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Investigation of possible relationship between atopic dermatitis and salivary biomarkers, stress, and sleep disorders

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Abstract

Atopic dermatitis (AD) is a chronic, relapsing, multifactorial inflammatory disease with genetic, environmental, and immunological characteristics. The quality of life and sleep of patients and their families are affected by AD, which triggers stress, described as one of the factors that worsens AD. Salivary biomarkers such as cortisol, alpha-amylase, chromogranin A, and melatonin have been associated with stress and sleep disturbances. Therefore, the evaluation of stress and sleep disorders using salivary biomarkers in AD patients is important. This review aims to describe the possible relationship between atopic dermatitis and stress, sleep disorders, and salivary biomarkers, seeking to contribute to better understanding and clinical management of AD. This descriptive study is characterized as a narrative literature review. A literature search was conducted of studies published in English and Portuguese between January 2012 and October 2022 that are available in electronic media from various databases, such as Scientific Electronic Library Online, Latin American and Caribbean Literature on Health Sciences, and PubMed. AD is associated with different degrees of impact on the lives of individuals who present with the disease. Psychological stress may induce

changes in saliva composition and worsen AD; at the same time, the severity of the disease may be associated with emotional impact. Further studies are needed to assess and correlate AD severity, stress, and sleep disturbances with salivary biomarkers in order to better understand this association.

Key Words: Atopic dermatitis; Sleep; Psychological stress; Chromogranin A; Melatonin; Cortisol

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Core Tip: The quality of life and sleep of patients and their families are affected by atopic dermatitis (AD), which triggers stress, described as one of the worsening factors. Salivary biomarkers have been associated with stress and sleep disturbances, and psychological stress may induce changes in saliva composition and worsen AD. Therefore, evaluating stress and sleep disorders using salivary biomarkers in AD patients is important. This review aims to describe the possible relationship between AD and stress, sleep disorders, and the presence of salivary biomarkers, seeking to contribute to its better understanding and clinical management.

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INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, recurrent inflammatory disease characterized by xeroderma and eczematous lesions that evolve in flare-ups and present pruritus of varying intensity[1]. AD can have a major impact on the lives of patients and their families, interfering with their quality of life in social, academic, and occupational spheres. Pruritus, especially at night, can lead to sleep disturbances that impact sleep quality. Satisfactory sleep is fundamental to welfare and health; in children, acute and chronic sleep disturbances have been associated with an extensive range of cognitive, behavioural, and mood impairments that have been associated with poor school learning performance[2]. In addition, there is an economic impact on patients, their families, and society, with medical and medication costs and decreased productivity[3].

Psychological stress can aggravate the symptoms of AD, which can generate more stress due to the aforementioned impacts. The severity of stress depends on factors such as individual sense, subjective evaluation, and intensity of the stressful event. However, the actual effect of stress on AD is still meanly understood. We know that some salivary biomarkers, such as cortisol, melatonin, chromogranin A, alpha-amylase, and immunoglobulin A (IgA), can reflect psychological stress and sleep alterations and are good indices for evaluating stress[4]. Thus, the objective of this literature review is to describe the possible relationship between AD and stress, sleep alterations, and salivary biomarkers, aiming to contribute to better understanding and clinical management of AD.

LITERATURE REVIEW

A narrative literature review was conducted, with a literature search of studies published between January 2012 and October 2022 that are available in electronic media from several databases, such as Scientific Electronic Library Online, PubMed, and Latin American and Caribbean Literature on Health Sciences. Health Sciences Descriptors "atopic dermatitis", "psychological stress", "sleep", and "salivary proteins and peptides" were used.

Justification

The importance of this review is based on the lack of scientific literature associating AD with salivary biomarkers, stress, and sleep disturbances. It is known that AD influences the physical health and emotional and social well-being of individuals[5]. On the other hand, psychological stress is considered to be a worsening factor in AD[6]. Moreover, patients with AD usually have sleep disorders, which leads to a worsening of their quality of life, school performance, and their and their family's behaviour, generating more stress[7,8].

Stress induces changes in saliva composition. Most compounds that appear in the biofluids can be identified in saliva[9], with easier access, which excludes the possible stress bias of needle puncture in blood collection.

ATOPIC DERMATITIS

AD is a chronic and frequent disease that goes through periods of remission and relapse; it predominantly affects children and its main symptom is pruritus. Characterized by eczematous lesions and xeroderma, AD is one of the most common chronic recurrent allergic inflammatory skin diseases and has an increasing prevalence in the population over time[1]. It affects 20% of children and 10% of adults worldwide[10] and is more frequent in individuals with a family or personal history of atopies, such as rhinitis and asthma, or AD itself[5]. The onset of AD is usually during the first six months of life, observed in approximately 45% of cases, and signs and symptoms may continue throughout life[1].

AD progresses with very diverse clinical manifestations characterized by recurrent xeroderma, erythema, eczema, and pruritus[11]. An assessment of disease severity is recommended for treatment choice and follow-up. There are several assessment tools, including SCORAD (Severity Scoring of Atopic Dermatitis) and EASI (Eczema Area and Severity Index)[12].

AD is a complex disease that has a genetic component and is influenced by innate and adaptive immune responses[7]. The pathophysiology is still not fully understood[7] and different factors are involved in its emergence and evolution, which include skin barrier defects, immune dysregulation, skin dysbiosis, and environmental factors[10,13]. This condition may be associated with several symptoms, including pruritus, pain, and sleep disorders, affecting the quality of life of patients and their families, in addition to triggering psychological stress, which has been described as one of the aggravating factors of the disease[10,14]. AD may be associated with higher rates of anxiety and depression, with a negative impact on self-esteem, educational performance, and work[10,15].

Atopic dermatitis and sleep

Sleep disorders are observed in up to 60% of individuals with AD[7,10] and can negatively impact neurocognitive function, behaviour, and mood[7], leading to worse quality of life, school performance, and behaviour of patients and their families. Additionally, sleep disturbances in children with AD have been associated with greater severity of AD and scratching[7,16].

A cohort study by Ramirez *et al*[2] in the UK evaluated 13988 children and demonstrated that AD was associated with impairment of sleep quality, but not sleep duration, throughout childhood. Sleep impairment was more common in more severe diseases and when associated with rhinitis or asthma, but the chance of sleep alteration remained high even among children with mild AD and with no activity[2].

A cohort of children and teenagers aged 6–7 years with moderate to severe AD underwent an actigraphy assessment during sleep, which showed that sleep was altered in approximately 60% of participants[17]. The pathophysiology of sleep disturbance in children with AD is mainly understood. Itching and scratching may lead to sleep disarrangement but it is improbable to be the isolated cause. The circadian rhythm of cytokine expression, the immune system, cutaneous physiology, and environmental factors may be related[7]. Decreased melatonin secretion in individuals with AD may be involved in sleep disturbances because of its effects on sleep, immunomodulation, and antioxidant activity[7,8].

A study conducted by Chang *et al*[8] demonstrated through actigraphy and polysomnography that children with AD have the following sleep alterations: Significantly reduced efficiency, longer latency time to sleep onset, more fragmentation, and less non-rapid eye movement (non-REM) sleep compared to healthy individuals.

Atopic dermatitis and psychological stress

AD influences the physical health and emotional and social well-being of the children affected[5]. There is great interindividual variability in neurally mediated responses to psychological stress and AD flare-ups[10]. With the influence of stressful stimuli, physiological activation of some specific areas of the peripheral and central nervous system occurs. The stress response includes stimulation of the hypothalamus and brainstem and also activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. These systems work together with the immune system and are intimately implicated in the pathogenesis of stress-associated illnesses. These compensatory responses of the body involve the production of substances that can be found in serum and saliva. The relationship between stress and the concentrations of cortisol, IgA, melatonin, alpha-amylase, and chromogranin A in the saliva has already been described in the literature[18].

Activation of the HPA axis and the adrenomedullary sympathetic system is adaptive mechanisms that allow the maintenance of physiological stability in response to stress signals. Dysregulations between the HPA axis, the adrenomedullary system, and chronic stress-induced stimulation may trigger metabolic changes[19,20]. Stress activates the HPA axis and results in the release of cortisol[21].

Neuroendocrine mediators play an important role in the pathogenesis of AD. The HPA axis has important functions, such as responses to physical and psychological stress and inflammatory agents. Dysfunction of the HPA axis is observed in AD patients, presenting as a decreased response of serum corticosteroids after exposure to stressors compared to individuals without AD. Regardless of whether the HPA axis is initially activated by pro-inflammatory cytokines, there is an attenuated corticosteroid response to stress in chronic AD. Thereby, in individuals with AD, insufficient corticosteroid production may result in a T-helper type 1 (Th1)/T-helper type 2 (Th2) imbalance and trigger inflammation[1].

Acute stress can induce an individual's adaptive response to environmental demands by rapidly triggering an elevated release of cortisol and adrenaline or noradrenaline, which stimulate the immune system, primarily Th1, to produce pro-inflammatory cytokines, resulting in a cellular immune response and inflammation. Chronic and excessive stress causes cumulative negative health impacts by increasing basal cortisol levels and decreasing acute stress responsiveness, with the immune system shifting from a cellular to a humoral response. The keratinocytes of the skin have receptors for neurotransmitters and hormones (adrenergic, muscarinic, glucocorticosteroid, oestrogenic, and androgenic), actively participating in psychoneuroimmunological pathways[11].

Stress impairs the epidermal barrier function and favours alterations in the Th2 immune response. Individuals with AD appear to have an inherited hypothalamic deficiency that impairs the normal function of the HPA axis under stress, altering some hormones and proteins, which trigger deleterious effects in these patients[6]. The impaired response of the HPA axis under stress may be an explanation for the stress-induced exacerbation of AD[21].

Atopic dermatitis and salivary markers

Saliva is secreted by three main glands - parotid, submandibular, and sublingual[22] - and contains stress-related biomarkers (Table 1). The secretion process is regulated by the autonomic nervous system; salivary electrolytes and fluid secretion are mainly controlled by the parasympathetic system, while protein secretion is triggered by sympathetic stimulation. Stress induces changes in saliva composition and most compounds that appear in the blood circulation can also be identified in saliva, but in different concentrations[9].

After a stressful stimulus, there is activation of the HPA axis, which stimulates the release of salivary cortisol, as well as the activation of the adrenomedullary sympathetic system, with stimulation of catecholamine secretion, which induces the release of salivary chromogranin A, alpha-amylase, and IgA [23].

Cortisol is a hormone produced by the adrenal cortex, principally in the second half of the night, and its serum levels are highest between 7 am and 8 am. During the day, cortisol levels drop significantly, and at night only about 10% of the morning cortisol remains in the body. When exposed to physical or psychological stress, the adrenal glands produce greater amounts of cortisol. This activates the metabolism, which supplies the body with energy and changes the conditions for mental reactions, increasing the activity of other hormones and generating additional energy stimuli to cope with stressful situations. Permanent stress can leave the body exposed to the effects of constantly elevated cortisol levels. It is hypothesized that after long exposure to physical and/or mental stress, the HPA axis becomes less sensitive, resulting in decreased cortisol production by the adrenal glands[18].

A study was conducted to measure baseline serum cortisol levels and cortisol levels after a low-dose adrenocorticotrophic hormone (ACTH) stimulation test in patients with AD before and after treatment with topical corticosteroids. Three groups of patients with AD were evaluated: Mild, moderate, and severe. Eighteen patients in the severe group at the beginning of the study had HPA axis impairment with cortisol levels < 250 nmol/l during the first visit. A total of 13 of the 18 patients recovered HPA axis activity when baseline cortisol was measured after the use of topical corticosteroids, resulting in a 75% improvement in disease activity. Thus, the authors concluded that disease activity is responsible for the low baseline levels in patients with severe AD[24].

Mizawa *et al*[4] conducted a study that evaluated 30 patients with AD aged 15–62 years and a control group; the SCORAD and salivary cortisol levels suggested that patients with AD may be under chronic stress and the severity of AD may be correlated with the intensity of stress. It was also reported in the same study that dosing through saliva has the advantage of being non-invasive, allowing for multiple sample collection, easy access, and no stress of needle puncture. The results suggested that the salivary cortisol level is a useful biomarker to assess stress in patients with AD and to help physicians plan their management for each case[4].

Meštrović-Štefekov *et al*[25] conducted a study of 84 patients with AD (42 symptomatic and 42 asymptomatic) to compare salivary cortisol levels with severity of AD and stress. Elevated cortisol levels were found in both groups and were not associated with disease severity (SCORAD). Individuals with severe AD had significantly lower cortisol levels than those with mild and moderate AD ($P = 0.042$). The study suggested that the intensity of perceived stress in patients with AD is not adequately measured by salivary cortisol levels or by SCORAD; it correlates with the impact of AD on the emotional profile and personality characteristics (anxiety and depression). The authors suggest that all patients with AD, regardless of disease severity, should be assessed for the impact of stress and should receive a multidisciplinary approach to psychological well-being[25].

Table 1 Atopic dermatitis and salivary biomarkers

Salivary biomarker	Specifications	Effect on atopic dermatitis	Ref.
Cortisol	Activates the metabolism, after physical or psychological stress, which supplies the body with energy and changes the conditions for mental reactions, increasing the action of other hormones and generating additional energy stimuli to cope with stressful situations	Salivary cortisol level may be a useful biomarker to assess stress in patients with AD. Patients with AD may present elevated cortisol	[4,18,25]
Chromogranin A	Reflects catecholamine secretion in the blood and functions as a marker of sympathetic adrenomedullary system activity	Severe AD is associated with elevated stress levels and salivary measurements of chromogranin A may be useful as a marker in the objective investigation of stress. In the most severe cases of AD, the chromogranin A levels in saliva were higher	[28,29]
Alpha-amylase	Digestive enzyme and a biomarker of the autonomic nervous system. Both sympathetic and parasympathetic nervous system innervations stimulate salivary alpha-amylase secretion <i>via</i> α - and β -adrenergic mechanisms	Salivary alpha-amylase activity increases in individuals with chronic psychosocial stress and can be used as a biomarker of chronic stress	[31,33,36]
Melatonin	Hormone with a function in sleep regulation. The literature suggests that melatonin has immunomodulatory, anti-inflammatory, and antioxidant effects and may improve skin inflammation and help to maintain a functional epidermal barrier in patients with AD	Decreased nocturnal secretion is associated with sleep disturbances and greater AD severity in children. It has been shown that salivary melatonin levels are reduced in patients with AD. In parallel, melatonin production is reduced by stress	[8]
IgA	Plays a role in defence against bacteria and viruses. IgA may help to prevent the development of allergic inflammatory reactions, and IgA deficiency could promote allergic sensitization and also be a marker of stress	Low serum IgA levels have been related to AD severity	[23,40,43,45]

AD: Atopic dermatitis; IgA: Immunoglobulin A.

Topical corticosteroids are widely used in the treatment of AD. Percutaneous absorption may occur mainly in high-potency topical formulations and when used on large areas of inflamed skin for long periods. It is believed that younger children would have a higher risk of systemic effects due to high percutaneous absorption because of the higher body surface area-to-weight ratio. However, there is doubt as to whether this is relevant in clinical practice. The presence of synthetic corticosteroids in the circulation would exert a negative response on the release of corticotrophin-releasing hormone, with reduced ACTH by the pituitary gland and decreased cortisol production by the adrenal glands[26].

A cohort study by Haeck *et al*[26] demonstrated that low baseline serum cortisol values are not caused by previous use of potent topical corticosteroids in patients with moderate to severe AD. However, the baseline serum cortisol levels of hospitalized patients showed an increase during intensive treatment with large amounts of potent topical corticosteroids[26].

A study conducted to investigate baseline serum cortisol levels and anxiety in paediatric patients with AD evaluated 36 patients (9–16 years old) and 36 controls (9–15 years old). Anxiety was assessed using the TAI-C (trait anxiety subscale of the State-Trait Anxiety Inventory for Children) and severity of AD was assessed by SCORAD. The study showed no statistical difference in baseline serum cortisol level ($P = 0.383$) or TAI-C score ($P = 0.730$) between the two groups. Also, no significant correlation was found between baseline cortisol values and TAI-C scores in the AD group ($P = 0.290$). The SCORAD index was correlated with TAI-C scores ($P < 0.05$) but not with baseline serum cortisol values in patients with AD ($P = 0.06$). Thus, the authors suggested that children with AD do not have more anxiety or altered cortisol levels compared to children without, but the severity of the symptomatology may cause anxiety levels to increase in children with AD[27].

Another salivary marker present in the ducts of the submandibular glands that is released into saliva following autonomic nerve stimulation is chromogranin A, a dissociated acidic glycoprotein from chromaffin granules in the adrenal medulla, which reflects catecholamine secretion in the blood and functions as a marker of sympathetic adrenomedullary system activity[28].

Kaneko *et al*[29] proposed that severe AD is associated with elevated stress levels and that salivary measurements of chromogranin A may be useful as a marker in the objective investigation of stress. A study by Cai *et al*[28] compared the assessment of AD severity and psychological stress with stress protein levels in saliva, and a correlation between stress and salivary chromogranin A level in patients with AD was suggested: In the most severe cases of AD, the chromogranin A levels in saliva were higher[28].

Lee *et al*[30] evaluated stress by measuring salivary chromogranin A and cortisol in distracted children using a kaleidoscope and also in non-distracted children, both undergoing venipuncture. They concluded that the level of salivary chromogranin A immediately after venipuncture was higher than that found before and 60 min after. The level of salivary cortisol did not show significant differences

[30]. According to the results of the above studies, it has been suggested that chromogranin A may be a reliable marker of stress in children[28-30].

Salivary alpha-amylase is a digestive enzyme and a biomarker of the autonomic nervous system[31]. Alpha-amylase exhibits a diurnal pattern opposite to that of cortisol: Its concentrations show a substantial decrease during the 30 min after waking up and then an increase throughout the day, with peaks in the late afternoon or evening[32]. Both sympathetic and parasympathetic nervous system innervations stimulate salivary alpha-amylase secretion *via* α - and β -adrenergic mechanisms[33] and it has been suggested that salivary alpha-amylase increases in response to cognitive function and psychosocial stress in healthy volunteers[34,35].

A study performed by Kaneko *et al*[29] investigated AD severity, stress levels, and consequent changes in stress proteins in saliva, observing no correlation between the SCORAD index and salivary alpha-amylase levels or between State-Trait Anxiety Index scores and amylase levels.

A study to evaluate salivary alpha-amylase activity as an indicator of chronic stress analysed 50 subjects with chronic stress-related problems and 50 subjects in the control group. Salivary alpha-amylase levels were compared between the groups. The study showed significantly higher salivary alpha-amylase levels in the study group ($P = 0.002$). The authors concluded that salivary alpha-amylase activity increases in individuals with chronic psychosocial stress and can be used as a biomarker of chronic stress[36].

Melatonin is a hormone secreted by the pineal gland, with a function in sleep regulation. Decreased nocturnal secretion is associated with sleep disturbances and greater AD severity in children[8]. The literature suggests that melatonin has immunomodulatory, anti-inflammatory, and antioxidant effects and may improve skin inflammation and help to maintain a functional epidermal barrier in patients with AD. In this context, it is known that activation of the immune system leads to the production of free radicals, which may be associated with decreased melatonin levels and reduced antioxidant enzyme activity in several inflammatory diseases[37].

One study compared the sleep quality and nocturnal salivary melatonin profiles of Canadian armed forces military personnel diagnosed with post-traumatic stress disorder[38]. Participants were monitored for a week *via* actigraphy to assess sleep quality and 24-h salivary melatonin levels were assessed every 2 h. It was concluded that post-traumatic stress disorder is associated with attenuated nocturnal melatonin secretion[38].

In the acute phase, AD lesions are related to Th2 cytokines, particularly IL-4, IL-5, and IL-13. Experimental data suggest that melatonin may reduce serum levels of total IgE and IL-4, related to the pathogenesis of AD, and thus could inhibit the development of the disease[37].

It has been shown that salivary melatonin levels are reduced in patients with AD. In parallel, melatonin production is reduced by stress. However, a study in Japan conducted on 24 patients with AD with a mean age of 14 years observed increased salivary melatonin levels after a stimulus, which in this case was "watching a comedy movie"[39].

IgA plays a role in defence against bacteria and viruses by interfering with epithelial adhesion and improving the properties of mucus in trapping and removing antigens. Similarly, it has been suggested that IgA may help to prevent the development of allergic inflammatory reactions[40]. IgA deficiency could promote allergic sensitization. Although the mechanism is not yet well known, it is suggested that IgA may competitively bind to allergens, preventing it from encountering other immunologically active factors[41,42].

Salivary IgA could also be a marker of stress[23] as it could interact with the autonomic nervous system, changing its concentration in response to physical and psychological stressors[43]. However, a study conducted by Tzira *et al*[44] observed no change in IgA levels when seeking to correlate salivary stress biomarkers in children admitted to a paediatric intensive care unit: 65 patients aged 2–14 years old were evaluated, with saliva samples collected at 8 am, 2 pm, and 8 pm.

The level of IgA in saliva changes in response to psychological factors, with an increase during good mood and a decrease during bad mood or stressful stimuli. Chronic stress is related to activation of the HPA axis, measured by an increase in the concentration of salivary cortisol, and to decreased activity of the immune system, measured by a decrease in salivary IgA concentration[18].

It has been described that atopy is frequent among children with low immunoglobulin levels, and the frequency and severity of allergic manifestations are more prominent in patients presenting low IgA levels[41,45]. A study in Turkey aimed to define the characteristics of 125 children with AD aged < 4 years with low serum immunoglobulin levels. It was suggested that low serum levels of IgA and IgM were related to the severity of AD[45].

A study evaluated 31 third-year dental students regarding self-perception of stress, measured by a stress scale and salivary cortisol, IgA, and chromogranin A levels, immediately before and after a 1-h written test[46]. Pre-test stress scores were associated with increased salivary cortisol, but no change was observed in the level of IgA or chromogranin A[46].

Results that demonstrate no association between stress and changes in IgA level could be due to the possibility of influence by bacterial contamination, even under refrigeration[23]. A study by Ng *et al*[47] demonstrated that salivary IgA concentration remains stable for up to 3 mo when the sample is stored at -30 °C. It is debatable whether salivary IgA would be a good marker of psychological stress in real time because its half-life is very long[23].

Atopic dermatitis and its impact on the patient's life

Stress-induced pruritus is a frequent problem for patients with AD[28]. A higher incidence of behavioural changes is also observed throughout the lifespan of children with AD[10].

AD influences the physical health and emotional and social well-being of children with AD[5]. It impacts life quality, imposes enormous responsibilities regarding prevention and treatment on children, families, and caregivers, and can also lead to interpersonal conflicts, financial difficulties, and significant impairment of mental health. Likewise, the presence of emotional and behavioural problems can interfere with the child's and the family's ability to manage the success or failure of the disease[48]. One study showed that children with severe AD have a higher risk of presenting behavioural problems, with potential impact on treatment of the disease[49].

Psychological monitoring in individuals with AD is of utmost importance and should be seen as an integral part of the care approach[10]. It is suggested that all individuals with AD, regardless of disease severity, should be assessed for psychological impacts and a multidisciplinary approach should be indicated[25]. Although many scientific advances have been made regarding the biological response to specific triggers, many unknowns and challenges remain in AD[10].

CONCLUSION

AD can negatively affect the physical, emotional, social, and economic spheres of individuals. Stress induces changes in saliva composition, and most compounds that appear in the biofluids can be identified in saliva, although in different concentrations. The severity of AD may correlate with its emotional impact and also with the patient's personality characteristics (anxiety and depression). It is therefore suggested that patients with AD, regardless of disease severity, should be assessed for the impact of stress and receive a multidisciplinary approach for psychological well-being. Further studies are needed to assess and correlate AD severity, stress, and sleep disturbances with salivary biomarkers, seeking to better understand this association and how these findings can assist in the follow-up of these individuals. The results of this narrative review suggest that salivary biomarkers such as melatonin, chromogranin A, cortisol, IgA, and alpha-amylase may be associated with AD.

FOOTNOTES

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