PSYCHONEUROIMMUNOLOGY OF ORAL DISEASES – A REVIEW

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Review Article

ABSTRACT

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Background: Various oral stimuli that are perceived by the brain as stressful can trigger patterns of neurological activity which then directly influence immune and endocrine response.
Objective: To analyze the psycho-neuro-endocrine-immunological interactions involved in oral diseases and conditions.
Data sources: Web of Science, PubMed, Google Scholar were databases researched for peer review articles in indexed journals.
Study selection: A literature search limited to peer-reviewed articles in indexed journals published before January 2019 was performed using specific keywords. 107 articles were selected.
Data extraction: The aspects related to psycho-neuro-immune interactions relevant for dental practitioners were synthesized and presented in the form of narrative review. Oral diseases and conditions in which psychological factors act through neurological, endocrine and immunological mechanisms are discussed. The following clinical entities were included: periodontitis, oral lichen planus, recurrent aphthous stomatitis, temporomandibular disorders, herpes labialis, burning mouth syndrome, and atypical odontalgia. Additionally, the role of psycho-neuro-immunological factors on bacterial adherence and oral microbiome is briefly discussed.
Data synthesis: Various oral diseases and conditions of multifactorial etiology can be influenced by psycho-neuro-immunological interactions. In daily practice, clinicians should be aware of the interplay between mental and general health and consider addressing psychological disturbances as a supplement for conventional treatment modalities. Recognizing these interactions should help to better understand the relationship between mental and physical health.
Keywords: Periodontitis; Lichen planus, oral; Stomatitis, aphthous; Temporomandibular joint disorders; Herpes labialis.

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1. Introduction

Psychoneuroimmunology is an interdisciplinary field which represents the convergence of psychology, neuroscience, endocrinology, and immunology. Various stimuli that are perceived by the brain as stressful can trigger patterns of neurological activity which then directly influence immune and endocrine response. Since many cells of the nervous, immune, and endocrine systems share common signaling pathways, these systems do not act as isolated functional units, but instead interact with each other to yield an integrated response. By recognizing these interactions, psychoneuroimmunology helps to better understand the relationship between mental and physical health. The idea of the interplay between psychological factors and physical health is not new – its origins can be traced back to Galen, who in the year 200 presented the observation that melancholic women are more susceptible to breast cancer than sanguine women [1]. Almost two millennia later, contemporary studies have collected a great deal of experimental data and clinical evidence which support the hypothesis that stress-induced immunosuppression, stress-induced inflammation, and various subtle changes in the regulation of the endocrine and immune system caused by psychological factors can modify the course of different diseases. This review is focused on the diseases affected by psycho-neuro-immunological factors which occur in the oral cavity.

2. Methodology

A literature search limited to peer-reviewed articles in indexed journals published before January 2019 (1983-2018) which were identified by searching the Web of Science, PubMed (Medline) and Google Scholar using the following keywords: (psychoneuroimmunology OR psychological OR psychiatric OR mental health OR stress OR depression OR cortisol OR hypothalamic-pituitary-adrenal) AND (oral OR dental OR dentistry OR periodontitis OR oral lichen planus OR recurrent aphthous stomatitis OR temporomandibular disorders OR herpes OR burning mouth syndrome OR atypical odontalgia OR eating disorders OR microbiome). The aspects

Table 1. Systematic division of the cited articles according to the discussed topics.

Topic	Reference No.
Periodontitis	2-40
Oral lichen planus	41-54
Recurrent aphthous stomatitis	55-62
Temporomandibular disorders	63-82
Herpes labialis	83-87
Burning mouth syndrome	88, 89
Atypical odontalgia	90
Eating disorders	91-97
Oral microbiome	4, 98-107

of psycho-neuro-immune interactions relevant for dental practitioners were synthesized and presented in the form of a narrative review.

3. Results

Oral diseases and conditions in which psychological factors act through neurological, endocrine and immunological mechanisms are discussed. The following clinical entities were included: periodontitis, oral lichen planus, recurrent aphthous stomatitis, temporomandibular disorders, herpes labialis, burning mouth syndrome, and atypical odontalgia. Additionally, the role of psycho-neuro-immunological factors on bacterial adherence and oral microbiome is briefly discussed. The systematic division of referenced articles regarding individual topics is presented in Table 1.

3.1. Periodontitis

Periodontitis is an inflammatory disease which progressively damages periodontal tissues, eventually leading to tooth loss. Although periodontitis is clearly associated with the presence of certain microbial species, it cannot be regarded as a classical infective disease because the damage to periodontal tissues results from an inappropriate inflammatory reaction and not from the destructive action of the microbes alone [2]. The pathophysiology of periodontitis is thus related to a complex interplay between the microbial challenge and host immune response [3], while the differences in immunological reactivity and susceptibility to periodontal destruction between individual persons are determined genetically. These differences explain why the presence of a certain microbial community can cause an aggressive disease in some individuals, whereas in others the same microbial species may not trigger any destructive reaction. Additionally, it is still unclear whether the bacterial strains found in active periodontal pockets truly initiate the disease or these strains simply prefer the new environment created by pocket formation and active inflammation, without an active role in its initiation and perpetuation [4]. The effect of periodontitis on systemic health has been extensively studied and many connections with illnesses of remote organs have been hypothesized [5, 6]. Many of these connections have also been supported by evidence, although to varying extents. Rather compelling evidence exists for the association of periodontitis with cardiovascular disease [7] and diabetes mellitus [8]. Obstetric complications, respiratory diseases, chronic kidney disease, and cancer have also been linked to periodontitis [9-12]. Two major mechanisms of systemic action involve (I) invasion of periodontal pockets bacteria, leading to bacteremia and dissemination of living bacteria or products of their decomposition; and (II) excessive production of long-range pro-inflammatory cytokines, resulting in their elevated systemic levels. The latter mechanism clearly represents an immuno-endocrine response, while the former mechanism is also immunologically-mediated since the presence of bacterial antigens in the bloodstream causes a cross-reactive immunological response which then leads to the destruction of host tissues [5]. The relationship between periodontitis and systemic health is often bidirectional: a complex immuno-endocrine response initiated by the microbiome in periodontal pockets modulates various systemic conditions, while the impaired systemic health, in turn, affects the progress of periodontal disease. For example, elevated levels of pro-inflammatory cytokines due to periodontitis can increase insulin resistance, while the resulting hyperglycemia and formation of glycosylation end products enhance the destructive potential of periodontitis [13]. Without going further into detailed descriptions of the pathophysiology of periodontitis and the related systemic conditions, it is evident that many of the interactions stem from the underlying dysregulation of the immune system and can be affected by psycho-neurological factors. Although the psycho-neurological influence on the complex interactions between periodontitis and systemic diseases currently remain unexplored, the psycho-neurological aspects of periodontitis itself have been well documented. Clinical observations and epidemiological studies have indicated that stress [14], depression [15], and inadequate coping behaviors [16] are related to the onset and progression of periodontitis. Psychological factors have long been known to present a risk factor for acute necrotizing ulcerative gingivitis and periodontitis – these aggressive forms were the first to be related to psychological factors about 50 years ago [17-20]. A systematic review from the year 2013 analyzed 14 studies and showed that 8 studies identified a positive relation between psychosocial factors and periodontitis, 4 studies identified a positive relation between some characteristics of psychological factors and periodontal disease, whereas only 2 studies were unable to identify any

relation [19]. Contrary to early beliefs that stress response mediated through catecholamines and cortisol is primarily immunosuppressive, the immune system may be affected by psychological stress in both directions. This happens because the individual cell or tissue reaction to elevated levels of stress hormones depends on the presence or absence of particular receptors [21]. Short-term stress appears to suppress cellular immunity, whereas chronic stress leads to a more comprehensive dysregulation of the immune system, affecting both cellular and humoral immunity [15]. Psychological status was found to correlate with salivary levels of cortisol and β-endorphin, which were in turn identified as determinants for tooth loss due to periodontal disease [22]. Depression has also been associated with increased risk and severity of periodontitis. Various psychometric factors, such as depression and anxiety scores, subjective well-being, somatic complaints, quality of life, and introversion have been correlated with periodontitis [23]. Traumatic life events such as the loss of a spouse, as well as the personality trait of exercising extreme external control were shown to increase the risk for severe periodontitis [24]. Stress-related depression and exhaustion have been associated with increased levels of cortisol and IL-6 in the gingival crevicular fluid, as well as higher levels of gingival inflammation and plaque accumulation [25]. Women on long-term sick leave for depression had more severe periodontitis and elevated levels of IL-6 in gingival crevicular fluid compared to healthy controls [26]. Patients with rapidly progressing periodontitis presented significantly higher depression and loneliness scores compared to patients with chronic adult periodontitis and healthy controls [27]. Depression was associated with a more extensive periodontal breakdown [28]. Psychosocial measures of stress and depression associated with financial strain were shown to be significant risk indicators for severity of periodontitis in adults [16]. The effectiveness of coping behavior has also been identified as a modulating factor for periodontitis in patients exposed to psychological stress. Adequate coping behaviors, such as problem-based coping were shown to reduce the stress-associated risk [16]. Conversely, patients with inadequate coping techniques (passive coping) were shown to be at greater risk for severe periodontitis [29]. Ineffective coping was also associated with poorer responses to nonsurgical periodontal treatment, whereas patients with active coping had less severe forms of disease and better treatment outcomes [30]. Although psychological factors have been identified as risk factors for periodontitis in multiple studies, rigorous analyses highlight the issue of heterogeneity of study designs, methodology and assessment criteria, thus claiming that it is not yet possible to regard psychological stress as a definitive risk factor [19,21]. In any case, a relation between psychological factors and periodontal health has been repeatedly observed. In studies on the relation between stress and periodontitis, it is generally difficult to distinguish between the contribution of stress-related behavioral factors (poor oral hygiene, poor nutrition, smoking, and generally neglected health) from exclusively psychoneuroimmunological stress-related factors which directly affect the progress of the disease, without a behavioral intermediary [15]. The psycho-neuro-immunological mechanism is evidenced by the role of cortisol and other stress-related hormones. In an experimentally induced periodontitis in rats which had genetically different responsiveness of the hypothalamic-pituitary-adrenal axis, the high-responding rats developed more severe periodontal disease. Additionally, they showed elevated corticosterone blood levels due to a local inflammatory response induced by experimentally enhancing the accumulation of subgingival microbiome, indicating a positive feedback loop between the hypothalamic-pituitary-adrenal axis activation and local periodontal inflammation [31]. In a rat model of depression induced by olfactory bulbectomy, the role of psycho-neuro-endocrine factors has been demonstrated by a decreased expression of glucocorticoid receptors in the hippocampus, different response to injected lipopolysaccharide and more extensive periodontal bone loss in depressive animals [32]. The association between cortisol and periodontitis has also been observed in humans; patients undergoing stressful life events had higher cortisol levels and more severe periodontitis [33]. Other studies have confirmed that hyperactivation of the hypothalamic-pituitary-adrenal axis and the resulting increase in cortisol level was positively related to the extent and severity of periodontitis [34]. Psychological stress, depression, and salivary cortisol levels were found to be positively correlated with the extent of periodontal destruction, independent of the level of oral hygiene [35]. In addition to cortisol, levels of another stress-related hormone whose secretion is regulated by corticotrophin, dehydroepiandrosterone, were also related to the extent and severity of periodontitis, adding to the evidence for the role of hypothalamic-pituitary-adrenal axis hyperactivation in the pathogenesis of periodontitis [36]. The outcome of periodontal treatment can be negatively affected by stressful life events [37], occupational stress [38], and clinical depression [39], indicating that psycho-neuro-immunological factors play a role in wound healing and recovery following an invasive treatment. From a clinical standpoint, these findings indicate that routine periodontal treatments may benefit from an adjunctive stress-management therapy which would comprise the assessment of patient's stress levels and their ability to cope with stress, followed by implementation of stress-

reduction protocols [40]. Similarly, addressing depression in patients with periodontitis may help to alleviate the course of periodontitis through immunologic and behavioral changes conducive of periodontal healing [35].

3.2. Oral lichen planus

Oral lichen planus is a chronic inflammatory disorder which clinically manifests on the oral mucosa as multiple bilateral papular, reticular, erythematous, and erosive lesions. Besides the significant negative effect on the quality of life due to its chronic course, oral lichen planus lesions have a potential for malignant transformation at an overall frequency of 0.3-3 % [41]. Although the etiology of oral lichen planus is unclear, the underlying pathophysiology has been known to involve a dysregulated T-cell immune response to an induced antigenic change in the oral mucosa. The hypothesized etiologic factors which have the potential to induce that antigenic change include dental amalgam, non-steroid anti-inflammatory drugs, and hepatitis C virus [41].

The association of oral lichen planus with psychological stress has generally been acknowledged and reported in multiple studies [42-45]; however, the causal relationship is less clear since chronic discomfort due to persistent lesions may itself act as a stressing factor [46]. An interesting approach for evaluating a possible etiological role of psychosocial stressors on oral lichen planus was employed in a double-controlled study which involved healthy individuals as a negative control and patients with burning mouth syndrome, atypical facial pain, and myofascial pain dysfunction syndrome as a positive control [45]. That study found significantly higher stress, anxiety, and depression levels in oral lichen planus patients and positive control compared to the general population, whereas no significant differences were found between the oral lichen planus patients and the positive control group. These results have led the investigators to hypothesize that psychological disturbances in susceptible persons may indeed play a causative role in the pathophysiology of oral lichen planus, probably by acting as a starting point for the initiation of autoimmune reactions.

In a study which assessed the psychiatric status of 56 patients with clinically and histologically verified oral lichen planus, 52% of patients were diagnosed with mental disturbances (12 patients with slight, 3 with moderate, and 14 with severe disturbances); that percentage was significantly higher than in healthy participants in the control group and the general population [42]. In a study on anxiety, depression, and stress in patients with oral lichen planus, no differences were found between the acute and remission stage, while patients diagnosed with oral lichen planus reported encountering stressful life events more frequently and received higher scores on anxiety and depression tests compared to healthy controls [43]. Higher sensitivity to stress perception and reduced capability of coping with stress was also observed [44]. A study evaluating psychological personality profiles of patients with oral lichen planus found significantly higher scores for hypochondriasis, depression, and hysteria compared with controls, whereas the scores at other clinical scales (psychopathic deviate, paranoia, psychasthenia, schizophrenia, and hypomania) were not different from controls [47]. In that study, a two-fold increase in serum cortisol levels was found between patients with erosive lesions and controls, whereas patients with reticular lesions had similar cortisol levels as controls. Elevated plasma cortisol levels were also found to be associated with more aggressive erosive lesions in another study [48], suggesting that cortisol levels may be predictive of the severity of the disease. Cortisol levels were positively correlated with scores on clinical scales for hysteria, hypochondriasis, and depression [47]. Conversely, a study on diurnal cortisol production reported that patients with oral lichen planus had decreased salivary cortisol production in the morning hours compared with healthy controls [44]. Despite some inconsistencies in the studies of cortisol levels, the findings indicate that oral lichen planus may be related to the dysregulation of the hypothalamic-pituitary-adrenal axis triggered by psychological factors. Considering the autoimmune background of oral lichen planus, additional evidence for the role of neuro-immune crosstalk for the systemic immune response is the finding that bilateral transection of glossopharyngeal nerves can attenuate the dose-dependent febrile response to injection of lipopolysaccharide or IL-1-β into the soft palate of rats [49]. This demonstrates that the communication between the central nervous system and the immune system is not exclusively mediated by cytokines and other humoral pathways, but instead requires a local neural route linked to the site at which the antigen was administered. The common treatment for oral lichen planus is symptomatic and involves topical, intralesional, and systemic administration of corticosteroids, while other immunosuppressive agents (cyclosporine and tacrolimus) or retinoids can also be used in more severe cases [46]. Although the disease can be successfully controlled by these medications in most cases, the effects of the treatment are usually transient and the side effects of long-term treatment may outweigh the benefits. Addressing the psychical health as a possible adjunctive therapy in treating oral lichen planus has been suggested decades ago [42,47,50], however, no studies evaluating the effectiveness of this approach have been published up to date. A multidisciplinary approach to the treatment of oral lichen planus could be beneficial because the psychological well-being of patients

with oral lichen planus can be severely affected by the disease itself. Psychological support may help in breaking the vicious circle formed by the disease that is both causing and being perpetuated by impaired psychological status [51]. Oral microbiome in patients with oral lichen planus has been shown to be altered in comparison to healthy controls [52]. Also, different colonization patterns were observed at the sites of oral mucosa affected by lesions compared to healthy control sites within the same patient [53]. However, it has not yet been clarified if the dysbiosis associated with oral lichen planus has some causative role, for example by invading the epithelial barrier and modifying the immune response [54]. Alternatively, the dysbiosis may simply be an epiphenomenon due to the changed oral environment, without having an active role in the immunopathology of oral lichen planus.

3.3. Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is a chronic disease of unclear etiopathogenesis, characterized by a recurrent onset of solitary or multiple painful ulcerations and erosions appearing predominantly on unattached oral mucosa. Clinical characterization distinguishes three main types of oral lesions: minor, major and herpetiform. The disease is considered to be caused by a hyper-reactive immune response, which is influenced by genetic predisposition and modulated by a multitude of factors, some of which include: viral and bacterial infections, nutritional deficiencies, food allergies, psychological stress, mechanical trauma, and hormonal imbalance [55]. The exacerbation of RAS is often related to psychological stress. Higher anxiety levels coupled with elevated cortisol levels in plasma and saliva have been associated with RAS [56]. Exposure to stressful situations and conditions appears to be more important for the onset of RAS than personality profiles and stable psychological traits [57]. However, some evidence exists that trait anxiety may be a predisposing factor for RAS [58]. A study in which 160 RAS patients were followed by weekly phone surveys over 1 year found a significant association of stressful life events and exacerbations of RAS, while a stronger association was found for psychological than physical stressors [59]. However, no association of stressful life events with the duration of RAS episodes was identified in that study. There are also reports of no association of RAS with alterations in cortisol levels [60] and psychological factors (stress and depression) [61], which is in line with the complex and multifactorial etiology of RAS. Frequent exacerbations of painful RAS lesions interfere with normal daily activities and negatively affect the quality of life [62]. The psychological consequences may then influence the course of disease thus forming a vicious circle in a similar manner as mentioned for oral lichen planus. Since the conventional treatment for RAS is symptomatic and ineffective in the long-term, a supportive psychotherapy may be beneficial for alleviating the discomfort that RAS patients experience [56].

3.4. Temporomandibular disorders

Temporomandibular disorders (TMD) encompass several clusters of symptoms involving chronic pain in the temporomandibular joint and masticatory muscles, limitations in the range of mandibular movement and sounds occurring during movements. Pain can be spontaneous or triggered by mandibular movement or palpation of the masticatory muscles. The etiology of TMD remains poorly understood and involves psychological, behavioral and environmental factors. TMD usually presents no observable organic pathology and shares many features with other chronic pain conditions. TMD is often comorbid with other chronic pain conditions, such as fibromyalgia, headaches, spinal pain, and back pain [63]. Although it causes significant distress to affected patients, TMD is self-limiting and usually does not lead to a progressive structural or functional deterioration [64]. Being predominantly a functional rather than structural disorder, TMD appears more as a symptom than a disease.

The inseparable interplay between psychological stress and the experience of pain is biologically based on the fact that most of the molecules which regulate the stress response are the same as those involved in pain modulation [65]. As in other chronic pain conditions, psychological factors are generally implicated in the occurrence of TMD, with the involvement of the hypothalamic-pituitary-adrenal axis, as well as the serotoninergic and opioid system [66]. In addition to the psycho-neuro-immunological dysregulation, the symptoms can be aggravated by hyperactivity of masticatory muscles which often accompanies TMD. However, the stress-induced parafunctional activities are not necessarily related to muscle pain and [67] and thus cannot be regarded as the primary source of TMD symptoms. This is supported by a study evaluating the association of masticatory muscle pain and nocturnal electromyography activity with psychological factors demonstrating that muscle pain is more related to psychological stress than to parafunctional activity [68].

Studies have indicated that patients with TMD tend to present higher levels of anxiety [69], depression and somatization [70]. Stress and emotional distress have also been shown to be associated with TMD pain, as well as muscular tension and parafunctional habits which can independently contribute to the painful experience [71]. TMD patients showed higher electromyographic activity during experimentally induced stress compared to patients with other chronic painful conditions (e.g. chronic back pain) and healthy controls [72].

Subjects with maladaptive coping were at greater risk for TMD pain than the subjects with adaptive coping [73]. A prospective cohort study of 171 healthy female volunteers identified the first-onset TMD in 8.8% of the participants over the course of 3 years and demonstrated a high predictive value of depression, perceived stress, and mood for the onset of TMD [74]. Some of the TMD patients showed cortisol hypersecretion in response to stress, which could be regarded as a biological predisposition to TMD [75]. However, the excessive cortisol secretion may represent a response to a painful stimulus, as evidenced in a study which showed that cortisol hypersecretion occurred mostly while the subjects were awake, i.e. aware of pain [76].

Sleep disorders may also be implicated in the pathophysiology of TMD through increasing central sensitivity to pain, but also by being associated with muscular parafunctions leading to myofascial pain [77]. The relation between sleep bruxism and TMD is unclear, as it has been shown that not all patients with parafunctional habits develop myofascial pain [78]. The cause and effect relation between sleep disorders and related parafunctions of masticatory muscles are difficult to establish since sleep disorders are commonly accompanied by depression and other psychological disturbances which may independently influence TMD symptoms [79].

The usual symptomatic treatment of TMD involves the use of orthopedic appliances which are intended to improve the biomechanics of temporomandibular joint thus reducing muscle activity and joint loading, while simultaneously increasing patient awareness of parafunctional habits [80]. Due to multifactorial etiology of TMD, a multidisciplinary treatment approach encompassing physiotherapy, biofeedback, and cognitive behavioral therapy seems reasonable [81]. Therapeutic modalities targeting psychological factors may be beneficial for reducing painful symptoms and functional limitations; however, the level of evidence for their effectiveness is currently low [82]. In any case, it appears that combined treatment modalities can be more effective and yield longer-lasting results than the conventional treatment which employs orthopedic appliances alone [81]. Also, as in other chronic pain conditions, the TMD pain can in many patients be mitigated by antidepressants regardless of their possible comorbidity with depressive disorder [66].

3.5. Herpes labialis

Most individuals have been exposed to herpes simplex virus through their lifetime, as evidenced by the presence of antibodies in up to 90% of the general population. About 75% of the general population is affected by clinically evident herpes labialis at some time in life [83]. After a primary infection on skin or mucosa, herpes simplex virus establishes a latent infection in ganglionic neurons which can be reactivated under conditions of impaired immune surveillance, thus causing a recurrent infection. The potential of psychological stress to exacerbate the recurrence of herpes virus infection has been well documented and various factors such as short-term stress, stressful life events, dysphoria, anxiety, anger, and negative mood were associated with viral reactivation at both oral and genital sites [84]. Since cellular immunity plays an important role in maintaining the infection in a latent stage, an exacerbation is considered to occur when the cellular immune response is impaired due to the stress-induced imbalance in the secretion of catecholamines, glucocorticoids, and pro-inflammatory cytokines (IL-1, IL-6, and TNF) [85]. For example, it has been demonstrated that adrenaline and glucocorticoids can be used to experimentally induce herpes simplex virus reactivation in animal models [86]. A longitudinal study which evaluated daily mood states and weekly levels in neuroendocrine markers found that the number of natural killer cells and serum levels of adrenaline were associated with herpes labialis exacerbations [83]. Additionally, that study found that adrenaline levels were positively correlated to scores of affect intensity. Although the role of psychoneuroimmunological interaction in the recurrent herpes infections has been well confirmed, it remains difficult to quantify psychological stress and its etiological significance for the onset of the disease [87].

3.6. Burning mouth syndrome

Burning mouth syndrome is a chronic pain condition of unknown etiology, usually characterized by burning or stinging sensation coupled with a subjective feeling of dryness and altered taste. Besides sensory disorders, clinically no oral lesions or other objective signs can be identified. The condition is usually associated with a number of psychological factors, leading some authors to refer to it as psycho-stomatodynia [88]. Higher levels of neuroticism, anxiety, depression, exposure to stressful life events have been associated with the syndrome and the involvement of some personality disorders as well as cortisol dysregulation have been hypothesized [89]. The treatment should aim at identifying and treating underlying psychological disturbances.

3.7. Atypical odontalgia

Atypical odontalgia is persistent idiopathic pain which mimics toothache but lacks any identifiable organic cause. It may occur at a healed extraction site or in a healthy, restored or endodontically treated tooth which presents with no evidence of pathology on clinical or radiographic examination. Etiopathogenesis of atypical odontalgia is unclear and the involvement of psychogenic and neuropathic

factors has been proposed, although the primary cause remains unclear and thus no causal treatment exists [90].
The symptomatic treatment is generally difficult and unsuccessful, usually leading to unnecessary extractions of multiple teeth due to patients' persistent requests for treatment driven by persistent pain. Thus psychological factors need to be thoroughly considered in patients with atypical odontalgia in order to avoid irreversible iatrogenic damage.

3.8. Eating disorders: anorexia and bulimia nervosa

Eating disorders which are characterized by restricted food intake (anorexia nervosa) or purging behavior by means of induced vomiting or laxative use (bulimia nervosa) are psychiatric disorders of unclear etiology with probable involvement of serotoninergic dysregulation in the brain [91]. Frequent exposure of dental hard tissues to gastric acid due to vomiting can lead to cumulative demineralization and extensive erosions on enamel and dentin. The resulting defects usually require comprehensive restorative or prosthodontic treatment. Eating disorders are associated with elevated levels of pro-inflammatory cytokines such as TNF- α and IL-6, indicating a psycho-neuro-immune interplay [92,93].
Also, eating disorders are related to psychological stress and inadequate coping behaviors and are often comorbid with other psychiatric disturbances such as anxiety and depression, with a probable bidirectional interaction [94]. The acute phase of anorexia nervosa has been associated with increased levels of salivary cortisol, secretory immunoglobulin-A, and alpha-amylase, reflecting dysregulation of hypothalamic-pituitary-adrenal axis [95]. Some patients with bulimia nervosa have shown changes in the enzymatic activity of proteases, collagenase, and pepsin in resting and simulated saliva, which contributes to the progression of dental erosions [96]. Gut microbiome can also play a role in the regulation of food intake. For example, bacterial metabolic products such as short-chain fatty acids exert a neuroactive effect which affects the host appetite, possibly playing a role in the pathophysiology of eating disorders [97].

3.9. The role of the oral microbiome

Besides the gut and the skin, as two sites of the human body that are most heavily populated by microbes, the oral cavity is also an important habitat for 500-1000 bacterial species [4, 98, 99]. The discrepancy in the number of species which is encountered in the literature stems from the fact that approximately half of the bacterial species found in the mouth cannot be cultured under laboratory conditions [100]. Most of the species present can be regarded as commensal, while some are symbiotic (e.g. ammonia-producing species which elevate oral pH values) and pathogenic (e.g. acidogenic species which cause tooth caries through demineralization of dental hard tissues).
In fact, two most frequent diseases in the oral cavity, i.e. caries and periodontitis, are caused by complex changes in the microbial community, rather than by infection with a specific pathogen [101]. Especially in the case of periodontitis, well-known shifts of microbial ecology in favor of specific bacterial species are associated with the destructiveness of the disease. Healthy periodontal tissues express a low-grade controlled inflammation which represents the host response to periodontal microbiome, whereas the transition towards destructive inflammation occurs in susceptible individuals when the microbial dysbiosis occurs [102].
The primary local beneficial effect of the commensal microbiome is the inhibition of colonization of the oral cavity by pathogenic species, the so-called colonization resistance [103]. Disbalances of the commensal microbiome can lead to opportunistic infections by Candida spp. or Staphylococcus aureus, which are commonly seen as a side-effect of antimicrobial therapy. Oral microbiome also has some systemic effects, as exemplified by its role in the metabolism of nitrates. Nitrate is secreted into the saliva (about 25% of the total ingested amount) and reduced by oral bacteria into nitrite which is then absorbed through gastric mucosa and converted into nitric oxide. Nitric oxide has an important role in regulating vasodilatation and maintaining blood pressure homeostasis. For example, orally ingested nitrates in the form of food supplements help to reduce blood pressure by exploiting this mechanism [104]. It is clear that the oral microbiome plays a complex role in both local and systemic health, whereas its imbalances reach beyond a straightforward infective disease caused by a single pathogen. However, the effects of psycho-neuro-immunological factors on the oral microbiome and the consequences of that interaction on systemic health have not been extensively studied. Considering the better-established links of psycho-neuro-immunological factors with the gut microbiome, it is plausible that a similar interplay may occur in the oral cavity. If the link is to be established and mechanisms elucidated, the oral microbiome could be altered by using probiotics in a manner similar to what is now commonly accepted for gut microbiome [105]. In such a scenario, modifying the oral microbiome could aid in mitigating the course of periodontal destruction through two major mechanisms: (I) inhibition of microbial adhesion, colonization, growth, and biofilm formation; and (II) altering the destructive host response involving inhibition of pro-inflammatory pathways and inflammation-induced enzymes [106].

3.9.1. Bacterial adherence

Psychoneuroimmunological factors have been shown to affect the adherence of oral and non-oral microorganisms: experimentally induced stress was shown to increase saliva-mediated adherence of *S. sanguis*, *S. gordonii*, and *H. pylori*, whereas the co-adherence of *C. albicans* with *S. gordonii* was decreased [107]. These results suggest that stress-induced changes in salivary composition may predispose oral mucosa to various diseases associated with changes in the oral microbiome.

4. Limitations of the current analysis

Due to the scarcity of published research on psychoneuroimmunological interactions related to oral diseases, the data from available literature are summarized in the form of a narrative review. A qualitative approach was used without attempting to address a specific research question, therefore the presentation limited to the general overview of the current state of research.

5. Conclusion

Various oral diseases and conditions of multifactorial etiology can be influenced by psycho-neuro-immunological interactions. Due to complex and insufficiently elucidated etiopathology of these conditions, it is difficult to isolate and quantify the significance of psychological factors. Further research should attempt to investigate intricate interactions of a number of psychological, neurological, endocrine, and immunological factors, as well as their impact on the onset and progress of oral diseases.

Also, the potential benefit of psychological support for alleviating the course of oral diseases needs to be assessed. In daily practice, clinicians should be aware of the interplay between mental and general health and consider addressing psychological disturbances as a supplement for conventional treatment modalities.

Author Contributions

MP: wrote the manuscript. ZT: critically revised the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Questions

1. Why should dental practitioners consider psycho-neuro-immune interactions in their daily practice?

❑a. Dental treatment may have a negative long-term effect on the psychological status in susceptible patients;
❑b. Certain oral diseases may be affected by psychological disturbances;
❑c. Early signs of some psychiatric disorders can be recognized in the mouth;
❑d. Major modifications of dental treatment are needed in patients with some personality disorders.

2. Which of the following is incorrect?

❑a. Periodontitis can affect systemic health, and some systemic diseases can influence the course of periodontitis;
❑b. Severity of periodontitis can be affected by stress, depression, and coping behavior;
❑c. Some forms of periodontitis can be successfully treated using psychotherapy, without the need for local periodontal treatment;
❑d. Despite considerable amount of evidence, psychological factors cannot be yet regarded as definitive risk factors for the onset of periodontitis.

3. Which of the following conditions usually does not present with painful symptoms?

❑a. Periodontitis and tooth caries;
❑b. Herpes labialis and recurrent aphthous stomatitis;
❑c. Temporomandibular disorder;
❑d. Burning mouth syndrome.

4. Choose the correct statement:

❑a. Oral microbiome consists of 500-1000 bacterial species; diseases such as caries and periodontitis occur in cases of imbalances in microbiome in which only one bacterial species becomes dominant over others;
❑b. Exacerbations of periodontitis and oral lichen planus have been shown to correlate with certain psychological states but no association of these diseases with stress-related hormones such as cortisol was observed;
❑c. Necrotizing ulcerative gingivitis and periodontitis are the only forms of periodontal disease which are not associated with psychological factors;
❑d. Burning mouth syndrome and atypical odontalgia usually present with no clinical or radiological signs of organic pathology but the patients affected by these conditions often show some psychological disturbance.

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