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NEUROIMMUNOENDOCRINE RESPONSE TO STRESS AND ITS CONTRIBUTION TO THE PATHOGENESIS OF SKIN DISEASES

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ABSTRACT

The neuroimmunoendocrine response to psychological stress plays a key role in the pathogenesis of dermatological diseases. This integrative literature review summarizes recent findings on the interactions between stress and skin diseases, focusing on the neuroimmune-cutaneous system (NICS) and its clinical implications. Psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, triggering the release of stress hormones, neuropeptides, and inflammatory cytokines, which disrupt skin immunity and exacerbate diseases such as psoriasis and atopic dermatitis. This bidirectional relationship is compounded by the psychosocial burden of visible skin lesions, which negatively affect self-esteem and mental health, creating a feedback loop of stress and inflammation. Key findings highlight the role of neurotransmitters such as serotonin and substance P in amplifying immune responses and pruritus, as well as the prevalence of psychiatric comorbidities among dermatological patients. Evidence supports the integration of stress management techniques such as psychotherapy and mindfulness into dermatological therapies to interrupt this cycle and improve patient outcomes. This review highlights the need for holistic clinical approaches that address both the physical and emotional aspects of dermatological conditions, emphasizing the importance of further research into neuroimmunoendocrine pathways and psychodermatological interventions to improve patient care and quality of life.

Keywords: Skin. Skin diseases. Neurotransmitters. Atopic dermatitis. Psoriasis. Quality of life. Immune system. Mental disorders.

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Revista ARACÊ
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INTRODUCTION

Mental health is a state of well-being in which the individual is aware of his or her capabilities, can cope with the stresses faced in daily life, can work productively, and can contribute to his or her community (World Health Organization, 2019). Therefore, it is understood as a state of emotional, cognitive, and behavioral balance, essential for quality of life. In contrast, psychological stress; a complex interaction between environmental demands and individual responses, characterized by feelings of anxiety, tension, and emotional overload, which can negatively impact mental health and general well-being (Thomas et al., 2021); can profoundly compromise this balance.

The impact of stress on quality of life is significant, reflected in reduced well-being, functional impairment, and lower satisfaction in different aspects of life. This condition can trigger mental disorders, such as depression and anxiety, in addition to contributing to the progression of physical diseases, especially dermatological ones. Some skin conditions, such as psoriasis and atopic dermatitis, have their onset and progression strongly associated with chronic stress. In this context, studies highlight the interrelationship between the nervous, endocrine, and immune systems, forming the neuro-immunocutaneous system (NICS), as one of the main underlying mechanisms (Mar et al., 2023; Rivers et al., 2023).

NICS explains how psychological stress directly affects the skin's immune system, triggering inflammatory processes that result in the exacerbation of dermatopathies. For example, in psoriasis, stress activates inflammatory pathways that lead to increased keratinocyte proliferation and the emergence of characteristic lesions. Similarly, in atopic dermatitis, elevated cortisol due to chronic stress can reduce the skin barrier and increase susceptibility to irritation and infections. Approximately 30 to 60% of dermatological conditions have some psychiatric component, highlighting the relevance of this bidirectional connection (Mar et al., 2023; Rivers et al., 2023).

The interaction between psychological stress and dermatological diseases is remarkably bidirectional. Stress can aggravate skin pathologies, while skin diseases negatively impact patients' self-image and self-esteem, leading to the development of mental health problems. This vicious cycle not only worsens dermatological symptoms but also further impairs the emotional balance of individuals, making clinical management and recovery difficult.

Revista ARACÊ
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Understanding this relationship is essential for effective clinical interventions. To this end, integrated therapeutic strategies that address both physical and emotional aspects are indispensable. Thus, the use of stress management techniques, such as psychotherapy, mindfulness, and psychosocial interventions, combined with dermatological therapies, can help to interrupt the inflammatory cycle and alleviate symptoms. In addition, pharmacological treatments, such as immunomodulators, when associated with the control of psychological stress, prove to be a promising approach for the management of these conditions. Finally, understanding the pathophysiological mechanisms that link psychological stress to dermatological diseases, as described in the NICS framework, provides a solid basis for more holistic clinical interventions. These approaches not only alleviate symptoms but also promote a better quality of life, considering the physical, emotional, and social aspects of patients. As Thomas et al. (2021) emphasize, mental and physical well-being should be addressed in an integrated manner, especially in conditions that clearly illustrate the interdependence between mind and body.

OBJECTIVES

To synthesize and analyze scientific findings related to the influence of psychological stress on dermatological diseases, focusing on the biological mechanisms and interactions between the nervous and immune systems and the skin.

METHODOLOGY

This is an integrative literature review, developed from the question: “What mechanisms and interactions between psychological stress and dermatological diseases are evident in recent literature, and what implications do these interactions have for clinical treatment?”. The searches were conducted in November 2024, on the PubMed platform, using the descriptors indexed in the Health Sciences Descriptors (DeCS): “Psychological Stress” “Stress Response” AND “Dermatologic Diseases”. Eighty-three articles in English were identified, which included reviews, meta-analyses, and original research, freely accessible, and published in the last five years.

For screening, some exclusion criteria were considered, to ensure greater relevance to the topic. In this sense, studies whose central focus was on conditions unrelated to dermatology - such as cancer or metabolic diseases - were excluded, as well as those that did not

Revista ARACÊ
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explore in detail the biological mechanisms involved or the role of the neuroimmunoendocrine axis in the relationship between stress and skin diseases. In addition, articles that broadly dealt with psychological aspects, without a direct relationship with specific skin diseases, were eliminated.

Based on these parameters, three studies met the objectives of the review, as they demonstrated evidence of biological interactions and their implications for the clinical management of dermatological conditions influenced by psychological stress.

RESULTS

DYSREGULATION OF THE NEUROIMMUNOENDOCRINE AXIS IN RESPONSE TO STRESS

Zhang et al. (2023) explore how dysregulation of the neuroimmunoendocrine (NIE) axis in response to stress contributes to the emergence and worsening of skin diseases. This axis, which integrates the central nervous system, the endocrine system, and the immune system, is activated by the brain when it detects stressful stimuli. Activation of the hypothalamic-pituitary-adrenal (HPA) axis promotes the release of corticotropin-releasing hormone (CRH) by the hypothalamus, which stimulates the production of adrenocorticotropic hormone (ACTH) by the pituitary gland. ACTH induces the adrenal glands to release glucocorticoids, such as cortisol, as well as stress hormones such as epinephrine and norepinephrine.

These stress hormones alter the immune function of the skin, promoting the release of neuropeptides and the activation of immune cells such as mast cells, dendritic cells, and keratinocytes. These alterations result in increased inflammation, impaired skin barrier function, and increased susceptibility to infections, exacerbating skin diseases such as psoriasis and atopic dermatitis. In the long term, persistent activation of the NEI leads to chronically elevated levels of stress mediators in the circulation, generating a dysfunctional immune response that amplifies inflammation and exacerbates stress-related skin diseases.

INFLAMMATORY MEDIATORS AND CYTOKINES ASSOCIATED WITH STRESS AND DERMATITIS

According to Mar and Rivers (2023), psychological stress increases the production of inflammatory mediators and cytokines, exacerbating conditions such as atopic dermatitis

Revista ARACÊ
ISSN: 2358-2472

(AD). Activation of the HPA axis in response to stress leads to the release of cortisol, adrenocorticotropin, and β-endorphins, which exert immunosuppressive effects on Th1 cells and increase the differentiation of T-helper cells into Th2. This process promotes the production of immunoglobulin E (IgE), which binds to mast cells, triggering their degranulation and releasing lipid mediators and pro-inflammatory cytokines (TNF-α, TGF-β, IL-1, IL-4, IL-13), contributing to the development of skin lesions in AD. The article also addresses the influence of stress on the serotonergic system, showing that patients with AD have elevated levels of serotonin receptors (5-HT1A) and serotonin transport protein (SERT) in skin lesions. This increase in serotonin activates and prolongs the life of monocytes, which secrete IL-16 and recruit T cells, contributing to inflammation and pruritus. These findings indicate a correlation between elevated serotonin levels and psychiatric comorbidities in patients with AD, suggesting that inadequate regulation of this neurotransmitter may intensify the psychological and dermatological suffering associated with the disease.

Neurogenic inflammation is also prominent in stress-induced AD. Patients with AD often have elevated levels of neuropeptides such as nerve growth factor (NGF), substance P (SP), and neuropeptide Y (NPY) in the blood. This increase is associated with a greater density of sensory nerve fibers in contact with mast cells in AD lesions, promoting the release of SP and CGRP, which intensifies pruritus and perpetuates the itch-lesion cycle.

INTERACTION BETWEEN CUTANEOUS IMMUNE SYSTEM CELLS AND NEUROTRANSMITTERS

The interaction between cutaneous immune system cells and neurotransmitters is discussed by Marek-Jozefowicz et al. (2022), emphasizing its role in the pathophysiology of psoriasis. Psychological stress induces the release of neurotransmitters and neuropeptides, such as serotonin, substance P (SP), and nerve growth factor (NGF), which interact directly with immune cells in the skin, increasing inflammation and pruritus.

Substance P, for example, when released under stress, binds to NK-1 receptors on mast cells, promoting their degranulation and releasing pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, increasing inflammation and aggravating symptoms of skin diseases. Furthermore, NGF, secreted by keratinocytes and fibroblasts in response to stress, increases the density of nerve fibers around lesions and activates mast cells, intensifying symptoms such as pain and itching.

Revista ARACÊ
ISSN: 2358-2472

Keratinocytes also express receptors for neurotransmitters such as adrenaline, noradrenaline, and dopamine, suggesting that the skin acts as an active component in the stress response.

SSE. These interactions form a communication network between the brain and the skin, which amplifies inflammation and contributes to the perpetuation of stress-related skin diseases.

PSYCHODERMATOLOGY AND PSYCHIATRIC COMORBIDITIES IN DERMATOLOGICAL DISEASES

Mar and Rivers (2023) also address the relationship between stress and skin diseases from the perspective of psychodermatology, discussing how psychiatric comorbidities, such as anxiety and depression, are frequent in patients with dermatological diseases. Visible lesions can trigger an intense emotional response, worsening the dermatological condition and creating a feedback loop between mental health and skin.

The presence of elevated neurotransmitters, such as serotonin and substance P, in patients with conditions such as atopic dermatitis (AD) and psoriasis is directly related to the worsening of dermatological and psychiatric symptoms. These findings suggest that multidisciplinary management, including psychological support, may be essential to break the cycle of stress and cutaneous inflammation, promoting more effective treatment of these conditions.

CONCLUSION

The findings of this review reinforce the crucial role of the neuro-mucocutaneous system (NICS) in the response to psychological stress and its contribution to the pathogenesis of dermatopathies. Evidence shows that the activation of the neuroimmunoendocrine axis by stress triggers a cascade of biochemical reactions, promoting the release of inflammatory mediators and neuropeptides, which result in inflammation and immune dysregulation of the skin. This mechanism has profound implications for the development and severity of skin diseases.

In addition, the interaction between neurotransmitters and cutaneous immune cells in response to stress indicates a bidirectional communication, where mental and dermatological health influence each other, establishing a feedback loop that aggravates the clinical manifestations of these conditions. The visibility of skin changes amplifies the

Revista ARACÊ
ISSN: 2358-2472

impacts on well-being, with significant effects on self-esteem, social relationships, and daily performance. For example, a study published in the journal “Dermatology Times” in 2024 revealed that 88% of patients with acne report embarrassment and decreased confidence, while diseases such as psoriasis and atopic dermatitis increase the risk of anxiety and depression.

The psychosocial impact of dermatitis and the high prevalence of psychiatric comorbidities among patients with skin diseases, associated with impaired well-being and quality of life, emphasize the need for therapeutic approaches that combine dermatological interventions and psychological support. Therefore, this study suggests that integrated clinical interventions, which consider stress management and the patient's mental health, can be strategic in the management of skin diseases, to reduce the frequency and intensity of outbreaks and promote an improvement in quality of life. New studies are needed to deepen the understanding of neuroimmunoendocrine pathways and the effectiveness of psychodermatological approaches in the treatment of skin diseases, aiming at more holistic and effective care.

Revista ARACÊ
ISSN: 2358-2472

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