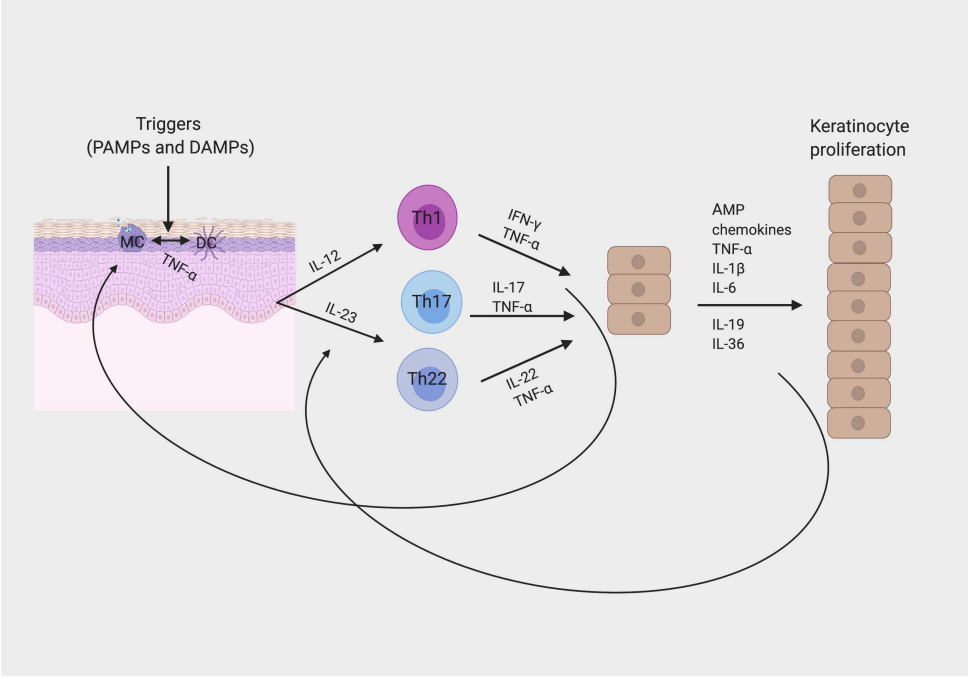

Figure 1. The TNF-α/IL-23/Th17 and keratinocyte interplay in psoriasis.
After activation from a trigger factor, dendritic cells (DC) and macrophages (MC) are stimulated and secrete inflammatory mediators that lead to differentiation of Th1/Th22/Th17 cells. T cells release key inflammatory cytokines that stimulate keratinocytes to an abnormal hyperproliferation. Activated keratinocytes produce antimicrobial peptides (AMP), chemokines and cytokines that lead to subsequent amplification of the psoriatic skin process.

Although the chronic stage of psoriasis is predominantly featured by an adaptive immune response, there is a complex interaction between the innate and the adaptive immune responses. Key cytokines in psoriasis, e.g. interferon (IFN), IL-12, IL-22 and IL-23 activate janus kinase (JAK) and signal transducer and activator of transcription (STAT) intracellular pathways. JAKs are localized at the intracellular region of cell-

surface receptors. Once a proinflammatory cytokine or another ligand binds to its receptor, JAKs phosphorylate and activate downstream signalling pathways including STATs. Activated STATs translocate to the nucleus and activate target genes resulting in modulation of proinflammatory gene transcription (29). Furthermore, extracellular stimuli can activate nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), another inducible transcription factor that orchestrates inflammation involved in the psoriasis pathogenesis (13). These signalling pathways are common in many chronic inflammatory conditions.

During the early phases of psoriasis development, IFN-γ seems to play a pivotal role. IFN-γ is also a predominating inflammatory cytokine in unstable and acute forms such as erythrodermic psoriasis or guttate-type psoriasis (8). Increased concentrations of IL-1β , IL-36α and IL-36γ have been found in pustular psoriasis compared to psoriasis vulgaris (30). Neutrophils, which are found in low numbers in the epidermis and stratum corneum in chronic plaque lesions, are the dominating leukocytes in pustular psoriasis. Neutrophils are key inducers of the IL-36 group of cytokines which triggers IL-1β production in dendritic cells. Although, IL-17 signalling is also operative, the IL-36/IL-1 pathway seems to have an important role in pustular psoriasis.

Altogether, adaptive mechanisms seem to be in the foreground in stable and mild disease while innate mechanisms seem to be more prominent in patients with active disease. The active signalling pathways in plaque psoriasis and the other clinical variants may well be overlapping, and the abovementioned separation is not absolute. Nevertheless, separation of the different signalling pathways might shed light on the immunophysiological reasons for why one therapeutic approach is effective in some psoriasis patients, but fails in others.

1.1.5 Immune activation

It is hypothesized that an altered microbiota may trigger an immune activation in autoimmune disease. Microbiota is a term meaning all bacteria, vira, or other microorganisms that colonize different areas of the body such as the skin, nasal cavities, oral cavities, the gut, eyes and genitourinary tracts. Several skin diseases, including psoriasis, reveal a differential colonizing microbiota compared to healthy skin (31). It is possible that the skin microbiome plays a regulating role by stimulating the production of antibacterial peptides. Proliferating keratinocytes in psoriasis patients overexpress antimicrobial peptides such as LL37 (a 37 amino acid C-terminal cleavage product of the antimicrobial peptide, cathelicidin), β-defensin and S100A7 (psoriasin) (32). Antimicrobial peptides could alter the skin microbiome and resistant microbial species to these antimicrobial peptides could be favoured (33). LL37 was the first antimicrobial peptide identified in mammalian skin. Physical trauma (cell damage) or bacterial products can trigger release of extracellular self-nucleic acids (DNA and RNA) and LL37 from damaged cells. Self-nucleic acids forms complexes with LL37. These complexes stimulate dendritic cells through toll like receptor (TLR)s, but can also be presented by HLA-Cw6 molecules and specifically activate T-cells (34). Further research is required to explore the more exact role of the microbiome in the pathogenesis of autoimmune diseases.

Furthermore, it has been suggested that reactive oxygen species (ROS) are involved in psoriasis pathophysiology (35). ROS are reactive molecules which can damage cell components such as proteins, carbohydrates, lipids and DNA, and are important weapons that innate immune cells use to kill pathogens. The body has a well-controlled defence system to counterbalance these highly reactive molecules and during normal physiological conditions there is a balance between oxidants and the ability to detoxify these reactive molecules. However, in inflammatory conditions there is an increased production of ROS. These molecules can increase the production and release of proinflammatory cytokines through activation of NFκB (31). Oxidative stress is defined as an imbalance in which ROS dominate over the antioxidant defence system.

1.1.6 Associated disorders

Psoriasis may not be limited to the skin only. Psoriatic arthritis occurs in 20% to 30% of patients (36, 37). Other coexisting conditions include, but is not limited to, obesity, cardiovascular disease, diabetes mellitus and inflammatory bowel disease (38). The total comorbid disease burden increases with increasing psoriasis disease severity (39). Several studies have shown that patients with severe psoriasis have increased mortality, most commonly caused by cardiovascular disease (CVD) (40, 41). The increased risk of CVD may be due to the increased systemic inflammation. However, there is also an over-representation of general risk factors for CVD such as smoking, hypertension, dyslipidaemia, obesity and diabetes (42). Incomplete adjustments for traditional risk factors will consequently form uncertainty regarding to what extent the skin disease itself is an independent risk factor for CVD.

1.1.7 Quality of life

The physical and emotional burden associated with psoriasis affects daily life and work, even in patients with mild disease (43, 44). Psoriasis is known to deteriorate quality of life (QoL) to the same degree as other major chronic illnesses such as heart disease and diabetes (45). The psoriatic patients frequently encounter problems with depression and anxiety, alcohol abuse and smoking (46-48).

Depression plays a major role to the lower QoL (49). Inflammatory mechanisms involving pro-inflammatory cytokines have been implicated in the aetiology of mental illness (50). Epidemiological evidence demonstrate an increased prevalence of mood disorders also in patients with autoimmune conditions other than psoriasis, and the relationship between inflammation and depression is gaining increased attention (51). The World Health Organizations defines QoL as an “individual´s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (52). QoL covers the physical, functional, emotional and social-well-being of the patient (53). This is a highly subjective experience by definition and is therefore measured by self-report

questionnaires. Patient reported outcome measures are key assessments tools which are increasingly being emphasized in clinical trials of psoriasis patients.

1.1.8 Treatment

Therapy is administered according to disease severity. Topical corticosteroids and vitamin D_3 analogues are usually sufficient to achieve adequate improvement in cases with mild disease. Topical calcineurin inhibitors are used for localized difficult to treat sites such as the face and intertriginous areas. If not sufficient effect of topical therapy alone, UVA/UVB phototherapy can be applied to induce remission (5).

Systemic treatment with immunomodulating drugs is indicated in moderate to severe disease. The therapeutic spectrum is relatively broad and includes cyclosporine, methotrexate, acitretin, fumaric acid esters which are often used as first line of treatment. Since the beginning of this century there has been a substantial increase in systemic psoriasis treatment regimens. While previous conventional drugs influenced the immune system in a more or less non-specific manner, biological drugs that directly targeted specific inflammatory mediators lead to a marked improvement in treatment effects. The TNF-α inhibitors infliximab, etanercept and adalimumab were the first biologic agents to be approved for psoriasis. From 2009 onwards the IL-12 and -23 antibody ustekinumab, the IL-17 inhibitors (secukinumb, ixekizumab and brodalumab) as well as the IL-23 inhibitors (guselkumbab, tildrakizumab and risankizumab) have emerged (54). With these highly effective, specific targeted drugs, the treatment goal has moved towards complete skin clearance of psoriasis (55). One disadvantage is that biological drugs are large molecular drugs (>1000Da) and need to be administered by injection. New small molecular drugs which directly target immune regulating checkpoints have emerged in the past decade. These drugs have the advantage that they can be administered orally, due to cutaneous permeability they could potentially also be formulated for topical administration, and they are less expensive to produce (8). To date small molecule drugs have shown moderate efficacy compared with biologics in psoriasis. Apremilast, a

phosphodiesterase-4 inhibitor, and tofacitinib, a JAK inhibitor, have demonstrated reduction of psoriasis disease activity in clinical trials, the latter was only FDA approved for psoriatic arthritis (PsA) and not for plaque type psoriasis only. However, there are more small molecule drugs currently undergoing clinical testing.

The presence of comorbidities such as PsA and inflammatory bowel disease is highly relevant when treatment options are considered. The responses to immune modulating treatments vary within individuals with the same disease and disease severity. This is likely caused by different genetic setup and immune signaling pathways. It has for example been demonstrated that HLA-Cw6 positive patients respond better and more quickly to ustekinumab than patients with other psoriasis susceptibility polymorphisms.

Precision medicine is a strategy in which medical treatment is tailored to “the individual characteristics of each patients”. Patients can be subclassified into groups that differ in their response to specific treatment based on their individual genetic, epigenetic and molecular characteristics (56). In the future this will obviously optimize treatment response, reduce health costs and potential side effects and individualize care for patients with psoriasis (57).

Despite all of these effective therapeutical options available, still many psoriasis patients remain untreated. A multinational survey of psoriasis and psoriatic arthritis revealed that 80% of psoriasis patients with moderate to severe disease are treated with topical drugs alone or no treatment at all (58).

1.2 Fatigue

1.2.1 Definition

Fatigue is a subjective experience, and has been defined as "*an overwhelming, debilitating, and sustained sense of exhaustion that decreases one´s ability to carry out daily activities including the ability to work effectively and to function at one´s usual level in family and social roles*" (59). Fatigue is associated with reduced motivation and is also recognized as "*the failure to initiate and/or sustain attentional tasks and physical activities requiring self-motivation*" (60). Fatigue can be distinguished from the normal tiredness everyone can feel during stressful periods in life by not being restored by sleep. In a qualitative study intending to capture the difference between fatigue and normal tiredness in patients with primary Sjogren's syndrome, patients reported that fatigue was often experienced as a feeling of bodily heaviness and could unexpectedly fluctuate in intensity (61). Importantly, patients suffering from fatigue therefore have to adjust their activity according to these flares.

1.2.2 Fatigue in chronic diseases

It has been said that a patient suffering from fatigue could have nearly any condition listed in a joint edition of the Oxford textbook of Medicine and Psychiatry (62).Yet, for the patients it is vitally important and often rated as the most troublesome phenomenon of their disease (63).

Fatigue is common in depression, hypothyroidism, chronic sleep disorders, cancer and chronic neurological diseases. In chronic inflammatory diseases such as Crohn´s disease, primary Sjögren's syndrome (pSS) and rheumatoid arthritis, the prevalence can often be up to and above 50% (64-66) .

Fatigue should be separated from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in which no other underlying condition associated with fatigue can be identified (67). Only a small minority of patients presenting with chronic

fatigue have ME/CFS, the vast majority having a recognized or unrecognized underlying disease or condition. The prevalence of this disorder has been estimated to be 0.4% and 2.6% in community and primary care-based studies respectively (68, 69).

There is an unclear relationship between disease activity and the severity of fatigue. In chronic inflammatory diseases some studies show an association between increased fatigue and increased disease severity. Notably, use of generic fatigue instruments that lack disease associated items, frequently fail to demonstrate such an association (70, 71).

While psychosocial aspects have been widely studied in dermatological diseases, less is known about fatigue. There are only a few genuine studies on fatigue in psoriasis, and the majority of available data are from therapeutic clinical trials investigating new biological agents.

1.2.3 Measurement

Fatigue is a subjective experience hence difficult to measure. Objective markers for fatigue do not exist. Instruments measuring this phenomenon are therefore based on self-reporting, and most instruments are questionnaires. Some are unidimensional, while others attempt to measure several aspects or domains of fatigue, e.g. central, peripheral, cognitive, etc. Some instruments are disease specific, and thus validated only for one single condition. Such instruments also capture disease specific factors other than fatigue like elements associated with disease activity, pain and inflammatory items. Other fatigue measuring questionnaires are intended to be used across a number of diseases, and referred to as generic instruments. There is no consensus regarding the optimal choice of instrument to use. The generic unidimensional instruments; Fatigue Visual Analog Scale (fVAS), Short Form 36 Health Survey Vitality Subscale (SF-36 VS) and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) have been extensively applied by

our research group, is easy to use, short and simple to interpret, sensitive to change over time, and is widely accepted (72).

1.2.4 Consequences

Chronic fatigue is often rated by the patients as their most debilitating phenomenon, and has a major impact on QoL (63, 73). Fatigue has substantial sosio-economical implications as it can lead to long term sick leave and work disability (74). Fatigue can lead to social withdrawal, and can be background for conflicts both at home and at work. Many patients do not acknowledge fatigue as a symptom of their underlying disease and may therefore interpret themselves as being lazy. Excessive rest and day time sleep can create a disturbed sleep cycle which results in increased perceived fatigue levels. A vicious circle between distorted sleep rhythm and experienced fatigue may therefore become inevitable.

1.2.5 Mechanisms for fatigue

There is an increasing understanding of the neurobiological basis of disease associated fatigue. A conceptual model for a scientific understanding of fatigue is the "sickness behavior response". This is a coordinated set of behavioural changes seen in all animals during infections and bodily harm. The behaviour is characterized by weariness, fatigue, reduced appetite, -thirst, -initiative, -grooming, -social activities, and depressed mood. Fatigue is a prominent feature of this response. In an evolutionary perspective this represents a strongly conserved and complex survival mechanism, and is supposed to protect the animal from predators while the immune system is fighting the pathogen. It therefore increases the probability that genes are forwarded to the new generations. In this regard, sickness behaviour is not a maladaptive response, but a subconscious strategy for the survival of the individual and the species (75).

Although the underlying biological mechanisms for fatigue is not fully understood, emerging evidence points to a key role for the innate immune system. One major source for activation of the innate immune system is stimulation by pathogen associated molecular patterns (PAMPs) and damage-associated molecular pattern (DAMPs) molecules. PAMPs are evolutionary conserved structural motifs found on bacterial cells walls, DNA, lipoproteins or other structures on pathogens, while DAMPs represent the body´s own biomolecules released by damaged or dying cells. Innate immune cells react to PAMPs and DAMPs through activation of pattern recognition receptors (PRRs). TLRs are one type of PRRs, C-type lectin receptors, nucleotide-binding oligomerization domain-like receptors and retinoic acid inducible gene-I-like receptors are other examples. Activation of innate immune cells like macrophages, dendritic and granulocytes follows and leads to production of pro-inflammatory substances like IL-1, IL-6 and TNF-α (76).

Several studies have revealed that IL-1β is a key cytokine for induction of sickness behaviour in animals (59). Despite being protected by the blood brain barrier (BBB), the central nervous system (CNS) is influenced by peripheral inflammation. Peripherally produced IL-1β enter into the brain through active and passive transport systems across the BBB (50). IL-1β can also be produced intrathecally by activated microglia in response to systemic stimuli (77). Inside the brain IL-1β binds to a complex of IL-1 receptor type 1 (IL-1RI) and the brain isoform of IL-1R accessory protein (IL-1RAcPb) on cerebral neurons (78). This does not cause inflammation, but leads to neuronal activation, followed by sickness behavior, in which fatigue is a prominent feature (79). Notably, IL-1R1 knock out mice are resistant to sickness behavior (80).

Whereas more thoroughly studied in animals, also clinical studies in humans highlight a fundamental role of IL-1β in promoting sickness behavior. Up-regulation of IL-1 in the brain is seen in a variety of acute and chronic disease (81). Furthermore, treatment with IL-1 blocking agents has been shown to alleviate fatigue

in rheumatoid arthritis, pSS, Cryopyrin-Associated Periodic Syndromes, cancer, and diabetes type 2 (82).

Although IL-1β it is important for generation of fatigue, it is possible that other immune regulatory mechanisms as well as cellular stress responses are potential mediators (83). One hypothesis for alternative fatigue generation is through oxidative stress mechanisms that occur in acute and chronic inflammatory diseases (84). Oxidative stress results from an imbalance in which ROS dominate over antioxidant defences. One mechanism to protect the cells against oxidative stress and other inducers of cellular stress is through upregulation of heat shock proteins (HSPs). HSPs are highly conserved proteins present in all animals and plants. They are mainly found intracellularly and have housekeeping, as well as protective roles in situations of different cellular stresses. Some HSPs are secreted out of the cells, have signaling properties and regulate functions in other cells. Extracellular HSPs influence immunological functions and some can activate TLRs (85, 86). Binding of lipopolysaccharide from the cell wall of Gram-negative bacteria to TLR4 on macrophages and microglia induces production of IL-1β and leads to sickness behaviour (87). Extracellular HSPs may therefore act as a DAMP on innate immune cells by activating their TLRs. Notably, we recently demonstrated that severe fatigue was associated with high plasma concentrations of HSP90α in patients with the autoimmune disease pSS and Crohn´s disease (88, 89). Generation of fatigue through cellular defense mechanisms could potentially shed light on the frequently reported lack of association between fatigue and disease activity in many studies.

1.2.6 Fatigue cofactors

In all studies performed there is a consistent association between depression and fatigue. Fatigue is one of the most commonly reported somatic complains indicating underlying depression, and is listed as one of the core symptoms in the clinical criteria for depression according to the 10-revision of the International Classification of Diseases (90, 91). There is an overlap in phenomenology and questionnaires for fatigue and depression often capture similar aspects, and therefore a circular

reasoning regarding causality may follow. Nevertheless, there are some distinctions. Whereas the patient with fatigue may keep their self-esteem and attribute their symptoms to physical limitations, depression often involve a negative view of self (92).

Pain has been associated with fatigue in many chronic diseases (93, 94). Chronic pain negatively affects sleep, mood and quality of life (95). Traditionally, pain has been conceived as a somatic phenomenon, while fatigue and depression has been interpreted to be of more psychological origin. Pain is a subjective phenomenon that has been defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain results from a combination of a peripheral stimuli and central processing. In chronic inflammatory diseases pain does not necessarily correlate with the degree of inflammation, and chronic pain may persist despite remission (96). Psoriasis is often accompanied by altered pain and thermal thresholds, also in non-involved skin tissue (97, 98). This could be caused by damage to nociceptors or peripheral nerves that can cause hypersensitivity to stimulus. Also, nociceptive sensory neurons express receptors for pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-17. Influence by these cytokines may directly decrease the excitation threshold of nociceptive neurons (99). Pain is a warning sign of proceeding tissue damage and as such it may induce a sickness behavior response.

Chronic sleep deprivation is associated with fatigue. Sleep is a basic biological need for all complex organisms and serves an essential restorative function. Psoriasis patients often suffer from sleep disorders (100). There is no Norwegian word for fatigue and the term "tiredness and exhaustion" is therefore often used concurrently. This is in accordance with Piper´s expression "in contrast to tiredness, subjective fatigue is perceived as unusual, abnormal or excessive whole-body tiredness, disproportionate to or unrelated to activity or exertion" (101). Furthermore, disturbances in sleep are well known as a core symptom of depression.

In summary, co-factors such as pain, mood-, and sleep disorders may overlap and exacerbate each other and may increase the severity of fatigue. This complex interplay could potentially be explained by an overlap in biological pathways in the genesis of these manifestations.

1.2.7 Treatment

Up to date there are no specific effective fatigue treatment. There is substantial evidence for some beneficial effect of biological drugs in chronic inflammatory diseases (102). Furthermore, some evidence supports a beneficial effect of aerobic exercise on fatigue in a variety of underlying diseases (62).

In the clinical approach to fatigue, treatment of the underlying condition/disease process may not be sufficient. Supportive management e.g. addressing treatable cofactors which could contribute to fatigue and help patients to develop techniques to better self-manage are generally recommended. Treatment of conditions which could potentiate the fatigue experience like anaemia, hypothyroidism and severe vitamin D deficiency may give small improvements in fatigue, which could improve QOL. Comorbidities like type II diabetes and cardiovascular disease could independently cause fatigue. Disrupted sleep due to e.g. obstructive sleep apnoea or any other cause of fragmented sleep like pain or pruritus should be sought and managed or referrals to appropriate services should be offered. Although mood disorders could be a consequence of, or a source to fatigue, patients suffering from emotional disturbances should be optimally treated. Nevertheless, the effect of antidepressants in treatment of depression associated with an underlying immune mediated disease is somewhat unclear (103). The most likely explanation for this is that peripheral immune activation in both human and other vertebras consistently induce sickness behavior in which the predominating features are consistent with major depression. This is highly suggestive of an interaction between inflammatory components and pathways involved in depression.

Further research into the molecular mechanisms for fatigue genesis could alter the understanding of psychological aspects of chronic inflammatory diseases, and lay foundation for further research into specific treatment options for this phenomenon.

2. Aims of the study

- Write a review of the current knowledge of fatigue in psoriasis
- Investigate the prevalence and severity of fatigue in psoriasis patients compared to healthy subjects
- Investigate biomarkers of oxidative stress and fatigue in psoriasis patients
- Explore the influence of selected cytokines on fatigue in psoriasis patients
- Investigate HSP gene expression levels in psoriasis patient with high compared to low fatigue
- Analyse the effect of biological treatment on fatigue in patients with psoriasis vulgaris

3. Subjects and methods

3.1 Study design

Paper I was a non-systematic review of fatigue in psoriasis, Papers II, III, IV and VI are based on case-control studies, and Paper V was a meta-analysis where we assessed the effect of biological drugs on fatigue in patients with psoriasis.

3.2 Psoriasis patients

A total of 120 patients were consecutively screened for potential participation based on referrals letters to the outpatient clinic at Department of Dermatology, Stavanger University Hospital. Three patients were recruited from the follow-up clinic. Thirty-six patients were excluded due to not meeting the inclusion criteria (n=30), lack of healthy control subjects that matched patients for age and gender (n=5), or withdrawn consent (n=1). Thus 84 patients were included for study. Recruitment was from November 2012 to May 2015. Inclusion criteria were Norwegian-speaking people of Caucasian origin, with chronic plaque type psoriasis, age 18 - 80 years, Psoriasis Area Severity Index (PASI) score > 0. Exclusion criteria were other non-plaque forms of psoriasis, psoriatic arthritis, other systemic inflammatory disease, cancer, and uncorrected hyper- or hypothyroidism.

3.3 Healthy subjects

The 84 healthy control subjects were predominantly recruited from acquaintances of the patients and were matched by age (± 3years) and sex with the individual patients. They fulfilled the same inclusion and exclusion criteria as the patients, except for the diagnosis of psoriasis.

3.4 Clinical examination and disease activity

All subjects underwent a clinical examination by IMS. Demographic and clinical data, medical history, current medication and tobacco smoking were recorded. Psoriasis severity was measured by the Psoriasis Area and Severity Index (PASI), and skin-related quality of life by the Dermatology Life Quality Index (DLQI). PASI takes into account the extent and the appearance of the lesions. PASI scores range from 0 to 72 (104). Severity may be graded into the following subgroups; mild disease (PASI<7), moderate disease PASI 7-12 and severe disease PASI > 12 (105). In clinical practice severe psoriasis is commonly defined as PASI >10 (106). DLQI is a QoL instrument used in dermatology. It consists of 10 questions concerning the patients` perception of the different aspects of QoL over the last week. It includes aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and side-effects of treatment. Each item is scored on a 4-point scale: not at all/not relevant = 0, a little = 1, a lot = 2 and very much = 3. The individual scores are added to yield a total score ranging from 0-30; higher scores indicate greater impairment of QoL.

3.5 Measures of fatigue

Fatigue was evaluated by three different generic fatigue instruments. fVAS consists of a 100 mm line with vertical anchors in both ends, where 0 denotes “no fatigue” and 100 “worst possible fatigue”. A cut-off score of ≥ 50 was defined as clinically important fatigue (71). The SF-36 VS comprises four questions regarding fatigue. The subscale score yields a result ranging from 0 to 100, where lower scores represent more fatigue. Clinically important fatigue was defined by a cut off score of ≤ 35 (107). The Fatigue Severity Scale (FSS) includes nine statements regarding fatigue over the last two weeks. To each item the patient assigns a score from 1 (completely disagree) to 7 (completely agree) which are summed and divided by nine to get a summary score. A cut off of 4 was applied to define clinically important fatigue (108).

3.6 Measures of pain and depression

Pain was rated using the pain subscale of the SF-36. Two questions regarding the last four weeks intensity of pain, and if it has interfered with daily activities, comprise the subscale score. Higher scores indicate less pain (109).

Depression was scored by the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) (110). The scale has seven items on depression of which all are answered from 0 to 3, and the responses are summed to obtain a depression score. A cut off of ≥ 8 has previously been used as cut off for depression (111).

3.7 Laboratory analyses

Blood was drawn by venous puncture in the morning after an overnight fast. Serum for routine laboratory analyses were separated from blood cells (centrifuged 7 min at 2600×*g* at 22 °C) within 2 h and analyzed within 5 h after collection. Peripheral venous EDTA blood samples for research purposes were centrifuged (15 min at 2500×*g* at 4 °C) within 30 min of sampling, and aliquots of plasma were stored at −80 °C until analysis. Furthermore, whole blood samples were collected from each patient into two PAXgene blood RNA tubes (Qiagen) per patient and kept for 2 h at room temperature, placed in a freezer at -20°C for 24 hours, and thereafter kept at -80°C for storage.

3.8 AOPP and MDA

Advanced oxidation protein products (AOPP) is an unspecific measure of oxidized proteins that is generated by oxidative changes of amino acids. Di-tyrosine is a main contributor to AOPP, but AOPP also comprises other chromophores including carbonyl and pentosidine. Di-tyrosine is formed by dimerization of tyrosine generated as a result of activation of neutrophil granulocytes observed in inflammation. UV-spectrometry is the current standard monitoring method for detection of AOPP. The

analysis is based on absorbance of light at 340 nm. The more light that has been absorbed at this wavelength, the higher estimated AOPP concentration (112).

Malondialdehyde (MDA) is a relatively stable end-product of lipid peroxidation. It can be analyzed by different methods which vary in selectivity and sensitivity. In this study we used high-performance liquid chromatography (HPLC) connected to a fluorescence detector. MDA is a small molecule that occur in very low concentrations in biological samples. It does not fluoresce and its molar extinction coefficient for UV and visible light is very low. In order to improve the detection limit, derivatization is necessary. The most widely used derivatization reagent is thiobarituric acid (TBA). The reaction of MDA with TBA in an acidic environment leads to formation of a MDA-TBA_2 complex that can be detected by visible spectrometry at wavelength 532nm or by fluorescence spectrometry at excitation/emission wavelengths 525/560nm. There are other compounds than MDA that can react with TBA, and they are often referred to as TBA-reacting substances (TBARS). To improve specificity for the MDA-TBA_2 complex, it can be separated from other TBARS by HPLC before detection by visible or fluorescence spectrometry. The fluorescence detector improves the specificity compared to visible light spectrophotometry by only detecting chromophores with fluorescent abilities (113).

3.9 Immunologial methods for cytokine analyses

Immunological methods are based on the interaction between antigens and antibodies, but varies in techniques for immobilizing a capture antibody and detection-system for quantification of the antigen. For analyses of IL-1RII plasma concentrations, we utilized sandwich enzyme-linked immunosorbent assay (ELISA). Plasma concentrations of IL-1β, IL-1Ra, IL-6 and IL-10 were measured by electrochemiluminescence (ECL) based Meso Scale Discovery (MSD) assay.

3.9.1 Sandwich ELISA

Sandwich ELISA is a frequently used method for quantitative detection of cytokines that utilizes two specific antibodies to form a sandwich with the cytokine of interest. Briefly, a capture antibody with specificity for the cytokine is immobilized on the microtiter wells. Biological samples and standard samples (containing a known concentration of the cytokine) is added. The cytokine binds with the capture antibody. A detection antibody linked with horseradish peroxidase (HRP) is added to form a sandwich with the captured cytokine. A colourless tetramethylbenzidine (TMB) solution is added. TMB is oxidised by HRP to yield the blue TMB diimine which turn yellow after acidification (Figure 2). The intensity of the color is proportional to the amount of cytokine in the sample. Finally, the absorption is measured with a spectrophotometer at 450 nm. The unknown plasma concentration of cytokine in the samples is calculated by use of calibration curve made from the standard samples containing known concentration of the cytokine (114).

3.9.2 ECL assay

Specific capture antibodies for IL-1β, IL-1Ra, IL-6 and IL-10 are immobilized at corresponding spots on microplate wells with an electric surface. The capture antibodies bind to the corresponding cytokine when the samples are added. The bounded cytokines are then detected by a secondary antibody that is conjugated to a SULFO-TAG™ (MSD). Upon electrochemical stimulation initiated at the electrode surfaces a redox reaction commences, and the SULFO-TAG™ emits light at 620nm. By measuring the intensity of the emitted light one can quantify the concentration of the concentration of the cytokines (Figure 2) (114).

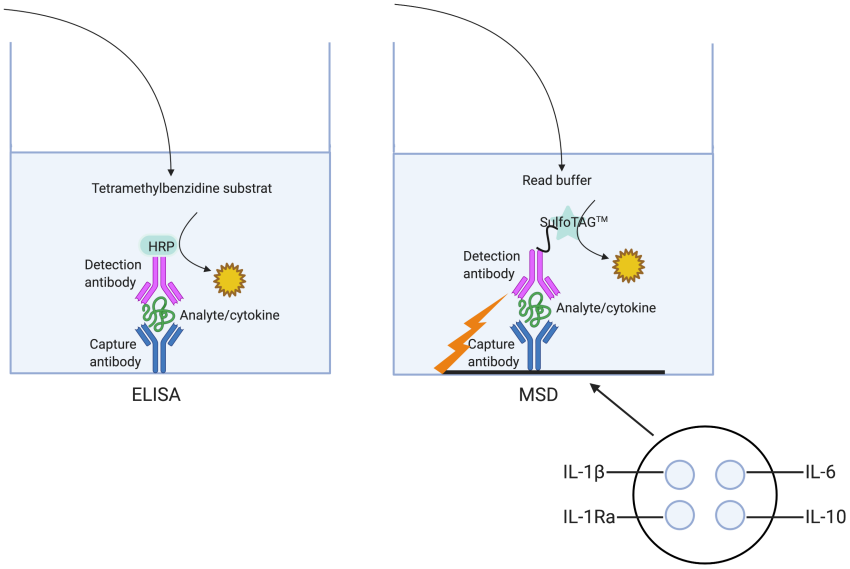

Figure 2. Illustration of ELISA and ECL principles.
In both assays specific capture antibodies are fixed to the well bottom of the assays. The ELISA method we used can only detect one cytokine at the time, MSD can detect up to 10 different cytokines. The detection or secondary antibodies have different tags attached. In ELISA the tag is an enzyme (e.g. horseradish peroxidase (HRP)) that create a colorimetric reaction when exposed to a chemical substrate (e.g. tetramethybenzidine). In MSD, however, the detection antibody is attached to an elctrochemiluminescence label (SULFO-TAG^{TM}) that emits light when excited by electric energy

All samples were run in triplicates. The intra-assay variation, expressed as coefficient of variations (CV) were < 15%. The inter-assay variation was assessed by measuring the same control on each plate (n=10 plates for cytokines measured on ECL, and n=9 plates for ELISA) and were 29.5% (IL-1β), 11.6% (IL-1Ra), 10.8% (IL-1RII), 29.1% (IL-6) and 12.3% (IL-10). This is in agreement with variations given from the assay manufacturer for IL-1Ra, IL-1RII and IL-6, but slightly higher for IL-1β and IL-10. These deviations can be explained by low concentrations of the cytokines in the internal control samples. In the low concentration end of the standard curve the measurements will often have greater variation thus higher CV. The

concentrations of our internal controls were comparable to samples from the study population, unlike the concentrations used by the manufacturer to assess CV.

3.10 HSP gene expression studies

Gene expression is a term meaning transcription from deoxyribonucleic acid (DNA) to ribonucleic acid (RNA) into protein**.** RNA is a highly regulated, single stranded molecule. It is not possible to sequence RNA directly. However, we can sequence RNA indirectly by reverse transcriptase from RNA to complementary DNA (cDNA). The cDNA molecule is more stable than RNA and can be amplified by polymerase chain reaction (PCR). The PCR process is based on a series of temperature changes (cycles), which are repeated 40 to 45 times. Each cycle consists of three steps, DNA denaturation (95°C), binding of primers (annealing) (55°C) and extension of single-stranded DNA molecules (72°C). The amplified cDNA will give an estimate of the expression level of the RNA.

3.10.1 RNA-sequencing (RNA-seq).

The transcriptome is the sum of all RNA transcripts in a cell or sample, i.e. it captures a snapshot of the total transcripts present at a given timepoint. There are different methods that can be used to generate transcriptome data. RNA-seq uses high-throughput sequencing to quantitate transcripts present in an RNA extract (115). High-throughput sequencing is the current dominant transcriptomics technique. This technique gives information on which genes are active and the magnitude of transcription.

The process involves three main steps; prepare a sequencing library, sequencing and data analyses. The total RNA is isolated from a sample and messenger RNA (mRNA) is selected for downstream analyses. As the sequencing machine can only sequence short (200-300 bp) fragments, mRNA is broken into small fragments which are converted into double stranded cDNA.

Sequencing adaptors are added that allow the sequencing machine to recognize the fragments to create a library for sequencing. Sequencing of these fragments involves generation of "read pairs" with two reads in either end of each fragment (separated by a fixed distance). The library is thereafter polymerase chain reaction (PCR) amplified to enable enough reads for measurement. Only the fragments with sequencing adapters are amplified.

The read pairs will then be aligned to the reference genome and the number of reads per gene counted. The number of RNA molecules that came from a specific gene should correspond directly to how many reads mapped to that gene. However, longer genes will have more reads. Therefore, the reads need to be normalized by gene length to determine expression. Furthermore, the number of reads that was sequenced need to be normalized, i.e. how deep was the sequencing. Instead of raw read counts, expression values are generally given in terms of FPKM. This unit stands for fragments (fragments are read pairs) per kilobase of gene (per length of the gene in units of kilobase) per million mapped reads (how many reads per million reads) (116). This normalized value will allow comparing one gene to another gene within the same sample because we have normalized by gene length. Furthermore, one can compare across different samples because we have also normalized by sequencing depth (i.e. library sizes; the total number of mapped reads).

We used principal component analysis (PCA) to visualize potential patterns in the selected HSP dataset. In the resulting PCA plot there was a clear tendency that the patients clustered in groups based on reported fatigue levels along the first principal component. To make the clusters more visible in the plots, the symbols were color-coded according to high or low fatigue. Based on the corresponding loading plot a set of candidate HSP genes, strongly congregating to the first principal component, were selected for re-evaluation by reverse-transcription real-time quantitative polymerase chain rection (RT-qPCR) in a larger patient set.

3.10.2 RT-qPCR

RT-qPCR is a widely used method for gene expression analyses. While the RNAseq is a hypothesis-free approach that does not require prior knowledge of sequence information, RT-qPCR can only be used for analyses of known sequences (117).

The RT-qPCR system detects the products at the extension step of each PCR cycle by using a non-specific fluorescent dye, SYBR Green, which binds to double-stranded DNA. An increase in PCR product will cause increased fluorescence intensity (118). The quantitation of PCR product is relatively compared to an internal reference gene. Reference genes are genes that are expressed at a constant level in different tissues of an organism. Reference genes are used as internal reaction control to normalize mRNA levels between different samples in order to allow for a more optimal comparison of mRNA transcription levels.

At the end of an RT-qPCR process, the system allows to analyze several aspects of the procedure e.g. the melting curve analyses are used to verify single PCR products and absence/presence of primer dimers.

Genes were measured in triplicates as a necessary means to control for PCR imprecision and to enable outlier removal.

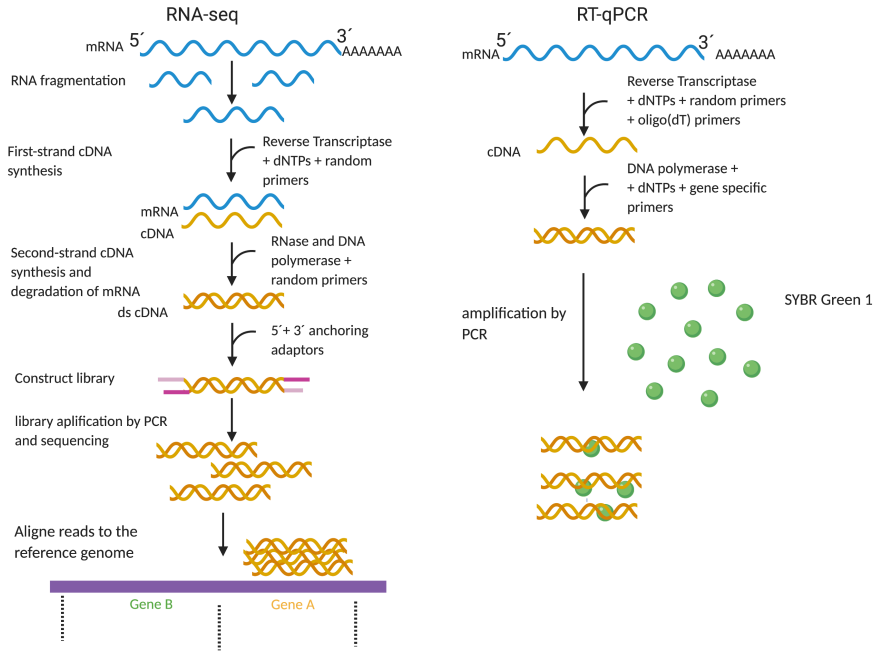

Figure 3. Schematic presentation of RNAseq and RT-qPCR.
After RNA extraction mRNAs are isolated from other varieties of RNA based on binding of their poly(A) tail to complementary oligo-dT chains attached to magnetic beads. The mRNA is used to make the second strand of cDNA. This double stranded cDNA is enzymatically fragmented. Adaptors attached to the ends of these molecules allow the sequencing to recognize the fragments. Only fragments with sequencing adaptors are amplified. Finally, sequences are mapped to a reference genome for quantitation of expression levels. The more reads the higher expression level of the specific gene. In RT-qPCR, specific primers are added to the cDNA. SYBR green binds to all double-stranded DNA and emits a fluorescent signal. In its unbound state, SYBR green does not fluoresce. Template amplification is measured in each cycle by the corresponding increase in fluorescence

3.11 Ethical considerations

The study was approved by the Regional Committee for Medical Research in Norway (REK vest 2010/1455) and conducted in accordance with the Declaration of Helsinki. Prior to their scheduled outpatient appointment, information about the study was posted to the participating patients. Written informed consent were obtained from all included participants.

3.12 Statistics

Unless otherwise stated, the statistical analyses were performed using the most recent IBM SPSS Statistics version available. We generally used two-sided tests with level of significance $P < 0.05$, and point estimates are supplied with 95% confidence intervals (CI).

Descriptive statistics of continuous variables were presented as mean and standard deviation (SD) if symmetrically distributed or median and interquartile range (IQR) if skewed. Distributions were assessed by visual inspection of histograms and QQ-plots. Most continuous data were not normally distributed, and for the purpose of simplicity median and IQR were sometimes preferred for all variables. Comparison of continuous variables between groups was similarly performed using respectively the independent samples t-test or the Mann-Whitney U test. Categorical variables were presented with counts and percentages. For comparison of categorical variables between groups, the Chi-square test or the Fisher´s exact test was used. In Paper II, the Wilcoxon paired sample test was used to test for differences in paired continuous data, and McNemar´s test was used for pair-wise categorical data.

Except for Paper VI, simple or multiple linear regression analyses were used to estimate associations between continuous dependent variables. Dependent variables which were not normally distributed were transformed using the natural logarithm before employed in regression analyses. Overall model fit was assessed by R^2. For each individual independent variable, estimated effect (beta) and 95% CI were determined, as well as the *P* value for Wald test of hypothesis of no effect. Change in R^2 (ΔR^2) was used to assess the contribution of the individual variables in the model. Variables with a $P < 0.25$ in univariable analyses were included in multivariable linear regression modelling. Both stepwise forward and backward selection procedures were performed to identify variables that should be included in the final model. In Paper VI logistic regression analyses were used for analyses of associations between fatigue as a dichotomous variable and HSP gene expression levels. The

estimated odds ratios (ORs) and 95% confidence intervals (CIs) and p-values from Wald tests of hypotheses of no association were determined. Unadjusted odds ratios (OR)s, as well as ORs adjusted for clinical variables were presented.

For Paper V we conducted meta-analysis using Stata v. 15.1. The standardised mean difference (SMD) in change from baseline in fatigue scores between biologic and placebo therapy was used as the primary outcome measure. Random effects and fixed effects meta-analyses was performed using the DerSimonian and Laird and reverse-variance methods, respectively (119) . The consistency between studies was measured by I^2 (119) and potential publication bias was assessed using a funnel plot.

Statistician and co-author Ingvild Dalen was the statistical advisor. Further details of the statistical procedures are given in the respective papers.

4. Summary of results

4.1 Paper I:

This is a non-systematic review article related to fatigue in psoriasis. The concept of sickness behaviour was used as an explanatory model for fatigue. The literature search included articles that described hypotheses regarding immunological mechanisms for fatigue. Available evidence for presence of fatigue in psoriasis was explored. Knowledge gaps on this topic in psoriasis research were identified such as the prevalence and severity of fatigue, the pathophysiological mechanisms as well as the evidence on the effects of pharmacological therapies for fatigue in psoriasis patients.

4.2 Paper II:

In this study we investigated the prevalence and severity of fatigue in 84 patients with plaque psoriasis compared with 84 age- and gender-matched healthy subjects, and explored the potential influence of essential clinical and demographic factors on fatigue among the patients. Severity of fatigue was assessed using three different generic and well-validated fatigue instruments: fVAS, FSS and the SF-36 VS .

We found that in the patients and healthy subjects the median fVAS scores were 51 and 11, FSS scores were 4 and 1.6, and SF-36 VS scores were 43 and 73, respectively. Among patients versus healthy subjects, the rates of clinically important fatigue were 51% vs 4% (fVAS), 52% vs 4% (FSS), and 42% vs 2% (SF-36) (all $P <$ 0,001). There was no association between fatigue and psoriasis disease activity (PASI), while smoking, pain and depression significantly influenced the severity of fatigue.

In conclusion, nearly 50% of psoriasis patients suffer from clinically important fatigue, a considerable higher prevalence than among the healthy subjects.

4.3 Paper III

Many studies claim that oxidative stress is involved in the pathophysiology of psoriasis, although typically, systemic inflammation is very low grade. In this study we compared plasma concentrations of AOPP and MDA between 84 patients with psoriasis and 84 age- and gender-matched healthy subjects. We also explored whether AOPP or MDA were associated with clinical characteristics of patients including fatigue. Plasma AOPP was measured with spectrometry and MDA concentrations were measured with HPLC connected to a fluorescence detector.

Median (interquartile range, IQR) AOPP concentrations were 66 μmol/l (IQR: 54−102) in patients and 69 μmol/l (IQR: 55−87) in healthy subjects ($P = 0.75$). Median plasma MDA concentrations were significantly lower in patients than in healthy subjects (0.68 μM, IQR: 0.54−0.85 vs. 0.76 μM, IQR: 0.60−0.97; $P = 0.03$). Higher AOPP concentrations were associated with male gender, high body mass index, and high hemoglobin values. Likewise, higher MDA concentrations were associated with advanced age and male gender. No significant associations with disease severity nor with fatigue were revealed.

In conclusion, oxidative stress was not increased in patients with psoriasis compared to healthy subjects. Several non-disease related factors might influence the measured levels of AOPP and MDA. These issues should be considered when interpreting results regarding these biomarkers in patients with psoriasis.

4.4 Paper IV

It has been suggested that pro-inflammatory cytokines play a causative role in fatigue. With reference to this we conducted a controlled study and explored the plasma levels of select cytokines in 84 patients with psoriasis and 84 age- and gender matched healthy subjects and compared them with fatigue severity and other clinical

factors. IL-1RII was measured by ELISA and IL-1β, IL-1Ra, IL-6, and IL-10 by ECL.

IL-1Ra and IL-6 concentrations were significantly higher in patients than healthy subjects. (203 pg/mL, IQR: 150 – 274 vs. 166 pg/mL, IQR: 128 – 212; $P = 0.008$ and 0.82 pg/mL, IQR: 0.18 - 1.40 vs. 0.50 pg/mL, IQR: 0.18 - 0.91; $P = 0.009$, respectively). Higher levels of IL-1Ra and IL-6 were associated with increased body mass index. Cytokine concentrations and disease activity did not influence fatigue.

In conclusion, these findings do not support an association between fatigue and blood concentrations of selected pro- and anti-inflammatory cytokines. Furthermore, the cytokine plasma concentrations are predominantly influenced by higher BMI, and not disease severity.

4.5 Paper V

Biologic therapy is effective in treating psoriasis skin symptoms. In this study we undertook a PubMed search and performed a meta-analysis of randomized controlled trials on the effect on fatigue from biological therapies used for psoriasis vulgaris. Eight trials were included. We found a consistent small to moderate effect of biological drugs on fatigue compared to placebo, with a standardized mean difference of -0.40 (95% CI, -0.46 to -0.34). The effect was independent of the type of biological drug used.

4.6 Paper VI

Recent evidence suggests a role for HSPs in generation of fatigue in chronic inflammatory diseases. Therefore, we investigated the expression levels of selected HSP genes in peripheral blood mononuclear cells (PBMC) of psoriasis patients with high and low fatigue. Total mRNAs from PBMC of 10 patients with high fatigue

scores (fVAS 63-92) and 10 with low fatigue (fVAS 0-31) were analysed by RNA-seq. Principal component analyses (PCA) was utilized to screen for differentially expressed HSP genes between patients with high and low fatigue. RT- qPCR was thereafter applied to confirm the expression profiling of 4 selected candidate HSP genes from PBMCs of 20 patients with high (fVAS 64-97) and 20 patients with low (fVAS 0-25) fatigue scores.

RNA-seq analyses demonstrated that *HSPB11*, *HSPBAP1*, *HSPA14* were upregulated in patients with high fatigue and *HSPA9P1, HSP90B1*, *HSP90AB1* downregulated. The expression levels of these upregulated and downregulated HSP genes contributed most to the separation of patients with high and low in an unsupervised PCA.

RT-qPCR levels of *HSPB11* and *HSP90B1* displayed a similar mode as the RNA-seq results. Patients with high fatigue scores had higher expression levels of *HSPB11* and lower expression levels of *HSP90B1* compared to patients with low fatigue. Psoriasis disease activity did not influence the expression levels of any HSP genes in our study.

These results indicate a role for HSP signaling in fatigue in patients with psoriasis.

5. Discussion

Fatigue is a common phenomenon across inflammatory conditions, but is somewhat underrecognized in dermatological contexts. There was a knowledge gap regarding fatigue in psoriasis and the overall aim of this thesis was therefore to investigate and describe fatigue in psoriasis patients and compare with an age- and gender matched control group consisting of healthy subjects. Furthermore, the project aimed to uncover biological mechanisms that signal fatigue to the brain.

5.1 Main findings

Initially we performed a non-systematic review of selected articles on fatigue and psoriasis. A lack of genuine investigations on fatigue prevalence and severity in patients with psoriasis was identified.

The case-controlled study demonstrated that approximately 50% of psoriasis patients reported clinical important fatigue. This figure was much higher than in healthy subjects. Fatigue severity was associated with depression, pain and smoking, but with not disease activity.

Oxidative stress, assessed by plasma protein oxidation and lipid peroxidation, was not increased in psoriasis patients compared to healthy individuals. In addition, we could not reveal any association between measures of oxidative stress and psoriasis disease activity nor with fatigue.

There were no associations between plasma concentrations of selected cytokines and fatigue. The cytokine plasma concentrations in psoriasis patients were predominantly influenced by higher BMI, and not disease severity.

Biological drugs have a small to moderate effect on fatigue in psoriasis patients. It was not identified any subgroup effects among the different types of biological drugs

in the study. Intriguingly, the majority of reported clinical trials on biological drugs for treatment of psoriasis vulgaris did not include fatigue measures as either primary or secondary endpoints.

There was an association between expression levels of some of the selected HSPs genes and fatigue severity in psoriasis patients. HSP gene expression was influenced by BMI, but not disease activity.

5.2 Discussion of main results

5.2.1 Fatigue severity and associated factors in psoriasis

The prevalence of clinically important fatigue in psoriasis patients that we revealed is in line with studies in other inflammatory diseases. In a controlled study of newly diagnosed and untreated patients with inflammatory bowel disease; 48% of patients with Crohn's disease and 42% with ulcerative colitis reported fatigue (64).

A lower mood state occurs more often in patients with psoriasis than in the normal population (47) and was in our study strongly associated with fatigue. “Loss of energy” is one of the criteria for a severe depressive episode (90). The association between fatigue and depressive symptoms may therefore be partly due to overlapping symptomatology. A leading hypothesis is that fatigue and depression both are parts of the sickness behavior response. This is a well-preserved defence mechanism in humans and animals with the advantage of improving survival during conditions with infections and bodily damage. The behaviour encompasses several phenomena, such as reduced physical activity, fatigue, depression, social restraint, and loss of thirst and hunger. Features of sickness behavior are likely to share common molecular signalling pathways (120).

The association between pain and fatigue is well documented, and was also confirmed in our study. Nociception involves a central nervous response to painful

stimuli in which the signals are transmitted from the periphery to the cerebral cortex and perceived as pain by the individual. The perception of pain leads to behavioral changes displayed as features of sickness behaviour. It is therefore to be expected that these phenomena are tightly correlated.

Smokers reported more fatigue than non-smokers. The association between smoking and fatigue was not statistically significant when smoking was kept as a continuous variable, i.e. numbers of cigarettes daily. The interpretation of this is not perfectly clear. In the cohort there was a relatively low number of smokers and it would have been interesting to study this further in a larger data set. Whether smoking per se is associated with fatigue or if the amount of smoking is related to more severe fatigue remains unclarified. Nicotine may have antidepressant effects due to stimulation of release of neurotransmitters including serotonin, dopamine and norepinephrine (121). Although it has been demonstrated that nicotine reduces fatigue, little research has investigated this effect further (122). We hypothesize that smoking probably identifies a subgroup of people in which psychosocial factors may influence fatigue.

5.2.2 Endproducts of oxidative stress do not influence fatigue

Some studies have revealed increased oxidative stress in psoriasis, and hypothesize a role in pathogenesis of psoriasis (123). Indicators of oxidative stress have also been linked to increased disease severity (124). The results in our study were therefore somewhat unexpected. A possible reason for the conflicting results is that the majority of our patients had predominantly mild psoriasis, which reduces the possibility to identify differences between the groups. Our study provided evidence to suggest that there are several contributing factors which are important to adjust for in analyses of AOPP and MDA including BMI, the latter closely related to disease severity (42). An association between chronic fatigue and measures of oxidative stress has been demonstrated in chronic fatigue syndrome / myalgic encephalomyelitis (CFS/ME) and in SLE (125, 126). The lack of association between

measures of end-products of oxidative stress and fatigue in our study does not necessarily mean that oxidative stress is not involved in the generation of fatigue. A possible explanation might be that the analytical methods are not accurate enough to detect minor and physiological increased amounts of ROS in this condition. Also, slight elevation of the markers in the periphery may not necessarily lead to activation of fatigue signaling pathways to the brain.

5.2.3 Plasma cytokine concentrations do not influence fatigue

Our results indicate that peripherally produced cytokines do not directly influence the severity of fatigue in psoriasis patients with mild disease. However, in inflammatory conditions IL-1β pass through the BBB into the brain and activate neuronal cells and microglia cells to produce IL-1β that binds to specific IL-1 receptors on nearby cerebral neurons. Intrathecal cytokine concentrations may therefore be more applicable when studying the influence of cytokines on fatigue.

The fact that fatigue is not associated with plasma concentrations of selected cytokines could partly explain the frequently reported lack of association between fatigue and disease severity (70). This may direct future research towards other pathways. Such alternative pathways could be cellular stress responses. However, a larger study group that included patients with more severe psoriasis and presumably higher cytokine concentrations would have been necessary to robustly exclude a correlation between blood cytokine levels and fatigue in psoriasis patients.

It would have been useful to measure potential influence of other relevant cytokines, such as TNF-α, but this was beyond our time and resources when the analyses were conducted. Future research on the relation between the peripheral inflammation and fatigue could therefore be directed towards other pathways such as cellular stress responses.

In the present patient cohort, the concentrations of IL-1Ra and IL-6 were predominantly influenced by higher BMI, and not disease severity. So-called adipokines i.e. cytokines released by adipose tissue play an important contributing role to the low-grade systemic inflammation seen in this patient group (127). Our finding highlights the importance of BMI as a confounder between psoriasis per se and systemic inflammatory markers.

5.2.4 Effect of biological treatment on fatigue in psoriasis

The effect of biological interventions on fatigue in psoriasis had not previously been systematically reviewed. We found the effect of biological treatment to be mild to moderate, and could not identify any subgroup effects of different types of biological drugs. Among the identified relevant trials, fatigue was only at best reported as secondary outcomes. This reflects the relatively little attention that has been given to the phenomenon in dermatology. The scores were usually measured quite early in the trial periods (i.e. at, or before 16 weeks), and the long-term effect on fatigue is yet to be established. Our findings are in agreement with studies in other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (102, 128).

5.2.5 Altered HSP gene expression may be related to fatigue

Our study demonstrated that HSPs gene expression pattern profiles in PBMC differed between patients with high and low fatigue. In psoriasis patients with high fatigue the expression levels were increased for of *HSPB11* and decreased for *HSP90B1* compared to patients with less fatigue. These findings were consistent in the RNA-seq and RT-qPCR mRNA analyses.

In the light of HSPs' important roles for protecting cellular life it is possible that mechanisms that induce fatigue through HSP signalling have evolved during evolution. Our study was exploratory with small number of patients and needs to be

confirmed in future studies with larger sample size. Furthermore, the gene expression profiles must be confirmed on protein levels before a more valid conclusion can be drawn. However, to the best of our knowledge, this is the first time a study has demonstrated findings suggestive of genetic mechanisms as contributors of fatigue in psoriasis patients. This opens the possibility to future studies in the same area.

5.3 Methodological considerations

5.3.1 Study design:

The patient cohorts in Papers II, III and IV was recruited from our local hospital catchment area and presumed representative for the average patients receiving treatment at hospital level in this health trust. A relatively large sample size has been investigated in the studies reported in Papers II, III and IV. It can therefore be assumed that the results can be generalised to patients with the same diagnosis in our hospital region. To avoid bias towards different levels of education and social adjustments, the healthy subjects were mainly recruited from acquaintances and friends of the patients. Furthermore, the healthy subjects were age- and gender matched with the patients.

We used validated, and internationally widely accepted, generic fatigue measuring instruments. This permits access to valid data that can be used to compare with non-dermatological diseases and healthy control subjects.

Many biomarkers are susceptible to degradation or other changes in the preanalytical processing of samples, as well as influenced by temperature and duration of storage. Blood was drawn at fasting state with equal pre-processing steps. All samples were subsequently stored at one biobank at -80˚C and processed at one site under similar conditions by the same personnel. None of the samples were frozen and thawed more than once before analyses.

There are some shortcomings. The cross-sectional design prevents any conclusion about causality. Only associations can be described in an observational study like this. One important weakness in our study is the relatively low disease activity. This might have influenced some of the associations or lack of these. Low number of patients with severe disease limits the statistical power of comparisons between patients with various degree of disease severity. Lack of statistical significance must therefore be interpreted with caution. However, despite this limitation, it was revealed that fatigue is a prevalent and severe phenomenon even in the subgroup of psoriasis patients with predominantly low disease activity.

5.3.2 Measures of oxidative stress

There are several biomarkers for oxidative stress. In Paper III, two frequently used biomarkers of oxidative stress were utilized; AOPP and MDA, which assess the end result of two different oxidation processes. We developed, modified and validated methods for MDA and AOPP and used them in several different patient cohorts, thereby minimizing the errors introducing new markers. One limitation is that we did not measure other indicators of oxidative stress e.g. biomarkers of the antioxidant defence system, nor DNA oxidations. A major obstacle in the interpretation of results regarding biomarkers of oxidative stress, is the lack of international standards for analyses and quality assurance of the data. As a result, it is difficult to compare studies from different laboratories.

It is puzzling that AOPP and MDA have been known as measures for oxidative stress for more than 20 and 40 years, respectively. Yet, one cannot use a measured value as a meaningful diagnostic, prognostic or predictive tool. Established general reference values are lacking. Therefore, each study must include a reference group.

Increased oxidative stress seems to be associated with several diseases and conditions. In addition, redox reactions also play an important part of the normal metabolism. Given the complexity of these processes, the meaning of oxidative stress

biomarkers in specific diseases remain somewhat uncertain even with available standardized monitoring methods.

AOPP is measured by UV-spectrometry which is a fast, simple and inexpensive method to determine the concentration of an analyte in a solution. AOPP was first described by Witko-Sarsat et al. in 1996 (112). The method and modified versions of it have been used in a large number of reports and studies thereafter. Absorbance at 340 nm is not specific for AOPP since other compounds, such as hemoglobin also absorb at 340 nm. Furthermore, a major disadvantage is that it can be disturbed through interference of turbidity in the samples, often due to lipemic plasma. Thus, this method allows only a screening of the degree of oxidative stress and is not a very specific measure of oxidized proteins. During the last years we have optimized the method to reduce spectrophotometric interference from lipids and hemolysis that cause falsely elevated optical densities.

The majority of studies on oxidative stress in psoriasis patients have investigated the levels of lipid peroxidation products. In contrast to our findings, higher concentrations in patients compared to healthy subjects are commonly revealed (123). A reason for this could be the choice of analytical method. MDA levels can be determined by different methods which vary in selectivity and sensitivity. Simple UV-spectrophotometric methods without chromatographic separation have often been used, but few publications mention the weaknesses of this method. HPLC connected to a fluorescence detector is a more specific method that separates MDA from other interfering compounds. This might be of particular importance in psoriasis patients who have a propensity to hypertriglyceridemia, a phenomenon possibly associated with disease severity.

5.3.3 Cytokine analyses

Immunological analytical methods based on specific binding between antigens and antibodies were utilized for cytokine measurements. There are several techniques available, including, but not limited to, ELISA and ECL.

ELISA is a frequently used method for cytokine analyses. However, the method we used is limited by its ability to measure only one cytokine at a time and is therefore time consuming and costly. No commercial MSD multiplex kit for IL-1RII was available at the time of our study, and ELISA was utilized for its quantification.

MSD is a multiplex assay that can simultaneously measure up to 10 cytokines from a single sample, and plasma concentrations of IL-1β, IL-1Ra, IL-6 and IL-10 were quantified by this method. Multiple excitation cycles of each SULFO-TAG™ (i.e. each cytokine) enhance the emitted light and thus improves the sensitivity and dynamic range compared to ELISA

Cytokines are not routinely measured in clinical practice although frequently used in research. This is partly due to challenges associated with rapid degradation and lack of established reference values for these compounds.

It has been demonstrated that cytokines should be analysed in immediately cooled and centrifuged EDTA or citrate blood to avoid release of cytokines from blood cells after sampling. The cytokine levels are lower and more stable in plasma than in serum, suggesting that coagulation factors and thrombin present in serum enhance cytokine release from leukocytes (129).

Psoriasis is generally associated with a low level of systemic inflammation and some cytokines are not measurable or found in very low- level similar to healthy subjects. In the present study, the concentrations of IL1β, IL-6 and IL10 were below the lower limit of detection (LLOD) in a high percentage of the patient plasma samples. LLOD of a method is defined as the lowest concentration that can be distinguished from the absence of the cytokine (a blank value). An important consideration in the interpretation of the results is that the values close to LLOD are usually less accurate and precise. There are different ways of approaching this problem. One method is to ignore data with measurements lower than LLOD, however omission of data below

LLOD is generally not recommended to avoid overestimation of mean concentration. Although the values are low, they may strongly impact the distribution of the data. A widely accepted used substitution method is by LLOD/$\sqrt{2}$ which was used in our study.

The immunoassay analyses for detecting cytokines were conducted by experienced laboratory personnel.

5.3.4 HSP gene expression

RT-qPCR is a much used technique to measure cDNA and genomic DNA levels. The primary disadvantage of the SYBR Green dye detection of PCR products is that it is not sequence specific (118). The SYBR green dye binds to any double stranded DNA and may therefore generate false positive signals. This was overcome in our study by using highly specific primers that binds specifically to the gene or sequence of interest. Furthermore, the primer specificity was ensured by melting curve analysis. Melting curve analysis is an assessment of the dissociation characteristics of double stranded DNA during heating. SYBR Green only fluoresces when it is bound to double-stranded DNA.
The temperature at which the two DNA strands is broken depends on their length thus a unique melting curve of the changing rate of fluorescence versus temperature will be produced for each specific double-stranded DNA fragment. If more than one DNA fragment is produced during the qPCR reaction, this will be reflected in the melting curve analysis.

5.3.5 Systematic review

Multiple databases are generally recommended when searching for relevant referenced in systematic reviews. A combination of Embase, MEDLINE, Web of Science Core Collection and Google Scholar has been shown to be the most optimal search strategy for systematic reviews (130). Due to time constraint the literature

search for in paper V was performed in PubMed only. PubMed began as an online version of MEDLINE index more than twenty years ago, but today also include PubMed Central (PMC). One can therefore risk that non-indexed articles are listed in PubMed as this is a back door from PMC.

Given the nature of the studies (randomised controlled trials of biological drugs for psoriasis) we found it overly likely that any study covered in the analyses would be indexed in MEDLINE or PMC. The InCite Journal Citation Reports, which is the trusted and most widely used publication to identify relevant information on the impact of an academic journal based on citation metrics, lists a total of 68 journals in the field of dermatology. A search through these revealed that only four were not indexed for in MEDLINE or PMC. In our opinion all the relevant influential randomised controlled trials of approved biological drugs for psoriasis at the time of data collection were listed in PubMed and therefore this was an adequate source for this literature search.

6. Conclusions and future perspectives

The results of the studies included in this thesis gives information of an overlooked aspect of psoriasis. We identified that clinically important fatigue is common among patients. Fatigue was strongly associated with pain and depression. This thesis also aimed to increase the understanding of biological mechanisms for fatigue in the context of sickness behavior. Although, several studies have indicated activation of the innate immune system, especially IL- Iβ, as important fatigue generating mechanisms, we could not reveal a relation between blood circulating cytokines and fatigue nor between measures of oxidative stress and fatigue. A plausible explanation is that fatigue is not influenced by the peripheral inflammatory profile and that signalling molecules in low concentrations in blood do not reach the brain through BBB. Another hypothesis is that the complex behavioral aspect of chronic inflammation has its biological fundament in protective mechanisms against inflammation like the heat shock response. Our study is the first to reveal altered expression of selected HSP genes between psoriasis patients with high and low fatigue. Furthermore, we demonstrated a low to moderate effect of anti-inflammatory biological drugs used for treatment of psoriasis on fatigue.

Our studies can inspire future studies on fatigue in psoriasis which in turn may lay foundation for further research into therapeutic possibilities of this phenomenon. Challenges for these studies would be to design larger cohorts and to include patients with more severe psoriasis disease. Additionally, it is desirable to confirm alteration of gene expressions related to fatigue on a protein level and especially perform CSF analyses of candidate molecules. Our study was cross-sectional and follow up changes were not evaluated. Longitudinal studies could potentially follow changes in severity of fatigue, therapeutic response to anti-inflammatory and immunosuppressive drugs and associated molecular changes over time.

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8. Appendix

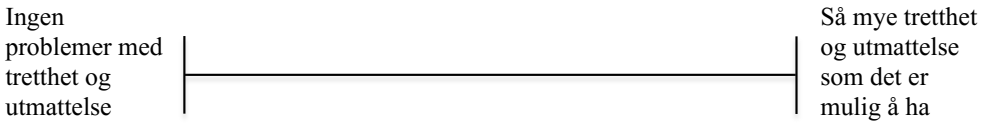
8.1 Fatigue Visual Analog Scale

Tretthet og utmattelse

Dette spørreskjemaet spør om hvordan du har opplevd følelse av tretthet og utmattelse den siste uken.

Linjen nedenfor er et mål på hvor mye tretthet og utmattelse du har opplevd den siste uken. Helt til venstre på linjen er "ingen problemer med tretthet og utmattelse" og helt til høyre er "så mye tretthet og utmattelse som det er mulig å ha".

Vi ber deg sette et merke med blyant eller penn på linjen nedenfor som passer med den følelse av tretthet og utmattelse som du har.



8.2 Fatigue Severity Scale

Skala for tretthet og utmattelse (fatigue severity scale)

Dette skjemaet utfylles av forsøkspersonen under veiledning av intevjuer. Til høyre for hver påstand skal det skrives et tall. Velg et tall fra 1 til 7, der 1 betyr *helt uenig med påstanden* og 7 betyr *helt enig med påstanden*.

		Tall
1.	Mitt pågangsmot blir dårligere når jeg er utmattet	____
2.	Jeg blir fort utmattet ved anstrengelser	____
3.	Jeg har lett for å bli utmattet	____
4.	Utmattelse nedsetter min fysiske funksjonsevne	____
5.	Utmattelse skaper ofte problemer for meg	____
6.	Utmattelse fører til at jeg har dårlig fysisk utholdenhet over lengre tid	____
7.	Utmattelse virker negativt inn på mine gjøremål og forpliktelser	____
8.	Utmattelse er ett av mine tre mest plagsomme symptomer	____
9.	Utmattelse virker negativt inn på mitt arbeid, min familie og mitt øvrige sosiale liv	____

Ikke skriv under denne linjen
IKM/UiTø 1995

Mean: ____

8.3 Short Form 36 Health Survey

SF-36 SPØRRESKJEMA OM HELSE
INSTRUKSJON: Dette spørreskjemaet spør om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål skal besvares ved å krysse av det alternativet som passer best for deg. Hvis du er usikker på hva du skal svare, vennligst svar så godt du kan.

SF

1 Stort sett, vil du si helsen din er:

(Kryss av ett alternativ)
1 ☐ Utmerket
2 ☐ Meget god
3 ☐ God
4 ☐ Ganske god
5 ☐ Dårlig

1

2 Sammenlignet med for ett år siden, hvordan vil du si helsen din stort sett er nå?

(Kryss av ett alternativ)
1 ☐ Mye bedre nå enn for ett år siden
2 ☐ Litt bedre nå enn for ett år siden
3 ☐ Omtrent den samme som for ett år siden
4 ☐ Litt dårligere nå enn for ett år siden
5 ☐ Mye dårligere nå enn for ett år siden

2

3 De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er helsen din slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

	(Kryss av ett alternativ på hver linje) **Ja, begrenser meg mye**	**Ja, begrenser meg litt**	**Nei, begrenser meg ikke i det hele tatt**	
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	1 ☐	2 ☐	3 ☐	3-12
b. Moderate aktiviteter som å flytte et bord, støvsuge, gå tur eller drive med hagearbeid	1 ☐	2 ☐	3 ☐	
c. Løfte eller bære en handlekurv	1 ☐	2 ☐	3 ☐	
d. Gå opp trappen flere etasjer	1 ☐	2 ☐	3 ☐	
e. Gå opp trappen en etasje	1 ☐	2 ☐	3 ☐	
f. Bøye deg eller sitte på huk	1 ☐	2 ☐	3 ☐	
g. Gå mer enn to kilometer	1 ☐	2 ☐	3 ☐	
h. Gå noen hundre meter	1 ☐	2 ☐	3 ☐	
i. Gå hundre meter	1 ☐	2 ☐	3 ☐	
j. Vaske deg eller kle på deg	1 ☐	2 ☐	3 ☐	

4 I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

(Kryss av ett alternativ på hver linje)

	JA	NEI	
a. Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter	1 ☐	0 ☐	13
b. Har du utrettet mindre enn du hadde ønsket	1 ☐	0 ☐	14
c. Har du vært hindret i visse typer arbeid eller andre aktiviteter	1 ☐	0 ☐	15
d. Har du hatt vanskeligheter med å utføre arbeidet ditt eller andre aktiviteter (f.eks. fordi det krevde ekstra anstrengelser)	1 ☐	0 ☐	16

5 I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (f.eks. fordi du har følt deg deprimert eller engstelig)?

(Kryss av ett alternativ på hver linje)

	JA	NEI	
a. Har du redusert tiden du har brukt på arbeidet ditt eller andre aktiviteter	1 ☐	0 ☐	17
b. Har du utrettet mindre enn du hadde ønsket	1 ☐	0 ☐	18
c. Har ikke arbeidet eller utført andre aktiviteter like nøye som vanlig	1 ☐	0 ☐	19

6 I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger? (Kryss av ett alternativ) 20

1 ☐ Ikke i det hele tatt
2 ☐ Litt
3 ☐ En del
4 ☐ Mye
5 ☐ Svært mye

7 Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene? (Kryss av ett alternativ) 21

1 ☐ Ingen
2 ☐ Meget svake
3 ☐ Svake
4 ☐ Moderate
5 ☐ Sterke
6 ☐ Meget sterke

8 I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)? (Kryss av ett alternativ) 22

1 ☐ Ikke i det hele tatt
2 ☐ Litt
3 ☐ En del
4 ☐ Mye
5 ☐ Svært mye

9 De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

(Kryss av ett alternativ på hver linje)

	Hele tiden	Nes-ten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. Følt deg full av tiltakslyst?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
b. Følt deg veldig nervøs?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
c. Vært så langt nede at ingenting har kunnet muntre deg opp?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
d. Følt deg rolig og harmonisk?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
e. Hatt mye overskudd?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
f. Følt deg nedfor og trist?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
g. Følt deg sliten?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
h. Følt deg glad?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
i. Følt deg trett?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

10 I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

(Kryss av ett alternativ)
1 ☐ Hele tiden
2 ☐ Nesten hele tiden
3 ☐ En del av tiden
4 ☐ Litt av tiden
5 ☐ Ikke i det hele tatt

11 Hvor RIKTIG eller GAL er hver av de følgende påstander for deg?

(Kryss av ett alternativ på hver linje)

Påstander om din helse	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
a. Det virker som om jeg blir lettere syk enn andre	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b. Jeg er like frisk som de fleste jeg kjenner	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c. Jeg forventer at helsen min vil bli dårligere	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d. Helsen min er utmerket	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

80
83

8.4 Hospital Anxiety and Depression Scale

HAD

Hospital Anxiety & Depression Scale (januar 1999)

Navn: _____ Fødselsdato: _____

Dato for utfylling: _____ Pasient nr.: _____

Behandler: _____

Rettledning

Legen er klar over at følelser spiller en stor rolle ved de fleste sykdommer. Hvis legen vet mer om følelser, vil han/hun bli bedre i stand til å hjelpe deg.

Her kommer noen spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret – de spontane svarene er best.

1. Jeg føler meg nervøs og urolig

- ❑ 3 Mesteparten av tiden
- ❑ 2 Mye av tiden
- ❑ 1 Fra tid til annen
- ❑ 0 Ikke i det hele tatt

2. Jeg gleder meg fortsatt over tingene slik jeg pleide før

- ❑ 0 Avgjort like mye
- ❑ 1 Ikke fullt så mye
- ❑ 2 Bare lite grann
- ❑ 3 Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig vil skje

- ❑ 3 Ja, og noe svært ille
- ❑ 2 Ja, ikke så veldig ille
- ❑ 1 Litt, bekymrer meg lite
- ❑ 0 Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner

- ❑ 0 Like mye nå som før
- ❑ 1 Ikke like mye nå som før
- ❑ 2 Avgjort ikke som før
- ❑ 3 Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer

- ❑ 3 Veldig ofte
- ❑ 2 Ganske ofte
- ❑ 1 Av og til
- ❑ 0 En gang i blant

6. Jeg er i godt humør

- ❑ 3 Aldri
- ❑ 2 Noen ganger
- ❑ 1 Ganske ofte
- ❑ 0 For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet

- ❑ 0 Ja, helt klart
- ❑ 1 Vanligvis
- ❑ 2 Ikke så ofte
- ❑ 3 Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere

- ❑ 3 Nesten hele tiden
- ❑ 2 Svært ofte
- ❑ 1 Fra tid til annen
- ❑ 0 Ikke i det hele tatt

9. Jeg føler meg urolig som om jeg har sommerfugler i magen

- ❑ 0 Ikke i det hele tatt
- ❑ 1 Fra tid til annen
- ❑ 2 Ganske ofte
- ❑ 3 Svært ofte

10. Jeg bryr meg ikke lenger om hvordan jeg ser ut

- ❑ 3 Ja, jeg har sluttet å bry meg
- ❑ 2 Ikke som jeg burde
- ❑ 1 Kan hende ikke nok
- ❑ 0 Bryr meg som før

11. Jeg er rastløs som om jeg stadig må være aktiv

- ❑ 3 Uten tvil svært mye
- ❑ 2 Ganske mye
- ❑ 1 Ikke så veldig mye
- ❑ 0 Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

- ❑ 0 Like mye som før
- ❑ 1 Heller mindre enn før
- ❑ 2 Avgjort mindre enn før
- ❑ 3 Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

- ❑ 3 Uten tvil svært ofte
- ❑ 2 Ganske ofte
- ❑ 1 Ikke så veldig ofte
- ❑ 0 Ikke i det hele tatt

14. Jeg kan glede meg over gode bøker, radio og TV

- ❑ 0 Ofte
- ❑ 1 Fra tid til annen
- ❑ 2 Ikke så ofte
- ❑ 3 Svært sjelden

Takk for utfyllingen!

Sum A:

1+3+5+7+9+11+13= _____

Sum D:

2+4+6+8+10+12+14= _____

Sum A + D: _____

8.5 Dermatology Life Quality Index

Hensikten med dette spørreskjemaet er å finne ut hvor mye hudproblemene dine har påvirket livet ditt **DEN SISTE UKEN**. Vær vennlig å krysse av ett svar for hvert spørsmål.

Sykehusnr. Dato: Score:
Navn:
Adresse: Diagnose:

Formålet med dette spørreskjemaet er å vurdere i hvilken grad hudproblemene dine har påvirket din livssituasjon I LØPET AV DEN SISTE UKEN. Vennligst sett en hake i en av boksene for hvert spørsmål.

1. I hvilken grad har du hatt **kløe, sårhet, smerte** eller **sviing** i huden den siste uken?

   Veldig mye ❒
   Mye ❒
   Lite ❒
   Ikke i det hele tatt ❒

2. I hvilken grad har du følt deg **brydd** eller **forlegen** p.g.a. huden din den siste uken?

   Veldig mye ❒
   Mye ❒
   Lite ❒
   Ikke i det hele tatt ❒

3. I hvilken grad har huden din hindret deg i **å gå i butikker** eller **gjøre hus- eller hage arbeide** den siste uken?

   Veldig mye ❒
   Mye ❒
   Lite ❒
   Ikke i det hele tatt ❒
   Ikke aktuelt ❒

4. I hvilken grad har huden din påvirket **klesvalget** ditt den siste uken?

   Veldig mye ❒
   Mye ❒
   Lite ❒
   Ikke i det hele tatt ❒
   Ikke aktuelt ❒

5. I hvilken grad har huden din hatt innvirkning på ditt **sosiale liv** eller dine **fritidsaktiviteter** den siste uken?

   Veldig mye ❒
   Mye ❒
   Lite ❒
   Ikke i det hele tatt ❒
   Ikke aktuelt ❒

6. I hvilken grad har huden din gjort det vanskelig for deg å utføre **sportslige aktiviteter** den siste uken?

Veldig mye ❒
Mye ❒
Lite ❒
Ikke i det hele tatt ❒
Ikke aktuelt ❒

7. Har huden din forhindret deg i å **arbeide** eller å **studere** den siste uken?
Ja ❒
Nei ❒
Ikke aktuelt ❒

Hvis "Nei", hvor mye problemer har du hatt pga huden når du har **arbeidet** eller **studert** den siste uken?

Mye ❒
Lite ❒
Ikke i det hele tatt ❒

8. I hvilken grad har huden din skapt problemer i forhold til **partneren din** eller noen av dine **nærmeste venner** eller **slektninger** den siste uken?

Veldig mye ❒
Mye ❒
Lite ❒
Ikke i det hele tatt ❒
Ikke aktuelt ❒

9. I hvilken grad har huden din ført til **seksuelle problemer** for deg den siste uken?

Veldig mye ❒
Mye ❒
Lite ❒
Ikke i det hele tatt ❒
Ikke aktuelt ❒

10. I hvilken grad har **behandlingen** av huden din vært et problem for deg den siste uken? f. eks. ved å tilgrise hjemmet ditt, eller ved at det har tatt mye av din tid?

Veldig mye ❒
Mye ❒
Lite ❒
Ikke i det hele tatt ❒
Ikke aktuelt ❒

9. Original publications

I

REVIEW ARTICLE

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Fatigue in psoriasis: a phenomenon to be explored*

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Summary

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 consider 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-1β, IL-6 and tumour necrosis factor (TNF)-α.[23,26] Among these cytokines, IL-1β seems to have a pivotal role.[27] IL-1β possesses an early and strong proinflammatory effect and is secreted mainly by activated monocytes, macrophages and dendritic cells.[28–30] IL-1β 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-1β in promoting sickness

behaviour. IL-1β 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-1β 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-1β.[31] All these observations point strongly to IL-1β 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 sclerosis[54] 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	($P < 0{\cdot}001$)[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. [a]Scores 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] Tyring *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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Fatigue in psoriasis: a controlled study

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Summary

Background Fatigue is associated with various chronic inflammatory diseases, but few studies have focused on its occurrence in psoriasis.

Objectives To describe fatigue prevalence and degree among patients with chronic plaque psoriasis vs. age- and sex-matched healthy subjects, and to examine how fatigue is influenced by essential clinical and demographic factors.

Methods In 84 patients and 84 healthy subjects, fatigue severity was assessed using three different generic fatigue instruments: the fatigue Visual Analogue Scale (fVAS), the Fatigue Severity Scale (FSS) and the Short Form 36 (SF-36) Vitality scale. Cut-off scores for clinically important fatigue were defined as ≥ 4 for FSS, ≥ 50 for fVAS and ≤ 35 for the SF-36 Vitality scale. Disease activity was evaluated using the Psoriasis Area and Severity Index (PASI), and the impact on quality of life with the Dermatology Life Quality Index (DLQI).

Results Patients and healthy control subjects, respectively, showed median fVAS scores of 51 [interquartile range (IQR) 21–67] and 11 (IQR 3–20); FSS scores of 4 (IQR 2·5–5·3) and 1·6 (IQR 1·1–2·2); and SF-36 Vitality scores of 43 (IQR 25–85) and 73 (IQR 65–85). The rates of clinically important fatigue among patients vs. healthy controls, respectively, were 51% vs. 4% (fVAS); 52% vs. 4% (FSS); and 42% vs. 2% (SF-36 Vitality) ($P < 0{\cdot}001$ for all differences). Fatigue was associated with DLQI scores, but not PASI scores, in univariate analysis but not in multivariate analysis.

Conclusions Nearly 50% of patients with psoriasis suffered from substantial fatigue. Fatigue severity was associated with smoking, pain and depression, but not with psoriasis severity.

What's already known about this topic?

- Fatigue is prevalent in patients with chronic inflammatory diseases, cancer and some neurological diseases.
- Depressive mood and pain are strong factors influencing fatigue.
- Emerging evidence points to genes and molecular signalling pathways as important contributors to fatigue.

What does this study add?

- Clinically significant fatigue occurs in nearly 50% of patients with psoriasis.
- Objective measures of psoriasis disease activity do not correlate with fatigue severity.
- There is a need for more research to understand the factors that generate and regulate fatigue in psoriasis.

Fatigue, defined as 'an overwhelming sense of tiredness, lack of energy, and a feeling of exhaustion',[1] is a prevalent phenomenon among many patients with chronic inflammatory and autoimmune conditions, such as inflammatory bowel disease, rheumatoid arthritis, primary Sjögren syndrome and systemic lupus erythematosus.[2–4] In fact, patients with these conditions often identify fatigue as the most troublesome aspect of their disease, as it interferes with physical and social activities and frequently leads to social withdrawal and long-term sick leave.[5]

In clinical experience, fatigue is a common complaint among many patients with the chronic inflammatory immune-mediated disease psoriasis. However, few studies have explored this association in depth, and the majority of available data are from therapeutic clinical trials investigating new biological agents. Such studies often include patients with psoriatic arthritis, a condition that could possibly influence the severity of fatigue. There remains a lack of unbiased investigations focusing on how fatigue presents and is experienced by patients with psoriasis alone.

Fatigue associated with other diseases is clearly influenced by pain and depression, but such a relationship is not documented in psoriasis. Moreover, the impact of disease activity on fatigue in inflammatory diseases remains a controversial issue. Some investigators claim that fatigue increases with high disease activity, while others have not confirmed such a relationship.[6–11] This issue has not yet been thoroughly studied in patients with psoriasis. Thus, there remains a need to elucidate the extent and severity of fatigue in psoriasis, and to uncover any genetic basis and signalling mechanisms that lead to fatigue.[12]

Here we performed a controlled study with the aim of describing fatigue prevalence and severity among patients with chronic plaque psoriasis. We further investigated how fatigue was related to essential clinical and demographic factors.

Patients and methods

Patients

Eligible patients were consecutively identified based on referral letters to the outpatient clinic, Department of Dermatology, Stavanger University Hospital, from 6 November 2012 to 19 May 2015. Additionally, three patients were recruited from the follow-up clinic. The inclusion criteria were white Norwegian-speaking individuals, age > 18 years and a clinical diagnosis of chronic plaque-type psoriasis. Patients were excluded if they had other types of psoriasis (guttate, unless associated with a typical plaque of psoriasis; erythrodermic; or pustular psoriasis), or prior history of cancer, psoriatic arthritis, chronic inflammatory diseases other than psoriasis, or untreated hyper- or hypothyroidism. Written information about the study was posted to the patients prior to their scheduled outpatient appointment.

A total of 120 patients were screened for potential participation; of these 84 were included (Fig. 1).

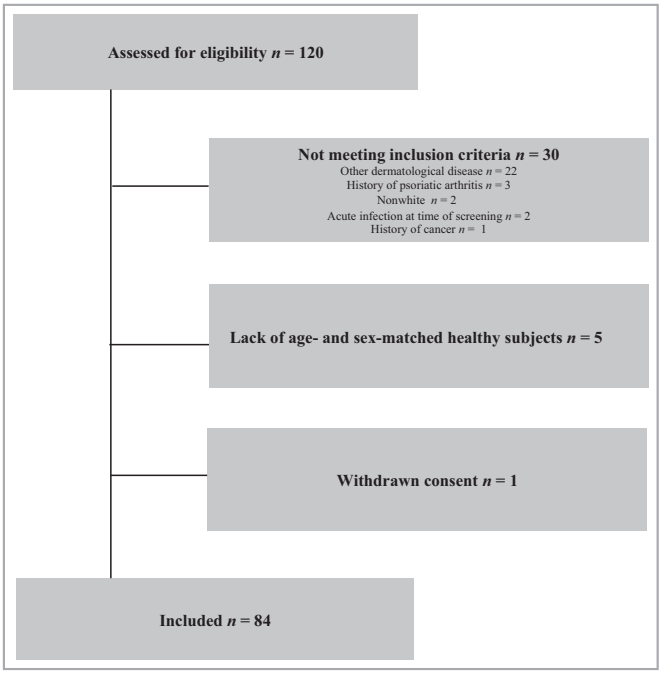

Fig 1. Flowchart of included patients.

Healthy subjects

The 84 healthy control subjects were predominantly recruited from acquaintances of the patients. Some control subjects (8%) were also recruited from employees of the service division of the hospital and their acquaintances. The healthy control subjects were matched by age (± 3 years) and sex with the individual patients, and fulfilled the same inclusion and exclusion criteria as the patients, except for the diagnosis of psoriasis.

Demographic and selected clinical data

The patient and control groups were similar with regard to education level, marital status and comorbidities, except for hypertension (Table 1). Compared with healthy controls, patients exhibited a somewhat higher body mass index (BMI) and significantly higher rate of smoking. Median [interquartile range (IQR)] Psoriasis Area and Severity Index (PASI) score was 6·0 (4·5–7·3) and Dermatology Life Quality Index (DLQI) score was 10 (6–13). Among the patients, 70% had a PASI score < 7, indicating mild disease.[13] Only two patients were taking oral medication (methotrexate or acitretin). The remaining 82 patients received, at most, topical treatment, but no systemic treatment. All except for one were naïve to biological medications. Disease duration of > 10 years was reported by 73% of the patients.

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or receiving antihypertensive therapy at the time of examination. Other comorbidities were also noted, including history of diabetes, overt cardiovascular disease (e.g. myocardial infarction, angina pectoris, stroke, transient ischaemic attack or cardiac dysrhythmia), migraine or respiratory disease (e.g. asthma or chronic obstructive pulmonary disease).

Clinical assessment and disease activity

All participants underwent a general clinical examination during which we collected demographic and clinical data, and recorded information about medical history, current medication and tobacco smoking (Table 1).

Psoriasis severity was evaluated using the PASI.[14] The PASI assesses psoriasis severity and extent by accounting for the percentage area affected by psoriasis in four body regions (head and neck, upper limbs, trunk and lower limbs), as well as the intensity of the plaque redness, thickness and scaling. The final PASI result is a single severity score ranging from 0 to 72.[13] Severity has been categorized as follows: PASI < 7 indicates mild plaque psoriasis; PASI 7–12 indicates moderate plaque psoriasis; and PASI > 12 indicates severe psoriasis.[13]

The DLQI is a patient-reported outcome measuring the impact of the dermatological disease on the patient's quality of life (QoL). The DLQI is simple, practical and widely used instrument consisting of a 10-item questionnaire that evaluates the impact of skin disease on QoL with a score ranging from 0 (no impairment) to 30 (maximal impairment). A DLQI > 10 implies a skin disease with a considerable influence on the patient's QoL.[15]

Table 1 Demographic and clinical characteristics of the subjects

	Patients with psoriasis (n = 84)	Control subjects (n = 84)	P-value
Demographics			
Mean ± SD age (years)	45 ± 14	45 ± 14	
Male sex	51 (61)	51 (61)	
Median (IQR) psoriasis duration (years)	14 (8–24)		
Current smoking	25 (30)	13 (15)	0·04
Educational status (college/university)	35 (42)	46 (55)	0·07
Married/common-law	61 (73)	65 (77)	0·59
Clinical data			
Median (IQR) BMI (kg m^{-2})	27 (24–30)	26 (23–29)	0·04
Median (IQR) PASI	6·0 (4·5–7·3)		
PASI < 7	59 (70)		
Median (IQR) DLQI	10 (6–13)		
Biochemical data			
Median (IQR) CRP (mg L^{-1})	2 (0·7–4·9)	1·3 (0·5–3·3)	0·05
Median (IQR) Hb (g 100 mL^{-1})	15 (14–16)	15 (14–16)	0·72
Median (IQR) GFR (mL min^{-1} 1·73 m^{-2})	98 (89–108)	96 (81–109)	0·10
Comorbid disease			
Hypertension	44 (52)	28 (33)	0·01
Diabetes	4 (5)	1 (1)	0·38
CVD	5 (6)	1 (1)	0·22
Respiratory disease	8 (10)	5 (6)	0·58
Depression (HADS-D ≥ 8)[a]	20 (24)	1 (1)	< 0·001
Medication			
Antidepressants	4 (5)	0 (0)	0·13
Levothyroxine	1 (1)	0 (0)	1·00
Immunosuppressive drugs	2 (2)	0 (0)	0·50
Beta blockers	8 (10)	2 (2)	0·11

Data are n (%) unless otherwise indicated. IQR, interquartile range; BMI, body mass index; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; CRP, C-reactive protein; Hb, haemoglobin, GFR, glomerular filtration rate; CVD, cardiovascular disease; HADS-D, depression subscale of the Hospital Anxiety and Depression Scale. [a]n = 82.

Fatigue measures

Fatigue severity was assessed using three different generic and unidimensional fatigue instruments: the fatigue Visual Analogue Scale (fVAS);[16] the Fatigue Severity Scale (FSS);[17] and the Vitality subscale of the Short Form 36 (SF-36 Vitality).[18]

During the examinations of the subjects, information was given about comprehension of the questions and how to score the fatigue instruments.

The FSS is an instrument that includes nine statements regarding the patient's fatigue over the last 2 weeks. To each item, the patients assign a score of between 1 (completely disagree) and 7 (completely agree), and these scores are summed and divided by nine to generate the FSS score. A higher FSS score indicates greater fatigue. An FSS score of 3 or 4 has been used as the cut-off to define clinically important fatigue. In the present study, we applied a conservative cut-off score of ≥ 4.[19]

The fVAS utilizes a 100-mm-long horizontal line with vertical anchoring lines labelled 'no fatigue' at the left end (0 mm) and 'worst possible fatigue' at the right end (100 mm). Patients are asked to rate their fatigue level by placing a marker at the point along the line that best represents their perception of fatigue over the last week. In this study, we used a conservative cut-off value, with clinically important fatigue defined by an fVAS score of ≥ 50 mm.[20]

The vitality subscale of the SF-36 questionnaire comprises four questions about energy and fatigue. The subscale score is calculated according to standard procedures, yielding score values between 0 to 100, with higher scores indicating greater functioning.[21] Clinically important fatigue was defined by a vitality score of ≤ 35, in accordance with previous data showing that this cut-off indicates relevant fatigue.[22]

Depression and pain

To detect concomitant depressive mood, we used the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D).[23] The HADS questionnaire comprises seven items on anxiety and seven on depression, which are each answered with a number from 0 to 3, and these responses are summed to obtain the anxiety and depression subscales, respectively. A score of ≥ 8 indicates possible depression and a score of ≥ 11 indicates probable depression. A HADS-D score of ≥ 8 was previously found to be adequate as a cut-off for depression and was used as the cut-off in this study.[24]

Pain was assessed using the bodily pain subscale of the SF-36 (SF-36 Pain). The SF-36 Pain is a two-item scale that assesses bodily pain intensity and the interference of pain with normal activities during the last 4 weeks. The score ranges from 0 to 100, with higher scores representing less pain.[25]

Statistical analyses

Our calculations revealed that we required a minimum sample size of 33 patients and 33 healthy subjects to detect a meaningful difference in fatigue measured as a fVAS score of 25, with a power of 80 and significance of 5%. We considered this a robust measure as a prior study of primary Sjögren syndrome had applied a 20% reduction in fVAS score.[26]

Most continuous descriptive data were not normally distributed, and are thus presented as median (IQR) and as n (%) for categorical data. For comparisons between two groups of paired data, we used the Wilcoxon signed-rank test for continuous data and the McNemar test for categorical data. Associations between fatigue and possible influential factors were first assessed using linear regression models for determination of estimated effect (beta) and 95% confidence interval (CI), P-value for hypotheses of no effect and R^2 value to evaluate model fit. Variables that showed P-values $< 0{\cdot}25$ in univariate analyses were subsequently included in multiple regression analyses. The final regression model included only explanatory variables with a P-value $< 0{\cdot}05$ in stepwise backward selection, and it was determined that no excluded variable would attain this level of significance and/or substantially change other effect estimates when subsequently included in forward selection. Most statistical analyses were performed using SPSS Statistics version 23 (IBM, Armonk, NY, U.S.A.). In situations with zero count categories, McNemar tests were performed using Vassarstats online calculator (http://vassarstats.net/propcorr.html).

All three fatigue instruments were used to assess fatigue severity and prevalence among patients and healthy subjects. However, as visual analogue scales are considered to provide a more optimal scoring spread, fVAS was used for further statistical analyses. Regression analyses applying FSS and SF-36 Vitality as dependent variables are given in Tables S1 and S2 (see Supporting Information). The analyses excluded data for one patient and one healthy subject owing to missing HADS-D scores.

Ethical considerations

This study was approved by the Regional Committee for Medical Research Ethics in Norway (REK vest 2010/1455). All participants gave their written informed consent, and the study was conducted in accordance with the latest revision of the Declaration of Helsinki.

Results

Fatigue severity and prevalence

On all three fatigue instruments utilized, patients showed significantly higher fatigue scores than age- and sex-matched healthy subjects. In the patients and healthy subjects, respectively, median fVAS scores were 51 (21–67) and 11 (3–20); FSS scores were 4 (2·5–5·3) and 1·6 (1·1–2·2); and SF-36 Vitality subscale scores were 43 (25–55) and 73 (65–85) (Fig. 2). Based on the defined cut-off values, the rates of clinically important fatigue in patients vs. healthy subjects, respectively, were 51% vs. 4% (fVAS); 52% vs. 4% (FSS); and 42% vs. 2% (SF-36 Vitality), with all differences being highly significant ($P < 0{\cdot}001$) (Fig. 3). No difference in fatigue prevalence was seen between patients with mild disease (PASI < 7) vs. moderate-to-severe disease (PASI ≥ 7) ($P = 0{\cdot}92$).

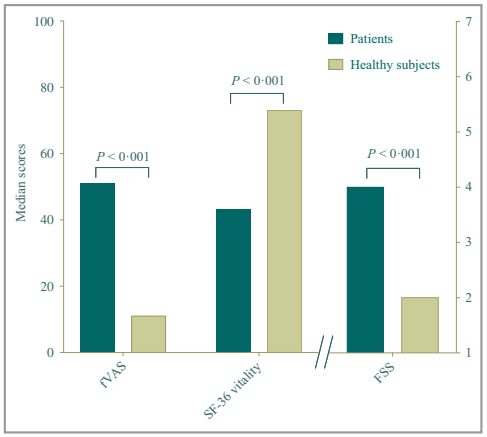

Fig 2. Median fatigue Visual Analogue Scale (fVAS), Short Form 36 (SF-36) Vitality and Fatigue Severity Scale (FSS) scores measured in the 84 patients with psoriasis compared with 84 age- and sex-matched healthy subjects.

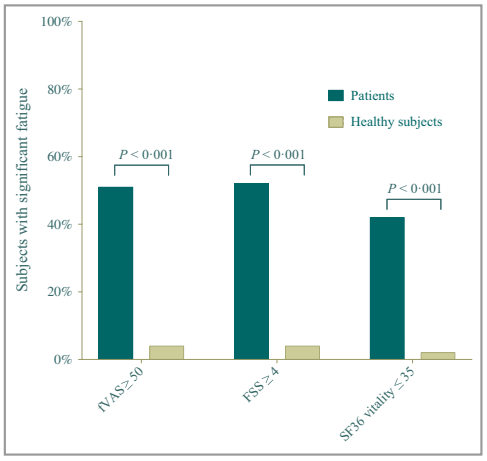

Fig 3. Percentages of subjects with clinically important fatigue, as determined using fatigue Visual Analogue Scale (fVAS), Fatigue Severity Scale (FSS) and Short Form 36 (SF-36) Vitality, among the 84 patients with psoriasis and the 84 age- and sex-matched healthy subjects.

Factors associated with fatigue (fatigue Visual Analogue Scale)

Selected demographic and clinical variables were tested in univariate analyses (Table 2). Fatigue was associated with smoking, DLQI, SF-36 Pain and HADS-D, and was not associated with age, sex, psoriasis duration, education level, BMI, C-reactive protein (CRP), haemoglobin, hypertension or other comorbidities, or PASI scores.

Table 2 Associations between fatigue Visual Analogue Scale and selected demographic and clinical variables among patients with psoriasis (n = 83)[a]

	β	95% CI	P-value
Demographics			
Age (years)	−0·28	−0·72 to 0·15	0·20
Male sex	1·92	−10·54 to 14·38	0·76
Psoriasis duration (years)	−0·01	− 0·51 to 0·48	0·96
Current smoking	14·94	1·98–27·91	0·02
Education level (college/university)	−4·33	−16·59 to 7·91	0·48
Clinical data			
BMI (kg m^{-2})	−0·42	−1·38 to 0·53	0·38
PASI	0·28	−1·54 to 2·10	0·76
DLQI	2·01	1·11 to 2·91	< 0·001
Biochemical data			
CRP (mg L^{-1})	0·06	−1·30 to 1·41	0·94
Hb (g 100 mL^{-1})	2·63	−2·79 to 8·04	0·34
Comorbid disease			
Hypertension	1·51	−10·64 to 13·66	0·81
Diabetes	−2·46	−30·78 to 25·86	0·86
CVD	0·71	−24·79 to 26·20	0·96
Respiratory disease	6·13	−14·38 to 26·64	0·55
Pain			
SF-36 Pain	−0·55	−0·76 to −0·34	< 0·001
Mood disturbance			
HADS-D	4·24	2·81–5·67	< 0·001

Results from univariate linear regression analyses. CI, confidence interval; BMI, body mass index; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; CRP, C-reactive protein; Hb, haemoglobin; CVD, cardiovascular disease; SF-36 Pain, Short Form 36 Bodily Pain Scale; HADS-D, the depression subscale of the Hospital Anxiety and Depression Scale. [a]One patient excluded owing to missing HADS-D score.

Table 3 Factors associated with fatigue Visual Analogue Scale for patients with psoriasis (n = 83)[a]

	β	95% CI	P-value
Current smoker	11·81	1·57–22·06	0·02
SF-36 Pain	−0·36	−0·56 to −0·16	0·001
HADS-D	3·11	1·68–4·54	< 0·001

Results from the final multiple linear regression model. Final model (n = 83), R^2 43%. CI, confidence interval; SF-36 Pain, Short Form 36 Bodily Pain Scale; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale. [a]One patient excluded owing to missing HADS-D score.

Variables with P-values < 0·25 were included in multiple regression analyses. Stepwise backward and forward model selection was used to construct a final multiple regression model (Table 3) that explained 43% of the variance in fatigue. In this model, higher fatigue was associated with current smoking, lower SF-36 Pain scores (more pain) and higher HADS-D scores. Fatigue was not associated with age, sex,

education level, BMI, CRP, haemoglobin, hypertension or other comorbidities, PASI scores or disease duration. Further, we observed no signs that any of these variables were important confounding factors for the variables in the final model. Notably, the significant positive association between fVAS and DLQI detected in univariate analyses disappeared following adjustment for the other variables.

The full model, including all of the tested variables listed in Table 2, explained 51% of the variance (Table 4). When smoking, SF-36 Pain, DLQI and HADS-D were excluded from the model, only 9% of the variance in fVAS was explained by demographic and objective clinical observations (age, sex, psoriasis duration, education level, BMI, PASI, CRP, haemoglobin, hypertension or other comorbidities) (Table 5). Inclusion of smoking and pain in the model explained an additional 4% and 32%, respectively.

Discussion

The major finding of the present study was that approximately 50% of patients with psoriasis suffered from fatigue, consistent with previous observations in other chronic inflammatory and autoimmune diseases.[2,4,27] This rate was considerably higher than the rate of fatigue among healthy age- and sex-matched individuals, indicating that fatigue is a prevalent problem associated with psoriasis. Our results were similar with all three fatigue instruments – fVAS, FSS and SF-36 Vitality – and thus provide a good estimation of the size of the problem.

Our second important finding was that objective measurements of disease activity and inflammatory variables, such as PASI and CRP, were not significantly associated with fatigue severity. This result is in agreement with prior studies that have applied generic and unidimensional fatigue instruments not containing the elements of disease-associated factors that are intrinsic to most disease-specific fatigue instruments. It is commonly thought that higher disease activity will correlate with greater fatigue. However, the lack of association between fatigue severity and disease activity or inflammatory variables suggests that the fatigue response may be controlled by pathways other than genuine proinflammatory pathways.

Emerging evidence suggests that the innate immune system may be an important 'fatigue generator'.[28–31] When pathogens or other danger signals activate innate immunity cells, proinflammatory cytokines cross the blood–brain barrier into the brain, triggering an evolutionarily conserved behavioural response (i.e. sickness behaviour), of which fatigue is a prominent feature. In chronic inflammatory conditions, this signalling is constantly active, leading to chronic fatigue.[32] As

Table 4 Fully adjusted associations between fatigue Visual Analogue Scale and selected demographic and clinical variables among patients with psoriasis (n = 83)[a]

	β	95% CI	P-value
Demographics			
Age (years)	−0·39	−0·87 to 0·09	0·11
Male sex	1·08	−12·91 to 15·07	0·89
Psoriasis duration (years)	−0·12	−0·60 to 0·35	0·60
Current smoking	10·52	−2·28 to 23·32	0·11
Education level (college/university)	4·54	−6·62 to 15·69	0·42
Clinical data			
BMI (kg m^{-2})	−0·67	−1·82 to 0·49	0·25
PASI	−0·79	−2·74 to 1·17	0·42
DLQI	0·28	−1·03 to 1·59	0·67
Biochemical data			
CRP (mg L^{-1})	0·91	−0·63 to 2·46	0·24
Hb (g 100 mL^{-1})	0·09	−5·77 to 5·94	0·98
Comorbid disease			
Hypertension	9·94	−2·44 to 22·32	0·11
Diabetes	−6·19	−30·26 to 17·88	0·61
CVD	4·13	−17·10 to 25·36	0·70
Respiratory disease	10·06	−8·37 to 28·48	0·28
Pain			
SF-36 Pain	−0·41	−0·69 to −0·13	0·005
Mood disturbance			
HADS-D	2·87	1·11–4·62	0·002

Results from the linear regression model, including all candidate variables. Full model (n = 83), R^2 51%. CI, confidence interval; BMI, body mass index; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; CRP, C-reactive protein; CVD, cardiovascular disease; SF-36 Pain, Short Form-36 Bodily Pain Scale; HADS-D, Depression subscale of the Hospital Anxiety and Depression Scale. [a]One patient excluded owing to missing HADS-D score.

Table 5 Adjusted associations between fatigue Visual Analogue Scale and the candidate variables for the patients with psoriasis (n = 83)[a] when current smoking, Short Form 36, Dermatology Quality Life Index, and Hospital Anxiety and Depression Scale are excluded

	β	95% CI	P-value
Demographics			
Age (years)	−0·50	−1·08 to 0·09	0·09
Male sex	−3·19	−20·33 to 13·10	0·71
Psoriasis duration (years)	0·27	−0·32 to 0·85	0·37
Education level (college/university)	−3·81	−17·47 to 9·85	0·58
Clinical data			
BMI (kg m^{-2})	−1·16	−2·62 to 0·31	0·12
PASI	0·42	−1·62 to 2·46	0·68
Biochemical data			
CRP (mg L^{-1})	1·09	−0·95 to 3·13	0·29
Hb (g 100 mL^{-1})	2·74	−4·68 to 10·16	0·46
Comorbid disease			
Hypertension	7·47	−8·58 to 23·52	0·36
Diabetes	2·95	−28·30 to 34·20	0·85
CVD	1·57	−26·15 to 29·30	0·91
Respiratory disease	12·75	−10·42 to 35·92	0·28

Results from multiple linear regression analysis. Full model (n = 83), R^2 9%. CI, confidence interval; BMI, body mass index; PASI, Psoriasis Area and Severity Index; CRP, C-reactive protein; Hb, haemoglobin; CVD, cardiovascular disease. [a]One patient excluded owing to missing HADS-D score.

inflammation is upregulated, mechanisms immediately start to control and downregulate this response. Immune downregulation and cellular defence mechanisms against oxidative stress and other dangers could potentially act as redundant and strong triggers of fatigue. This hypothesis is supported by our recent finding of elevated heat shock protein 90α levels in patients with severe fatigue.[30]

Another observation that may support this theory is that smokers reported more fatigue than nonsmokers. Others have also reported this association.[33] Smoking causes oxidative stress, with subsequent increases of antioxidative defence and other mechanisms to protect cellular life. Fatigue is associated with oxidative stress in many chronic inflammatory disorders.[34] On a pathophysiological level, this may contribute to the greater prevalence of fatigue among smokers. However, history of depression is more common among smokers than nonsmokers, and this relationship could also contribute to the association between smoking and fatigue.[35]

Fatigue was most strongly influenced by depressive mood and pain, which is a well-known constellation in both chronic inflammatory and noninflammatory disorders.[36,37] In the complex relationship between fatigue and depression, at least three interrelated factors are regarded as important. Firstly, there is an overlap in phenomenology between fatigue and depression. Secondly, questionnaires used to assess fatigue and depression often share similar wording, tapping more or less the same dimensions, and leading to a causal chain with a 'false' association between the two factors. Notably, compared with depression, fatigue seems to be less responsive to antidepressant treatment.[38] Thirdly, increasing evidence from animal and human studies suggests that depression and fatigue may be signalled through shared molecular pathways.[39,40]

Chronic pain influences feelings of energy and coping abilities, but the exact mechanisms that lead to fatigue remain unclear. The process may involve psychological and adaptive factors, including the development of depressive mood. In psoriasis, muscular and articular complaints frequently occur in the absence of clinical signs of arthritis, and are not related to psoriasis severity or extent.[41] Further studies are needed to explore the complex relationship between depressed mood, pain and fatigue in psoriasis, as well as in other conditions.

Fatigue was not associated with age or disease duration. This is in accordance with previous findings in patients with psoriatic arthritis and other chronic inflammatory diseases.[2,7] The present results also suggest that fatigue was independent of the extent and severity of skin inflammation. Psoriasis severity is defined by the signs and symptoms, disease history and the disease's effects on the patient's QoL. A patient with very few psoriasis plaques or limited psoriasis in special locations such as the scalp, genitals, hands and feet may nevertheless be devastated by the disease. Accepted clinical tools for defining psoriasis severity include the PASI, body surface area and the DLQI, which can be used individually or in combinations.[15,42,43] While the PASI is an objective measure of psoriasis severity, the DLQI includes elements related to mood, pain and fatigue. Thus, it is unsurprising that DLQI score covaried with fatigue in univariate analyses, and that this association disappeared when depressive mood and pain were introduced in the multiple regression analyses. The choice of an objective disease activity instrument is crucial for correctly interpreting the effects of psoriasis severity on fatigue.

One major strength of the current study was the matched case–control design that prevented confounding effects of age and sex. Additional strengths included the assessment using well-validated measures of fatigue, and the relatively large and well-characterized study population. All patients were interviewed and assessed by the same researcher, and were consecutively recruited from the same clinic. Moreover, all patients except for one were naïve to biological medication. The study also had several limitations. Firstly, the study patient population mainly comprised patients with psoriasis with PASI scores indicating mild disease. Another limitation was the lack of follow-up or repeated examination. Furthermore, we did not measure sleep disruption, itch or physical activity, which could potentially be important determinants of fatigue. We selected cut-off values that have been used in previous studies (VAS > 50, FSS > 4, SF-36 < 35), and the prevalence obtained with fVAS matched the results with SF-36 and FSS. However, the validity of these cut-off values is debatable, particularly as it is not logical to dichotomize this complex behavioural response into simply 'fatigue' or 'no fatigue'.

In conclusion, the present results indicate that nearly 50% of patients with psoriasis suffer from fatigue, and that fatigue was strongly associated with pain and depression. Fatigue was not significantly associated with markers of disease activity. These findings suggest a need to accept fatigue as an important and prevalent aspect of psoriasis. A better understanding of the link between psoriasis and fatigue could promote the development of better care and self-management options for these patients, and possibly lay the foundation for more effective therapeutic approaches in the future.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Associations between selected demographic and clinical variables among patients with psoriasis.

Table S2. Factors associated with fatigue for patients with psoriasis.

Video S1. Author video.

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