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ATOPIC DERMATITIS: FROM MOLECULAR SPECIFICITY OF ORAL MANIFESTATIONS TO CLINICAL IMPLICATIONS

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ABSTRACT

Atopic dermatitis (AD) is considered a systemic disease that also manifests itself in the oral cavity. The presence of oral pathologies in patients with atopic dermatitis can result in the worsening of the atopic disease, and on the other hand, the presence of AD can favour the development of oral diseases. As changes in the expression of AD-specific molecules can be observed in AD patients both in the skin and in the oral mucosa, the investigation of the expression levels of some salivary molecules could be possible biomarkers of risk for the onset, diagnosis and progression of the disease. The evolution of lesions diagnosed in patients with atopic dermatitis can be significantly improved by early and correct treatment of infectious odontogenic foci.

Key words: atopic dermatitis, biomolecules, biomarkers, oral cavity, oral mucosa

INTRODUCTION

Initially considered a chronic inflammatory dermatosis, atopic dermatitis is now considered a systemic disease affecting multiple organs and systems, associating besides the cutaneous expression, clinical respiratory (allergic rhinitis, allergic bronchial asthma), renal, ophthalmological, autoimmune manifestations, food allergies, psychological comorbidities, but also oral manifestations [1].

In the last 30 years, the incidence and prevalence of AD has shown significant increases, directly related to the heterogeneity of environmental factors [1,2] .

The onset of AD is usually in the first 6 months of life (in 45% of cases) or during childhood, up to the age of 5 years [2]. Often, the onset of skin or systemic diseases with an immune mechanism of action, such as atopy, occurs in the oral cavity [3].

Also, many immune-mediated dermatoses have a direct effect on the oral mucosa, with a remodelling process taking place that includes disruption of the epithetlial barrier and release of inflammatory signals [1-3].

The algorithm for assessing the clinical and developmental severity of AD is not fully elucidated [4].

A higher prevalence of AD has been found in people with oral pathologies, with some authors suggesting that these may be involved in the pathogenesis of AD [5].

Also, the presence of oral manifestations such as class I occlusion, reduced overbite, susceptibility to cariogenic activity, reactivation of the Herpes Simplex Virus type 1 (HSV-1) is correlated with AD, and some research data show that the presence of focal odontogenic infections in patients with AD leads to the atopic disease getting worse [6]

Given that there is currently little data in the literature on oral mucosal changes associated with autoimmune diseases, the aim of this review is to mention them by highlighting aspects related to specific molecular features of oral mucosal remodelling in atopic dermatitis in order to use them as a potential tool for early diagnosis and for guiding therapy.

IMPACT OF ORAL PATHOGENS

Periodontal disease is one of the most common inflammatory diseases encountered in the adult population and is caused by dysbiotic microbial communities in the subgingival sulcus that result in the destruction of tooth anchoring structures in the jawbone followed by subsequent tooth loss [7].

Periodontitis is mainly caused by *Porphyromonas gingivalis, Treponema denticola* and *Actinobacillus actinomycetemcomitans* [5,8].

Dysbiosis of the oral microbiota, which is the 2nd largest microbiota in the human body, and the proliferation of the aforementioned anaerobic gram-positive bacteria will initiate the immune response, causing chronic inflammation and periodontal tissue destruction [10,11].

Thus, a number of pathogens and significant levels of inflammatory mediators, including TNFα, IL-1, IL-2, IL-8 and prostaglandin PGEs, are identified in the diseased periodontium pocket and released from the diseased periodontium into the circulation, contributing to systemic inflammation evidenced by increased levels of C-reactive protein in both acute and chronic forms of periodontitis [12,13].

Also, involved in immune responses to oral pathogens and allergic diseases, Treg. CD4+CD25+ cells have been identified in gingivitis and periodontal lesions [7].

The results of research by Jee Hye Wee et al. revealed a correlation between oral health and atopic dermatitis, asthma and allergic rhinitis in Korean adolescents, based on the premise of the common Ig-E-mediated pathophysiological mechanism of the three conditions [14].

In the same line, the research results of Ji-Su Shim & Min-Suk Yang also indicate that oral lesions can aggravate AD, and *S.aureus* skin infections and *C.albicans* oral infections influence the severity of AD [15].

Thus, Matsumura et al. showed that *C.albicans* infection correlates with AD, with *C. albicans*-specific antibody production being associated with disease severity and with IgE antibody levels being significantly higher in AD patients than in the control group [16].

On the other hand, Javad et al. found that IgG levels for *C. albicans* in AD patients are statistically significantly lower than in the control group, while the use of inhaled corticosteroids contributes to the development of candidiasis [17].

Given the role of saliva in antimicrobial defence in the oral cavity, a decreased salivary flow due to antihistamines or mouth breathing commonly seen in AD may increase susceptibility to oral infections. Antihistamines have CNS side effects and antimuscarinic effects, including xerostomia, due to inhibition of M3 receptors in salivary glands, and a decreased salivary flow leads to increased cariogenic activity. Xerostomia may also occur in AD patients treated with immunosuppressants or antibiotics, which would result in the transformation of commensal *Candida albicans* in the oral cavity into a pathogenic form favouring the development of oral lesions [18,19,20].

At the same time, anti-allergic drugs may contribute to poor oral health by decreasing salivary flow and ph, leading to increased incidence of DMFT (decayed, missing due to caries, and filled permanent teeth) [21,22].

It is also known that skin barrier dysfunction can lead to an increased risk of microbial infections of both the skin and the oral cavity. From this point of view, the interrelationship between AD and oral pathology can be explained by several possibilities. Thus, patients with AD are prone to colonisation and skin infections in particular with *Staphylococcus aureus* and *herpes simplex virus* (HSV) due to both skin barrier dysfunctions caused by alterations in the expression of structural proteins such as filaggrin (FLG), and immune system disturbances including low levels of antimicro-

bial peptides. These aspects may also lead to increased susceptibility of the oral cavity to infection [23,24].

Igawa et al. observed that in patients with AD, poor oral health (caries, gingivitis) can interfere with treatment and thus exacerbate clinical manifestations. In this regard, after 3 months of dental treatment in adult AD patients with focal odontogenic infections (30%), they show significant improvements in skin lesions [25].

MOLECULAR BIOMARKERS

Given the concept of targeted, personalised medicine, research in the field aims to find new and more specific biomarkers for the diagnosis, prognosis and assessment of the outcome of therapies used in AD so that evaluation of their expression can provide clinicians with useful information for an appropriate therapeutic strategy.
Due to the heterogeneity of clinical manifestations and molecular characteristics, as well as the difficulties in biological sampling, there are few data on AD-specific bio-markers in the oral mucosa [25-27].

In this regard, the investigation of the expression levels of molecules such as FLG, TNF alpha, IL-17, antimicrobial peptides, toll-like receptors and other salivary biomarkers, which could be possible diagnostic and risk biomarkers for the development and progression of AD, is considered.

1. FILAGGRIN

FLG, a protein expressed in epithetlial tissues, has important functions in maintaining barrier integrity at both the epidermal and oral mucosal levels. It is identified in granular and horn-like tissue cells where it stabilizes cytokeratins, the intermediate filaments of the cytoskeleton. In addition, changes in synthesis and secretion of this protein may be correlated with the development of infectious pathology in the oral cavity. Thus, some gene defects may favour and condition the etiopathogenesis of caries identified in about 60% of AD patients. At the same time, this variability in filaggrin expression is also correlated with xerostomia, a synergistic factor in the development of *Streptoccocus mutans* infections [5,26-28].

As early as 2015, based on the hypothesis that filaggrin is involved in the terminal differentiation of keratinocytes, Pendaries et al demonstrated the important role of FLG and FLG2 gene expression in defining and maintaining epidermal barrier function, with particular impact on AD progression [29].

Using the results of this research, recent studies correlate the presence of various mutations in the FLG filaggrin gene with AD-specific tissue changes in both the skin and oral mucosa. At the same time, it is suggested that some oral cavity lesions represent the clinical expression of allergic mechanisms initiated by exposure to Ni- and Cr (Chromium) III-containing amalgams [30,31].

However, Kim J. et al. obtained conflictting results on the interrelationship between the degree of FLG gene expression and/or filaggrin promoter methylation with the development of allergic-type lesions in the oral mucosa [32].

In normal oral mucosa, both filaggrin and filaggrin-2 are expressed to different degrees in keratinized and non-keratinized epithelia. In addition, filaggrin-2, resulting from filaggrin proteolysis, was found to show reduced expression in the oral cavity of AD patients [33].

In this context, it is considered that filaggrin expression may be influenced by certain inflammatory biomarkers. While IL-17 production reduces filaggrin and involucrin expression, cytokines such as IL-4, IL-13, IL-31, IL-33 also have similar inhibitory action on keratin, loricrin, and cell adhesion proteins [34-38].

2. TNF-α

Involvement of key immune pathways in the initiation and development of AD-specific lesions is also strongly

supported by the action of the proinflammatory cytokine TNF-α. While at the cutaneous level the intervention of internal and external triggers on cell signalling pathways controlled by TNF-α is known, at the oral mucosal level the role of this molecular checkpoint in the progression and prognosis of AD-associated lesions is not yet well documented[34-39].

Similar to other proinflammatory cytokines such as IL1β and IL6, the degree of TNFα expression is conditioned by the action of pathogens influencing both local inflammation in periodontal tissue and systemic inflammation [8,40].

According to the population-based study conducted by Shim & Yang, this increased susceptibility to infection, characteristic of AD patients, is directly proportional to the lesional aggressiveness mediated by the concomitant action of proinflammatory cytokines and matrix metalloproteinases (MMPs). In this case, data obtained from an 8-year analysis of the Korean cohort indicated the interdependddence between pathognomonic tissue changes in gingivitis and periodontal destruction and microbial antigens with tropism in oral cavity epithelial cells [15].

Also, Ebersole et al. indicate that expressions of TNF-α, salivary macrophage inflammatory protein-1α, matrix metalloproteinase-8, interleukin (IL)-1β, IL-6, prostaglandin E2 can be used as markers in establishing diagnostic algorithms for gingivitis and periodontitis [41].

All these cellular and molecular interactions define the local inflammatory microenvironment, with systemic repercurssions, allowing the creation of a vicious circle infection-inflammation-AD. Therefore, Igawa et al. revealed that the clinicotherapeutic evolution of lesions diagnosed in patients with AD is significantly conditioned by the correct treatment of odontogenic infectious foci, even before the onset of symptoms in the oral cavity [25].

Some studies in the research literature have shown that both the expression of TNF-α and other proinflammatory molecules, such as IL-1β, MMPs and prostaglandins (PE2), are associated with the severity of periodontal disease [25] .

On the other hand, inhibition of the secretion of these proteins has positive effects on the clinical course of the disease, independently of the etiopathogenic mechanisms involved [42].

Also, at the tissue level, TNF-α can influence the morphofunctional architecture of the skin barrier by direct and indirect action on the synthesis and secretion mechanisms of involucrin, loricrin and filaggrin. The latter can be inhibited by TNF-α via the c-Jun-mediated signalling pathway, with particular impact on epithelial keratinization [43].

3. IL-17

According to research conducted by Shimizu et al, IgE levels are a true mediator of Th17 cell activation, with stimulation of IL-17 secretion, considered the "eye" of the cytokine storm in AD pathogenesis. Therefore, serum IgE concentrations can be correlated with the degree of IL-17 expression in epithelial tissue [44].

Moreover, the intensity of cellular immunoreactivity for IL-17 is greatly increased in AD patients with a personal pathological history of invasive orthodontic treatments. These therapeutic procedures influence cell turn-over by maintaining the balance of osteoclastogenesis/odontoclastogenesis via IL-8 and IL-6, molecules secreted by IL-17-stimulated fibroblast cells. This explains the increased level of these cytokines in AD patients [44].

On the other hand, in root resorption, IL-17 has been shown to play a synergistic role in stimulating orthodontically induced inflammation. Moreover, in his study, Hayashi et al. revealed that the balance of bone remodelling is tilted towards osteoclastogenesis in AD patients. This mechanism involves both the dental pulp and the periodontal ligament, under the active control of mechanically stimulated Th17

cells. Consequently, orthodontic movements amplify IL-17 production, with direct impact on root resorption [39,45].

4. ANTIMICROBIAL PEPTIDES

Similar to the skin epithelium, the variable expression of 3 types of human β-defensins (hBD1-3) is also identified in oral mucosal cells. The secretion of these antimicrobial peptides is the result of the action of infectious factors, bacterial or viral, via proinflammatory cytokines and growth factors [46].

In AD patients, susceptibility to infection is directly proportional to the reduced expression of antimicrobial peptides, such as β-defensins 2 and 3 and cathelecidin LL-37, in response to increased levels of interleukins 4 and 13 (IL-4, IL-13) [9,47].

This hypothesis was also supported by the results of research conducted by Perugia et al. [5].

Among the pathogens frequently involved in cutaneous-mucosal infections diagnosed in AD patients are *S. aureus* and *HSV* [48].

The observations made by Kim et al. that *S. aureus* colonisation induces and activates the interdependence between the development of AD and the immune response mediated by antimicrobial peptides were also supported by research conducted by Ong et al. [32,49].

These molecules are also responsible for the clinical expression of secondary bacterial infections [32,49].

Furthermore, Waasdorp et al. indicated that saliva containing antimicrobial peptides and enzymes such as defensins, histatins, cathelicidin (LL37), lysozyme, lactoferrin and lactoperoxidase also exhibit protective anti-infective role by killing microorganisms [50].

Histatins, histidine-rich peptides, are produced in the salivary and parotid glands and secreted in the saliva where they have antimicrobial action. Histatins are known to have bactericidal activity for *Streptococcus mutans* and *Porphyromonas gingivalis.* At the same time, Histatin-3 1/24 (Histatin-5) is effective against *Candida albicans* and *Cryptococcus neoformans* [51-54].

The antiviral activity of saliva is also controlled by HNPs (Human Neutrophil Peptide) (Human alpha defensins 1-4). Thus, the low level of salivary HNP explains the increased risk for oral infections in these patients. HNP-1 and HNP-3 are found in the junctional epithetlium of healthy gums, but also in the pocket epithelium of gums with periodontitis. Low concentrations of HNP-1 are associated with increased keratinocyte proliferation, and moderate and high concentrations are correlated with significantly increased cell death [51-54].

Another key peptide in defining oral biology is the antimicrobial peptide AM (adrenomedullin), a molecule involved in the formation and development of mineralized tissues, expressed by oral keratinocytes. Its secretion is stimulated by the presence of bacteria such as *P. gingivalis*, *S. mutans* and *E. corrodens*.

In addition, this protein is sequestered in the extracellular matrix of dentin during the process of dentinogenesis [55-57].

5. TOLL-LIKE RECEPTORS

Some genetic mutations of tooth structural proteins are involved in the etiopathogenic mechanism of early caries. These include the Dlx-3 gene with an important role in enamel formation and epidermal differentiation and the MBL2 gene. Similar to toll-like receptor 2 (TLR2), polymorphism of these genes is associated with both AD and early development of dental caries. These observations were also supported by the studies conducted by Kalhan et al, the author of the "structural defect hypothesis". AD cases with a positive SPT (skin prick test) result would have a higher risk of ECC at 2 and 3 year dental examinations.

In periodontitis patients, salivary

levels of TLR4, IL-18, uric acid, aspartate transaminase and procalcitonin are elevated, correlating positively with clinical parameters [58-60].

6. VITAMIN D3

Analysing the action of vitamin D on specific and nonspecific immune response, Hui Mei Cheng et al. showed in a cohort study in the Korean adult population an inverse correlation between the level of this neurohormone and the severity of AD. Similar results were not obtained for RA, asthma and/or IgE sensitization. At the same time, 25(OH) vitamin D3 deficiency eludes the immune system controlling the periodontal endothelial tissue, with alteration of the lymphocytic infiltrate predisposing to periodontal disease. In this regard, it is considered that a one standard unit improvement in vitamin D3 levels is associated with an approximately 25% reduction in periodontitis severity. Vitamin D has been shown to play an anti-inflammatory role by intercepting the transcriptional mechanisms of antimicrobial cathelicidin-like peptides [61].

CYP27A1 (sterol 27-hydroxylase), the gene encoding cytochrome P450-oxidase, is expressed in many morphofunctional units of skin tissue and oral mucosa, with particular impact on vitamin D3 metabolism. Recent studies associate vitamin D receptor polymorphism and the CYP27A1 variant with atopic dermatitis [62,63].

7. SALIVARY STRESS BIOMARKERS
CORTISOL

A wide range of biomolecules is transported through the epithelium of the salivary glands, which is why saliva can be considered a mirror of the body's health.
Salivary cortisol levels are known to be used as a biomarker of psychological stress, an important element in the diagnostic management of AD [64].
CHROMOGRANIN A (CgA)

Cai L, Kaneko S and Morita E correlated AD and stress severity with salivary stress protein levels. CgA level in saliva of AD patients may be an objective marker of disease severity. In severe AD, salivary CgA levels are maintained at a higher level independent of serum marker levels [65,66].

CONCLUSIONS

Over the years it has been demonstrated that the oral mucosa, the "mirror" of the systemic health of the human body, also plays an important role in the diagnostic and therapeutic management of AD. Thus, the inflammatory status of the oral mucosa, initiated and maintained by the action of local and systemic pathogens, influences the clinical course of AD.

The tissue microenvironment specific to acute and chronic lesions of atopic dermatitis is defined at the molecular level by the interaction of genetic and epigenetic factors. The clinical variability identified at both cutaneous and oral mucosal levels is explained by the heterogeneity of triggers predisposing and favouring the activation of the two main immune pathways.

In this regard, extensive cellular and molecular biology research is needed to identify and define the main molecular biomarkers of the specific lesional profile of atopic dermatitis, with the aim of improving the prognosis and quality of life of these patients.

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