The Impact of Pyschological Stress on Acne

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ABSTRACT Acne is one of the most common skin disorders. It is a multifactorial and complex disease, originating in the pilosebaceous follicle where a hereditary background, androgens, skin lipids, disorders of keratinization, inflammatory signaling, and regulatory neuropeptides seem to be mainly involved. Even though emotional stress has long been suspected to trigger or exacerbate acne, its influence on acne severity has been mostly underestimated until recently when studies have brought new data about the different mechanisms and possible factors involved in this interaction. A point to note is that there have been relatively few studies examining stress as a possible cause of acne or acne exacerbation; more studies have focused on stress and mental health problems occurring as a result of acne. In this review, we have tried to identify the underlying mechanisms that link stress to acne according to the latest scientific findings, and we summarize this perplexing connection. The basis for the association between emotional stress and the onset or exacerbation of acne is in several cutaneous neurogenic factors which interact with a pathogenic cascade in acne. This bidirectional intimate relationship of the skin and the mind emphasizes the importance of a holistic and interdisciplinary approach to caring for patients with acne that involves not only dermatologists but also psychologists and psychiatrists.

KEY WORDS: acne, psychological stress, sebaceous gland, neuroendocrinology

INTRODUCTION

Acne vulgaris is, along with eczema and psoriasis, one of the most commonly seen chronic inflammatory skin diseases affecting individuals of all ages. Eighty-five percent of people between the ages of 12 and 24 will have some form of acne (1). Direct costs related to acne, including loss of productivity and related depression, exceed $2.2 billion annually in the United States (2). It is a multifactorial and complex disease, originating in the pilosebaceous follicle. Four primary inter-related pathogenic factors of acne have been recognized for decades: overproduction of sebum, abnormal shedding of follicular epithelial cells, *Propionibacterium acnes* follicular colonization, and inflammation (3-6). However, other endogenous and exogenous factors like psychological stress, diet, smoking, hormone concentrations, oxidative stress, and genetic predisposition have been considered as factors that can trigger or worsen acne (7-15). In the past, most of the studies have focused on stress and psychological consequences occurring as a result

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of acne with only a few studies examining stress as a possible cause of acne or acne exacerbation. Even though emotional stress has long been suspected to exacerbate acne, previous reports on its influence on acne severity have mostly been scientifically unfounded until the recent decade when psychoemotional stress was confirmed as a pathogenetic aspect in acne vulgaris (16,17). Additionally, studies have shown that psychological stress can alter the immune functions of the skin (18,19) and cutaneous barrier function (20,21). The association between the mind or mental health and dermatology has been clarified by the mounting evidence that microbial residents and the functional integrity of the intestinal tract may play an interceding role in both skin inflammation and emotional behavior (the gut-brain-skin theory). The physiological association between intestinal microbiota, psychological symptoms such as depression, and inflammatory skin conditions such as acne was examined long ago and was recently validated further by modern scientific investigations (22-26). It has become evident that gut microbes and oral probiotics may be related to the skin, specifically acne severity, through their ability to influence systemic inflammation, oxidative stress, glycemic control, tissue lipid content, and even mood (27-29).

Acne is undoubtedly a cause of anxiety and stress in those who suffer from it, and these patients suffer mainly from social limitations and reduced quality of life (30-33). Psychological factors associate with acne in at least three ways, described below.

First, emotional stress can exacerbate acne, as reported by a high number of acne patients. Second, as a consequence of acne, it is common for patients to develop psychiatric problems like social phobias, low self-esteem, or depression. Last but not least, some mental diseases like psychosis and obsessive-compulsive disorder may be dependent on an acne-related issue (34).

The main difficulty in evaluating the significance of acne on quality of life is resolving the chicken or the egg dilemma: does acne cause psychiatric distress, or do the stress and daily life changes exacerbate acne?

DOES STRESS EXACERBATE ACNE?

Yes, it seems to. Many patients report that emotional stress makes their acne worse, and these statements were confirmed in several studies by a significant percentage of affected adolescents and adults (varying between 50-80%) (35-38). Griesemer found that patients with acne reported a lag time of two days between a stressful episode and the exacerbation of acne (39). Lorenz *et al.* found that intense anger also may aggravate acne severity (40). An Australian survey that included 215 graduating medical students, reported that 67% of them identified stress as one of the factors leading to acne exacerbations (37). Two Korean epidemiological studies found psychological stress to be the main triggering or aggravating factor influencing acne as reported by the majority (80-82%) of patients (38). A prospective cohort study, published in 2003, which comprised 22 university students, showed increased acne severity during stressful exam periods by using previously validated scales measuring acne severity and perceived stress. Acne severity was significantly associated with increased stress levels in comparison with the period without exams despite adjusting for confounding factors such as lack of sleep and changes in diet (17). Similar findings have also been reported by other, mostly questionnaire-based studies (41-44). One study conducted with high school students also found that increased stress correlated with increased acne severity; there also did not seem to be any increased sebum production during times of stress (45). On the other hand, conflicting findings were presented in a recent study consisting of 40 patients with acne vulgaris (46). The authors concluded that the intensity of stress does not correlate with the severity of acne and they hypothesized that course of the disease may depend on the tolerance to stress and methods of coping with stress.

ADULT FEMALE ACNE

Over the last few years, there has been more and more discussion on adult acne, specifically adult female acne that differentiates itself from adolescent acne by its specific clinical aspects, its evolution, and different physiopathological mechanisms (47). Frequently, stress is reported as a factor triggering female acne. For Dumont-Wallon, it is part of the four most often described factors promoting acne (48). Dreno *et al.* conducted a large-scale prospective observational international study evaluating clinical characteristics of acne and lifestyle in adult women (≥25 years). There was an association between job stress and acne severity, which could bolster the relationship between stress and acne. The significant majority of subjects (83.2%) reported at least moderate stress, including 15.5% who reported high-stress levels. A total of 23.0% examinees reported that their jobs were psychologically stressful, and job stress was correlated with more severe acne in women. It has also been shown that compared to women without localized acne, those with mandibular acne were more likely to be employed, reported greater daily stress levels (5.8% vs. 5.1%), and were more likely to

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define their jobs psychologically stressful (71.4% vs. 57.5%) (49). Similar findings were published by Poli *et al.* who reported that stress was recorded as causal factor for acne in 50% of women aged 25-40 years who completed a self-administered questionnaire (36).

Adult female acne has increased in prevalence in recent years, reaching up to a reported percentage of 41-54% (47); this can be partly explained by the fact that social pressure is high for adult women, specifically the demands of work or a career in addition to the duties of a mother and wife. Women also have a greater risk of developing psychiatric disorders such as depression and anxiety (50,51). Moreover, large cities demand a lifestyle which requires sleep deprivation, an intrinsic stressor which is increased in the modern lifestyle and has several negative consequences on health, including hormonal secretion and the immune system (21,52). Thus, the stress caused by worsened sleep quality may exercise a relevant role in adult female acne, as this disease has increased significantly in the last decade (53).

HOW STRESS GETS UNDER THE SKIN

Stress is a term we are faced with in everyday life, being a stimulant for some but pressure for many others. Psychological stress is an accepted fact of life, usually triggered by a stimulus that induces a reaction in the brain. As a consequence, additional physiological systems are activated in the body, including the immune, endocrine, and nervous systems (54,55). The concept of the skin neuro-endocrine was formulated twenty years ago, and recent advances in this field additionally strengthened evidence of its role. We may say that skin is a bi-directional platform for a signal exchange with other peripheral organs, such as endocrine and immune system (56). Skin cells and appendages not only respond to neuropeptides, steroids, and other regulatory signals but also actively synthesize a variety of hormones (57). The skin represents the first line of defense against many noxious environmental inputs. Some researchers have indicated that the skin is especially sensitive to psychological stress. Experimental findings demonstrate that stressors affect cutaneous and adaptive immunity (18); furthermore, psychological stress alters cutaneous barrier homeostasis (20,21,58). For example, it has been shown that the recovery time of the stratum corneum barrier is reduced after elimination of psychological stress (innate immunity) (59). Antigen presentation by epidermal Langerhans cells (adaptive immunity) was also altered (60). Moreover, psychological stress may trigger or exacerbate immune-mediated dermatological disorders. As an evolutionary adaptation to the fight-or-flight response, psychological stress generates some responses that can be detrimental in some states. Stress signals initiate the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system, while also inducing secretion of different neurotransmitters, cytokines, and hormones that possess skin receptors and can aggravate several skin diseases, including acne (24-27). The exact mechanisms of stress-induced triggering or aggravation of acne have not yet been completely understood; however, various mechanisms have been proposed. Some believe that glucocorticosteroids and adrenal androgens are released during emotionally stressful periods and lead to acne worsening. The skin expresses specific genes involved in pathways associated with inflammation and extracellular matrix remodelling at higher rates in acne-affected parts compared to acne-unaffected skin, including genes encoding for matrix metalloproteinases 1 and 3, interleukin-8, human β-defensin 4, and granzyme B (61). Facial skin from patients with acne is characterized by rich innervation, by increased numbers of substance P-containing nerves and mast cells, and by high expression of neutral endopeptidase in the sebaceous glands (SG) compared with healthy skin (62).

New data regarding the physiology of SG indicate that SG have receptors for numerous neuropeptides (β-endorphin, corticotropin-releasing hormone (CRH), urocortin, proopiomelanocortin, vasoactive intestinal polypeptide, neuropeptide Y, and calcitonin gene-related peptide), and these receptors modulate inflammation, proliferation, and sebum production and composition, as well as androgen metabolism in human sebocytes. These neuroendocrine factors with their autocrine, paracrine, and endocrine actions appear to mediate centrally and topically induced stress towards the SG resulting in the clinical course of acne (16).

Corticotropin-releasing hormone (CRH)

As acne is apparently exacerbated by acute or chronic psychological stress, the corticotropin-releasing hormone (CRH) appears to be an important aspect in the development of acne lesions (63,64). CRH is a 41-amino acid polypeptide; the innate effect of CRH and related peptides involves interactions with membrane-bound CRH receptor type 1 (CRHR-1) and type 2 (CRHR-2), and it can be modified by its binding protein (CRH-BP) at the central, local, or systemic levels (65). Pro-CRH processing into CRH appears to be similar at the central and peripheral levels, including the skin (66). CRHR-1 is said to be the predominant form of CRHR expressed in the human skin and possibly plays a significant role in coordinating responses

to external stress in analogy to the central response. CRHR-2 expression was fully documented in cells of adnexal structures, smooth muscle, blood vessels, and selected cells of immune origin, and rather plays a modulatory role. CRH is one of the main components of the stress system, the HPA axis, acting to stimulate attention, inhibit appetite, and promote secretion of adrenocorticotrophic hormone (ACTH), α-melanocyte-stimulating hormone, other proopiomelanocortin (POMC) derived peptides, and β-endorphin in the pituitary gland via the activation of CRHR-1 (67). ACTH, in turn, stimulates the production and secretion of cortisol or corticosterone by the adrenal cortex through the activation of melanocortin receptor type 2 (MC2R). CRH is synthesized among others by keratinocytes, immune cells, and human mast cells under the influence of stress. *Propionibacterium acnes*, a commensal bacteria of the skin whose proliferation is linked to acne, can stimulate the production of CRH by keratinocytes (68). CRH is also reported to act as a growth factor in the skin by activating CRHR-1. It plays a role in the regulation of keratinocyte proliferation and differentiation, representing an important step in the early stages of the development of acne lesions (69). It is also an inhibitor of the early and late apoptosis of many skin cell types such as keratinocytes, dermal fibroblasts, and melanocytes (70). Moreover, CRH is known to act on inflammation by inducing the degranulation of mast cells (71), the release of inflammatory cytokines, and the modulation of immune cells; CRH enhances interleukin-6 and inhibits IL-1β production in human keratinocytes (72). On the other hand, a study examining the concentrations of cortisol, 11-deoxycortisol, and adrenal androgen in women aged 19-39 years with idiopathic acne before and after inducing prolonged adrenal stimulation via ACTH infusion reported there were no significant differences in the levels of these hormones among women with acne and controls (73). However, this does not undermine the importance of these hormones in acne development but rather leads us to the findings that acne development and its clinical course depend on the neuroendocrine factors that mediate stress towards the SG (17,74).

It has become apparent that SG is an organ with an independent peripheral endocrine function which, together with the sweat glands, encompasses the vast majority of androgen metabolism in the skin. The presence of a complete CRH system in human sebocytes has been confirmed in vitro and in vivo (75,76). CRH is a major autocrine hormone in these cell types with homeostatic differentiation activity. It directly induces lipid synthesis and steroidogenesis and enhances mRNA expression of Δ5-3β-hydroxysteroid dehydrogenase, independently from the HPA axis (16,76). CRH regulates the lipid synthesis in human sebocytes, promoting up-regulation at lower concentrations of lipid content and inducing a decrease when the levels are higher (76). Testosterone and growth hormone, which also enhance sebaceous lipid synthesis, were found to antagonize CRH activity and CRHR expression; precisely, testosterone suppresses CRHR-1 and CRHR-2 mRNA expression in SZ95 sebocytes while growth hormone switches CRHR-1 mRNA expression to CRHR-2 (76). These findings implicate the involvement of CRH in the clinical development of acne and seborrhea, as well as in further skin diseases associated with alterations in the formation of sebaceous lipids. Ganceviciene *et al.* analyzed CRHRs by immunohistochemistry in three groups of biopsies; the facial skin biopsies of 33 acne patients, non-involved thigh skin of these patients, and normal skin of eight age-matched healthy volunteers (74). There was a definite positive reaction for CRH in acne-involved skin in all types of SG cells, regardless of their differentiation stage. The results differed in noninvolved and healthy skin biopsies where SG exhibited a weaker CRH staining depending upon the differentiation stage of sebocytes. The most positive reaction for CRH-BP in acne-involved SG was in differentiating sebocytes. CRHR-1 and CRHR-2 showed the strongest expression in sweat glands and SG, respectively. They concluded that expression of the complete CRH system is abundant in acne-involved skin, especially in SG, possibly activating pathways that affect immune and inflammatory processes leading to the development and stress-induced exacerbation of acne. Concerning the clinical perspectives of CRH and its receptors in the pathogenesis and the course of acne, CRHR antagonists could soon arise as possible therapeutics. At this time, there have already been some studies demonstrating this effect (77).

Melanocortins

Melanocortin (MC) peptides can also directly affect the function of human sebocytes via MC receptors. Alpha-melanocyte-stimulating hormone (α-MSH) has been demonstrated to act as a modulator of the preputial rat gland, a specialized sebaceous gland-like structure of rodents. The effect of α-MSH is mediated through binding to G-protein-coupled MC receptors (MC-R) on the cell surface of the target cell. To this point, five different MC-Rs have been cloned (78). The presence of both MC-R, specifically MC-1R and MC-5R, which bind α-MSH, were detected in human sebocyte cultures established from the facial skin as well as in immortal human sebocyte cell line – SZ95 (79-81). In SZ95 sebocytes, α-MSH partially

prohibited the inductive effect of IL-1β on the secretion of IL-8, an important chemokine that directs neutrophils to inflammatory sites including SG (79). In acne-involved skin, sebocytes and keratinocytes of the ductus seboglandularis showed MC-1R expression to a high degree in contrast with less intense dispersed immunoreactivity in normal skin samples, suggesting that this receptor is involved in the initiation of acne. It has been shown that proinflammatory signals up-regulate MC-1R (82). Since proinflammatory cytokines are upregulated in acne lesions (83), based on the previously mentioned data, sebocytes would respond to these cytokines with increased MC-1R expression, thereby generating a negative feedback mechanism for α-MSH which exerts direct anti-inflammatory actions as it inhibits IL-1β-mediated IL-8 secretion.

The expression of MC-5R is weaker than that of MC1-R, but it has been shown to be a marker of human sebocyte differentiation, since it is only expressed in differentiated, lipid-containing sebocytes. The targeted disruption of MC-5R in mice resulted in reduced sebaceous lipid production and a severe defect in water repulsion (81). These findings of Zhang *et al.* stimulated a search for MC-5R antagonists as potential sebum-suppressive agents. As anticipated, an antagonist-inhibited sebocyte differentiation in vitro and reduced sebum production in human skin transplanted onto immunodeficient mice. These data suggest that antagonists of MC-1R and MC-5R could be active sebum-suppressive agents, clinically useful for the treatment of disorders with excessive sebum production, such as acne (81,84). Clinical trials with MC-5R antagonists, like topical gel MTC896, have been initiated for the treatment of excessive sebum production in subjects with acne and other skin conditions. MTC896 has completed Phase II clinical trials (85).

Substance P

There have been various reports that demonstrate an association between human sebocytes and neurogenic stress axes. Nerve fibers release neurogenic neuromediators, neuropeptides (NEP), that exert proinflammatory responses on immune system cells and/or cells of many peripheral tissues as well as the skin (86,87). Substance P (SP), an important neuropeptide related to stress response and pain, also plays a fundamental role in acne (88). The sebaceous gland of patients with acne expresses SP (6,62). In 2002, Toyoda *et al.* demonstrated for the first time in cultured sebocytes that SP stimulates NEP expression by sebaceous cells in a dose-dependent manner, in addition to the fact that more numerous SP-containing nerve fibers were present around SG of the facial skin in patients with acne compared with controls (62). Later, Lee *et al.* demonstrated that the addition of SP induced less proliferation and differentiation. Furthermore, the addition of SP increased immunoreactivity to interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), demonstrating the influence of SP on the production of inflammatory mediators (89). Since these findings, the active pathogenic role of SP as a potential mediator of neurogenic inflammation in acne has been acknowledged. These results indicate a connection of neurogenic factors such as neuropeptides with the pathogenesis of acne and represent a plausible mechanism for the exacerbation of acne from a neurological point of view (90).

CONCLUSION

There is increasing evidence that psychological stress is an important factor in acne pathogenesis. Emotional stress associated with the production of hormones, neuropeptides, and inflammatory cytokines influences the chronic course and exacerbation of acne by altering the activity of the pilosebaceous unit. These mechanisms involve the HPA axis and the neuro-immuno-cutaneous system where neuropeptides and hormones such as CRH, melanocortins, and substance P play a substantial role. On the other hand, great emotional distress and dysmorphic tendencies may develop as the consequence of this disease. Therefore, dermatologists should be capable of recognizing the psychological factors which either contribute to the exacerbation of acne or influence the self-perception of patients with acne. Additionally, an interdisciplinary therapeutic approach should be employed in qualifying patients, involving not only dermatologists but also psychologists and psychiatrists.

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