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The influence of stress and other behavioural factors on the onset and exacerbation of acne - a review of pathogenetic mechanisms, interactions between body systems and directions for therapeutic strategies

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Abstract

Introduction and aim

Acne vulgaris, which is one of the most common inflammatory skin diseases, affects millions of people worldwide. It is most common during adolescence, but also occurs in adults. Its pathogenesis is the result of a complex interaction of genetic, hormonal, environmental and psychosocial factors. Traditional models have focused on excessive sebum production, impaired keratinisation and colonisation by *Cutibacterium acnes*. Recent studies show that, in addition to hormonal, genetic and environmental factors, psychological stress is recognised as an important factor influencing the pathogenesis and exacerbation of acne. This review examines the mechanisms by which stress influences the development and severity of acne (considering the role of the skin microbiome, diet and lifestyle), presenting current scientific reports from recent years, and discusses modern therapeutic strategies combining standard pharmacotherapy with mental health support interventions, dietary modification and probiotic therapy.

Review methods

More than 20 studies, available on PubMed and Google Scholar, were analysed and critically reviewed to understand the relationship between stress and the occurrence of acne, discussing neuroendocrine mechanisms (activation of the HPA axis, secretion of cortisol, catecholamines and neuropeptides), increasing oxidative stress, the impact of the skin and gut microbiome, skin barrier dysfunction, the importance of diet and psychosocial aspects. This has provided a comprehensive picture of the impact of stress and other factors on skin condition. Keywords used to search for scientific articles: acne, stress, HPA axis, oxidative stress, microbiome, skin barrier, diet, mental health, probiotics

Brief description of the state of the art

Acne vulgaris is one of the most common dermatological diseases, characterised by blackheads, papules, pustules and cysts. Although the pathogenesis of acne is multifactorial, the role of psychological stress in its development and exacerbation is receiving increasing attention.

Stress, both acute and chronic, can affect the endocrine system, immune system and skin microbiome, leading to increased inflammation and sebum production. Diet is also an important factor in modulating the body's inflammatory response. In recent years, studies have shown that stress and other behavioural factors like lifestyle and diet can not only exacerbate existing acne lesions, but also contribute to their initial onset. Patients with acne often experience reduced self-esteem, anxiety and depression, which further increases stress levels. In addition, stress can lead to poor skincare habits, such as over-cleansing the skin or squeezing acne lesions, which can damage the skin barrier and increase inflammation. Studies have shown that people with severe acne have a higher risk of mental disorders compared to those with mild acne.

Lifestyle, which includes sleep habits and physical activity, is another important factor affecting skin condition. Insufficient sleep leads to hormonal disturbances that can worsen the condition of the skin. On the other hand, lack of regular physical activity negatively affects metabolism and circulation, which can impede the removal of toxins.

Acne treatment should include not only pharmacological therapy (topical/ systemic retinoids, antibiotic therapy, anti-androgens), but also stress reduction interventions.

It is important to introduce intervention programs to improve the quality of life of people with acne, such as learning proper skin hygiene and healthy eating habits, participating in relaxation therapies and providing psychological support and help in dealing with the emotional consequences of acne

Summary

Analysis of the literature clearly indicates that stress and other behavioural factors influence the pathogenesis of acne through a number of related mechanisms, such as: activation of the HPA axis and increased cortisol levels, increased secretion of neuropeptides, excess ROS.

Despite the abundance of evidence pointing to a link between stress and acne, many issues remain unexplained. Existing studies are often based on self-reported indicators of stress or on small study groups. In addition, the authors emphasise the need for further research to develop treatments for acne exacerbations by stress and other external factors, such as diet and lifestyle, to significantly improve patients' quality of life. An integrated approach to acne treatment, including both pharmacological and non-pharmacological interventions, seems to be the most promising.

Examples of effective strategies include:

- Combining appropriately selected pharmacological therapies (e.g. retinoids or antibiotics) with psychological support programs,
- Use of probiotic preparations to modulate the skin and gut microbiome,
- Introduce dietary changes, such as lowering the glycemic index of meals,
- Implementing educational programs on healthy lifestyles.

Keywords: acne, stress, HPA axis, oxidative stress, microbiome, skin barrier, diet, mental health, probiotics

1. Introduction

Acne is one of the most common inflammatory skin diseases, affecting millions of people worldwide, not only in adolescence but also in adults. It manifests itself by the formation, papules, pustules and, in more severe cases, cysts and scars, affecting the appearance and quality of life of patients [1, 2]. Its pathogenesis is multifactorial and includes hormonal disorders, excessive sebum production, abnormal keratinisation of the hair follicle outlet, *Cutibacterium acnes* colonisation and inflammatory processes [2,3,4]. In recent years, the influence of psychosocial factors, particularly stress, on the course of the disease and the incidence of exacerbations has received increasing attention. Many studies confirm that chronic

stress can affect the functioning of the immune, endocrine and nervous systems, which promotes the occurrence of acne and exacerbates its inflammatory changes. Additionally, environmental factors, diet and disruption of the skin and gut microbiome (gut-skin axis) further modulate these processes [5, 6, 7, 8]. The aim of this article is to comprehensively present a multifaceted model of acne pathogenesis and the mechanisms through which stress and related factors influence its onset and severity.

2. Review methods

More than 20 studies, available on PubMed and Google Scholar, were analysed and critically reviewed to understand the relationship between stress and the occurrence of acne, discussing neuroendocrine mechanisms (activation of the HPA axis, secretion of cortisol, catecholamines and neuropeptides), increasing oxidative stress, the impact of the skin and gut microbiome, skin barrier dysfunction, the importance of diet and psychosocial aspects. This has provided a comprehensive picture of the impact of stress and other factors on skin condition.

Keywords used to search for scientific articles: acne, stress, HPA axis, oxidative stress, microbiome, skin barrier, diet, mental health, probiotics

3. Impact of stress on the pathogenesis of acne

3.1. Activation of the hypothalamic-pituitary-adrenal (HPA) axis

Stress is defined as the body's response to external and internal stimuli. During stressful situations, the hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the adrenal glands to produce cortisol, a hormone that plays a key role in the stress response [9, 10], and its elevated levels correlate with increased inflammatory processes in the skin.

Cortisol affects the skin through:

- Increased sebum production: High cortisol levels stimulate sebocytes, leading to excessive sebum secretion and creating an environment conducive to the proliferation of *C. acnes*.
- Keratinization of the hair follicle outlet: Changes in the differentiation process of keratinocytes cause a blockage of the follicle outlet, resulting in inflammatory lesions.
- Modulation of the immune response: Cortisol affects the secretion of cytokines, which can modify (both inhibit and stimulate) the response to inflammatory stimuli - particularly under conditions of chronic stress [9, 11].

3.2. The role of neuropeptides

Stress causes increased secretion of neuropeptides, such as substance P, which is released by nerve endings. Substance P stimulates sebocytes to increase lipid production, which contributes to the overproduction of sebum. The presence of neuropeptide receptors on sebocytes allows direct modulation of the function of these cells, which can lead to pathological changes in hair follicles [12, 13]. In addition, substance P activates local immune cells and increases the secretion of pro-inflammatory cytokines.

3.3. Effects of stress on the immune system

Elevated cortisol and neuropeptide levels increase the production of cytokines such as IL-1, IL-6 and TNF- α , which cause an influx of inflammatory cells into the hair follicles, intensifying inflammatory processes and contributing to the development of acne lesions [9, 10, 11]. Long-term exposure to stress leads to chronic dysregulation of the immune response, maintaining inflammation in the skin. This creates a local environment favouring dysbiosis of the skin microbiome.

4. Oxidative stress and skin condition

4.1. ROS production and lipid peroxidation

Oxidative stress results from the overproduction of reactive oxygen species (ROS), which damage cell membranes through lipid peroxidation [3, 14, 15]. This leads to increased permeability and promotes inflammatory reactions in the hair follicles.

4.2. Regulation by microRNAs as a potential therapeutic strategy

MicroRNAs, in particular miRNA-21, play a key role in regulating the expression of genes responsible for the production of pro-inflammatory cytokines and the activity of antioxidant enzymes. Regulation of miRNA-21 expression opens up new possibilities in the precise modulation of inflammatory and oxidative processes. Therapies targeting miRNAs may enable precise inhibition of molecular pathways involved in acne pathogenesis, which represents a new therapeutic perspective [16].

5. Importance of diet

People experiencing stress are more likely to consume an unhealthy diet, rich in simple sugars and saturated fats. In turn, diet is an important factor in modulating the body's inflammatory response. High-glycemic-index products lead to spikes in insulin and IGF-1 levels, which stimulates sebum production and keratinisation of hair follicles, resulting in a higher incidence of inflammation [1, 2, 8]. Studies have shown that high milk consumption correlates with acne severity [1], and that changing to a low-glycemic diet can improve skin conditions [8,17]. Dietary modification may therefore be an effective strategy to help treat acne.

5.1. Environmental and lifestyle factors

Improper skincare habits, poor sleep quality, exposure to air pollution and lack of physical activity are other important factors affecting the condition of the skin. They disrupt hormonal and immune balance, increasing cortisol production and exacerbating oxidative stress [5, 6]. Air pollution has been shown to damage the skin barrier, which promotes colonisation with pathogens [5]. In addition, stress can lead to inappropriate skincare habits, such as over-cleansing the skin or squeezing acne lesions, which also leads to damage of the skin barrier and increased inflammation. A lack of regular physical activity, on the other hand, negatively affects metabolism and circulation, making it more difficult to remove toxins. Regular

exercise and improved sleep quality help to reduce stress levels, which stabilises the body's hormonal balance and can improve skin condition.

6. The role of the skin and gut microbiome

The skin microbiome plays an important role in maintaining skin health, and disturbances in its composition can lead to the development of dermatological diseases. The skin is the largest organ of the human body. It is inhabited by numerous microorganisms, predominantly *Cutibacterium acnes*. Stress on the body can affect the composition of the microbiome.

Dysbiosis of the skin and gut microbiota contributes to chronic inflammation, exacerbating acne symptoms [7,18]. In addition, studies on the gut-skin axis indicate that the normal composition of the gut microbiota has a direct impact on immune function and cytokine production. The use of probiotics, prebiotics and cosmetics that modulate the microbiota can restore microbial balance, reducing inflammatory reactions, improving skin barrier integrity, alleviating acne symptoms.

7. Skin barrier disorders and immune response

7.1. Mechanisms of skin barrier damage

The skin barrier is the first line of defense against external agents. Its integrity depends on the correct production of ceramides, protein and lipid structures that maintain hydration and protect against pathogens, forming the stratum corneum. In acne, a number of disorders occur, including lipid peroxidation or changes in sebum composition.

Excessive ROS production leads to lipid oxidation, which damages cell membranes and weakens the protective barrier. Decreased ceramide synthesis and damage to cell membranes result in increased permeability of the skin, allowing the penetration of pathogens and allergens [19].

The keratinisation of hair follicles and overproduction of sebum promote the formation of blackheads, which provide a habitat for *C. acnes* and other pathogens. This leads to the initiation of inflammatory reactions that exacerbate barrier damage. Furthermore, exposure to pollutants, aggressive cosmetics and inadequate care can cause micro-damage to the barrier, further exacerbating inflammation.

7.2. Immune response and its modulation by barrier disruption

Damage to the skin barrier results in an immune imbalance. Increased skin permeability allows pathogens and allergens to penetrate, which activates macrophages, lymphocytes and other immune cells, leading to the secretion of pro-inflammatory cytokines (IL- 1, IL- 6, TNF- α) [19].

The persistence of inflammation due to continuous activation of immune cells promotes the development of chronic acne, hindering the healing and regeneration process of the skin. Furthermore, barrier disruption and oxidative stress affect the expression of microRNAs, such as miRNA-21, which further modifies the immune response and contributes to the maintenance

of chronic inflammation [16].

The above mechanisms demonstrate that restoration of barrier integrity is a key component of acne therapy. Barrier restoration not only limits skin exposure to pathogens, but also reduces chronic immune activation, which promotes a reduction in inflammation. This may represent a key target in acne therapy.

8. Therapeutic strategies - a comprehensive approach

8.1. Stress reduction - psychological interventions and lifestyle changes

Acne, especially in its more severe forms, significantly affects patients' quality of life. Not only is it a result of stress, but it can also exacerbate it, creating a vicious circle that significantly impedes the healing process. There is an association between the severity of the disease and the occurrence of psychological problems such as reduced self-esteem, anxiety and depression.

Acne treatment should include not only pharmacological therapy (topical/systemic retinoids, antibiotic therapy, anti-androgens), but also stress reduction interventions. It is important to introduce intervention programs to improve the quality of life of people with acne, such as learning proper skin hygiene and healthy eating habits, participating in relaxation therapies, and providing psychological support and help to cope with the emotional effects of acne.

Psychological therapies such as cognitive behavioural therapy, meditation, autogenic training or relaxation techniques help to lower cortisol levels, reduce neuropeptide production and reduce the secretion of pro-inflammatory cytokines [20, 21]. Psychological support programs improve patients' quality of life, which has a positive impact on immune function and overall skin condition.

In addition to stress reduction, lifestyle changes including:

- **Regular physical activity:** Exercise improves metabolism, lowers insulin and IGF-1 levels, which translates into reduced sebum production.
- **Improved quality of sleep:** Adequate recovery enables the body to maintain hormonal balance and improve immune function.
- **Limiting exposure to pollution:** Using protective cosmetics and avoiding aggressive environmental factors helps protect the skin barrier.
- **Diet optimisation:** A low-glycemic diet and limiting dairy intake stabilise insulin levels, reduce sebum production and reduce inflammation [1,17].

8.2. Pharmacological treatment and supportive preparations

Standard acne treatment includes drug therapies. Standard medications include: retinoids,

antibiotics and hormonal therapies, antioxidant preparations and cosmetics that rebuild the skin barrier. Retinoids act by regulating keratinocyte differentiation, reducing sebum production and inhibiting the secretion of inflammatory cytokines. They are effective in the treatment of acne, often leading to long-term remission [2, 22, 23].

Antibiotics, such as tetracyclines or macrolides, have antibacterial and anti-inflammatory effects. Hormonal therapies, especially in women, help to regulate androgen levels, which reduces sebum production. However, it is important to use these drugs for appropriate indications to avoid increasing antibiotic resistance and disruption of the microbiome [2, 22, 24]. Supplementation with vitamin C, E, ferulic acid and plant extracts helps neutralise ROS, reducing lipid peroxidation and protecting skin cells from oxidative damage [3, 14, 19]. Emollients, moisturising creams and ceramide-containing preparations promote the restoration of the damaged skin barrier, reducing skin permeability and limiting pathogen colonisation [19]. Their use with aggressive drug therapies is beneficial.

8.3. Probiotic therapy

Topical preparations containing bacterial strains (e.g. *Lactobacillus*, *Bifidobacterium*) help to rebalance the skin microflora, inhibit pathogen growth, stimulate ceramide production and reduce local inflammatory responses [7, 18]. By affecting the gut-skin axis, oral probiotic therapy improves the intestinal microbiota, which translates into reduced production of pro-inflammatory cytokines, improved hormonal balance and an overall reduction of inflammation in the skin [7,18].

Moreover, combining probiotics with prebiotics or plant extracts shows a synergistic effect, enhancing the antibacterial, anti-inflammatory and antioxidant effects. This approach may become a valuable complement to traditional acne treatments [18].

9. Innovative drug delivery methods

Modern technologies, such as micropuncture, carrier systems based on nanoparticles or liposomes, allow precise delivery of drugs to the deeper layers of the skin. These methods increase the effectiveness of anti-inflammatory preparations and antioxidants and minimize side effects by reducing systemic drug absorption [23,24].

10. Discussion

Research indicates that acne is a disease with a complex aetiology, in which the synergistic interaction of stress and neuroendocrine, immunological, microbiological and behavioural factors plays a key role. An integrated therapeutic approach, including dietary modification, stress reduction and interventions aimed at restoring the microbial balance of the skin, represents a promising direction in the treatment of acne.

Stress reduction, both through psychological interventions and lifestyle modification, reduces the production of cortisol and neuropeptides, which consequently reduces inflammatory responses. Pharmacological treatment, based on retinoids, antibiotics and hormonal therapies, effectively controls the underlying mechanisms of acne pathogenesis. In addition, antioxidant

preparations and cosmetics that rebuild the skin barrier promote tissue regeneration, and probiotic therapy - both topical and oral - helps restore the microbial balance of the skin and gut.

New technologies, including miRNA targeting and innovative drug delivery systems, may increase the efficacy of therapies in the future by enabling precise modulation of acne-related molecular pathways. The implementation of multidisciplinary treatments may not only reduce the severity of skin lesions, but also significantly improve patients' quality of life, especially in terms of psychosocial problems associated with the disease.

11. Conclusions

Analysis of the literature clearly indicates that stress and other behavioural factors influence the pathogenesis of acne through a number of related mechanisms, such as:

- Activation of the HPA axis and increased cortisol levels, leading to overproduction of sebum and keratinisation of hair follicles, creating a favourable environment for *C. acnes* [9,10].
- Increased secretion of neuropeptides, such as substance P, inducing local inflammatory responses, which aggravates acne lesions [12,13].
- Excess ROS, formed as a result of oxidative stress, cause lipid peroxidation and damage to cell membranes, which increases inflammation and skin barrier dysfunction [3, 14, 15,16].
- Penetration of pathogens and allergens, as a result of a disrupted skin barrier, which induces chronic activation of the immune system, leading to increased inflammation and impeding skin regeneration [19].
- Environmental factors, diet and dysbiosis of the skin and gut microbiome further modify these processes by increasing the production of pro-inflammatory cytokines and altering the hormonal balance [1, 5, 6, 8,17].

A comprehensive therapeutic approach, combining stress-reducing interventions (psychological and lifestyle modification), pharmacological treatment (retinoids, antibiotics, hormonal therapies), antioxidant supplementation and probiotic therapy, appears to be most effective in achieving long-term acne remission. Rebuilding barrier integrity is a key goal of therapy. Restoring balance in the skin microflora and reducing chronic inflammation makes it possible not only to improve the dermatological condition, but also to reduce complications and improve patient wellbeing. A multifaceted therapeutic approach produces the best results in the treatment of acne.

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