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Effect of Daily Stressors on Psoriasis: A Prospective Study

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TO THE EDITOR

Many patients (37–88%) with psoriasis believe that there is a causal relationship between stressors and their skin disease (Gupta *et al.*, 1989; Nevitt and Hutchinson, 1996; Yosipovitch *et al.*, 2000; O'Leary *et al.*, 2004; Zachariae *et al.*, 2004; Fortune *et al.*, 1998, 2005), and this relationship has received increasing attention over the years (Pacan *et al.*, 2003; Reich *et al.*, 2003; Gaston *et al.*, 1991). Although some earlier studies have found that over 60% of the patients with psoriasis retrospectively report to have experienced stressful life events in the month before the exacerbation of their skin disease (Gupta *et al.*, 1988; Pacan *et al.*, 2003; Reich *et al.*, 2003), evidence for a prospective relationship between stressors and disease outcome is, thus far, lacking. The aim of this study is therefore to investigate the relationship between the experience of daily stressors and the change in disease outcome (disease severity and itch) 4 weeks later in patients with psoriasis. We hypothesized that only at moments of relatively high levels of daily stressors there would be a relationship between stressors and an increase in itch and disease severity 4 weeks later.

Participants for this study were recruited from the Departments of Dermatology at the University Medical Centre St Radboud and the Canisius Wilhelmina Hospital, Nijmegen, the Netherlands. This study was approved by relevant ethics committees and conducted according to the Helsinki principles. Written inform consent was obtained from all participants. For the purpose of this study, the participants were followed up for over 6 months with monthly measures of disease severity (Psoriasis Area and Severity Index (PASI); Frederiksson and Pettersson, 1978), itch impact of skin diseases on daily life (ISDL; Evers *et al.*, 2008), and daily stressors (everyday problem check list (EPCL); Dekkers *et al.*, 2001; Vingerhoets *et al.*, 1989). The study sample consisted of 62 patients with a mean age of 52.3 years (SD 13.2 years, range 21.9–79.7) at the start of the study. Of all the participants, 72.6% were male and 27.4% were female. Furthermore, 4.8, 66.1, and 29.1% of them had a primary, secondary, and tertiary education level, respectively. For each participant, the month in which the participant reported the most daily stressors (highest EPCL score), as well as the month in which they reported the least, (lowest EPCL score) was determined. Prospective relationships between daily stressors and changes in disease outcome 4 weeks later were subsequently examined by calculating Pearson's correlation coefficients between the EPCL daily stressor scores and the change in disease severity (PASI) and itch. For this purpose, residual gain scores were used to measure the change in PASI and itch. These scores take into account the individual baseline levels and the control for regression to the mean effects (Kerlinger, 1975).

Mean levels of disease severity, itch, and daily stressors in the month in which patients experienced the highest and lowest levels of daily stressors are presented in Table 1, showing significant differences between the moments of highest and lowest reported daily stressors. When patients reported the highest level of daily stressors, they also experienced significantly more itch and a more severe disease than when they reported the lowest level of daily stressors. In addition, Pearson's correlation coefficients between daily stressors and changes in disease severity (PASI) and itch 4 weeks later are presented in Table 2. Only at the moment that patients reported the highest amount of daily stressors there was a positive, significant correlation between daily stressors and

Abbreviations: PASI, psoriasis area and severity index

Table 1. Level of daily stressors and disease outcome (means, standard deviations, and paired samples *t*-test) at the moments patients reported the most and the least daily stressors

	Most daily stressors	Least daily stressors	
Daily stressors	16.8 (SD 10.9)	5.1 (SD 5.8)	t=13.6, P<0.001
Disease severity	7.0 (SD 4.4)	6.0 (SD 4.3)	t=2.5, P<0.05
Itch	6.3 (SD 3.0)	5.6 (SD 3.0)	t=2.0, P<0.05

Table 2. Pearson's correlation coefficients between the change in disease outcome and daily stressors at the moments patients report the highest and lowest amount of daily stressors[1]

	Change disease severity	Change itch
High amount of daily stressors	0.28*	0.26*
Low amount of daily stressors	−0.01	−0.05

*P<0.05, **P<0.01.
[1]A positive correlation indicate that a high level of daily stressors is associated with an increase in disease severity/itch.

the increase in disease severity (PASI) and itch. No such relationships were found at the moment patients reported the lowest amount of daily stressors, nor any at other monthly measurement moments (data not shown). None of the demographic variables (gender, age, and educational level) was further related to the change in disease severity (PASI) or itch at this moment of highest or lowest stress (data not shown).

Our results are in line with those of other studies focusing on the relationship between stressors and disease outcome. For example, significant prospective relationships between daily stressors and an increase in disease severity have been reported in patients with atopic dermatitis (King and Wilson, 1991; Salewski and Lissner, 2002). For other chronic inflammatory diseases, such as rheumatoid arthritis, prospective relationships between daily stressors and disease severity have also particularly been found at moments when patients reported heightened levels of stressors (Affleck *et al.*, 1997; Zautra *et al.*, 1997, 1998). These findings support the idea that, in particular, the experience of a relatively high level of daily stressors can influence the course of chronic inflammatory diseases, including psoriasis.

When interpreting the results of this study, several limitations have to be kept in mind. Although the patients who completed this study did not differ from non-completers, there could have been a selection bias because more than half of our study population consisted of older males. Although gender differences have been reported, for example, in the hypothalamic–pituitary–adrenocortical axis response to psychological stressors, future studies should address the influence of gender on the stress–disease relationship (Kudielka and Kirschbaum, 2005). Furthermore, to control for medication effects, we included only patients whose medication regimen was stable in the 3 months before the start of the study, which might explain the rather low disease severity in the study sample. Moreover, during this study we had to exclude six patients because their medication regimen was changed, which suggests that the disease severity also showed less variability than usual. In addition, we cannot exclude the fact that the study design with repeated assessments might have influenced patients' attitudes and behavior, such as compliance with applying topical medication.

To our knowledge, only preliminary prospective results have been reported earlier about the influence of daily stressors on disease severity and itch in patients with psoriasis. Although our results should be replicated, our findings indicate that the possible effect of daily stressors on disease outcome should be noticed within daily practice, particularly when patients report that they are going through a stressful period.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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The Localization of Label-Retaining Cells in Eccrine Glands

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TO THE EDITOR

Stem cells are multipotent cells capable of self-replicating and differentiating into several lineages of cells. In the skin, stem cells reside in the hair follicle bulge areas throughout the hair cycling, growth (anagen), involution (catagen), and rest (telogen) stages (Cotsarelis *et al.*, 1990; Paus and Cotsarelis, 1999; Cotsarelis, 2006). The stem cells in the hair bulge can differentiate into cells of hair follicles, sebaceous glands, and interfollicular epidermis (Oshima *et al.*, 2001). The lack of hair follicles on the palms of the hands and soles of the feet in humans may suggest the presence of another source of stem cells for reepithelialization after severe wounds or burns in this volar skin. One candidate location is an eccrine sweat gland, as eccrine glands are abundant in the palm and sole. Eccrine glands are composed of four segments: the intraepidermal duct, the straight intradermal duct, the coiled intradermal duct (the most proximal duct), and the secretory portion. In contrast to the stem cells in hair follicles, however, the localization of stem cells in the eccrine gland has been poorly characterized.

Before exploring the localization of stem cells in the mouse eccrine glands, we examined the development of mouse eccrine glands by immunohistochemistry with anti-keratin 14 antibody. Mice have eccrine sweat glands only in their footpads. An immunohistochemical study of cryosections from the hind footpads of BALB/c Cr Slc mice showed that, at embryo day 17.5, the first sign of eccrine gland development appeared as an epidermal downgrowth in the mesenchymal condensation of the hind footpads (data not shown). The tips of eccrine gland rudiments penetrated deep into the dermis after birth, and began to produce epithelial columns, which extended further deeply into the dermis. One week after birth, intraepidermal ducts were formed and the whole sweat gland formation was completed around day 14 after birth.

To address the localization of stem cells in the mouse eccrine glands, we used a peculiar character of stem cells; they are very slow cycling cells and retain labels in the nucleus over several weeks (Cotsarelis *et al.*, 1990). We performed BrdU pulse-chase experiments in BALB/c Cr Slc mice as described earlier (Nakamura and Ishikawa, 2008). Five newborn BALB/c Cr Slc mice were purchased from the SLC Company (Hamamatsu, Japan) and maintained in the Institute of Laboratory Animals, Kyoto University. Subcutaneously, 100 mg/kg/day BrdU (Sigma-Aldrich, St Louis, MO) was injected daily for 5 days. Mice were killed after 4 weeks and the frozen hind footpad sections were stained with a BrdU IHC Kit (Kamiya Biochemical Company, Seattle, WA) according to the manufacturer's instructions. Label-retaining cells were present in the eccrine secretory gland and coiled duct, but not in the straight duct or intraepidermal duct (data not shown).

To investigate the localization of stem cells in the human eccrine glands, we transplanted human skin onto the back skin of BALB/c nude mice, after obtaining approval from the Kyoto University ethical committee and written informed consent from the patients. The study was conducted according to the Declaration of Helsinki Principles. Histologically normal skin was obtained from five patients (ages from 37 to 72 years), three males and two