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The role of psychogenic factors in the etiopathogenesis of autoimmune disorders in the oral cavity

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ABSTRACT

Autoimmune disorders (AD) represent a heterogeneous group of multifactorial chronic conditions, which are triggered secondary to the loss of self-antigen tolerance. Their etiology involves genetic, epigenetic, and environmental factors; however, AD cannot be explained by these factors alone. Recent studies have shown increasing stress levels in industrialized countries and also increasing trends in the prevalence of autoimmune diseases. The oral mucosa is extremely responsive to emotional influences such as stress, anxiety and depression. Therefore, oral diseases can appear as a direct expression of emotions or indirectly, due to various psychological mechanisms. The aim of this study is to find and present possible correlations in order to support the hypothesis that psychogenic factors can play a significant role in the etiopathogenesis of autoimmune disorders in the oral cavity. The review is focused on clarifying epidemiology, etiology, pathogenesis, course, clinical signs, and management of oral lichen planus, recurrent aphthous stomatitis, psoriasis, muco-membranous pemphigoid, pemphigus, and erythema multiforme. Existing literature suggests bidirectional links between psychogenic factors and autoimmune diseases, which influence patients' psychological well-being and quality of life. Consequently, research and medical practice must continue investigations related to the proper diagnosis and clinical management of these conditions. The first signs of several diseases first appear in the oral cavity, which means that dentists can play an important role in the early diagnosis and treatment of AD oral. Although the role of psychological factors in the etiopathogenesis of AD is still underestimated, a holistic multidisciplinary approach should be implemented to provide for these health problems an appropriate diagnostic and therapeutic procedures.

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Introduction

Autoimmune disorders (AD) represent a heterogeneous group of chronic multifactorial conditions, which occur secondary to the loss of self-antigen tolerance [1,2]. Their etiology involves genetic, epigenetic, and environmental factors. Unfortunately, autoimmune diseases cannot be explained by these factors alone [2]. Recent studies have shown in industrialized countries the increase in both stress levels and the prevalence of autoimmune disorders [3]. Additionally, psychological stress, including early life stress, has been suggested to precede autoimmune diseases and exacerbate their symptoms, causing long-term negative health effects [2,3]. In one of his works, Gabor Maté (2004) emphasized the psychological connection between life's stresses and emotions and the body mechanisms governing nervous activity, immune system, and hormones. He indicated that emotion and psychological stress play a strong role in the onset of chronic diseases, as suppressing one's emotions could directly affect the functioning of the immune system [4].

Besides psychological distress, other psychogenic factors may contribute to the development of chronic autoimmune disorders: lower quality of life, mental health impairments (increased levels of anxiety and depression) [5], as well as specifics factors in psychological functioning such as temperamental traits, self-esteem, action-oriented personality components, etc. [6]. Oral mucosa is extremely responsive to emotional influences such as stress, anxiety, and depression, and hence, oral diseases can occur as a direct expression of emotions or indirectly - because of various psychological issues [7,8]. Shamim (2014) offered a revised working type classification of psychogenic disorders pertaining to dental practice [9]. The latter were categorized under six major groups – pain-related disorders, disorders associated with altered sensitivity in the oral cavity, disorders caused by neurotic habits, autoimmune disorders, a disorder caused by altered perception of dentofacial form and function (dysmorphophobia), and miscellaneous disorders. Autoimmune disorders include oral lichen planus, recurrent aphthous stomatitis, psoriasis, muco-

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membranous pemphigoid, pemphigus, and erythema multiforme [9].

The aim of this study is to find and present possible correlations in order to support the hypothesis that psychogenic factors can play a significant role in the etiopathogenesis of autoimmune disorders in the oral cavity. The current review is focused on clarifying epidemiology, etiology, pathogenesis, course, clinical signs, and management of aforementioned conditions.

Discussions

Oral lichen planus (OLP)

Oral lichen planus is a chronic mucocutaneous disease that affects the skin, lips and other mucous membranes and is the most common dermatological disease affecting the oral cavity. It affects approximately one to two percent of the population, often women, and occurs most frequently in the fifth and sixth decades of life [10-12]. The highest prevalence was reported from Europe (1.43%) and the lowest in India (0.49%) [13]. It is associated with an increased risk of malignant transformation in about 1.1% of cases. The etiopathogenesis is unknown, but the prevailing opinion postulates that the disease is based on a dysregulated T-lymphocyte response to autologous keratinocyte antigens or exogenous triggers [11,14,15]. In general, there are various hypotheses regarding the etiology of the disease, including genetic, infectious, psychogenic, and autoimmune factors [8,16,17]. The role of psychosocial factors in the development of this condition has been suggested but is still underestimated and thus understudied [6,18].

Over the past few decades, multiple lines of evidence have indicated that psychological factors seem to play an important role in this chronic inflammatory disease [5]. Chaudhary (2004) found higher levels of anxiety, depression and stress in lichen planus patients compared to healthy controls [19]. Analyzing the history, lifestyle, and habits of individuals with lichen planus, Burkhart et al. (1997) noted the presence of stressful events at the onset of this condition in 51 percent of patients [20]. Rojo-Moreno et al. (1998) in a controlled study of 100 patients using various psychometric tests found greater anxiety and depression in patients with lichen planus than in controls [21]. Consistent with these previous results, Zucoloto et al. (2019) suggested that the greater severity of OLP and oral lichenoid lesions (OLL) was associated with increased levels of anxiety, higher scores of oral health impact profile, and decreased quality of life [5].

Sajewicz-Radtke et al. (2023) reported differences in psychological functioning of women diagnosed with lichen planus and other diseases of the oral cavity as compared with healthy women. Subjects with oral lichen planus demonstrated lower levels of maladaptive perfectionism, social support, and social resourcefulness as well as scored higher for moral self-approval. The authors concluded that patients with lichen planus generally used compensatory mechanisms that negatively affect their social functioning and hence, delineated the need for implementation of holistic approach, including psychologists, psychiatrists, and other healthcare workers, to properly diagnose and treat these groups of patients [6].

The cutaneous component of lichen planus is characterized by purple, polygonal, pruritic plaques or papules affecting the torso or extremities [22]. Up to 65% of patients with cutaneous lichen planus develop oral lesions at the same time. Oral lichen planus is usually bilateral and can be mainly categorized as reticular, atrophic, or erosive [11]. Reticular lichen planus is the most recognizable type and manifests as hyperkeratotic streaks in a characteristic lacy pattern (Wickham striae), keratotic plaques and papules [23,24]. The atrophic form presents as erythematous spots, and the erosive form as shallow ulcers. The clinical presentation of oral lichen planus is dynamic, and patients often have a combination of reticular, atrophic, or erosive form. The most commonly affected site is the buccal mucosa, but any area can be affected. Gingival lichen planus often presents as desquamative gingivitis, which is also commonly seen in mucosal membranous pemphigoid and pemphigus vulgaris [25]. Pain and sensitivity to spicy foods are often observed, most often in atrophic and erosive forms [26].

Treatment. Most patients respond positively to corticosteroid therapy with triamcinolone acetonide 0.1%, fluorinated steroids such as fluocinolone acetonide 0.05% and 0.1%, and high potency halogenated corticosteroids such as clobetasol propionate 0.05% [10,11]. Patients unresponsive to short-term systemic steroid therapy should be referred to a dermatologist for long-term combined immunochemotherapy, which may include glucocorticoids, azathioprine, cyclosporine, methotrexate, TNF-α inhibitors, and other immunomodulators [12,26,27].

Surgical excision, cryotherapy, CO2 laser and ND: YAG laser are also used [28,29]. Photodynamic therapy (as a particular form of photochemotherapy, may also be used [17]. Relaxation, meditation, and hypnosis have positive effects on many skin diseases and help calm and balance the inflammatory response, which can also improve the condition [29].

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is a commonly observed chronic inflammatory disease characterized by painful ulceration of the oral mucosa. It is believed to be the most common form of oral ulceration, with prevalence ranging from 5 to 60% [30]. Various factors such as trauma, psychological stress, allergies, microbial factors, nutritional factors (e.g., vitamin deficiency) and immunological imbalance have been discussed in the etiology of this disease, but in general it remains unresolved [8,30,31].

Previous studies have suggested that psychological disturbances such as stress and anxiety may play a role in the onset and recurrence of aphthous lesions [32]. A factor associated with disease exacerbations could be represented by stress [33]. Psychological stress induces immunoregulatory activity by increasing the number of leukocytes at sites of inflammation; this feature is often observed in the pathogenesis of recurrent aphthous stomatitis [34].

Aphthous ulcers can vary in size, but usually appear as round, shallow ulcers with a well-defined erythematous halo. Commonly affected areas are the tongue, lips, and buccal mucosa. Three clinical forms have been described - minor (MiRAS), major (MaRAS), and herpetiformis ulcers (HU) [31,35,36] (summarized in Table 1). Aphthous ulcers are very painful and may prevent the patient from eating, drinking, and speaking [7].

Table 1. Classification of aphthous ulcers

	Minor ulcers (MiRAS)	**Major ulcers (MaRAS)**	**Herpetiformis ulcers (HU)**
Prevalence	75% - 85%	10% - 15%	1% - 10%
Clinical signs	Painful, round or oval ulcers with shallow necrotic centers, raised edges, usually with a gray white pseudomembrane and an erythematous halo.		
Size	< 10mm	> 10mm	2mm - 3mm
Localization	Unattached mucosa (labial and buccal mucosa, the mouth floor)	Unattached mucosa (lips, soft palate, and fauces)	Attached mucosa (gingiva)
Duration	10–14 days	up to 6 weeks	< 1 month (7-10 days)
Scars	Yes	Sometimes	No

Treatment. Many patients consider RAS to be a trivial annoyance and do not seek treatment. However, for patients who experience significant discomfort, the goal of treatment is to relieve symptoms, shorten the healing time, and prevent recurrence [30,36]. In mild cases, local anesthetics (e.g., benzocaine) can be used, as well as a soothing mouthwash to improve patient comfort [35-37]. In more severe cases of RAS, the use of topical glucocorticoids such as dexamethasone (0.5 mg/5ml), fluocinonide (0.05% gel) and clobetasol (0.05% gel) is recommended. It is recommended to apply the gel directly to the lesion 2-3 times a day. For isolated recurrent ulcers, intralesional injections of triamcinolone acetonide (10 mg/ml, injection at 0.1 mg/cm3) are administered [36].

Patients with severe chronic disease require long-term systemic therapy with agents such as colchicine (suppresses leukocyte activation), pentoxifylline (suppresses neutrophil adhesion and activation), or thalidomide (a highly teratogenic drug available on a very limited basis in strict protocols) to maintain disease control. Long-term use of a systemic regimen requires referral to a physician who can monitor and manage the occurrence of potential adverse effects associated with systemic therapy [36,38]. In this aspect, to avoid side effects of systemic treatment, low laser therapy has also been recommended for aphthae treatment: CO2, Nd: YAG, diode, and Ga1AS [36,39].

Psoriasis

Psoriasis is a papulosquamous exfoliative dermatitis that presents clinically as discrete flat-topped papules or plaques covered with thin, white, loosely adherent scales [40]. It is a chronic, immune cell-mediated inflammatory skin disease, affecting approximately 125 million people worldwide [41,42]. According to data from the Outpatient Skin Clinic at King's College Hospital and the Psoriasis Association, about 60% of patients believe that stress/psychological factors are the cause of the disease [43]. One of the hypotheses regarding the pathophysiology of psoriasis, is that chronic stress influences the formation of hormonal changes, which favors the processes of autoimmunity [44]. Additionally, associations of psoriasis with psychological disorders, such as depression, low self-esteem, suicidal thoughts, and sexual dysfunction have also been well evidenced in the literature [45,46].

Some authors found oral lesions in only two of 100 cases of psoriasis they examined, while others noted that by 1971 only 15 cases of oral psoriasis had been documented, three of which had gingival involvement. Thus, the appearance of changes in the oral mucosa in patients with psoriasis is still a controversial issue [47]. Although oral lesions in patients with psoriasis are rare, the most characteristic and frequent symptoms are the geographic tongue and fissured tongue [48-50]. However, not all patients with geographic tongue present psoriasis [51,52]. Other possible oral changes in patients with psoriasis were also suggested. Psoriasis might affect the periodontal and teeth condition, saliva secretion, and the function of temporomandibular joint [48].

Treatment. Topical agents (corticosteroids, vitamin D analogues, calcineurin inhibitors, and keratolytics) are indicated for treating mild psoriasis. For treatment of moderate to severe plaque psoriasis, compounds that inhibit TNF-α, p40IL-12/23, IL-17, and p19IL-23, as well as oral phosphodiesterase 4 inhibitor are recommended. Narrowband UV-B phototherapy is also found to be useful in relieving the symptoms of psoriasis [42,53-55].

Mucous membrane pemphigoid (MMP)

MMP is a heterogenous group of chronic, autoimmune diseases characterized by the formation of subepidermal blisters, and usually affecting the mucous membranes and skin. Mucous membranes of the eye and oral cavity are most frequently affected (in 85% and 65% of all cases, respectively) [56-58]. The annual incidence of the disease is estimated to be 1.3–2.0 cases per million, the typical age of onset is from the sixth to the eighth decade of life, affecting more women than men (2:1) [58,59].

The etiopathogenesis of MMP is associated with the production of autoantibodies directed against various proteins in the basement membrane zone. Autoantibodies target BP180 (collagen type XVII), BP230, laminin 332, laminin 311, α6ß4 integrin and type VII collagen. The antibody-induced, complement-mediated process results in epithelial shedding and reactive migration of lymphocytes, eosinophils, neutrophils, and mast cells to the basement membrane zone [58,60].

The psyche, immunity, and skin are interconnected so that a pathogenic relationship between intense emotional stress and autoimmune skin diseases can be assumed [44]. The role of psychological stress in triggering these diseases (MMP, Pemphigus vulgaris, Erythema multiforme) is still underestimated among a significant number of scientists.

MMP most commonly affects the gingiva (almost 94% of the cases) and appears as desquamative gingivitis [61-63]. The lesions can be simple erythema or true ulcerations affecting both the fixed and the adherent gingiva. This condition is very often cofounded with periodontal disease. Other affected areas of the oral cavity include the palate, buccal mucosae, lips, tongue, and pharynx [62]. Extraoral involvement is rare, but MMP can affect the conjunctiva, nasopharynx, larynx, esophagus, and anogenital region [56,57]. A positive Nikolsky's sign is often noted [64].

Treatment. There is no cure for MMP, and therapeutic strategies are aimed at reducing inflammation, accelerating healing and relieving symptoms. For intraoral lesions, the use of topical corticosteroids such as fluocinonide, clobetasol, and betamethasone remains first-line therapy. The use of a soft elastic splint facilitates the application of the drug in cases of gum involvement. When using topical steroids for an extended period, it is important to monitor for side effects such as candidiasis. Strict oral hygiene and follow-up are mandatory for patients with oral MMP. Patients unresponsive to topical steroids can be treated with secondary agents such as topical calcineurin inhibitors (tacrolimus, pimecrolimus, etc.). Intralesional injections of triamcinolone acetonide (10 mg/ml, 0.1 mg/cm^3 injection) may be helpful in stubborn, symptomatic lesions in conjunction with topical therapy [62,65,66].

Patients with MMP who do not respond to topical or intralesional steroid injections should be referred to a dermatologist for long-term combination immuno-pharmacotherapy, which may include glucocorticoids, azathioprine, cyclosporine, methotrexate, TNF-α inhibitors, and other immunomodulators [59-61,67].

Pemphigus

Pemphigus includes a group of potentially fatal autoimmune vesiculobullous lesions affecting the skin and mucous membranes. Five forms of pemphigus have been described: pemphigus vulgaris (PV), pemphigus foliaceus, paraneoplastic pemphigus (PNP), drug-induced pemphigus, and IgA pemphigus [68,69]. However, only PV and PNP usually affect the oral cavity. Most cases are diagnosed in the fifth to sixth decade of life and in general, there is no gender predilection [62].

Ashkenazi Jews and persons of Mediterranean descent are at higher risk of developing PV [70]. Of importance to dentists is the fact that the first manifestation of PV is often an oral blister or ulcer without skin affecting, which hinders the diagnosis [62,69,71]. PV is an autoimmune condition in which autoantibodies targeting intraepithelial adhesion molecules (desmosomes) cause disruption of cell adhesion, leading to acantholysis. The target antigens in PV are the cadherin group antigens - desmoglein 1 (DSG1) and desmoglein 3 (DSG3) [62,63,69,72].

The etiology of pemphigus is associated with genetic and ethnic factors. Physical agents, viruses, hormones, different drugs and treatments, vaccines, nutrients, micronutrients, pregnancy, and stress might trigger the lesions [62,69,73]. However, the relationship between pemphigus and psychogenic factors is still a matter of debate. There is a real gap in the literature whether psychological factors are inducing for pemphigus onset, its possible complication, comorbidity, or an adverse reaction to conventional therapy for pemphigus [74].

PV is characterized by painful superficial ulcers affecting the oral mucosa and oropharynx. Gingival involvement often manifests as desquamative gingivitis. Intact oral blisters are rarely seen because of their fragility, and patients with PV exhibit a positive Nikolsky's sign [62,64,75].

The presence of skin lesions suggests worsening of the disease course and requires prompt medical evaluation and therapy. Oral PV progresses and involves skin areas in about 4-6 months on average. The diagnosis of PV is made based on the correlation between clinical findings and histological examination by direct immunofluorescence (DIF) [68,72]. Once diagnosed, patients with PV should be referred to a dermatologist.

Treatment. It is currently recognized that long-term topical glucocorticoid therapy, as described above for MMP, is insufficient for the treatment of PV due to its progressive nature. A patient diagnosed with PV should be referred to a dermatologist for a long-term combined immuno-pharmacotherapy, which may include rituximab, corticosteroids, azathioprine, mycophenolate mofetil,

cyclophosphamide, intravenous immunoglobulin, and other immunomodulators [69,71,72].

Erythema multiforme (EM)

EM is an acute, self-limiting immune-mediated mucocutaneous bullous disease characterized by the presence of symmetrically located lesions on the trunk and extremities. Oral manifestations are also present in more than 70% of EM cases, which often necessitates a rapid diagnosis by oral health professionals. Accurate epidemiological information is lacking, but the annual incidence of EM is less than 1% [76,77].

EM occurs as a result of a T-lymphocyte-mediated type IV cytotoxic reaction targeting the blood vessels of the skin and mucosa. Multiple precipitating factors have been identified, which include infectious agents, drugs, immune conditions, toxins, and chemicals. Infectious agents are implicated in up to 90% of cases, with herpes simplex virus (HSV) involving about 75% of these cases. Of the group of drugs, sulfonamides are most commonly associated with this disease [76-78]. While EM is usually preceded by viral infections and certain medications, a large portion of cases are due to an unidentifiable cause [78]. The most serious variants of EM, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are now considered distinct conditions based on their different clinical presentations, patient demographics, and potential causes [76,78]. Lefaucheur et al. (2021) suggested that psychological factors related to post-traumatic stress disorder play a key role in complex mechanisms leading to persistent chronic pain as a long-term sequela of SJS/TEN [79].

Oral lesions of EM can affect any area of the oral cavity and have a diverse clinical appearance, ranging from diffuse erythema to multifocal superficial ulcers and bullae. Lesions on the lips are characteristic hemorrhagic crusts. Oral pain and burning sensation can affect the patient's ability to swallow, eat, drink and speak [80,81].

Treatment. It depends on the severity of the clinical condition [78]. An essential element of treatment is the identification of potential triggering factors. Therapy for mild cases of EM with limited skin and mucosal involvement is symptomatic and supportive. Topical steroids, anesthetics, and analgesics, as well as preventive antiviral therapy (e.g., acyclovir, valacyclovir, famciclovir) are administered to reduce the risk of EM due to HSV [76,78]. Maintaining a diet and fluid intake is mandatory. Frequent monitoring of the condition is essential.

Conclusions

This study confirmed that psychological, emotional, or mental factors might affect the onset and clinical course of autoimmune diseases in the oral cavity. Conversely, the presence of AD causes adverse effects connected with various psychological comorbidities like depression, anxiety, elevated stress levels, social isolation, guilt, embarrassment, low self-esteem, substance abuse, etc. Bidirectional links between psychogenic factors and autoimmune disorders impact psychological well-being and quality of life of patients, as well as significantly challenge contemporary medical practice in terms of proper diagnosis and clinical management of these conditions. Sometimes the first signs of certain diseases manifest first in the oral cavity and therefore, dentists can play an important role in the early diagnosis and treatment of oral AD. Although the role of psychological factors in etiopathogenesis of autoimmune disorders is still underestimated, a holistic multidisciplinary approach should be implemented to provide a better insight and complex, etiology-based solutions towards these conditions.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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