RESEARCH PAPER

Psychological Stress and Cortisol Levels in Skin Inflammation

Deryne Anggia Paramita[1*], Elmeida Effendy[3], Ramona Dumasari Lubis[2], Putri Chairani Eyanoer[4], Khairuddin Djawad[5], Muhammad Rusda[6], Oke Rina Ramayani[7], Dewi Indah Sari Siregar[8]

[1]Philosophy Doctor in Medicine Program, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[2]Department of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[3]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[4]Department of Community and Preventive Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[5]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia
[6]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[7]Department of Pediatrics, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[8]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
Email: deryne.anggia@usu.ac.id, elmedia.effendi@usu.ac.id, ramona_lubis@yahoo.com, putrieyanoer@usu.ac.id, duddin@ymail.com, m.rusda@usu.ac.id, okerina@usu.ac.id, dewi.indah@usu.ac.id
***Corresponding Author:** deryne.anggia@usu.ac.id

ABSTRACT
Psychological stress is closely related to inflammatory skin diseases such as psoriasis, atopic dermatitis, and acne, which can be exacerbated or exacerbated by stress. The hypothalamic-pituitary-adrenal (HPA) axis mediates stress perception and skin physiology, with the main influence being the hormone cortisol. Stress-induced cortisol dysregulation, such as excessive or strong reactions, contributes to the development and worsening of these symptoms. The skin itself acts as an endocrine nerve organ, has a peripheral HPA axis, and expresses key regulatory factors such as 11β-hydroxystoid dehydrogenase type 1 (11β-HSD1), allowing for the conversion of cortisone to cortisol locally. Changes in glucocorticoid sensitivity and cortisol metabolism in the skin's morphological response to internal and therapeutic steroids. Patients with inflammatory skin disease often show changes in cortisol patterns, including decreased stress response and glucocorticoid resistance. These changes determine the activity and severity of the disease. Psychological interventions such as mindfulness-based stress reduction and cognitive behavioral therapy can improve post-mortem by regulating cortisol levels. Pharmacological approaches targeting the HPA axis, specifically selective serotonin reuptake inhibitors (SSRIs) and topical 11β-HSD1 inhibitors, offer additional therapeutic potential. However, differences in cortisol measurements and the confusing effects of topical corticosteroids have limited research comparisons. This review summarizes the relationship between psychological stress, cortisol dysregulation, and inflammatory skin diseases, emphasizing the importance of standardized cortisol assessments and rigorous clinical trials for patient care and health promotion.

Keywords: Psychological stress, Cortisol, Skin inflammation, HPA axis, Glucocorticoid, Inflammatory skin diseases.
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Introduction

Atopic dermatitis (AD) is a common skin disease characterized by chronic dermatitis. Clinically, the disease appears to be in a state of persistent inflammation, but tissue results mainly show leakage of inflammatory cells such as lymphocytes, orchids, and mast cells. Alzheimer's disease affects about 10-20% of children and 1-3% of adults in developed countries, and epidemiological evidence suggests that its prevalence continues to increase over time (Bieber, (2021).

The exact cause of Alzheimer's disease is still unknown, but laboratory and clinical results point to a multifactorial cause (Decourt et al., 2022). Genetic and environmental factors can contribute to stress, which leads to inflammation of the disease. This review discusses psychological stress, not physiological stress, in Alzheimer's disease (Mohammadi, 2021). Alzheimer's disease can also signal the onset of atopic processes, which can then progress to asthma and allergic rhinitis. Stress also affects biological processes related to clinical outcomes. These drugs can be used to reduce the onset and progression of tumors, and affect their metastases, and can promote tumor immune evasion through immunosuppression

(Joh et al., 2022). Stress is known as a risk factor for several skin diseases, such as psoriasis, alopecia areata (AA), and atopic dermatitis (AD), which contribute to their development and exacerbation (Goyal et al., 2023).

Hunter revealed that psychosocial stress significantly exacerbated skin diseases and was a major trigger reported by patients. Recent studies have increasingly focused on the brain-skin axis, which describes complex interactions between the nervous system, the immune system, and the brain. Evidence suggests that the physiological stress response works through the hypothalamic-pituitary-adrenal (HPA) axis and the locus coeruleus–norepinephrine (LC-NE), peripheral pathways that act as signaling molecules within the skin, and several peripheral neurocentral nervous organs. Therefore, stress plays an important role in regulating the balance of the skin and can be considered a biological factor that contributes to the pathological mechanisms of skin diseases (Jiao et al., 2024).

Chronic stress disrupts the balance of the body. With proper management, the activity of the hypothalamic-pituitary-adrenal (HPA) axis can gradually return to normal function, allowing the body to regain its physiological state before experiencing stress. In humans and many other mammals, the stress response involves the activation of the autonomic nervous system and the HPA axis. This physiological process triggers the release of stress-related hormones, especially cortisol and adrenaline. The parasympathetic nervous system helps the body restore balance (Anlia et al., 2025).

Increased inflammatory activity and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis are often associated with depression, at least in some subgroups with depressive disorders. Extensive evidence highlights that the HPA axis plays an important role in inflammatory processes, closely involved in the interaction between neuroendocrine regulation and immune responses. This activation specifically promotes the secretion of glucocorticoids such as cortisol, which play an important role in anti-inflammatory and immunosuppressive processes (Lei et al., 2025).

The skin is the largest organ in the body. It responds to various stimuli that come from inside and outside the body. The skin is essential for protecting the body and maintaining balance (Crucianelli et al., 2022). The function of the epidermal barrier depends not only on structural integrity, but also on the coordinated movement of the immune, endocrine, nervous systems of the skin (Table 1).

Table 1. Components of neuroendocrine and immune tissues in the skin.

System Name	"System Components"
Nervous system	"Sensory nerve fibers (β, Aδ, C) that secrete peptides, neuronutrients, and autonomic neurohormones (sympathetic and parasympathetic)
Endocrinology	"Hormones Secreted by Skin Cells, e.g., CRH, ACTH, cortisol, α-MSH, β-endorphins"
Immune system	"Immune cells (macrophages, monocytes, oranges, basals, neutrophils, T cells, commercial cells, dendritic cells, fungal lymphocytes)"

Components of this regulatory system, such as cortisol, catecholamines, and noropepeptides, influence the immune response. This can help promote or worsen the progression of the disease. The skin is the main barrier that the body guards against environmental threats. Previous research has shown that the skin reacts strongly to stress. Experiments have shown that stress can affect the skin's innate and adaptive immune responses (Gribonika, 2025).

The clinical manifestations of glucocorticoid resistance vary widely, with chronic fatigue associated with a lack of glucocorticoid function in the central nervous system, ranging from different degrees of hypertension that can occur regardless of alkaline status. The condition is often associated with high levels of cortisol, corticosteroids such as certain steroids that increase salt retention, and increased androgen production in the adrenal glands. In women, excessive androgen levels can lead to clinical features such as acne, hair growth, menstrual disorders, oligomeric formation, and infertility. In men, hyperandrogens can contribute to infertility, and in children, they can lead to premature puberty. Various molecular defects, such as spot mutations or microdeletions in the highly conserved glucocorticoid receptor genes, alter the functional properties or concentrations of intracellular receptors, and appear to cause glucocorticoid resistance (Huang & Wang, 2022).

Research questions are essential for leading investigations and forming scientific goals. By focusing on a specific phenomenon, the researchers created a clear framework for analysis (Alvesson & Sandberg, 2023). The clarification question explains how stress-induced cortisol dysregulation affects the onset, progression, and severity of psoriasis, atopic dermatitis, and acne. Examining glucocorticoid receptor sensitivity, peripheral cortisol metabolism via 11β-HSD1, and HPA axis integrity in the skin may

reveal the mechanism of the relationship between stress and dermatitis (Lee et al., 2023). Introduction examines the regulation of the HPA axis and the role of cortisol in dermatitis. The following sections systematically review and analyze the effects of psychological interventions such as attention-based stress reduction, cognitive behavioral therapy, and heart rate variability biofeedback on cortisol and skin outcomes (Zhang et al., 2026). The analysis was based on randomized controlled trials and took into account disruptors such as corticosteroid use, comorbid psychiatric disorders, and differences in cortisol measurements. This review highlights the ongoing need for standardized cortisol assessments and rigorous trial designs to support the treatment of stress-driven skin disorders.

Methods

This study will use a literature review approach. Literature searches will be conducted through online databases including Scopus, ScienceDirect, and Google Scholar. The research strategy will use keywords such as stress, cortisol levels, dermatitis, HPA axis, brain-skin axis, and skin neuroimmunology. All searches will be conducted in English to obtain comprehensive literature regarding the relationship between stress, cortisol regulation, and dermatitis mechanisms, without publication year restrictions.

The inclusion criteria will consist of: (1) original research articles and review articles discussing stress-related mechanisms in dermatitis; (2) studies examining cortisol regulation, HPA axis activity, brain-skin axis interactions, or skin neuroimmunology; (3) articles published in peer-reviewed journals; and (4) full-text articles available in English. Exclusion criteria will include duplicate articles, conference abstracts without full text, non-peer-reviewed sources, and studies not directly related to dermatitis or stress-mediated mechanisms.

The screening process will be conducted in several stages. First, titles and abstracts identified from the databases will be reviewed to determine relevance. Second, duplicate studies across databases will be removed. Third, full-text screening will be performed to ensure that the selected studies meet the inclusion criteria. The selection process is expected to identify approximately 80–120 relevant articles from an initial search yield of several hundred studies across Scopus, ScienceDirect, and Google Scholar databases.

Results and Discussion

Physiology of the brain-skin axis

Centralization of the HPA axis and regulation of cortisol.

The hypothalamic-adrenal axis (HPA axis) is the primary endocrine system that regulates the physiological response to stress in humans. The last hormone produced through this axis, cortisol, has immediate and long-term effects on the body's systems, including the metabolic system, cardiovascular system, and central nervous system. Advances in neuroimaging techniques have allowed researchers to study the neural networks and regulatory mechanisms that regulate cortisol activity in the central nervous system in different human populations. Studies in humans and animals have shown that several brain regions, including the hippocampus (HC), amygdala (AG), prefrontal lobe (PFC), and various brainstem nuclei, play an important role in regulating cortisol secretion during the stress response. In general, when discussing the impact of these structures on the regulation of the HPA axis, it is necessary to distinguish between the types of voltages (Rusch et al., 2023).

Sahin et al., (2023) showed that the flame rhythm of the HPA axis is regulated by the correlative nucleus, and cortisol is the main mediator between the central circadian clock and peripheral tissue. This regular disorder is manifested in shift workers and some clinical diseases, for example, and is associated with metabolic disorders, an increased risk of cardiovascular disease, and death. On the other hand, a decrease in cortisol rhythmic capacity persists in adrenal insufficiency, affecting quality of life even with medication.

In addition, Nunez et al., (2025) revealed that chronic stress results in HPA axis dysfunction and cortisol dysregulation, resulting in glucocorticoid resistance, cytokine imbalances, and inflammatory conditions. This imbalance is associated with an increased risk of autoimmune diseases such as lupus, rheumatoid arthritis, and multiple sclerosis, and the HPA axis has been identified as an important mechanism linking psychological stress to autoimmune stress.

The activity of the hypothalamic–pituitary–adrenal (HPA) axis is regulated by various afferent neural pathways, including sympathetic, parasympathetic, and limbic circuits. Brain regions such as the amygdala, hippocampus, and medial prefrontal cortex contribute to this modulation by providing direct or indirect neural input to the paraventricular nucleus (PVN) of the hypothalamus. The PVN integrates convergent excitatory stimuli, including catecholaminergic, glutamatergic, and serotonergic inputs, as well as inhibitory signals (Mclntyre et al., 2023). In addition, prolonged exposure to chronic stress is strongly associated with the development and development of neurodegenerative diseases, including Alzheimer's

and Parkinson's disease. This association is mainly caused by excessive cortisol secretion, disorders of the hypothalamic-pituitary-adrenal (HPA) axis, and neuroinflammatory processes in the central nervous system. In addition, the association between cortisol imbalance and major depressive disorder varies, often accompanied by HPA axis hyperactivity and persistent inflammatory responses. Finally, chronic pain is associated with abnormal cortisol patterns that increase pain sensitivity and sensitivity (Trevino et al., 2022)

Skin as an endocrine organ

The skin has an internal endocrine system that is closely related to the body's neuroendocrine glandular axis. These interactions are believed to maintain overall skin and physiological balance while improving the peripheral nerve response to stress (Slominski et al., 2025). This activity is regulated by endocrine axons within the skin, which are mainly made up of intracutaneous HPA axons. Slominski and Watzman were among the first researchers to show that human skin, which regulates the activity of the hypothalamic-pituitary-adrenal axis, expresses CRH, urocotine, and POMC, and secretes their products ACTH, α-MSH, and beta-endorphins.

These findings were later supported by Itoi et al., suggesting that the skin can produce cortisol again. The enzyme that converts the inactive hormone cortisone into active cortisol inside the cell is 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1). In addition Barukcic et al., (2025), it has been reported that the effects of glucocorticoids are determined not only by hormone levels in the bloodstream, but also by glucocorticoid receptor (GR) structure, synaptic morphological diversity, and tissue-specific signaling kinetics. As Jack Lockett et al. have shown, the classic dichotomy between the anti-inflammatory effects of metastasis inhibition and the metabolic effects of metastasis activation are no longer sufficient to explain the glucocorticoid response. Identification of different forms of GR and context-dependent receptor activity suggests that glucocorticoid sensitivity or resistance is caused by modulation of receptor levels.

The skin acts as a physical barrier that separates the biological milieu from the external environment. At the systemic level, the primary central regulator of responses to perceived stress is the hypothalamic–pituitary–adrenal (HPA) axis, whose activation follows a sequential pathway beginning with the release of corticotropin-releasing factor (CRF), followed by the involvement of corticotropin-releasing factor receptor 1 (CRF1), pro-opiomelanocortin (POMC), and the synthesis and release of adrenal glucocorticoids. In addition, the activity of this axis is modulated by cytokines (Tan et al., 2026. The same axis is also expressed in the skin, where it represents an important component of the local response to cutaneous stress. The skin should not be regarded solely as a passive physical barrier; rather, it operates as an active neuroendocrine organ capable of detecting, integrating, and responding to various environmental stimuli. It synthesizes and releases a broad spectrum of hormones, neuropeptides, and biologically active substances (Slominski et al., 2022).

Cortisol receptors in skin cells

Glucocorticoid (GC) derivatives are among the most effective and commonly prescribed therapeutic agents used in the management of inflammatory and autoimmune disorders. However, their therapeutic use is limited by an adverse side-effect profile that, in the skin, includes epidermal thinning, dermal atrophy, impaired wound healing, and increased fragility, dehydration, and infection risk (Lesovaya et al., 2022). De Mello et al., (2025) were among the first to demonstrate that human skin expresses functional glucocorticoid receptors, characterized by specific and saturable steroid binding, as well as biochemical properties consistent with classical steroid hormone receptors. Their findings further revealed that receptor density varies across different skin layers, anatomical locations, and age groups, providing early evidence that the skin's response to glucocorticoids is region-specific and subject to biological regulation.

Further, Veloso et al., (2025) shows that cortical receptors (MR) are widely expressed in the skin space and are activated by high-affinity glucocorticoids. These findings suggest that the skin's corticosteroid response is not only affected by glucocorticoid receptors but also by magnetic resonance signals, which contribute to therapeutic effects and side effects such as skin atrophy.

In addition, pharmacological evidence presented by Ali et al (2025) et al suggests that selective and dual interactions between GR and MRI modulate skin gene expression in different ways in old mice. Their results suggest that the presence of receptor dynamics as well as receptors modulates inflammatory signals and skin differentiation, reinforcing the idea that the cutaneous corticosteroid response depends on the complex interactions between GR-MR.

These studies have shown that cutaneous corticosteroid signaling is modulated not only by circulating glucocorticoids, but also by locally regulated receptor networks, including glucocorticoid receptors and mineralocorticoid receptors (Rosa et al., 2024). The density, distribution, and dynamic interactions of the GR–MR complex determine tissue-specific sensitivity, inflammatory regulation, and skin structural integrity (Sueyoshi et al., 2025). Therefore, this receptor-centred regulatory system is crucial in

shaping the therapeutic efficacy and side effects of glucocorticoids in dermatological contexts.

Cortisol kinetics in psychological stress

Acute stress response

Acute and chronic stress can be evaluated through physiological markers such as heart rate, blood pressure, and metabolic hormone levels. However, interpreting cortisol fluctuations remains challenging because serum and salivary cortisol mainly reflect short-term changes and are influenced by circadian rhythm and protein-binding variations (Shkvarok-Lisovenko et al., 2025).

Previous studies demonstrated that acute stress is associated with alterations in cortisol levels and selective cognitive regulation. Vidara et al. (2000) reported that reduced cortisol levels were linked to improved short-term memory and hippocampal-dependent cognitive performance. These findings suggest that cortisol fluctuations during acute stress selectively influence specific cognitive domains rather than producing uniform effects.

Expanding this perspective, Boucher & Plusquellec, (2019) proposed the concept of Cortisol Excess Load Proportion based on allostasis theory, emphasizing regulatory imbalance rather than cortisol elevation alone. Similarly, Floriou-Servou et al., (2021) showed that acute stress induces coordinated multi-omic changes across stress-sensitive brain regions, highlighting the complexity of neuroendocrine stress responses.

These results suggest that acute stress cannot be adequately characterized by cortisol measurements alone. In contrast, cortisol fluctuations selectively affect cognitive regions (Morales et al., 2026). Together, this evidence supports a multidimensional framework in which acute stress represents a dynamic regulatory process encompassing endocrine signalling (Schuler et al., 2026), cognitive modulation (Langer et al., 2023), and multiomic reorganization rather than simply an increase in circulating cortisol (Sitorus et al., 2025).

Chronic stress and rostatic load

Despite these challenges, studies using allostatic load (AL) markers such as cortisol, catecholamines, cholesterol, blood pressure, and cytokines consistently demonstrate that elevated AL is associated with impaired physiological functioning, poorer mental and physical health, increased cardiovascular risk, and higher mortality in older adults (e.g., Gruenwald, Seaman, Liv, Calamangla, Singer, 2006; Juster et al., 2010; MacYu, 2007).

Lennart-Bogle et al (2022) showed that an increase in heterogeneous load index is Lennart-Bogle et al. (2022) further reported that increased allostatic load is associated with structural and functional brain changes, particularly in stress-sensitive regions including the hippocampus, prefrontal cortex, and white matter tracts. Their systematic review confirmed that chronic stress-related biological dysregulation is linked to measurable neuroanatomical alterations in both clinical and non-clinical populations. Similarly, Miranda-Galves et al., (2025) found that higher allostatic load in patients with chronic myeloid leukemia was associated with poorer treatment outcomes, including lower probability of optimal molecular response and increased risk of disease progression and mortality. These findings support the role of allostatic load as an integrative biomarker reflecting the cumulative effects of chronic physiological stress on disease progression.

Overall, persistent elevation of allostatic load reflects chronic biological dysregulation associated with reduced physiological resilience, cognitive and functional decline, neurostructural changes, and increased morbidity and mortality (Rodriguez et al., 2019).

Glucocorticoid resistance

The results of previous studies indicate that chronic stress exposure is associated with the development of glucocorticoid receptor resistance (GCR). Cohen et al., (2012) demonstrated that individuals exposed to prolonged stress showed reduced glucocorticoid receptor sensitivity, increased inflammatory cytokine production, and a higher risk of symptomatic infection. These findings support the hypothesis that chronic stress impairs cortisol's anti-inflammatory function, contributing to persistent inflammation through reduced GR-α sensitivity in target tissues.

Similar evidence has been reported in inflammatory diseases. Zhang, (2022) found that patients with asthma exhibited differences in cellular sensitivity to dexamethasone and reduced inhibition of Th2 cytokine production, indicating impaired glucocorticoid responsiveness. This supports the broader concept that decreased receptor sensitivity weakens the regulation of inflammatory processes.

Furthermore, Care, (2022) emphasized that glucocorticoid–GRα signaling functions as a coordinated phase-specific regulatory system essential for maintaining physiological homeostasis during stress. Disruption of this mechanism may lead to persistent inflammatory activation, energy depletion, and increased allostatic load. Consistent with this framework, Meduri et al. (2022.) suggested that GC–GR signaling also contributes to maintaining barrier integrity and limiting inflammatory damage.

Overall, these findings suggest that impaired GRα sensitivity represents an important biological link between chronic stress and persistent inflammatory disorders, including inflammatory skin diseases such as dermatitis.

Evidence suggests a link between cortisol dysregulation and inflammatory skin disease

Psoriasis

Psoriasis is a chronic inflammatory skin disease characterized by red plaques covered with white-silver scales, often accompanied by systemic complications such as psoriatic arthritis and cardiovascular disease (Wang et al., 2025). In the analysis, patients with psoriasis had significantly lower salivary cortisol levels ($P< 0.01$) after exposure to social performance stress ($P = 0.016$) and lower serum cortisol concentrations, while patients who thought they were unresponsive to stress ($P = 0.016$) showed it. On the other hand, there was no difference between the groups in changes in pulse rate after stress. (Richards et al., 2005)

Andrea William M. Evers et al found that people with high levels of stress tended to have worse psoriasis more often. In addition, the relative risk (RR) of psoriasis recurrence in individuals exposed to stressful events was set at 4.92 compared to controls. The exact biological mechanism is unknown, but dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) is believed to play an important role. Evidence suggests that patients with psoriasis have a low cortisol response to stress, usually low cortisol levels, while levels of the hormones adrenaline and adrenocorticotropics are relatively high. These changes increase levels of inflammatory cytokines such as TNF-a, IL-1, IL-6, and interferon α (IFN-α), which have been shown to cause psoriasis (Potestio et al., 2024)

Tumor necrosis factor (TNF) has long been recognized as an important inflammatory cytokine in the pathogenesis of psoriasis. In the skin of psoriasis lesions, an increase in TNF and its receptors, TNFR1 receptors, TNFR2 receptors, are usually observed. In addition, TNF was the first cytokine to be therapeutically targeted against psoriasis, and its inhibition has shown clinically significant effects. In addition, members of the interleukin-1 family, especially interleukin-36α (IL-36α), interleukin-36beta (IL-36β), and interleukin-36gamma (IL-36γ), are regulated in the lesion family and are considered important contributors to disease progression. Experimental evidence suggests that IL-36α deficiency may protect against imikimod-induced dermatitis. In addition, the loss of functional mutations in IL36RN, which encodes normal antibodies in IL-36 signaling, has been identified as a genetic factor in some common cases of pustular psoriasis. Psoriasis recurrences are often observed in skin that heals after treatment is stopped, suggesting that the tendency to increase recurrence is still present in the tissues. Indeed, in psoriasis patients, non-lesion skin grafts caused by immunocompromised mice have resulted in psoriasis lesions that rely on local T cell proliferation. (Afonina et al., 2021)

Atopic dermatitis

Psychological stress is a contributing factor to many diseases, especially in skin diseases that worsen symptoms when stress increases. These conditions include psoriasis, vitiligo, atopic dermatitis, simple aneurysms, alopecia areata, urticaria, and flat algae, all of which can increase stress-related physiological and psychological changes. Stress can cause or worsen conditions such as itchy dermatitis, seborrheic dermatitis, and hyperhidrosis. (Afonina et al., 2021)

Psoriasis occurs primarily as a result of an immune response through the activation of helper T cells 17 (Th17) and interleukin-17 (IL-17). Atopic dermatitis, on the other hand, is characterized primarily by a helper T cell (Th2) immune response, which is associated with increased production of interleukin-4 (IL-4) and interleukin-13 (IL-13). Despite these differences, both diseases involve activation of the T-helper 22 (Th22) and T-helper 1 (Th1) pathways, which are accompanied by increased interleukin-22 (IL-22) and interferon-gamma (IFN-γ) pathways, respectively. Alzheimer's disease is often associated with increased IgE production, pronounced sensitivity, and asthma, which may be caused by increased Th2 activation, which is rare in psoriasis (Guttman-Yassky et al., 2017). Boskey-Kirschbaum et al (1997) conducted a series of studies showing that children with atopic dermatitis had a significantly weaker cortisol response to laboratory-induced psychosocial stress than healthy people who supervised both controls. This strong cortical non-neuronal reactivity suggests that the HPA axis is in a state of minus reactivity, which can limit the anti-inflammatory capacity of the inner cortex under stress exposure.

Hypoadrenal function is a condition in which the adrenal glands fail to produce sufficient amounts of cortisol (glucocorticoids responsible for maintaining blood pressure, blood sugar, and energy levels during physiological stressors such as illness, surgery, and injury) (Ahmet et al., 2011). Evidence suggests that there is a two-way relationship between sleep quality and cortisol regulation. A study by Jui Tsai showed a significant relationship between cortisol levels and sleep quality. Similarly, a study by Kai Roy et al reported that people with poor sleep quality tended to have a slower cortisol arousal response (CAR), an even tendency to release cortisol during the day, a decrease in total sleep time (TST), and a longer latency to sleep onset (SOL). Disruption of normal cortisol secretion patterns can contribute to sleep disorders, increasing the risk of insomnia, sleep deprivation, and the accumulation of sleep debt. In contrast, poor sleep quality leads to an increased stress

response in cortisol, changes in cortisol secretion patterns during the day, and lower cortisol levels in the morning. Activation of the hypothalamic-pituitary-adrenal (HPA) axis stimulates cortisol secretion, increases consciousness, increases brain activity, and inhibits slow-wave sleep. This study shows that cortisol is a mediator and consequence of sleep disorders in shift workers (Sukor et al., 2025).

Atopic dermatitis (AD) is a chronic inflammatory skin disease that arises from a complex interaction between environmental stress and psychological stress responses. An interactive relationship has been observed between Alzheimer's disease and stress. On the other hand, the presence of Alzheimer's disease contributes to increased stress in affected individuals. On the other hand, psychological stress can exacerbate the severity of the disease. Current evidence suggests that activation of the hypothalamic-pituitary-adrenal axis in the central and peripheral skin plays an important role in influencing the neuroimmune response and health of the skin barrier as a molecular mediator of the stress response. HPA axis dysregulation has also been reported in Alzheimer's patients. The study of the PS response is important because inflammation and skin barrier function are key factors in the pathogenesis of Alzheimer's disease. (Lin et al., 2017)

Acne vulgaris

Acne Vulgaris is a prevalent inflammatory skin disorder that affects more than 85% of adolescents globally. The development of this condition is multifactorial, involving several contributing factors. Among these, psychological stress has been identified as an important factor that can influence the onset and progression of various dermatological conditions, including acne. 24 Seventy-four percent of 178 patients and relatives in a questionnaire survey reported that they believed that anxiety is an exacerbating factor of acne (Zari et al., 2017).

Patients with acne may experience worsening of the disease during examinations. Furthermore, changes in acne severity correlate highly with increasing stress, suggesting that emotional stress from external sources may have a significant influence on acne (Chiu et al., 2003).

Findings from a study by Mathilde Mordaunt et al. showed that salivary cortisone measurements at 9:00 AM after a 1 mg overnight dexamethasone suppression test (ONDST) had excellent diagnostic performance compared to serum cortisol. In an analysis of 34 individuals, serum cortisol was not suppressed in 22 cases, and a strong correlation was found between salivary cortisone levels and post-dexamethasone serum cortisol ($r^2 = 0.65$; $p = 0.009$). The classification agreement between the two methods reached 94.1% with a kappa value of 0.87 ($p < 0.0001$). The sensitivity of salivary cortisone in detecting possible cortisol excess based on a serum cortisol cut-off of >50 nmol/L reached 100%, with a specificity of 84.6%, a positive predictive value of 90.5%, and a negative predictive value of 100%. Only two cases showed misclassification, with salivary cortisone/serum cortisol values of 5.9/23 nmol/L and 7/32 nmol/L, respectively, so that, overall, the analysis results support the potential of salivary cortisone as a reliable non-invasive alternative for the evaluation of suspected Cushing's syndrome (Mordaunt et al., 2025).

Corticotropin-Releasing Hormone (CRH) and Cortisol have been shown to stimulate sebaceous gland activity and are therefore considered important contributors to the pathogenesis of Acne Vulgaris. Experimental studies in rodents have demonstrated that prenatal exposure to Polychlorinated Biphenyls (PCBs) can increase cortisol concentrations in female offspring. In human studies, inhalation of the essential oil Salvia sclarea (clary sage) has been associated with reduced cortisol levels in postmenopausal women. Thus, while EDCs may alter endogenous cortisol levels, the link between cortisol, cutaneous CRH expression, and activity remains unclear [61](Rao et al., 2021).

Exposure to stress-related levels of Cortisol has been shown to suppress the expression of inflammatory cytokines, enhance Glucocorticoid Signaling pathways, and promote the activation of pro-fibrotic gene targets in human vocal fold fibroblasts (hVFF). The combination of stress-analogous cortisol exposure and LPS upregulated inflammatory cytokines, glucocorticoid signalling gene expression, and protein expression of a-SMA (Venkatraman et al., 2025).

Urticaria

Urticaria has been recognized as a dermatological condition since ancient times. Clinically, it can be categorized into several subtypes, including spontaneous urticaria (both acute and chronic forms), physical urticarias, specific variants such as Contact Urticaria, and diseases related to urticaria for historical reasons (e.g., urticaria pigmentosa). Most urticaria subtypes have a profound impact on quality of life, and effective treatment is thus required if diagnostic procedures do not reveal a treatable cause (Wedi et al., 2009).

Bettina Wedi et al. indicate that infection plays a clear causal role in acute spontaneous urticaria, whereas in chronic spontaneous urticaria, there is evidence that eradication of persistent infection, particularly Helicobacter pylori, is associated with significant clinical improvement. Analysis of studies evaluating the course of chronic urticaria after Helicobacter eradication showed a statistically

significant benefit compared with untreated patients or Helicobacter-negative controls without urticaria ($p < 0.001$). In contrast, in physical or other specific forms of urticaria, evidence of an association with infection is limited. Overall, these findings support the identification and treatment of infection, particularly Helicobacter pylori, as contributing to remission of spontaneous chronic urticaria and warrant consideration in routine diagnostic evaluation.

Maurer et al (2020) confirm that chronic urticaria (CU), particularly chronic spontaneous urticaria (CSU), is primarily driven by mast cell activation, including autoimmune forms mediated by autoantibodies targeting mast cells. This update emphasizes that the goal of therapy is complete disease control, i.e., the absence of signs and symptoms and normalization of quality of life, which is now monitored using an increasingly broad spectrum of patient-reported outcome measures (PROMs), including new instruments such as the Angioedema Control Test and the Cholinergic Urticaria Activity Score. Furthermore, therapeutic developments are focusing on agents that block signals that trigger mast cell activation and accumulation, inhibit intracellular degranulation pathways, or suppress mast cell activity through inhibitory receptors. Overall, this update demonstrates that understanding of the pathogenesis and management of CU continues to advance rapidly, although there is still a need for routine diagnostic tests to detect autoimmune CSU types I and IIb, as well as for more effective, well-tolerated long-term therapies.

Current understanding points to two main axes in the management of chronic urticaria: the identification and eradication of treatable triggers, such as infections, and interventions that target mast cell activation mechanisms more precisely. However, the need for routine diagnostics for autoimmune subtypes and more optimal long-term therapy remains a challenge.

Cortisol as a Biomarker: Measurement and Challenges

Salivary, serum, and hair cortisol

Stress-related activation of the Hypothalamic–Pituitary–Adrenal Axis (HPA axis) can be assessed using various biological samples and analytical matrices, each presenting specific advantages and limitations. For instance, blood cortisol measurements typically reflect short-term stress responses and enable evaluation of HPA axis activation following a particular event. However, the procedures involved in handling or restraining animals during blood collection may themselves induce stress, potentially elevating cortisol concentrations. Consequently, repeated blood sampling within short intervals is generally not recommended. To minimize such confounding effects, there has been increasing interest in non-invasive approaches for cortisol assessment using alternative matrices such as hair, feces, urine, and saliva. Cortisol and GC metabolite levels in hair and faeces reflect blood concentrations over months and days, respectively, and are useful to monitor cumulative and chronic aspects of stress (Verspeek et al., 2021).

Salivary Cortisol is widely utilized as a biomarker for assessing psychological stress. Nevertheless, the underlying psychobiological mechanisms that activate the Hypothalamic–Pituitary–Adrenal Axis (HPA axis) cannot be directly evaluated solely through salivary cortisol measurements. The reactivity of the HPA axis is regulated by multiple components, including the Hippocampus, Hypothalamus, Pituitary Gland, and Adrenal Glands, as well as by various modulators, receptors, and binding proteins that may influence cortisol levels detected in saliva. Consequently, a direct linear relationship between plasma Adrenocorticotropic Hormone (ACTH) and cortisol concentrations measured in blood or urine may not always be observed. This is particularly true under response conditions (Hellhammer et al., 2009).

In humans, under normal physiological conditions, a transient increase in Cortisol levels typically occurs following the consumption of carbohydrate-rich meals administered at intervals of approximately 6 to 12 hours. Accurate identification of this postprandial cortisol response requires strict standardization of both the timing and composition of meals among study participants to distinguish it from the hormone's natural pulsatile secretion pattern. The initial phase of glucose counter-regulation is triggered when blood glucose levels reach around 3.75 mmol/L (68 mg/dL), characterized by increased secretion of Glucagon, Adrenaline, and Growth Hormone. In contrast, cortisol secretion generally rises only when glucose concentrations decline below approximately 3.5 mmol/L (63 mg/dL). In nocturnal rodents (in which intermeal fasting periods are habitually short), a nutritional challenge consisting of restricting daily food access to a few daytime hours (i.e., during their resting period) results in the appearance of a food-anticipatory rise in circulating corticosterone before the mealtime, in addition to the nocturnal rise controlled by the master clock (Oster et al., 2017).

Serum or plasma cortisol measures total cortisol (both bound and free) and provides a snapshot at a single point in time. While useful for clinical assessment of adrenal function, its usefulness in stress research is limited by the stress of blood sampling itself, which can acutely increase cortisol levels (Iqbal et al., 2023).

Moreover, single measurements fail to capture the dynamic nature of cortisol secretion. (Manenschijn

et al., 2011) demonstrated that a single serum cortisol measurement is poorly reproducible and weakly correlates with integrated measures of cortisol exposure over time.

Measurement of Cortisol in scalp hair has recently emerged as a useful indicator of cumulative activity of the Hypothalamic–Pituitary–Adrenal Axis (HPA axis), offering advantages over traditional biological samples such as saliva, urine, or blood that are commonly used to evaluate cortisol levels and HPA function. Cortisol concentration in the most proximal 3 cm segment of scalp hair is considered a retrospective marker reflecting overall HPA axis activity during the previous three months. This measure is conceptually similar to Hemoglobin A1c, which serves as an indicator of average blood glucose control over a comparable three-month period. Cortisol obtained from scalp hair is a lipophilic substance that originates from the vascular supply that nourishes the hair shaft follicular cells (Wright et al., 2015).

In dermatology, hair cortisol has been used to study chronic stress in conditions like alopecia areata and chronic urticaria. Söder et al (2019) showed that individuals at high risk for psychosis, both clinical risk (n = 43) and familial risk (n = 32), did not have significantly higher hair cortisol concentrations than low-risk controls (n = 35), thus disproving the assumption that chronic HPA axis hyperactivation is an indicator of early vulnerability to psychosis. However, exposure to severe social stressors such as childhood abuse and traumatic events significantly predicted increased hair cortisol levels across the entire sample.

A comparative study conducted by Paolo Gisondi reported that Psoriasis was significantly associated with higher scores on the Perceived Stress Scale (PSS) and the Hospital Anxiety and Depression Scale (HADS). These associations remained significant after controlling for potential confounding factors, including sex, body mass index, diabetes, hypertension, dyslipidaemia, and occupational status. Furthermore, salivary Cortisol levels were significantly lower in patients with psoriasis than in control participants (9.6 ± 0.5 vs. 14.0 ± 1.1 nmol/L, $p < 0.001$). In conclusion, psoriasis was associated with higher psychological stress, anxiety, and depressive symptoms, and with impaired cortisol response to stress (Gisondi et al., 2021). Future studies should consider multi-matrix approaches to capture the full complexity of cortisol dynamics in inflammatory skin disease (Juliana et al., 2025).

Correlation studies with disease severity

A growing body of literature has attempted to correlate cortisol levels with clinical severity in inflammatory skin diseases, although findings are often inconsistent and sometimes contradictory, reflecting the complex and non-linear nature of HPA axis dysregulation. In psoriasis, several studies have reported an association between cortisol and disease activity. Evers et al observed that in people with high levels of stress, exacerbations of psoriasis were more frequent. In addition, an RR of 4.92 was calculated for psoriasis flares among those exposed to stressful events, compared with controls. 39 Although the exact mechanism is not known, it is believed that a disturbance of the hypothalamic-pituitary-adrenal axis underlies it (Potestio et al., 2024).

Psychosocial stress (PS) and hypothalamic-pituitary-adrenal (HPA) axis dysfunction contribute to inflammatory dynamics in inflammatory skin diseases such as atopic dermatitis (AD), psoriasis, and chronic urticaria (CU). AD is known to be associated with central and peripheral activation of the cutaneous HPA axis, which influences neuroimmune responses and skin barrier function, and is characterized by a predominance of Th2 (IL-4, IL-13) responses, in contrast to psoriasis, which is driven by Th17/IL-17, although both have Th22 and Th1 activation. A study by Angelika Buske-Kirschbaum showed that children with AD had a significantly lower cortisol response to psychosocial stress compared to healthy controls, suggesting HPA hypo reactivity that potentially limits endogenous anti-inflammatory capacity during stress, a mechanism that could theoretically worsen clinical severity.

In terms of measurement methodology, research by Mathilde Mordaunt showed that salivary cortisone after an overnight 1 mg dexamethasone suppression test correlated strongly with serum cortisol ($r^2 = 0.65$; $p = 0.009$), with a sensitivity of 100% and a specificity of 84.6%, thus providing a reliable non-invasive approach to evaluate HPA function in clinical studies. In urticaria, Bettina Wedi reported that eradication of Helicobacter pylori resulted in a significant improvement in chronic spontaneous urticaria ($p < 0.001$), while an update by Marcus Maurer confirmed that mast cell activation, including autoimmune forms, is a major driver of disease severity, with therapeutic targets aimed at comprehensive control of inflammation and normalization of quality of life.

However, interpretation of the correlation between cortisol levels and disease severity must consider confounding factors such as the use of topical or systemic corticosteroids that suppress endogenous cortisol production, the use of antidepressants or anxiolytics that modulate HPA activity, the chronicity of the disease that can lead to HPA axis exhaustion in later phases, and age and sex variations that influence basal cortisol profiles (Levin et al., 2002). Psychological factors such as depression and anxiety,

which very often co-occur with inflammatory skin diseases, independently influence cortisol secretion and may confound this relationship (Yang et al., 2025).

Chronicity of the disease also plays a role. Patients with long-standing disease may exhibit HPA axis exhaustion and low cortisol levels, whereas those with recent-onset disease may exhibit elevated cortisol levels (Sitorus et al., 2025). Age and gender are additional factors; premenopausal women exhibit different cortisol profiles than men, and children have different normative values than adults (Roelfsema et al., 2017).

Therapeutic Implications: Modulating the Stress-Cortisol Axis

Psychological interventions

Given the well-documented role of psychological stress in exacerbating inflammatory skin diseases, interventions aimed at reducing stress and modulating the HPA axis are gaining increasing attention as adjunctive therapies in dermatology. These interventions range from mind-body techniques to structured psychotherapy, with varying degrees of evidence supporting their effectiveness. Mindfulness-based stress reduction (MBSR), an 8-week program combining mindfulness meditation and yoga, is among the most rigorously researched interventions (Kriakous et al., 2021).

Psychiatry & 1982 (1982), reported the results of a 10-week mindfulness meditation-based stress reduction and Relaxation program in 51 chronic pain patients who had previously shown no improvement with conventional medical therapy. After the intervention, 65% of patients experienced a ≥33% reduction in the mean total Pain Rating Index (Melzack), and 50% showed a ≥50% reduction, along with significant reductions in other pain indices and the number of reported medical symptoms. In addition, there were large and significant improvements in mood disturbance and psychiatric symptoms that remained relatively stable at follow-up, with consistent effects across pain categories. Although this study did not evaluate endocrine parameters such as cortisol and lacked a control group, the authors suggest that mindfulness practice facilitates a "decoupling" between the sensory dimensions of pain and the affective-evaluative reactions, thereby improving self-regulation and reducing overall suffering.

Subsequent research by (Sanada et al., 2016)0] sought to clarify the effects of Mindfulness-Based Interventions (MBIs) on salivary cortisol levels in a healthy adult population through a meta-analysis. By analysing five randomized controlled trials (RCTs), they found a moderate positive effect (Hedges' g = 0.41) of these interventions on health-related cortisol levels. Further analysis showed that the effectiveness of MBIs was significantly influenced by participant age and program duration, with greater numbers of sessions and total training hours correlating with greater effects. These findings suggest potential physiological benefits of mindfulness in healthy individuals, although the researchers emphasized the need for more RCTs with standardized methodology to confirm these results.

MBSR training in patients with SAD may reduce emotional reactivity while enhancing emotion regulation. These changes might facilitate a reduction in SAD-related avoidance behaviours, clinical symptoms, and automatic emotional reactivity to negative self-beliefs in adults with SAD. Cognitive Behavioral Therapy (CBT) is a psychotherapeutic approach designed to help individuals recognize and modify maladaptive or distressing patterns of thinking that negatively affect their emotions and behaviours. Through this process, CBT encourages the reduction of avoidant and safety-seeking behaviours that may hinder the correction of inaccurate beliefs. By addressing these cognitive and behavioural patterns, CBT can support more effective stress management, thereby contributing to the prevention or reduction of stress-related disorders and the improvement of overall mental well-being. Under stressful conditions, some individuals tend to feel pessimistic and unable to solve problems (Nakao et al., 2021). Zachariae et al (1996) assigned random psoriasis patients to receive either guided imagery and relaxation recordings or standard care during phototherapy. The intervention group showed significant improvements in PASI scores and reported lower stress levels. The results indicated small but statistically significant changes in TSS and LDBF within the treatment group, whereas no significant differences were observed in the control group. When the analyses were conducted separately for each group, participants in the treatment group demonstrated significant reductions across all three measures of Psoriasis activity. In contrast, the control group did not exhibit any measurable changes.

Ribeiro et al. evaluated the effectiveness of a heart rate variability biofeedback (HRV-BF) protocol on mental health symptoms in 21 frontline healthcare workers. The intervention was implemented in five weekly sessions. Pre- and post-intervention measurements used psychometric questionnaires and electrophysiological parameters. Results showed a decrease in mental health symptoms, perceived stress, and chronic stress levels after the intervention. Physiologically, a decrease in respiratory rate and increases in SDNN, LFn, and the LF/HF ratio were observed. These findings indicate that HRV-BF is effective in improving autonomic regulation and reducing psychological stress burden.

Electrophysiological parameters have the potential to serve as objective indicators of response to stress-regulation-based interventions (Castro Ribeiro et al., 2023).

Psychological interventions, particularly MBSR and CBT, are promising adjunctive treatments for inflammatory skin diseases, with evidence suggesting they can reduce stress, modulate cortisol, and improve clinical outcomes. However, larger trials, with rigorous methodology, longer follow-up periods, and standardized cortisol measurements are needed to establish definitive efficacy and identify which patients are most likely to benefit (Ach et al., 2025).

Pharmacological approaches

While psychological interventions target cognitive and stress behaviors, pharmacological approaches offer alternative or complementary strategies to modulate the HPA axis and reduce the negative effects of cortisol dysregulation on skin health. This approach can generally be categorized as an approach that directly targets the HPA axis and indirectly affects mood, inflammation, and neuroendocrine function. (Choi et al., 2018)

CRH receptor antibodies are a direct pharmacological strategy to inhibit HPA axis activity during peak periods. Identification of corticotropin-releasing hormone receptors, development of corticotropin-releasing hormone (CRH) agonists and antagonists, and the application of advanced chemical immunochromatography techniques have provided strong evidence that CRH is involved in the regulation of several biological systems. The purpose of this review is to summarize the findings of recent research on these 41 amino acid peptides.(Caruso et al., 2022)

Glucocorticoid receptor modulators offer another straightforward approach. The physiological and pharmacological effects of glucocorticoids are primarily driven by NR3C1, which encodes glucocorticoid receptors (GR). GR belongs to the hypernuclear receptor family of ligand-activating transcription factors. When bound to glucocorticoids, GR is regulated by activating or inhibiting the transcriptional activity of some target genes. The effects of this regulation can be extended to about 10-20% of the human genome. As reflecting the broad biological function of glucocorticoids, GR is expressed in most human cells and plays an important role in postpartum survival. Cellular responses to glucocorticoids vary widely, with significant differences in specificity and sensitivity. (Oakley et al., 2022)

Psychotropic medications, particularly antidepressants, are commonly prescribed for dermatology patients with comorbid depression or anxiety and may have beneficial effects on mood and skin disease through HPA axis modulation. SSRIs, such as fluoxetine and sertraline, have been shown to normalize HPA axis function in depressed patients, reducing elevated cortisol levels and increasing feedback sensitivity. (Kenkare et al., 2025) confirmed the role of antidepressants, particularly SSRIs such as fluoxetine and sertraline, in the management of dermatology patients with psychiatric comorbidities. Medication selection is based on the precise diagnosis, individual response, and side effect profile. These findings support the concept that SSRIs not only improve affective symptoms but also potentially modulate the HPA axis, which plays a role in cortisol dysregulation in various skin conditions. Understanding psychotropic pharmacotherapy is crucial for dermatologists in a holistic approach and opens up opportunities to explore their systemic effects on stress response and tissue healing.

Benzodiazepines and other anxiolytics are sometimes used in the management of acute stress in patients with skin diseases. Although effective in reducing anxiety in the short term, chronic use is limited to tolerance, dependence, and potential inhibition of the HPA axis. While the risks of overprescribing benzodiazepines have been highlighted, scientific evidence continues to support the safety and effectiveness of these medications in managing anxiety disorders in the short and long term. An important research gap lies in the limited study of intermittent patterns used as needed, which are considered the most consistent and common for the pharmacological properties of benzodiazepines. As opposition to benzodiazepines becomes widespread, the number of prescriptions can decrease in the absence of alternatives such as cognitive behavioral therapy. More research is needed on the safety and effectiveness of long-term and intermittent use to improve anxiety management. (Krieger, 2025)

Beta-blocking drugs inhibitors of the sympathetic nervous system have been studied to inhibit stress dermatitis. We reviewed studies in which beta-blocker use went beyond cardiac markers, particularly in traumatic injuries and immunomodulatory injuries. Beta-blockers work by inhibiting sympathetic activation and post-injury hypermetabolism, thereby regulating glucose balance and cytokine expression. This review explores the clinical evidence for beta-blocker use in conditions such as traumatic brain injury, spinal cord injury, hemorrhagic trauma, burns, and sepsis. These results suggest that beta-blockers have broader therapeutic potential through metabolic and immunological effects on trauma patients. (Loftus et al., 2016)

(Simon et al., 2025) Consider what role melatonin plays outside of traditional circadian rhythm functioning, especially in dermatology. Melatonin acts as a multifaceted regulator, having different

antioxidant and immunomodulatory properties depending on the context. In the skin, melatonin directly neutralizes reactive oxygen species and stimulates internal defense mechanisms, contributing to protection against oxidative stress, UV rays, and various environments. Additionally, melatonin has been shown to influence the immune response to inflammatory skin diseases such as atopic dermatitis, aiding in tissue repair and contributing to relieving symptoms associated with skin aging. Topical dosing regimens, such as gels, creams, and patches, allow for the administration of insertions, increase skin penetration and reduce adverse reactions in the body. Current research also highlights ongoing clinical trials, advances in drug delivery technology, and the potential to combine melatonin with conventional skin care.

Due to the complexity and bidirectional nature of the HPA axis, pharmacological interventions run the risk of unintended consequences such as adrenal insufficiency, metabolic disorders, and worsening of diseases necessary for treatment. Future research should prioritize well-designed trials that evaluate efficacy and safety, focusing on patient selection based on initial cortisol status (hypercortisol or cortisol deficiency) and specific disease characteristics.

Conclusion

Investigating the role of more than just cortisol regulation in inflammatory dermatitis, it was found that bilateral interactions between psychological stress and skin lesions strongly determine the progression and progression of the disease and its clinical severity. The study highlights the importance of understanding central dysregulation, peripheral cortisol metabolism, and glucocorticoid receptor sensitivity as mechanisms of stress and dermatitis associated with diseases such as psoriasis, atopic dermatitis, rashes, and pathological urticaria. It is hypothesized that psychological interventions (e.g., attention-based stress reduction, cognitive behavioral therapy, biofeedback for heart rate changes) and pharmacological approaches (e.g., selective serotonin reuptake inhibitors, CRH antagonists, beta-blockers, melatonin, topical 11β-HSD1 inhibitors) modulate cortisol motility and improve clinical outcomes. This supports the possibility that there are therapies that target the stress-cortisol axis in dermatology. However, as noted throughout this review, significant challenges remain, including systematic variations in cortisol measurements, the association between cortisol levels and disease severity, and the confusing effects of topical steroids and comorbid psychiatric disorders. Therefore, further studies using standard multi-index cortisol assessments (e.g., hair, saliva, serum) and rigorous randomized controlled trials are needed to strengthen the evidence base. As psychiatric dermatology gains recognition as a specialty, it is encouraging to see that stress-focused interventions are increasingly integrated into comprehensive dermatological care, underscoring the need for multidisciplinary frameworks that bridge dermatology, endocrinology, and mental health. Bridging the gap between mechanistic understanding and clinical practice through personalized biomarker-based treatment strategies can lead to disease management and overall health promotion in patients with inflammatory skin diseases.

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