

The impact of lifestyle factors on evolution of atopic dermatitis: An alternative approach (Review)

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Abstract. Atopic dermatitis (AD) is a multifactorial chronic inflammatory disease with an incompletely understood etio-pathogenesis. With a significant impact on the quality of life of patients, AD has attracted the interest of many research studies aiming to investigate the complex cellular and molecular mechanisms and to identify new therapeutic pathways. Various studies have focused on psycho-immunology, emphasizing the involvement of stress, defined as a general response of the body to external or internal challenges to the AD pathology. Factors like lifestyle and leisure activities may change the behavior of immune cells in AD with a strong impact on the evolution of the disease. Moreover, the poor adherence of AD patient to standard treatment approach has led to the necessity to combine different therapies in the field of complementary and alternative medicine. Although there are still not enough data to conclude that adjuvant therapies are effective in a conventional sense, there are already promising results suggesting that alternative therapeutic strategies could be a main subject of further research.

Contents

1. Introduction
2. Psychoneuroimmunology of atopic dermatitis
3. Lifestyle factors and leisure activities in atopic dermatitis
4. Discussion

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1. Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease characterized by dry skin, cutaneous inflammation and intense itching which can be exacerbated by many trigger factors such as allergens, infections, season and climate changes or psychological stress. Almost half of the cases are diagnosed by the age of 1 year and more than one third of the patients have a persistent disease throughout adulthood (1,2). Nowadays, AD is one of the most common skin diseases worldwide. However, it is often perceived as a minor dermatologic condition, for which patients have to endure symptoms over time (3). At individual level, it has been depicted that AD has a significant effect on quality of life, more important than other common skin diseases, extending its negative effects on patient's family (4,5). Being frequently associated with asthma, allergic rhinitis, contact dermatitis, food allergies, AD deserves to be analyzed in the light of possible complications (6).

The severity of the disease is assessed based on the intensity of the eczema, by the presentation of elementary lesions (erythema, edema/papule, exudate/wounds, excoriations and lichenification), and on the repercussions of subjective symptoms, such as itching and sleep loss (7,8). Furthermore, it is important to take into account the effects of AD on patients' lives, the social impact of the disease, how the patients are managing their condition and their opinion regarding how well the disease is controlled.

The main functions of the skin are protection and defense. Impairment of skin barrier affect the defense against the action of external physico-chemical agents and aggression of microorganisms. Most of the barrier defects that have been described in AD originate in the stratum corneum, a main component of skin barrier owning a 'brick and mortar' structure. The surface lipids of stratum corneum provides a filmogenic feature. Also, filaggrin, after hydrolyzed, is responsible for pH maintenance, moisture and skin protection against microbial agents. On the other hand, proteins of the tight

junctions are essential to control the selective permeability of the epidermis (9).

There is a wide group of microorganisms that colonize the skin and influence the innate immune response. Predominance of *Staphylococcus aureus* in active lesions of AD, can exacerbate or contribute to persistent skin inflammation in AD by secreting toxins with antigenic properties, leading to activation of T cells and other immune cells (10). In the skin of AD patients were found specific IgE antibodies directed against the toxins and basophils are able to release histamine on exposure to the relevant toxin (11,12). Moreover, staphylococcal superantigens may induce mast cell degranulation after penetrating the epidermal barrier resulting in pruritus and acute inflammation.

Being a complex, multifactorial disease, therapeutic management of AD is directly dependent on the severity of the condition as well as the patient's compliance (13). Numerous efforts have been directed toward the development of the easiest and most reliable therapeutic strategy for this disease characterized by varied and recurrent symptoms (14). The management of AD is currently focused on avoiding triggers, improving skin hydration and reduction of skin inflammation (15).

In a simplistic note, nowadays, the therapeutic management of AD is represented primarily by emollients associated with the administration of topical steroids and oral antihistamines. This treatment offers a rapid and effective relief of AD symptoms but, it is important to take into consideration that long-term use of corticosteroids may lead to cutaneous adverse events as well as systemic side effects (16,17). Also, ultraviolet therapy may be considered, followed by immunosuppressants such as systemic corticosteroids and cyclosporine A and topical calcineurin inhibitors (18).

The poor adherence of the patient to drug therapy has made it necessary to combine different therapies in the field of alternative medicine involving the mobilization of physiological and psychological resources. Numerous studies have suggested that balanced lifestyle, healthy diet, hydration, massage, aromatherapy, leisure activities such as listening to classical music, socializing, attending cultural events, altogether could modulate the behavior of patients' immune cells, leading to a favorable evolution of the disease, with a significant decrease in frequency of exacerbations (19-22). Although there are still not enough data to be considered 'effective' in a conventional sense, adjuvant therapies can have promising results that could be the main subject of further research (23-25).

2. Psychoneuroimmunology of atopic dermatitis

Already known as a field of study that analyzes the mutual influence of the nervous and immune systems, psycho-neuroimmunology has become the focus of many research studies that seek to find new treatment pathways for diseases such as AD (26,27).

Being a constant aspect of modern life and widely used as a simple term, stress, is defined as a general response of the body to external or internal factors and it has the role of intensely enlivening the physiological and psychological resources of the individual (28). However, it results in an imbalance between the requirements of the body and its ability

to cope with it (29). Persistence of stress is known as chronic stress, with repercussions on various organs and systems, especially on the immune system. From the anatomical and physiological point of view, there are several links between the central nervous system (CNS) and the immune system. The most important are represented by the autonomic nervous system (ANS) composed of sympathetic (noradrenergic) and parasympathetic (cholinergic) systems, and the hypothalamic-pituitary-adrenal (HPA) axis (27).

It is well-known that stress related conditions are one of the most worrying political and economic issues in the countries of the European Union, being responsible for producing important social and health care costs (30-32).

Numerous studies have suggested the possibility of stress and neuroendocrine factors being involved in the onset, relapse or worsening of a series of dermatological disorders, such as melanoma and non-melanoma skin cancer, psoriasis, acne, rosacea, vitiligo, alopecia areata, lichen planus, seborrheic eczema, urticaria, prurigo nodularis or AD. Their actions seem to be mediated by neurohormones, neuropeptides, neurotransmitters and neuromediators that modulate the interactions between skin and nervous, immune and endocrine systems (33-38).

Although many studies have attempted to identify a clear-cut correlation between stress and allergic skin diseases, it cannot yet be stated that stress is able to induce an allergic response in any circumstance. However, certain subjects with genetic susceptibility could have a predisposition to develop such conditions.

Stress may induce AD lesions by impairing the skin barrier function (39) and by favoring a switching of the immune response towards a Th2 type lymphocyte response (40-42). These changes may underpin the pathogenic pathways in the onset of the disease. Furthermore, chronic stress is able to reduce the activity of NK cells, leading to an increased vulnerability to infection, hence an aggravation of skin lesions (43).

Another hypothesis of pathogenic mechanism in AD is the increased reactivity of the sympathetic-adrenal medullary system to stress (44) which leads to an imbalance between the adrenergic and cholinergic systems, clinically expressed by paradoxical vasoconstriction to mechanical stimulation of the skin (45).

The activation of neuroendocrine systems as an initial response to stress is different in intensity or duration in any individual subject. In chronic stress, the initial adaptation or adjustment mechanisms aimed to cope with the stress agent stimulate the secretion of various neuropeptides and neurohormones with an important role on the onset and course of the disease (46,47).

For example, secretion of catecholamines and cortisol, major stress hormones, have a significant influence on the immune system. They inhibit the production of IL-12 by antigen-presenting cells (APC), responsible for stimulating the Th1 cell response (48). Moreover, corticosteroids have a direct stimulatory effect on Th2 response, by increasing the levels of interleukins IL-4, IL-10 and IL-13 (49,50). Thus, chronic stress may induce an imbalance of Th1/Th2 responses in favor of the Th2-mediated response, with impairment of neuroimmunological homeostatic mechanisms, favoring the occurrence of an allergic inflammatory response.

Moreover, stress may induce modulatory actions on cutaneous nerve fibers and their neurons of origin. An increased density of nerve fibers has been emphasized, especially those containing substance P (SP), in AD lesions (51-57). In addition, patients with AD have significant changes in plasma and tissue levels of neuropeptides such as vasoactive intestinal peptide (VIP), nerve growth factor (NGF), and SP, neuropeptide Y (NPY). Another neuropeptide that could be involved in pathogenesis of AD is calcitonin gene related peptide (CGRP). Higher levels of neuropeptides such as SP, CGRP and VIP induce vasodilation and increased vascular permeability. SP action on monocytes and macrophages increases the production of TNF- α and IL-12, while CGRP stimulates Langerhans cell function to initiate immune responses of Th2 type (58). Furthermore, SP and CRH, released at the peripheral level in inflammatory outbreaks induces mast cell degranulation, thus aggravating the symptoms (59). Mast cells can be another link between stress and exacerbation of AD lesions not only by degranulation of mast cells induced by stress factors, but also by increasing the number of mast cells in the skin (60,61). It was also emphasized that plasma levels of histamine and its concentration in the skin of patients with AD are increased (54).

Thus, there are numerous neuro-pharmacologic agents such as neuropeptides (ACTH, NPY, VIP, SP, CGRP), neurotransmitters [(acetylcholine, noradrenaline, serotonin, histamine, glutamic acid, γ -aminobutyric acid (GABA)] and hormones (adrenaline and glucocorticoids) involved in the modulation of neuronal receptors that amplify circuits of inflammation. They are all viable options for not only the treatment of AD, but also for other stress-mediated inflammatory skin diseases.

At present it is not possible to explain a direct correlation between stress and several skin diseases, but it is important to take into account the evidence obtained from different studies that support the idea that chronic stress, in genetically susceptible individuals, can favor the onset of AD on the one hand, and can impair the therapeutic control of existing skin disease on the other.

3. Lifestyle factors and leisure activities in atopic dermatitis

Emotions. Recent studies have focused increasingly on the emotions rollercoaster, emphasizing their major impact on the development of skin disorders. Moreover, whether acute or chronic, skin conditions have a negative impact on the emotional status of social relationships and on daily activities, due to the stigma caused by the appearance of the lesions (62). Chronic pruritus is often difficult to treat; hence it has a major impact on the quality of life of patients and their families and may lead to psychiatric conditions (32). The decline in the quality of sleep is frequent, affecting the patient's behavior and productivity on a daily basis. Also, in children with AD, sleep loss can lead to hyperactivity disorders and attention deficit. In addition, sleep loss can inhibit recovery of skin barrier increasing natural killer cell activity and plasma proinflammatory cytokines which can worsen the clinical course of many dermatologic conditions (63,64).

Since negative emotions may aggravate the disease, and the disease induces negative emotions it can be said that their entire interaction can create a vicious circle. Also, positive

emotions can improve the symptoms of the disease with a significant impact on its evolution (65,66).

Numerous research papers reported the benefits of laughter and many medical researchers from different parts of the world proposed various experiments that measured the physiological effects and benefits of laughter (65). The link between emotion and significant changes on gene activity on cellular level was investigated by Hayashi *et al* starting from laughter's effect and its potential in treating type 2 diabetes affirming that 'positive emotions influence endocrinological and immunological response' (67).

Kimata showed in a study that laughter reduces the production of allergen-specific IgE, with decreased allergic skin response, significantly increasing the activity of natural killer cells (68).

Regarding deeper feelings, some studies revealed that kissing has a significant effect on allergen induced skin conditions, and decreasing NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4 levels in patients with AD (69). These results indicate that kissing have appreciable implication in the study of neuroimmunology in AD.

Music. Several studies have investigated the impact of music on skin pathophysiological processes. Kimata emphasized the effects of classical music on patients with latex allergy with a positive response in patients who listened to Mozart's music. However, no response was observed to the patients who listened to Beethoven (70). One of many benefits of music is distracting patients' attention from unpleasant experiences or thoughts with an important impact on patients' quality of life (71). However, the relationship between the immune system and music has been assessed in various research such as the study conducted by Bittman *et al* (72), who discovered an increased NK cell activity and lymphokine-activated killer cell activity in normal patients. In addition, Koyama *et al* (73) noted that recreational music modulates immunological responses with significant increases of lymphocytes, T cells, CD4⁺ T cells and memory T cells and higher levels of IFN- γ and IL-6. A more recent study by Bittman *et al* (74) confirmed the above-mentioned findings on a genetic level: their results support the hypothesis that different sets of genes play important roles in both stress and the relaxation response in humans. All these changes may have a huge impact on skin barrier function and the symptomatology of AD patients.

Even though the impact of music was successfully applied in various clinical settings, studies regarding its impact on skin disorders are limited. Nevertheless, nowadays, researchers suggest that listening to known and pleasant music may be included in a regular feature music therapy, aiming to improve the symptomatology of several diseases such as atopic dermatitis, cardiovascular disease, cancer pain, epilepsy, depression and dementia. It would be worthwhile to study the individual emotional responses to music as this would open pathways to tailored music therapy (75).

Humorous movies. Moreover, a considerable correlation between evolution of AD and watching entertainment TV shows was revealed; specifically, the blood parameters suffered changes as the allergic response diminished. It has been observed that the number of plasma neutrophils has been

significantly reduced following the viewing of films, thus improving the implicitly mediated allergic response (65).

Furthermore, it was reported that humorous movies are useful in relieving AD symptoms of children during the night by lowering ghrelin levels. Nighttime waking is quite common in particular in children with AD and disturbances of ghrelin production may be involved in this process. Ghrelin is a hormone produced in the digestive tract, mainly in the stomach and pancreas, which stimulates hunger. It also balances the effect of the hormone leptin produced in the adipose tissue that produces a satiety after the meal (76). Kimata measured salivary ghrelin levels overnight in 40 healthy children and 40 AD patients with nocturnal wake. Levels of salivary ghrelin at 2 AM were significantly elevated in patients with AD compared to those in healthy children. In addition, watching humorous videos before bedtime improved night waking and decreased salivary ghrelin levels in patients with AD (77).

Numerous studies have investigated fluctuations of dermcidin (DCD)-derived peptide, an antimicrobial protein expressed in human eccrine sweat glands. Individuals with atopic eczema have lower levels of DCD-derived peptide in sweat. Researchers measured the levels of DCD protein in the sweat of 20 people before and after watching a humorous movie. They noted a significant increase of this specific protein levels, which could be correlated with the improvement of the skin symptomatology (78).

Mobile phones and video games. Although the sound of mobile phones has come into the daily routine, text messages and video games are included now on the list of factors with a significant influence on AD, increasing both the severity of the symptomatology and the prevalence of the condition. It was estimated that the number of patients with AD increased significantly with the development of technology, making it more and more accessible (79). An interesting research on AD patients undergoing stressful situations (2-h fighting video games or repeated phone calls during a 30 min interval), highlighted increased values of the prick test response, as well as higher levels of Th2 cytokines, neuropeptides and neurotrophin activity (41). Video games enhanced allergen-specific skin wheal responses in patients with AD, increasing plasma levels of SP and VIP. In addition, mononuclear cells from peripheral blood are stimulated with the combination of IL-4, IL-10, IL-13 leading to allergen-specific IgE hyperproduction with concomitant decreased production of IFN- γ and IL-12 in patients with AD. Furthermore, frequent use of mobile phones induces a similar effect, being responsible for an amplification of allergic responses by release of SP, VIP and NGF. The IL-4 and IL-10-stimulated peripheral blood mononuclear cells, lead to an increase in allergen-specific IgE values in AD patients. Since stress can easily aggravate AD, these finding may have important implications in the treatment and pathophysiology of AD (80).

Diet. The importance of diet as a potential trigger of atopic dermatitis has been a subject of debate for long time (81,82). The pathogenesis of AD associated with food allergy is complex. Imbalance of intestinal flora may have an

important role in the development of food allergy in AD, increasing the intestinal permeability that initiates immune responses (83,84). Previous studies emphasized that there are several foods that can aggravate the skin lesions of atopic dermatitis, having an essential and yet unpredictable role in exacerbations of the disease (85,86). Clinical research documented the prevalence of food allergy in AD from 20% to 80% (87). Hence, foods such as chocolate, cheese, yogurt, potato chips, glutinous rice cake, instant noodles, eggs, peanuts, seafood, shellfish and milk have been found to be responsible for irregular aggravation of skin lesions in patients with the disease (88,89). Many studies have established several diet instructions that could relieve the symptoms of atopic dermatitis such as: moderation in eating meals with sufficient chewing, avoiding the ingestion of excess sweets, alcohol, coffee, juice, meats, fats, avoiding processed food and additives. However, it is important to adapt the diet as adjuvant therapy for individual patients. Also, a study by Dhar *et al* (90) on the effects of dietary elimination in 100 children showed significant decrease in the severity score of AD. After 3 weeks of maintaining a proper nutrition, the severity of AD was measured and showed significant improvement. However, there is not enough evidence that can demonstrate improvement in AD through dietary elimination so this is not recommended routinely as it may lead to a severe nutritional deficiency.

4. Discussion

Living with a chronic condition like AD can be both challenging and frustrating. The symptoms such as itching, rash, scaly skin, dryness, bumps, and papules have periods of remission and reappearance, with AD flaring up over and over again (3). It is essential to comprehend that psychological stress affects skin through its direct and indirect effects on immune response, cutaneous neuropeptide expression, and skin barrier function (9). Even though the mechanism underlying the association of AD with psychological stress has not been fully elucidated, many new insights for understanding the role of stress in AD were provided in the field of psychoneuroimmunology (26). There is a growing knowledge about all factors that influence not only the onset, but also the course and severity of this condition, but little is still known about the coping management that may improve its symptoms. There is evidence on the significance of factors such as emotions, sleep, laughter, human interactions, mobile phones, videogames and so on, therefore it is more than relevant to emphasize the link between them and AD (91).

Several studies depicted not only the connection between the nervous and immune system but also the biochemical and cellular links between them (92). It must be taken into account that during chronic stress various hormones and neuropeptides are released leading to immunological changes with imbalance between Th1 and Th2, in favor of the latter.

In conclusion, more and more studies focus on the idea that lifestyle and day-to-day challenges significantly affect susceptible people who are prone to AD. Having all the data, can we conclude that the factors listed are not only responsible for the worsening of AD but also for the increase of its incidence?

Studies regarding lifestyle, including every modality of coping with the stress in AD, have a great potential for identifying new therapeutic targets that can improve the treatment of this chronic and relapsing skin disease that has significant impact on patient's quality of life. Even though the research in medicine is continuously undertaken, it is important to emphasize well-being, humor as potential therapeutic interventions, ameliorating atopic eczema and dermatitis. Therefore, using positive emotions as part of the therapy is an outstanding advice not only for patients with AD but also for many other areas of clinical dermatology.

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Authors' contributions

IS, MAI, CD, VMV, CC, BD and SZ were responsible for gathering and analysis of the data, and contributed to drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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