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How stress gets under the skin: cortisol and stress reactivity in psoriasis

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Summary

Background Psychological stressors might contribute to the severity of chronic inflammatory diseases such as psoriasis by dysregulating hypothalamic–pituitary–adrenal (HPA) axis activity.

Objectives To evaluate the role of cortisol, a key component of the HPA axis, in reaction to psychological stress in patients with psoriasis.

Methods Serum cortisol, clinical indicators of disease severity (Psoriasis Area and Severity Index) and self-report measures of daily stressors were measured monthly for 6 months in 62 patients with psoriasis.

Results In addition to the previous findings in this sample showing that peak levels of daily stressors predicted an increase in disease severity a month later, the peak levels of daily stressors were also significantly associated with a lower cortisol level. Moreover, patients who persistently experienced higher levels of daily stressors had lower mean cortisol levels than patients who experienced lower levels of daily stressors.

Conclusions Results suggest that daily stressors influence disease outcome in patients with psoriasis by affecting cortisol levels at moments of high stress. Furthermore, patients with persistently high levels of stressors seem to have a specific psychophysiological profile of lowered cortisol levels and may be particularly vulnerable to the influence of stressors on their psoriasis.

There is increasing evidence that the experience of stressful events is associated with the course of chronic inflammatory skin diseases such as psoriasis.[1–10] For example, more than half of patients with psoriasis retrospectively report having experienced stressful life events before an exacerbation of the disease.[8,11–14] As a stress response involves activation of both the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system, both of which interact with the immune system, stressful events could contribute to maintenance and exacerbations of chronic inflammatory diseases such as psoriasis. For example, external stressors stimulate the secretion of hormones such as cortisol, with peripheral and central HPA axis activity,[15,16] that activate skin mast cells,[17,18] alter the barrier function of skin[3] and upregulate proinflammatory cytokines,[19] which in turn might exacerbate the severity of psoriasis.

There is preliminary support for a link between the psoriatic disease process and specific physiological stress responses. For example, exposure to experimental stress has been linked to altered HPA axis activity and immune function in patients with psoriasis.[4–6,20] Specifically, experimental stress repeatedly resulted in altered HPA axis activity with decreased cortisol levels in patients with psoriasis,[4,20] suggesting that lowered cortisol levels might act as an HPA axis mediator in this stress–disease process of chronic inflammation. Other studies have reported cortisol levels to increase in response to experimental stress in psoriasis.[5] So far, how cortisol levels change in response to real-life stressors has not been investigated in patients with psoriasis, and such knowledge might help unravel the complex interaction between HPA axis activity and the psoriatic disease processes.

The relationship between stressors and disease outcome may also be influenced by patient characteristics, such as differences in stress reactivity. For example, patients with psoriasis who consider stressful life events to influence their disease course have higher scores on clinical measures of disease outcome, are characterized by heightened distress, and react with decreased cortisol responses during an experimentally induced stressful experience in comparison with patients who consider stress to have less influence on their disease.[8,20] The lower

levels of cortisol during stressful events measured in high stress-reactive patients suggest that the HPA axis is hyporesponsive to stress in these individuals. A similar phenomenon has been described as hypocortisolism in a subgroup of patients with stress-related disorders such as post-traumatic stress disorders, as well as in patients with chronic inflammatory diseases such as rheumatoid arthritis or psoriasis.[21–24] In these patients, hypocortisolism might indicate a reduced responsiveness of the HPA axis as a consequence of chronic stress exposure and a prolonged hyperactivity of the HPA axis.[21,23,24] In patients with psoriasis, this blunted HPA activity might result in immune overactivity with increased inflammatory responses due to the diminished suppressive effect of the low level of cortisol.[20] Thus there may be a subgroup of patients with psoriasis whose disease course may be adversely affected by persistently high levels of stressors and low levels of cortisol. Patients might consequently differ in their cortisol reactivity to stressful events depending on the level of chronic stress exposure, which may influence the disease-related outcome.

The aims of the current study were prospectively to investigate the relationship between the experience of daily stressors and cortisol levels and changes in disease severity in patients with psoriasis. We have previously shown in this sample that when patients experienced peak levels of daily stressors, stressors predicted an increase in disease severity,[1,2] and we now report the results on cortisol in this sample. In line with these previous findings, we hypothesized that when patients experienced peak levels of daily stressors, these stressors would be associated with lower cortisol levels, and that both daily stressors and lower cortisol levels would be associated with an increase in disease severity a month later. Moreover, we investigated group differences between patients who experienced persistently low vs. high levels of daily stressors, hypothesizing that patients who experienced persistently higher levels of daily stressors would have relatively lower mean levels of cortisol.

Materials and methods

Participants and procedure

Seventy-six patients were recruited from the Departments of Dermatology at the Radboud University Nijmegen Medical Centre and the Canisius Wilhelmina Hospital, Nijmegen, the Netherlands, between 2005 and 2008. Inclusion criteria were a diagnosis of psoriasis, a minimum age of 18 years, and a stable medication regimen (no change of the type of systemic medication or start of phototherapy). Exclusion criteria were pregnancy, comorbid physical conditions (such as rheumatoid arthritis, malignancy, renal insufficiency) and psychiatric or mental disturbances that would severely interfere with adherence to the study protocol. Patients who used antidepressant medications were also excluded due to their possible effects on the HPA axis activity (including cortisol) that might interfere with the effects of daily stressors. Medication regimen and the possible occurrence of physical and psychological comorbidities were further checked at all assessment points. Patients whose medication regimen (type of systemic medication or start of phototherapy) changed during the study or who developed severe physical and psychological comorbidities during the study period were also excluded.

Clinical measures of disease severity, self-reported measures of daily stressors and serum cortisol levels were measured once a month for 6 months. Of 76 consecutive patients who participated in the study, the data of 14 patients were not suitable for analyses. Of these, eight patients dropped out during the first 4 months (three because of time constraints, two because of comorbid health problems of knee surgery or heart failure, and three because of life events of divorce or illness in the family). The data for the other six patients were not suitable because of changes in medication regimen during the first 4 months of the study (two patients started with systemic medication and four patients started with phototherapy).

For the remaining 62 participants, data were analysed for the available period of 6 months, with the exception of 11 patients who were followed for a shorter period of 4–5 months: seven patients because of changes in their medication regimen (five due to a change in systemic medication, one due to 1-week use of an antidepressant during the second month, one due to the start of phototherapy) and four patients because of the development of physical comorbidities (two patients) or for time management reasons (two patients). For these participants, the remaining five or six assessment points were included in the dataset. The cortisol data of two additional patients were finally excluded due to invalid serum cortisol measurements for four of the seven assessments.

Measures

Demographic variables were assessed using a general checklist for age, sex and educational level. The latter was measured using seven categories that can be classified as primary, secondary and tertiary levels of education, representing on average 7, 12 and 17 years of formal education.

Disease severity was assessed with the Psoriasis Area and Severity Index[25] (PASI), the most widely used clinical indicator of psoriasis severity. The PASI measures the average redness, thickness and desquamation of the lesions (each graded on a 0–4 scale), weighted by the area of involvement.

Daily stressors were assessed with a short 49-item version of a widely used and validated daily hassles questionnaire, the Everyday Problem Checklist[26,27] (EPCL), with items such as 'You had to wait a long time for an appointment', 'You blundered in company' or 'Important belongings got lost'. Patients were asked at the monthly assessment points to complete the list of 49 stressful events for the previous 4 weeks. When patients answered that they had experienced the event, they indicated the intensity of this event, ranging from 0 (no impact at all) to 3 (very high impact). The total score for daily stressors experienced was calculated by summation.

For measurement of *serum total cortisol concentrations*, blood samples were taken between 09:00 and 11:00 h at the monthly visits, which were always scheduled at the same time (e.g. 09:00 h) for every patient. Patients were asked not to smoke or to take caffeine, black tea or alcohol on the morning of the appointments. Blood samples were centrifuged and the serum was frozen at −80 °C for later analyses. Cortisol concentrations were measured with a luminescence immunoassay on an Architect random access analyser (Abbott, Hoofddorp, the Netherlands). Within-assay coefficients of variation were 3·9% at 0·16 μmol L^{-1} and 4·8% at 0·44 μmol L^{-1}, and between-assay coefficients of variation were 4·5% and 6·2%.

Statistics

In total, 1197 observations (105 missing from a maximum of 1302 observations) for the three outcome measures (daily stressors, cortisol and disease severity) were evaluated in the 62 participants with data sets being complete for 92% of all of the seven assessments made during the 6-month period (see also Participants and procedure). The month in which the participant reported the highest and lowest level of daily stressors (highest/lowest EPCL score) was determined for all participants as well as the same-month level of cortisol and the variables of disease severity for the same month and 1 month later. All variables used in the present analyses (highest and lowest levels of daily stressors and corresponding cortisol and disease severity levels at the same month or 1 month later as well as mean levels of daily stressors, cortisol and disease severity) were normally distributed in the present sample (skewness and kurtosis <1·5). Pearson correlation coefficients and partial correlations were calculated for all study variables in these months. Residual gain scores were used to measure the change scores and were calculated by regressing the outcome measure (e.g. PASI) at the next assessment on the score for this measure the previous month. For the between-group analyses of differences in daily stress reactivity, mean levels of daily stressors, cortisol levels and PASI were calculated for all assessments. Patient groups were subsequently distinguished according to the median split of daily stressors and compared by t-tests and ANCOVA on all outcome variables.

We also studied the possible confounding effects of demographic variables (sex, age and educational level) by calculating Pearson correlation coefficients for all outcome measures (daily stressors, cortisol and disease severity). No relationship was found between sex or educational level and any of these outcome measures. However, there was a significant relationship between lower age and the peak levels of daily stressors ($r = -0{\cdot}43$, $P < 0{\cdot}001$). Consequently, all analyses were controlled for age as covariate, reporting also results of partial correlations and ANCOVAS (two-tailed). Finally, we also conducted all analyses without the two female patients using oral contraceptives, revealing the same overall results (data not shown). The SPSS 16.0 program was used for all analyses (SPSS, Chicago, IL, U.S.A.).

Results

Patient characteristics

The sample consisted of 62 patients (47 men) with a mean ± SD age of 52·3 ± 13·2 years (range 21·9–79·7) (Table 1). Of these participants, 5%, 66% and 29% had a primary, secondary or tertiary education level, respectively. Mean ± SD PASI at the start of the study was 7·0 ± 4·6. Student's t-tests showed no significant differences between the patients in the final sample and the 14 patients who did not complete the study in terms of sex, age, educational level, measures of disease severity or daily stressors at the start of the study (data not shown).

Relationship between daily stressors, cortisol and disease severity at highest and lowest levels of daily stressors

When patients experienced peak levels of daily stressors, we previously showed that daily stressors were correlated with an increase in disease severity (PASI) the following month ($r = 0{\cdot}28$, $P < 0{\cdot}05$ and after controlling for age $r = 0{\cdot}22$, $P = 0{\cdot}09$).[1,2] In addition, daily stressors at peak levels were negatively correlated with the level of cortisol at peak levels ($r = -0{\cdot}23$, $P = 0{\cdot}08$ and after controlling for age $r = -0{\cdot}28$, $P < 0{\cdot}05$), but the level of cortisol was not significantly associated with the change in disease severity a month later. When daily stressors were at their lowest level, no significant relationships were found between daily stressors and cortisol or between daily stressors and increase in disease severity a month later.

Group differences in daily stressor reactivity

To explore group differences between patients who consistently experienced relatively high or low enduring levels of daily stressors, we first calculated total mean levels of daily stressors, cortisol and disease severity at all assessments and subsequently distinguished the groups according to the median split of the total mean level of daily stressors (median split

Table 1 Characteristics of 62 patients with psoriasis at study entry

Age (years), mean ± SD	52·3 ± 13·2
Sex (M/F)	45 (73%)/17 (27%)
Marital status	76% married or having a partner
Educational level, n (%)	
Low	3 (5)%
Moderate	41 (66)%
High	18 (29)%
Clinical severity of psoriasis (PASI), mean ± SD	7·0 ± 4·6

PASI, Psoriasis Area and Severity Index.

Table 2 Mean ± SD level of daily stressors, cortisol level and disease severity at the monthly assessments for patients who experienced high or low mean levels of daily stressors (median split)

	Patients with high daily stressors	Patients with low daily stressors	Group differences[a]
Daily stressors	17·31 ± 6·34	4·70 ± 2·91	$P < 0·001$
Cortisol (μmol L^{-1})	0·29 ± 0·10	0·37 ± 0·11	$P = 0·001$
Disease severity	7·34 ± 4·11	5·84 ± 3·83	n.s.

[a]Significance of F-value in ANCOVA, testing group differences with regard to daily stressors, cortisol and disease severity (Psoriasis Area and Severity Index), after controlling for the effect of age. n.s., not significant.

for all assessment points; $F = 71·54$, $P < 0·001$, see Table 2). Results indicated that the groups had different mean levels of cortisol ($F = -11·55$, $P = 0·001$), with the patients with higher mean levels of daily stressors having lower mean levels of cortisol. Disease severity did not differ significantly between the groups [$F = 0·83$, not significant (n.s.)]. When choosing other possible methods of group differences in the present study, for example extreme subgroups (33% high–low groups of 2×20 patients), results again showed that the groups of patients with high vs. low levels of daily stressors differed significantly with regard to mean cortisol levels ($P < 0·05$), but not with regard to disease severity. Also when calculating correlations between mean levels of monthly cortisol and mean levels of daily stressors for the whole study group, the results showed that mean daily stressors levels were negatively related to mean cortisol levels ($r = -0·36$, $P < 0·01$), while no significant correlation was found between daily stressors and disease severity ($r = 0·15$, n.s.).

Discussion

The present study is one of the first longitudinal studies to examine the influence of daily stressors on cortisol levels in patients with psoriasis. Results showed daily stressors to be negatively associated with cortisol levels when patients experienced peak levels of daily stressors, while we previously showed that at that moment daily stressors were associated with an increase in disease severity a month later.[1,2] Moreover, patients who persistently experienced high levels of daily stressors had lower mean levels of cortisol, which might reflect a general vulnerability to exacerbation of inflammation in these patients, such that relatively stressful periods may aggravate the course of psoriasis in these individuals in particular.

Our results are in line with those of other studies investigating the relationship between stressors and the outcome of chronic inflammatory diseases such as rheumatoid arthritis and which reported that high levels of daily stressors were a trigger of disease exacerbation, especially at moments when patients report heightened levels of stressors.[28,29] In line with these results, we previously showed in this sample that – only at peak levels of stress – levels of stressors were associated with an increase in disease severity over time.[1] Overall, these findings support the idea that relatively high levels of daily stressors can influence the course of chronic inflammatory diseases including psoriasis, and that cortisol might be a key parameter of this stress–disease process. A negative relationship between cortisol and stress levels has previously been reported in psoriasis after stress exposure and might reflect a blunted HPA axis responsiveness in psoriasis.[4,20] Similar findings of reduced HPA axis responsiveness have been reported for other chronic inflammatory diseases such as rheumatoid arthritis.[30] This dysregulation of the HPA axis with decreased release of cortisol is assumed to be involved in the stress-induced exacerbation of chronic inflammatory diseases, for example by leading to an upregulation of proinflammatory cytokines.[19] This dysregulation includes both central and peripheral HPA axis activity, for example by the release of corticotrophin-releasing hormone, that might be one of the central and peripheral mediators of the stress–skin connection in cutaneous inflammatory diseases.[15,16]

The result that patients who persistently experienced higher levels of daily stressors, and are possibly more stress reactive, had relatively lower mean cortisol levels suggests that the HPA axis is hypoactive in these individuals, which might directly influence the disease-related outcome. The finding of consistently lower cortisol levels in chronically stressed individuals is consistent with the reports of hypocortisolism in patients with stress-related disorders, possibly due to prolonged hyperactivity of the HPA axis.[21,23,24] Similar findings have been reported in patients with chronic fatigue or chronic pain, particularly in those who had experienced high levels of childhood stressful events.[31,32] It is also consistent with the observation that patients with psoriasis who consider themselves stress reactive report more distress and have diminished cortisol responses after exposure to experimental stressors.[8,20] The findings that the patients with persistently high and lower stress levels showed mean differences in cortisol, but no mean differences in disease activity, might indicate that the supposed stress–disease relationships of the high stress group might particularly occur during specific time periods, such as peak levels of stress.[1,28] For example, there is increasing evidence that the sensitivity of the immune system to glucocorticoids is diminished by chronic stress, suggesting that chronic stress interferes with the ability of cortisol to regulate the immune system, which might result at peak moments of stress in increased inflammation[33,34] and possibly even a higher prevalence of chronic inflammatory diseases including psoriasis.[22]

When interpreting the results of the study, several limitations and possibilities for future research should be kept in mind. We investigated the effect of stressors on disease outcome using daily stressors, as the enduring and cumulative impact of these minor daily stressors (e.g. running late for an appointment or losing keys) has been shown to be a substantially better predictor of health outcome than, for example, major life events.[26,35] Nevertheless, the role of specific stressors, for example interpersonal daily stressors, disease-related

daily stressors or childhood traumatic events,[10,29,32] should be studied to establish whether our findings concerning daily stressors and disease severity also apply to other categories of stressors. Also timing is known to play a crucial role when evaluating the role of stress on HPA axis activity,[24] and it could be argued that monthly assessments for 6 months might not be sensitive enough to detect real-life short- and long-term interactions, such as day-to-day changes or long-term effects of chronic stressors.[28,29,36] However, others have shown that it is likely that a person will experience increased levels of daily stressors at some stage in a 6-month period.[28,29] Future studies should also investigate the role of other markers of HPA axis activity, such as ACTH, which are known to be possibly differently involved in the phenomenon of HPA axis hypoactivity in post-traumatic stress.[24] In addition, key parameters involved in the pathogenesis of psoriasis, such as skin mast cells or specific immune-related responses (such as altered cytokine reactivity after stress exposure) should be investigated, to gain a better understanding of the underlying stress–disease relationships in psoriasis.[17,18] Although the patients who completed the study did not differ from the patients who did not complete the study regarding the study variables investigated, results may have been influenced by selection bias. For example, most of the participants were men, and thus future studies should aim to replicate findings in populations with a larger proportion of women, even though stress and cortisol responses did not differ between the sexes in this study. In addition, lower age was associated with the stress measures of daily hassles and was controlled for in the analyses. In order to control for medication effects, we included only patients with a stable medication regimen. This might explain the relatively moderate PASIs observed, with few fluctuations in disease severity during the study period. Also the variability of daily stressors might have been greater if groups of patients with high and low stress levels had been previously selected. Although medication regimen and the possible occurrence of physical and psychological comorbidities were checked at all assessment points, we did not ask the patients on a day-to-day basis about their drug or alcohol use or minor infections and therefore we cannot exclude that these factors might also have affected the results. Lastly, the study design with repeated assessments might have influenced patients' attitudes and behaviour in coping with the disease, resulting in closer monitoring of their skin condition or increased compliance with topical medication.

The present study is the first longitudinal study of patients with psoriasis to show a relationship between cortisol levels and daily stressors, of which the latter has previously been shown to be associated with more severe disease a month later.[1,2] The results further suggest that patients who continuously experience higher levels of daily stressors are characterized by persistently lower cortisol levels and might thus be more vulnerable to the effects of stress on their disease. Clinicians should be aware of the possible effect of daily stressors on disease outcome and endocrine function, particularly when patients are going through stressful periods and for those subgroups of patients who are most vulnerable to the enduring influence of daily stressors.

What's already known about this topic?

- There is preliminary evidence that psychological stressors contribute to the severity of chronic inflammatory diseases such as psoriasis by dysregulating hypothalamic–pituitary–adrenal (HPA) axis activity. For example, exposure to experimental stress resulted in altered cortisol levels in patients with psoriasis, suggesting that cortisol might act as an HPA axis mediator in the stress–disease process of chronic inflammation.

What does this study add?

- The present study is the first prospective study to examine the influence of daily stressors on cortisol levels in patients with psoriasis. Results indicate that daily stressors might influence disease outcome by affecting cortisol levels at moments of high stress. Furthermore, patients with persistently high levels of stressors were characterized by a psychophysiological profile of lowered cortisol levels and may be particularly vulnerable to the influence of stressors on their psoriasis.

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