How stress affects the skin

From designs to mechanisms

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How stress affects the skin: from designs to mechanisms

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The reciprocal relationship between stress and skin diseases is well known, showing that for example many chronic skin diseases induce moderate-to-severe stress responses,[1,2] such as subjective levels of psychological distress and a physiological stress response of altered hypothalamic–pituitary–adrenal (HPA) axis activity, that in turn might trigger a worsened disease course or progression.[3] Although there is considerable evidence showing that stress is a common psychological consequence of skin conditions,[1] there is much less 'hardcore' evidence from prospective studies about the possible causal effects of stress on the origin or course of a skin disease.[4] There are at least three ways through which stress can affect the skin that all ask for different designs.

(i) Stress as a causal factor for the origin of the disease: examples are psychiatric diagnoses of factitious disorders (e.g. dermatitis artefacta) or compulsive disorders (e.g. trichotillomania), without a specific dermatological cause. These cases are usually studied in a clinical context, showing for example that successful treatments can cure these conditions.[5]

(ii) Stress as a trigger for the worsening of a (chronic) skin disease. Examples are prospective diary studies showing that a worsening of chronic skin diseases, such as psoriasis or eczema, is temporally preceded by a phase of more stress, that for example induces maladaptive behaviour,[6,7] such as higher scratching response or less adherence, or an altered HPA axis response.[3] The number of prospective studies in this area is relatively low,[4] but increasingly confirms the large number of cross-sectional studies that suggest a relationship between stress and the course of skin diseases,[3,8] at least during periods of high stress.[6,7] Furthermore, experimental research showing that stress induction is related to increased itch severity in nonclinical populations underlines the potential relevance of experimentally examining stress-related disease processes in patients with skin conditions.[9]

(iii) Stress as a trigger for the onset of the skin disease: examples are many retrospective reports of patients with chronic skin conditions that report life events or other stressors in the period before the first onset of the condition, notwithstanding all the limitations of retrospective data.[4] In contrast, large prospective and epidemiological studies, as presented by Schmidt *et al.*[10] in this issue, are usually missing to demonstrate these possible causal relationships.

In the article by Schmidt *et al.*,[10] the authors present an example for stress as a trigger for the onset of a skin disease with a unique dataset of 77 310 Danish citizens, showing a relationship between higher perceived stress responses and the onset of herpes zoster (HZ). The study is characterized by several advantages in comparison with the existing literature, including its large, population-based sample, prospectively collected data and dose–response analyses. Although these types of studies are important to advance knowledge about the role of stress in the onset of skin conditions, the reported relationships are still descriptive and cannot explain the underlying mechanisms or really prove the causal effects of stress on HZ.

As a next step, it is crucial to disentangle the mechanisms underlying exactly how stress might affect these inflammatory processes. For example, future studies might focus on experimental (treatment) designs in patients with HZ and healthy participants to demonstrate, for example, specific psychoneuroimmunological [such as interleukin (IL)-6 or IL-8 responses, altered cortisol levels] as well as behavioural (e.g. scratch responses, low adherence, lifestyle factors) pathways to explain the specific mechanisms underlying the relationship between stress and disease processes in HZ and other skin diseases.

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What instruments should we add to our toolbox for measuring the severity and control of eczema?

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The severity of disease and its management are no longer merely measured by the objective and subjective measurements used by physicians and nurses. The patient perspective has become an important element in decision making regarding treatment choice. In dermatology, various objective instruments have been created and validated to score the visual aspects of the commonest of the skin and mucosal diseases, and subjective instruments have been validated to measure the effect of these diseases on our patients' quality of life. There are also validated instruments that are symptom specific, particularly the symptom of itch. Thus far, not many instruments have been developed and validated that measure the level of disease control.

In atopic dermatitis/eczema a particular group of international experts called the Harmonising Outcome Measures for Eczema (HOME) group, led by Professor Hywel Williams in the UK, has been attempting to meet annually to delineate by consensus which of these various outcome instruments should be performed in all clinical trials in eczema and which ones may be applicable in routine clinics. The group consists of dermatologists, nurses, methodologists, industry experts and patient support group leaders, as well as patients.[1]

Experts within the group are charged with performing an evidence-based review of a particular topic related to a clinical question to be addressed at each meeting and present this to the group, such as, which objective outcome measure has the highest validation according to COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) analysis.[2] There are small group discussions and at the end of the 2- to 3-day meeting there is anonymous voting on the best instrument. Consensus is defined by when there are less than 30% of the group who disagree; at least 70% of the group agrees or is neutral. These reviews are published independently and the outcome of the HOME recommendations are published. Earlier meetings of HOME endorsed the use of the Eczema Area and Severity Index and the Patient-Oriented Eczema Measure, and they have been working on analysing quality-of-life instruments, itch and long-term control.

In this issue, Thomas *et al* report on the latest HOME VII consensus.[3] In the meantime, two new instruments to measure long-term control of eczema have been validated, the independent Recap of Atopic Dermatitis (RECAP)[4] and the Sanofi-patented Atopic Dermatitis Control Test.[5] Six of the patient questions within them are almost identical, focusing on the patients' experience of their symptoms, itch, sleep, daily activities, mood and overall interference. The RECAP has the advantage of being validated both for adults and children (where it is completed by caregivers). Both tools ask about the past week, and because eczema fluctuates a lot, unless they are in a clinical trial with frequent visits, asking only about the past week may not reflect true long-term control over, say, a 3-month interval between visits. The numerical rating scale (NRS-11) over 24 h was recommended to assess itch and the Dermatology Life Quality Index/Children's Dermatology Life Quality Index/Infant's Dermatology Quality of Life Index to assess overall quality of life.[3]

Why is it important for dermatologists to be familiar with these instruments? The funding of biologics for AD is linked to the severity of AD using validated instruments and its response. Additionally, for caregivers, embracing the patient perspective about their disease will undoubtedly strengthen the relationship between caregiver and patient, and facilitate adherence to treatment and disease control. It is important that the instruments assessing disease control in AD are freely available for use in the clinic and in clinical trials to improve AD management in the years to come.

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Conflicts of interest: D.F.M. and C.F.P. are both members of the voluntary HOME group but did not attend the HOME VII meeting this article refers to. D.F.M. is an advisor and investigator for AD trials with Sanofi-Regeneron, Dermira, Galderma, Lilly, Leo and Pfizer.

C.F.P. has received grants and has been a consultant for Almirall, Amgen, AbbVie, BMS, Boehringer, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck, Mylan, Novartis, Pfizer, Pierre Fabre, Sanofi and UCB pharma. For atopic dermatitis C.F.P. has been an investigator or consultant for Eli Lilly, Leo Pharma, Pierre Fabre, Regeneron and Sanofi.