Psychological Stress: A Predisposing and Exacerbating Factor in Periodontitis

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Abstract

Purpose of Review This review focuses on recent advances in our understanding of the interactions between psychological stress, the immune system, and periodontitis, including the dynamic role of host stress responses in altering immune function, altering the oral microbiome and biofilm formation, and promoting local and systemic disease progression.

Recent Findings Within the context of periodontal health and disease, stress leads to an impairment of effective antimicrobial defense, shifts in oral microbiome profiles toward more pathogenic gene expression and taxa composition, increased translocation, and biofilm formation. The link between stress and periodontitis is multifaceted and includes hypothalamic–pituitary–adrenal (HPA) axis and catecholamine activation, production of immune mediators of inflammation and, clinically, syndromes of depression, bipolar disorder, anxiety disorders, and sleep-wake disorders.

Summary Psychological stress appears to be an important modifiable risk factor for the development and progression of periodontitis and other periodontal diseases.

Keywords Periodontal disease · Stress · Microbiome · Inflammation · Sleep · Biofilm

Introduction

Inflammation is a prominent feature of common chronic diseases, including atherosclerosis, cancer, and periodontitis. Many modifiable risk factors, such as smoking, contribute to increases in systemic markers of inflammation, which can further modify gene regulation through a variety of biologic mechanisms [1]. Mounting evidence points to the ability of psychological stress to dysregulate the inflammatory response, promoting the development and progression of disease [2]. Moreover, evidence continues to expand our understanding of the reciprocal interaction between psychological well-being and overall physical health. The significance of this interplay is perhaps most evident when adaptive capacities are overloaded by environmental demands and events in times of psychological stress, referred to simply as “stress” in this article [3]. Stress is associated with the predisposition, precipitation, perpetuation, and exacerbation of many illnesses, as well as worsening morbidity and mortality [4]. Stress has been shown to induce and worsen inflammation, an underlying factor in many major chronic illnesses, including cardiovascular, metabolic, digestive, pulmonary, and rheumatologic illnesses as well as conditions with an infectious, allergic, autoimmune, or neoplastic etiology [2, 5].

For over 100 years, stress has been recognized as a predisposing factor in the development of necrotizing gingivitis (aka, Vincent’s infection, trench mouth, acute necrotizing
ulcerative gingivitis [6]). Necrotizing gingivitis was first extensively documented in military personnel exhibiting acute psychological stress, poor oral hygiene, and malnutrition. Necrotizing gingivitis is clinically characterized by rapid onset with associated pain, bleeding, and ulceration of the gingival interdental papilla. *Spirochetes, Fusobacterium,* and *Bacteroides* species are commonly recovered from gingival lesions [7].

Periodontitis is a prevalent condition, affecting nearly 50% of US adults [8], that often exhibits chronicity and periodicity in progression. This review focuses on recent advances in our understanding of the interactions between stress, the immune system, and periodontitis, including the dynamic role of host stress responses in impairing normal protective immune defenses, altering the oral microbiome and biofilm formation, and promoting local and systemic disease progression. Stress is a potentially important modifiable risk factor causally associated with exacerbation of periodontitis and other inflammatory periodontal diseases.

**Stress**

Stress is the activation of the brain’s defensive motivational system to promote behaviors that protect the organism from perceived future danger; it is experienced when there is a mismatch between a person’s coping ability (i.e., ability to adjust to or tolerate) and actual or perceived environmental events or demands, such as an imminent threatening stimulus or situation [2, 9]. Stress can stem from external events originating in the environment (e.g., loss of job), or from one’s own perception of those experiences or thoughts. A person’s coping ability is largely determined by the dynamic interaction between resiliency mechanisms and vulnerabilities, which are inherent or acquired at different stages of neurodevelopment. Coping skills usually help in achieving two goals: managing emotions and altering the relationship between the individual and the stressor [9]. Resilient individuals are able to “capacitate” strain, threats, and losses, often responding to stress with humor and optimism; they are able to “move on” [10]. On the other hand, early childhood adversity can increase vulnerability to a maladaptive stress response that imprint onto the immature brain in a way that lasts far into adulthood [11••]. Children exposed to chronic stress experience accelerated aging and increased prevalence of systemic illnesses, including ischemic heart disease and cancers as adults [11–14]. Social support and positive relationships can increase resiliency and improve children’s ability to respond to stress in an effective way [15, 16].

**Clinical Implications of Stress**

It is important to note that stress is an active response and involves an organized system of communication between the brain and other organs, including endocrine and immune systems, to mobilize internal defenses for survival and safety [17, 18]. However, a significant cumulative biological damage is incurred by the body as an unintended consequence of allostatics (i.e., behavioral or physiological process of achieving stability in response to stressors), which has been referred to as “allostatic load” [17, 18].

Among clinical outcomes of stress, depression displays the strongest association [3]. Stress may also lead to substance use, sleep deprivation, and poor eating habits. Systemic illnesses significantly associated with stress include metabolic disorders such as diabetes, cardiovascular disease, infectious diseases, autoimmune diseases, and periodontal disease [17, 19–29].

Several studies have found a positive relationship between life stressors and periodontitis [30–35, 36••]. Dental phobia is a specific life stressor that often leads to more advanced disease and poorer clinical outcomes because dental care is sought at later stages of disease requiring more invasive treatment [37]. In the following sections, we explore the mechanisms involved in the stress-periodontitis relationship.

**Stress and Periodontitis: The HPA Connection**

A fundamental question is how stress contributes to disease, such as periodontitis, and whether the relationship is reciprocal (see Fig. 1). A growing body of research has identified various systems and pathways that are responsive to stress and mediate the mind-brain-body relationship [5, 38, 39••, 40•••, 41, 42]. Under physiological conditions, these stress pathways promote adaptation and survival via autonomic, endocrine, metabolic, and immune responses [17]. However, chronic stress can lead to dysregulation of these pathways which can lead to significant biological damage [4, 24, 43]. Specifically, the dysregulation of the HPA axis and immune system has been well established in the context of chronic stress.

The hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic-adrenal-medullary (SAM) system are two neuroendocrine substrates of stress. The paraventricular nucleus of the hypothalamus is activated in response to acute stress [44, 45], releasing arginine vasopressin and corticotropin-releasing hormone (CRH) which, in turn, stimulate the pituitary gland to secrete adrenocorticotropic hormone (ACTH), activating the cortex of the adrenal gland to secrete cortisol [42, 46]. Cortisol rises with stress, as do catecholamines, through the activation of the noradrenergic center in the locus coeruleus of the brainstem and the medulla of the adrenal gland, which releases epinephrine. Both cortisol and

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adrenergic molecules allow the body to respond to danger, real or perceived, by increasing vigilance, reactivity, and mobilizing the body’s resources for sustaining physiological “fight or flight” [47].

Persistent dysregulation of the HPA axis caused by stress, and especially in terms of cortisol levels, is implicated in many illnesses, such as autoimmune diseases, cardiovascular disease, HIV/AIDS progression, upper respiratory tract infection, osteoporosis, obesity, and periodontitis [26, 30, 44, 45, 48]. Cortisol levels rise after acute stress, such as after the loss of a child, and rise even further when coping skills are ineffective [49]. With chronic stress, cortisol levels may still be high, but cortisol is no longer able to blunt the immune response as it does acutely. The cascade of inflammation is initiated leading to the increase of circulating pro-inflammatory cytokines and modulation of their action [4], but the action of cortisol is then generally thought to be ineffective at blocking inflammatory pathways due to glucocorticoid receptor resistance [2, 50].

Regulatory T cells (Tregs) suppress the inflammatory cascade, producing Transforming Growth Factor (TGF)-β1 and Interleukin (IL)-10 as well as suppressing CD4+ and CD8+ effector cell responses. Regulatory T cells are reduced in depression and the ratio of Tregs to pro-inflammatory T cells is decreased with stress [51]. Additionally, a decrease in Tregs has been shown in patients with atherosclerosis that are periodontally infected by Porphyromonas gingivalis (P. gingivalis) [52].

Animal models have also been used to examine the effect of stress on the development and progression of periodontitis. Experimentally induced periodontitis in rats exposed to chronic stress was associated with increased blood glucose, plasma ACTH, corticosterone and adrenaline, as well as more severe alveolar bone resorption, when compared to rats not exposed to chronic stress. This relationship is hypothesized to be enhanced through adrenergic pathways suggesting that adrenergic antagonists could be a pharmacological treatment for periodontitis [53, 54].

Clinically, Peruzzo et al. (2007) reported that the majority of studies (7 case-control studies, 6 cross-sectional studies, and 1 prospective clinical trial) that met inclusion criteria in a systematic review found a positive association between psychosocial stress and periodontal disease [55]. Similarly, in a cross-sectional study of 235 individuals, a positive correlation was found between salivary cortisol levels and the severity of periodontitis with adjustments for age, sex, oral hygiene, bleeding on probing, smoking, and stress inventory scores in adults 50 years and older [47]. In a systematic review of the relationship between periodontal status and cortisol levels in saliva, it was found that only 3 of the 6 studies measured stress, whereas the other study used cortisol as a proxy for stress [56]. In conclusion, a positive association has been
found between cortisol levels and periodontal disease; however, causality cannot be inferred because of the cross-sectional nature of all studies [56].

**Stress and Periodontitis: Role of Inflammation**

Inflammation provides another potential mechanistic link between stress and periodontitis. Experiments with animal models of stress in the form of infections, exposure to toxins, physical injury, restraint, social deprivation, or mother–infant separation have found long-term changes in certain molecular and cellular immune markers [4, 57–61]. With chronic stress, there is an increase in circulating neutrophils and functional immunosuppression through the modification of the T-helper 1 cell (Th-1) and T-helper 2 (Th-2) cell response, including changes in the ratio of the Th-1 to Th-2 cells, thereby diminishing the proliferation of T cells and the antibody response, respectively [4, 50, 62]. It has been hypothesized that chronic increases in cortisol leads to glucocorticoid receptor resistance (GCR) causing a decrease in immunosuppressive actions of cortisol on lymphocytes [2]. The ratio of Tregs (cells involved in regulation of the intensity and duration of inflammation after exposure to inflammation triggers) to pro-inflammatory T cells is also decreased with stress [51]. A meta-analysis has identified elevations of blood levels of IL-6, Tumor Necrosis Factor (TNF-α), IL-1β, and C-reactive protein (CRP) in response to stress [63].

Pro-inflammatory mediators found in the gingival crevicular fluid are generally elevated in active or untreated periodontitis [64, 65]. Given that chronic stress leads to dysregulation of the immune system, with increases in the levels of cytokines and other pro-inflammatory mediators [47, 56, 65, 66], the inflammation-mediated damage may be one plausible explanation of increased risk of periodontal disease in stress.

**Stress and Periodontitis: The Biofilm Connection**

As stress leads to decreased immunity and to increased susceptibility to infections and bacterial proliferation, the role of the oral microbiome has gained significant attention in the context of stress and periodontal disease. Periodontal disease is thought to be driven by a complex dysbiotic microbiota [67–69]. Indeed, several species of bacteria, in particular, “red complex” bacteria *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola* as well as *Aggregatibacter actinomycetemcomitans* are recognized as important pathogens in periodontitis [70]. These pathogens were isolated in the subgingival plaque of patients with periodontitis and found to correlate with levels of oxidative stress markers (8-hydroxydeoxyguanosine and malondialdehyde) in saliva, with highest oxidative stress levels associated with the combination of the three red complex pathogens [71]. The persistence of the bacteria, as a component of dental plaque, results in a constant production of pro-inflammatory cytokines and other molecular mediators, which leads to extensive tissue destruction [66]. In particular, *P. gingivalis* has the ability to change the composition of plaque and the inflammatory milieu through one of the virulence factors of *P. gingivalis*, gingipains, which converts complement C5 to C5a, thereby inducing inflammation and also modulating the Toll-like receptor response, thus preventing leukocytes from being efficient killers [72]. Studies have shown a positive association between cortisol levels and the presence of *P. gingivalis* in subgingival plaques of localized periodontitis, after adjusting for age, sex, income, and smoking status [73]. *P. gingivalis* alters the host immune response, thereby contributing to dysbiosis of the periodontal microbiome and magnifying its capacity to produce periodontitis [74].

Oral microbiome signatures have been identified for chronic periodontitis, including in gene expression, relative to the oral microbiome of periodontally healthy individuals [75, 76]. A key question is whether stress or stress-induced biologic mediators contribute to the dysbiosis of the periodontal microbiome, impacting the initiation or progression of disease. Cortisol has been shown to significantly increase the in vitro growth of *P. gingivalis*, suggesting one mechanism underlying the association between stress and periodontal disease [77]. Moreover, recent research has demonstrated that cortisol, when administered *ex vivo*, directly induces changes in the gene expression profile of the oral microbiome, consistent with previous signatures of chronic periodontitis [75–77]. Thus, the elevation of cortisol in saliva observed during stress, generally thought to be simply a marker of stress, actually appears to be a direct mediator of the stress-periodontitis connection [78]. The latter scenario could certainly be the case of salivary levels of pro-inflammatory cytokines induced experimentally by stress [79].

**Stress and Periodontitis: The Sleep Connection**

Stress and sleep have a bidirectional relationship, with cascading effects between sleep disruption and stress. In a review, Medic et al. reported that sleep disruption leads to a multitude of negative physiological effects, including activation of the HPA-axis, increased secretion of catecholamines, ACTH and cortisol, a decrease in insulin sensitivity and leptin, with a concomitant increase in ghrelin and appetite, as well as an increase in oxygen consumption and CO₂ production [80]. Moreover, sleep disruption was found to be associated with an upregulation of inflammatory cytokines such as TNF-α,
IL-1, and IL-6, CRP, reactive oxygen species, and a decrease in the production of melatonin [80].

Sleep problems can be due to duration of sleep, sleep quality, and consistency in timing of sleep [80]. Sleep apnea is associated with the activation of the HPA axis and higher cortisol levels compared to persons without a sleep disorder [81]. Reductions in sleep time have been shown to be associated with higher reported stress levels the next day [82]. Conversely, chronic stress has been associated with reduced time spent in REM sleep [83, 84]. Early life stress is associated with insomnia [85, 86] and can result in increased serum concentrations of inflammatory cytokines [14, 57, 87]. Inflammatory cytokines have been found to alter and disrupt sleep [88]. Moreover, sleep disorders perpetuate the inflammatory pathway, further increasing inflammatory cytokines [89, 90], with potential cascading effects.

Sleep deprivation induces an increase in several biomarkers of stress, including cortisol and blood pressure [89], and leads to increased loss of alveolar bone in rat experimental models [91]. Insomnia related to stress has also been associated with periodontal disease [92]. Taken together, sleep deprivation and insomnia can be the consequence of stress and a contributor to increased vulnerability to stress, with vulnerability to infection and inflammation as one of the key mediators of the link between stress, sleep, and periodontal disease.

Conclusion

Current evidence indicates a relationship, presumably bidirectional, between stress and periodontitis, involving both dysregulation of the immune response and dysbiosis of the oral microbiome. This association underscores the importance of considering stress in the evaluation of patients with periodontitis. Patient education and referral for evaluation and counseling should be considered for patients exhibiting psychological stress or depression. A list of self-help book recommendations and referrals should be readily available. An interdisciplinary-team approach to patient management should include consideration of a physician or mental health care practitioner.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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