Fatigue in Psoriasis

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Inger Marie Skoie from the Department of Dermatology at Stavanger University Hospital defended her doctoral thesis titled *Fatigue in psoriasis: prevalence and biological methanisms* at the University of Bergen on June 18th, 2021 in Stavanger. Her supervisors were Roald Omdal, Thomas Ternowitz, Grete Jonsson and Katrine Brække Norheim. Petter Gjersvik and Arne Klungland, both from the University of Oslo, were first and second opponents. Available from: https://bora.uib.no/bora-xmlui/handle/11250/2826492.

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 behaviuoral 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 behaviour is signalled 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 behaviour 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.

The main aims of the thesis were to write a review article with focus on current knowledge, biological mechanisms and identifying research gaps on fatigue in psoriasis, to investigate and describe fatigue in chronic plaque-type psoriasis patients and to compare with age- and sex-matched healthy subjects to obtain a better understanding of the extent and severity of this phenomenon. Also, we wanted to estimate the efficacy of biological drugs on fatigue in psoriasis. Furthermore, we aimed to uncover biological processes and signalling pathways that cause fatigue in psoriasis.

From the public defence: From left to right: Hartwig Körner (acting dean), Inger Marie Skoie, Arne Klungland (2nd opponent; from behind) and Petter Gjersvik (1st opponent).

We found that fatigue is overlooked and an under-researched phenomenon in psoriasis (1). In a clinical study, fatigue was measured in 84 patients with chronic plaque-type and 84 age- and sex-matched healthy subjects (2). Nearly 50% of psoriasis patients reported to suffer from clinically important fatigue. Fatigue severity was associated with pain, depression and smoking, but not with psoriasis disease severity. In a systematic review and meta-analyses based on 8 randomized controlled trials, biological drugs had a small to moderate effect on fatigue in psoriasis (3).

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 (4). Plasma concentrations of AOPP and MDA were not associated with fatigue in psoriasis patients, but were strongly dependent on sex and other non-disease-related factors. In another study, plasma concentrations of IL-1β, IL-1Rα, IL-1RII, IL-6, and IL-10 were not associated with fatigue (5). In a third study, peripheral blood transcriptional profiles of heat shock protein (HSP) genes from 10 patients with high

fatigue and 10 patents with low fatigue were compared (6). The expression levels of 4 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 scores. Fatigue was found to be associated with altered expression of some HSPs. A tendency to higher expression levels of *HSPB11* and lower expression of *HSP90B1* was demonstrated in patients with high fatigue scores compared to those with low fatigue scores.

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

List of original publications

1. Skoie IM, Ternowitz T, Jonsson G, Norheim K, Omdal R. Fatigue in psoriasis: a phenomenon to be explored. Br J Dermatol 2015; 172: 1196–1203.
2. Skoie IM, Dalen I, Ternowitz T, Jonsson G, Kvivik I, Norheim K, et al. Fatigue in psoriasis: a controlled study. Br J Dermatol 2017; 177: 505–512.
3. Skoie IM, Dalen I, Omdal R. Effect of biological treatment on fatigue in psoriasis: A systematic review and meta-Aanalysis. Am J Clin Dermatol 2019; 20: 493–502.
4. 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; 311: 299–308.
5. 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; 30: 16–23.
6. 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. Manuscript.