

## ORIGINAL ARTICLE

**Sensitive skin: A relevant syndrome, be aware**A. Wollenberg<sup>1\*</sup> , A. Giménez-Arnau<sup>2</sup> <sup>1</sup>Department of Dermatology and Allergy, University Hospital, Ludwig Maximilian University, Munich, Germany<sup>2</sup>Department of Dermatology, Immunodermatology Section at Hospital del Mar, Institut Mar d'Investigacions Mèdiques, Autonomous University of Barcelona, Barcelona, Spain

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Sensitive skin is clinically defined by characteristic sensory perceptions including tightness, abnormal stinging, burning, tingling, pain and pruritus. Facial erythema may occur, and other body areas can be involved. Sensitive skin affects extremely the quality of life. According with the International Forum for the Study of Itch (IFSI), sensitive skin is defined as a syndrome. The unpleasant sensations described are in response to stimuli that normally should not provoke such sensations. Moreover, these unpleasant sensations cannot be explained by any skin disease. Sensitive skin is always considered when any new consumer health, cosmetic or household product is introduced in the market. Once sensitive skin is recognized, it is mandatory to identify specific triggers that commonly induce symptoms and even cutaneous visible signs. Sensitive skin syndrome can be exacerbated by an allergic setting and environmental factors (cold, hot, dryness, pollution, wind, chemicals ...), a source of intolerance and unpleasant sensations. Cosmetics are the main triggering factors of sensitive skin according to patient's reports. The presence of potentially irritant substances in their composition increases the clinical expression of symptoms. As sensitive skin is frequent, and it is increasing based on the current development of cosmetic use worldwide, there is a need to develop better skin care products. The continuous research of active and safe skin care products to prevent and treat sensitive skin is extremely welcome.

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**Introduction****Sensitive skin overview from social, dermatological and self-perception**

Sensitive skin (SS) has been defined as the occurrence of unpleasant sensations in response to stimuli that normally should not provoke such sensations.<sup>1</sup> It is considered to be a self-claimed condition or syndrome, rather than a disease, and is reported to occur in over 50% of the world's population. Indeed, in a Metabase compiling 26 studies in 18 countries, ~70% (23%–90%) of the general population claimed to have 'slight', 'moderate' or 'very' SS.<sup>2</sup> In the past, SS has been underreported, underestimated or even neglected; however, it is now recognized as a widespread problem that can have a significant impact on patients' quality of life. Therefore, much research has focused on the underlying causes, influencing factors and treatments of SS.

According to subjective feedback from patients, SS can affect all body locations but the most common reported location is the face, possibly due to a thinner barrier, a greater density of nerve endings and a higher exposure to multiple products (e.g. cleansers and cosmetics) and environmental factors. Various chemicals

have been associated with undesirable skin sensations, and according to patient's reports, cosmetics are the main triggering factors of SS. Therefore, SS should always be considered when any new consumer health, cosmetic or household product is developed.

There are multiple extrinsic and intrinsic factors thought to contribute to SS. Individual factors include age, hormonal changes, skin types and attributes, e.g. susceptibility to sunburn, blushing and/or flushing.<sup>3,4</sup> SS mainly manifests in women, but with increasing cosmetic use in recent years, there are also increased reports of SS in men.<sup>2</sup> SS can be exacerbated by an allergic setting, but there appears to be no direct link to SS and skin disease, except for light erythema in 74% of cases.<sup>2,3</sup> SS syndrome can also be exacerbated by environmental and external factors, such as UV radiation, wind, temperature extremes, dryness, pollution, wind, spicy food and chemicals.<sup>3</sup> Some geographical differences in prevalence have been noted, possibly due to cultural factors, specific climate and environmental factors, and beauty-related sensitivity.<sup>2,3</sup>

Efforts should be maintained to clarify the link between sensory symptoms and subjective signs, and to standardize a reliable

diagnostic. The use of epidemiology to identify patients with specific risks, as well as intrinsic and extrinsic contributors should help elucidate the pathophysiology of this condition and define integrated interventions for better patient care and comfort.

### Pathophysiology of cutaneous reactivity

A deeper understanding of both the clinical expression and the pathophysiology of sensitive skin can lead to a better care and the development of products for SS. Clinical manifestations of sensitive skin include pain and itching, which are essential phenomena that normally contribute to body protection. However, pain in atopic dermatitis is not associated with a retraction reflex; instead, it co-localizes with itching/stinging sensations, and differs from the sensation that people associate with the word pain. Since objective methods for pain assessment do not always detect SS, symptoms of pain that overlap with itch symptoms can be assessed using validated subjective questionnaires.<sup>3</sup>

Mechanistic studies have identified three major dimensions in SS pathophysiology, namely neurogenic- and immune-related effects, and an alteration of the skin barrier function. The neurogenic component has been investigated in several studies. In SS patients, the heat pain threshold was reported to be lower, and pain scores using neuropathic questionnaires were significantly higher.<sup>5</sup> This was confirmed by a transversal study performed in women with sensitive skin, which demonstrated that one-fifth of patients with sensitive skin showed neuropathic pain.<sup>6</sup> In another study, while epidermal thickness and markers of epidermal inflammation were not increased in SS, there was a significant decrease in intra-epidermal nerve fibre density, especially that of peptidergic C-fibres (involved in pain, itching and temperature perception) in the sensitive skin group.<sup>7</sup> These results suggest the presence of hyperalgesia, probably due to damage of C-fibres in sensitive skin patients.

The contribution of immune mechanisms to the pathogenesis of SS is evidenced by the activation of sensory neurons, e.g. transient receptor potential vallinoid 1 (TRPV1, linked to the induction of pain) and TRPV4 (linked to the induction of itch).<sup>8</sup> Activation of these neurones results in the local cutaneous release of neuropeptides such as substance P, which activates several skin cell types, e.g. keratinocytes, mast cells, antigen-presenting cells and T cells.<sup>9</sup> Receptor-mediated release of pro-inflammatory cytokines and chemokines by substance P results in the recruitment of additional immune cell subsets to the skin. All these factors are linked to itch and warmth sensations related to SS syndrome.

Clinical data show that individuals with SS present an altered epidermal barrier function.<sup>10, 11</sup> A weak epidermal barrier facilitates the penetration of irritants and allergens and is associated with poor protection of nerve endings and increased trans-epidermal water loss.<sup>11</sup> Topical creams can be

used to protect the integrity and strengthen the skin barrier of sensitized skin exposed to environmental stresses (cold, dryness).

These three dimensions, combined with environmental, lifestyle and endocrine factors allow to draw a consolidated approach of the condition and to seek topical interventions that are safe and well tolerated, that may restore normal skin function and favourably impact quality of life.

This special issue describes investigations into the underlying mechanisms of SS, as well as evaluations of dermocosmetic formulations designed to alleviate the condition based on the known mechanisms. Jacques et al. describe a novel base formulation designed to mimic the components and structure of the skin and thus provide a solution for sensitive skin. This paper describes the combination of an *in vitro* skin model with X-ray diffraction imaging to gain a mechanistic understanding of the structure of the formulation and its interaction with the skin. In addition, *in vivo* clinical studies investigated the tolerance and efficacy in soothing the effects of SS. Villaret et al. describe the outcome of a clinical evaluation of the anaesthetic-like effect of two dermocosmetic formulations containing the active component of Avène natural spring water, Aquaphilus dolomiaie extract-G3 (ADE-G3), in subjects with SS. This study used emotional endpoints (electrodermal response and verbatim/semantic analysis) and a technical endpoint (the Sensitive Scale) to conclude on the efficacy of the formulations. Viode et al. also evaluated ADE-G3-containing formulations for their efficacy in alleviating SS. In their studies, an *in vitro* model using 'sensitized' reconstructed human epidermis was employed to determine the impact of the formulations on barrier function. Complementary clinical studies were performed to demonstrate that the improved barrier function was also evident in patients with SS. In conclusion, the data presented here will improve our understanding of the mechanisms underlying the condition of SS, and will pave the road for upcoming, novel treatments targeting some of these mechanisms.

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