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Role of chronic stress and depression in periodontal diseases

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Psychological stress refers to the emotional and physiological reactions experienced when a person confronts a life event, such as marital conflict, financial debt or death of a loved one, that exceeds his or her ability to cope effectively with the situation. Stress evokes emotional and physiologic reactions and is an important modifiable risk factor for both mental and physical illnesses. A robust, and presumably causal, association exists between stressful life events and major depressive episodes (55, 68), with chronic stress being closely linked to depressive disorders. The neurobiology underlying stress and depression is thought to result from molecular and cellular abnormalities that interact with genetic and environmental factors (73). Epidemiologic studies provide strong evidence that chronic psychosocial stress and depression increase the risk of atherosclerotic cardiovascular disease, diabetes and other systemic conditions (51), as well as adversely affect the course and outcome of the conditions (85, 100, 138). Moreover, numerous studies show that stress and depression are associated with increased morbidity and mortality across a range of systemic conditions (23, 88, 113, 114, 130, 137).

Several pathophysiologic mechanisms may explain the association of chronic stress and depression with systemic diseases (54, 57, 64, 87, 120, 131). Basic and clinical studies demonstrate that stress and depression are associated with atrophy and loss of function of limbic brain regions that control mood and depression, including the prefrontal cortex and the hippocampus (9, 38, 39, 73, 86, 119). In addition, experimental animal models suggest that chronic stress induces vascular inflammation through elevations in circulating proinflammatory cytokines (80).

Prevalence estimates of depression and stress-related disorders in the United States vary across studies; however, a recent survey revealed that 9.0% of adults met the crieria for current depression, with 3.4% meeting the criteria for major depression (22). In addition, a national survey commissioned by the American Psychological Association found that 69% of employees perceived work as a significant source of stress and 41% typically felt tense or stressed during the work day (6). Health-care expenditures associated with stress and depression are high, especially those attributable to comorbities, such as cardiovasular disease and diabetes. Recent estimates suggest that nearly 25% of health-care costs are attributable to modifiable risk factors, such as depression, in the United States (51). In a study of 92,486 employees from seven organizations over an average of 3 years, Goetzel et al. (51) found that in the category of psychosocial risks, health-care costs for employees with depression were 48% more expensive than for those not at risk ($2,184 in higher costs). Similarly, the health-care costs of workers reporting high stress were 8.6% ($413) higher than the costs of those not reporting high stress.

The purpose of this narrative review was to summarize the literature on stress and depression as it relates to periodontitis, highlighting the emerging role of neuroendocrine and neuroimmune mediators in the pathophysiology of inflammatory diseases. We reviewed English language publications from 1970 to 2012, retrieved using the electronic database PubMed. The search terms psychiatry, psychological stress, depression, dental, periodontal disease, periodontitis, teeth, oral health, and immune function were used in the searches.

Psychoneuroimmunology

Central nervous system communication with both the immune and endocrine systems has given rise to the field of psychoneuroimmunology. Neuroendocrine-derived peptides and hormones have long been recognized as immune modulators. Early studies in animals found that stress was associated with increased susceptibility to infectious disease (106) as well as experimental models of inflammatory disease (4). Research in human psychoneuroimmunology has shown that immune-regulatory processes are an inextricable part of a complex network of adaptive responses (62). Individuals experiencing stress exhibit prominent abnormalities of behavior, such as depressed mood and impaired sleep, along with dysregulation of the neuroendocrine and sympathetic nervous systems – the latter systems are critical efferent pathways in the regulation of immunity by the brain. The pattern and magnitude of the response to stress appears to be influenced by mulitple factors, such as the duration of stress exposure (acute vs. chronic), the type of stress (physical vs. psychological) and gender, among others (64).

Multiple stress mediators, including monoamines, neuropeptides and steroid hormones, are necessary to convey the stress signal to the central nervous system and contribute to the resulting functional changes in the central nervous system. A basic understanding of the role of the limbic–hypothalamic–pituitary–adrenal axis and the cytokine regulatory loop are depicted graphically in Fig. 1.

Complex bidirectional interactions have been established between the central nervous system and the immune system, mediated by the endocrine system. Two important features of these interactions include the production of stress hormones by the limbic–hypothalamic–pituitary–adrenal axis and the sympathetic–adrenal–medullary axis (46). Hormones effect immune function through receptor binding and modulation of cytokines. The modulation of cytokines has been shown to feed back to the brain, producing changes in the hypothalamic–pituitary–adrenal axis, providing a mechanistic basis for common alterations in sleep patterns and depression. Acute, time-limited stressors appear to result in adaptive redistribution of cells and preparation of the natural immune system for possible infection or injury, or both. Chronic stressors have been associated with more global immunosuppression – cellular immunity followed by both natural and specific immunity, including T-helper 1 (e.g. T-cell-proliferative responses) and T-helper 2 (e.g. antibody to influenza vaccine) parameters (117). Therefore, the adaptiveness of immune changes appears to decrease with increasing chonicity of a stressor.

Psychological stress clearly exerts the capacity to modify the susceptibility of animals and humans to infectious agents, influencing the onset, course and outcome of certain infectious pathologies (12).

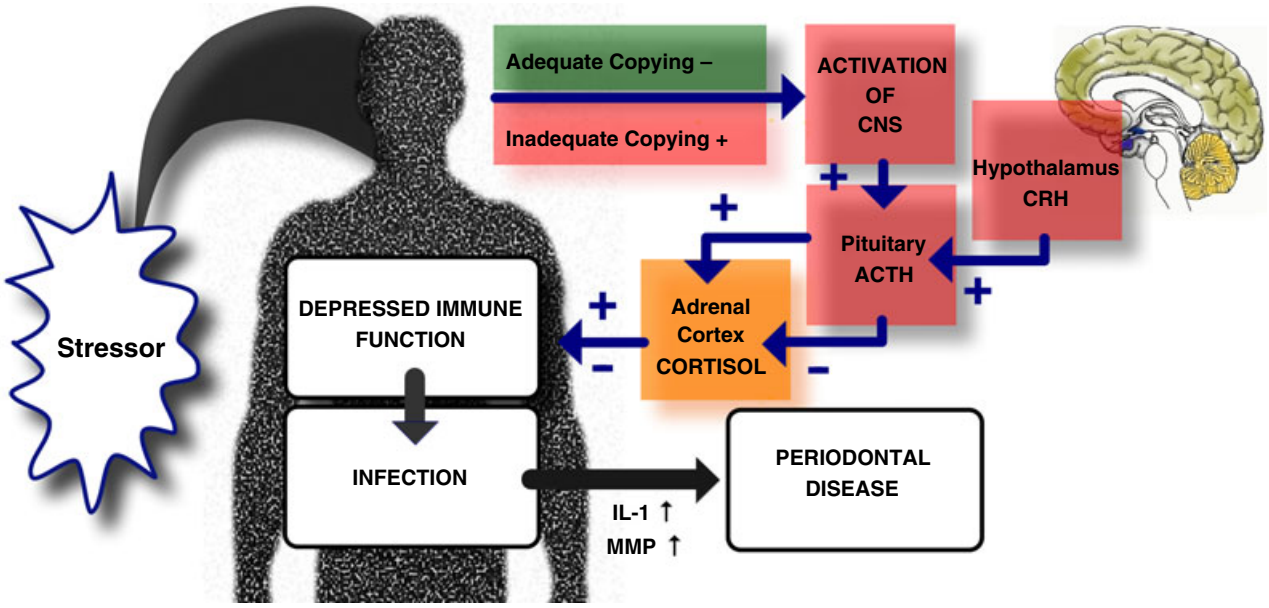

Fig. 1. Model of the effects of chronic stress on the immune system and periodontal disease. ACTH, adrenocorticotropic hormone; CNS, central nervous system; CRH, corticotropic-releasing hormone; IL-1, interleukin-1; MMP, matrix metalloproteinase. Adapted from Genco et al. (45). Graphic courtesy of Dr. Harlan Shiau, Baltimore, MD.

Psychological stress is generally recognized as a potential cofactor in the pathogenesis of infectious disease. Cohen et al. (30) prospectively studied the relationship between psychological stress and the frequency of documented clinical colds among subjects intentionally exposed to respiratory viruses. After completing questionnaires assessing the degree of psychological stress, 394 healthy subjects were given nasal drops containing one of five respiratory viruses (rhinovirus type 2, 9 or 14; respiratory syncytial virus; or coronavirus type 229E) and an additional 26 were given saline nasal drops. Stress was associated in a dose–response manner with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection. In a recent systematic review and meta-analysis, Pedersen et al. (101) conclude that the evidence supports the hypothesis that psychological stress is associated with increased susceptibility to upper respiratory tract infection, consistent with the potential importance of psychological factors in other infectious diseases.

Stress has a direct impact on the immune system , similarly to many other strategies which people use to cope with stress, whether healthy (e.g. exercise) or unhealthy (e.g. smoking). Genco et al. (44), for example, found a higher risk of more severe periodontal attachment loss (odds ratio = 2.24) and alveolar bone loss (odds ratio = 1.91) among individuals with financial strain and an inadequate coping style, when compared with those with low levels of financial strain within the same coping group, after adjustment for age, gender and cigarette smoking. There is also evidence for psychological modulation of the immune response to viral vaccines. One of the earliest studies was conducted in medical students who were inoculated with the hepatitis B virus vaccine. Both virus-specific T-cell and antibody responses were up-regulated in those students with more stress and less social support (46, 48). Chronic stress associated with caregiving for a spouse with Alzheimer's disease was associated with a less desirable antibody response to an influenza virus vaccine compared with matched controls (69). A similar study in Hong Kong compared 55 caregivers of spouses with chronic conditions that impaired their activities of daily living with 61 matched controls. Participants were injected with trivalent influenza vaccine and were assessed for symptoms of stress and depression. Caregivers had statistically significantly lower cell-mediated immune responses to the influenza vaccine compared with controls (136). Other studies show that caregivers of those with chronic illnesses are at higher risk of infection and immune reaction (20, 91, 133). Collectively, these studies and others (132) suggest that stress and inadquate coping strategies or social support can play a role in the activation or re-activation of herpesviruses and other viral infections in the periodontium. High periodontal loads of active Epstein–Barr virus and cytomegalovirus tend to be associated with aggressive periodontitis, whereas latent herpesvirus infections are more common in chronic periodontitis and gingivitis (125).

Stress also alters clinical wound healing and underlying immunologically mediated processes (72). Studies on the healing of acute experimental and surgical wounds consistently report slower wound healing in individuals with high levels of psychological stress, regardless of stressor duration (17, 70–72, 84). A decrease in local pro-inflammatory cytokines in the wound bed has been postulated as one biologic mechanism (49, 70), presumably caused by the immunosuppressant effects of cortisol, norepinephrine and epinephrine (40, 94). In animal models of psychological stress-impaired cutaneous wound healing (50), delay in healing is also associated with deficits in bacterial clearance (129) and susceptibility to opportunistic infection (109) at the wound site. Oral mucosal wound healing is also known to be impeded by stress (84). Depressive symptoms also predict the rate of mucosal wound healing in healthy young adults (15).

Stress modifies the host immune response

The mechanisms through which stress produces inflammation are complex and bidirectional (stress can produce inflammation and inflammation can produce stress). These processes involve networks of communication including genetic, neural, endocrine and immune interactions. It is clear from both animal and human studies that stress affects the immune system in multiple ways. Stress increases neuroendocrine hormones, such as glucocorticoids and catecholamines. Through the activation of these hormones, stress has detrimental effects on immune functions, including reduction of lymphocyte populations, lymphocyte proliferation, natural killer cell activity and antibody production and the re-activation of latent viral infections (134). The limbic–hypothalamic–pituitary–adrenal axis and the sympathetic nervous system are the major neural pathways activated by physical (i.e. pathogens or toxins) and

psychological (i.e. major life events, abuse, or work- or relationship-related factors) stressors (2, 13, 24).

Early conceptualizations accepted a global immunosuppressive action of stress, but it is now clear that both immunosuppression and immune activation occur in various types of stress states (93). Chronic or repetitive stress, of the sort that is quite typical for those individuals with mental illness, seems to provoke a state of chronic inflammation through the activation of macrophages, dendritic cells, microglia, adipocytes and endothelium, which secrete cytokines. Other effects include altered cell trafficking, natural killer cell cytotoxicity changes and alterations in the T-helper 1/T-helper 2 balance, all of which could contribute to the potential for poor immunoresponsiveness to microorganisms and vaccines, susceptibility to infections, re-activation of latent viruses and delays in wound healing (47). The chronic inflammation occurs often in the presence of limbic–hypothalamic–pituitary–adrenal activation and secretion of high levels of normally immunosuppressive glucocorticoids (122).

Chronic stress: a state of inflammation

Chronic stress acts through a variety of molecular mechanisms to produce a state of inflammation. Central to the production of this state is the release of proinflammatory cytokines responding to particular signals. Cytokines are signaling proteins that transmit information between immune cells and also between the immune system and the brain and endocrine system. Cytokines can act in autocrine, paracrine and endocrine manners to produce their effects (19). The cytokines with greatest involvement in producing a stress-associated state of chronic inflammation include interleukin-1beta, tumor necrosis factor-alpha and interleukin-6, a process that is mediated by nuclear factor-kappa B (14). Inflammation is normally a cell and tissue response to injury or infection, with safeguards to keep inflammation from becoming unchecked and chronic (18). There are also systemic effects of inflammation, largely accomplished through the release of cytokines, that produce the well-known 'sickness behavior' of inflammation through actions of cytokines on the brain (33).

The normal pathways for proinflammatory secretion are through liganding of receptors on cytokine-secreting cells. These receptors include toll-like receptors, which respond to pathogen-associated molecular patterns as well as to danger-associated molecular patterns (10). Danger-associated molecular patterns are classified as 'alarmins' (i.e. molecules that signal cell damage) and include heat shock proteins, DNA and many different products of injured tissue (e.g. high-mobility group protein B1, defensins, annexins and uric acid; 10). Inflammation produced through the alarmin pathway is considered 'sterile' as it is not provoked by pathogens. In the stress associated with mental illness, the inflammation is of this latter sort. Another important receptor-mediated pathway is through alpha- and beta-adrenergic receptors that bind norepinephrine, which may be increased in stress states through activation of the sympathoadrenal system (94).

Liganding of these receptors initiates secretion of proinflammatory cytokines through several signal-transduction pathways, one involving nuclear factor-kappa B and another involving mitogen-activated protein kinases. Both pathways act to increase the expression of tumor necrosis factor-alpha and interleukin-1beta genes (11). Interleukin-6 production is stimulated in an autocrine manner by interleukin-1beta, and the major signal transduction factor is signal transducer and activator of transcription 3 (92). Opposing these pathways are the glucocorticoid receptors. Glucocorticoid receptors are nuclear receptors that, when bound with cortisol, bind to glucocorticoid-response elements on the promotor regions of genes which code for proinflammatory (and other) molecules, inhibiting transcription (122). In stress, there may be activation of the sympathoadrenal system and the limbic–hypothalamic–pituitary–adrenal axis, both of which may be involved in the production of the chronically inflamed state. Adrenergic mechanisms may account for many of the short-term inflammatory effects of acute stress. Chronic stress, on the other hand, is more likely to be associated with a low-grade state of inflammation (25, 108). Glucocorticoids inhibit the reproductive axis on multiple levels by reducing secretion of gonadotropin-releasing hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol and progesterone. The latter inhibitory effects may contribute to sexual dimorphisms of stress-related behavioral syndromes and autoimmune inflammatory disorders (26).

Neurologic and behavioral characteristics of the chronically stressed or depressed state can be explained, in part, through the cytokine effects of fatigue, decreased mobility, anhedonia and depression (81). These states are characterized not only by higher plasma levels of proinflammatory cytokines, particularly interleukin-6, but also by higher than normal

levels of acute-phase reactants, the synthesis of which is stimulated in the liver by the proinflammatory cytokines. These include C-reactive protein, fibrinogen and various adhesion molecules (108). There is also evidence of limbic–hypothalamic–pituitary–adrenal axis activation and release of glucocorticoids in the face of ongoing inflammation (27). The latter is thought to take place through several mechanisms. One concept is that glucocorticoid receptors become down-regulated or impaired and insensitive or resistant to the high levels of cortisol. Without a damping mechanism through the glucocorticoid pathway, inflammation persists and exerts damage to vulnerable tissues (29). It is also now established that a number of glucocorticoid receptor gene polymorphisms exist that could play a role in susceptibility to stress-induced inflammation and also that epigenetic mechanisms can alter the glucocorticoid receptor gene (92, 122).

Genetic variability in the expression of inflammatory mediators in response to stress can also contribute to differences between individuals in systemic markers of inflammation and risk of morbidity and mortality (31). For example, the presence of the guanine/cytosine single nucleotide polymorphism (rs1800795) in the promoter of the interleukin-6 gene, -174 bp upstream of the transcription start site, affects the binding of a beta-adrenergic-sensitive transcription factor, GATA-1. Following a beta-adrenergic stimulus, only the interleukin-6 -174G single nucleotide polymorphism leads to increased interleukin-6 production. In a study of spousal bereavement in older adults, Schultze-Florey et al. (116) found that the interleukin-6 -174 single nucleotide polymorphism moderated the effect of bereavement on the vulnerability of an individual to higher circulating levels of inflammation. Moreover, epidemiologic analysis revealed an increased 10-year mortality risk associated with late-life depressive symptoms that occurred solely in homozygous carriers of the GATA1-sensitive G allele (31). Such studies underscore the importance of genetic variability in determining the biologic effects of environmental stressors.

Depression: is stress the tie that binds?

The connection between stress and depression is also complex and bidirectional. Evidence supports the hypothesis that psychosocial stress can lead to depression in susceptible individuals, which, in turn, can be aggravated by depression. In a recent meta-analysis, Howren et al. (60) reviewed the associations between depression and the inflammatory markers C-reactive protein, interleukin-1 and interleukin-6 in circulating peripheral blood from community and clinical samples. All three inflammatory markers had a positive association with depression. The strongest association (based on clinical interviews) was found in clinically depressed patients, but the association was also significant in the community-based samples. Depression was also found to be predictive of C-reactive protein and interleukin-6 levels in cardiac and cancer patients. Interestingly, the relationship between depression and circulating levels of interleukin-6 became weaker with increasing age (60). The latter finding may reflect, in part, age-related increases in circulating levels of interleukin-6, tumor necrosis factor-alpha and other inflammatory cytokines, even in healthy adults and in the absence of acute infection (123).

In a more recent meta-analysis, Hiles et al. (59) also found a moderate and significant elevation in serum interleukin-6 levels in depressed compared with nondepressed groups, consistent with earlier systematic reviews (36, 59, 60, 78). However, a high heterogeneity in the effect size was present among studies. Elevations in interleukin-6 were larger in studies of patients with major depressive disorders and no known comorbid conditions. Comorbidities associated with depression were found to reduce the effect size between depressed and nondepressed groups. Body mass index, for example, was shown to be a moderating factor, as reflected in smaller, but significant, positive associations between depression and serum inflammatory markers.

Studies evaluating the effect of antidepressants on systemic markers of inflammation provide additional evidence linking depression to elevations in markers of systemic inflammation. In a meta-analysis of 22 studies, Hannestad et al. (56) examined whether serum levels of tumor necrosis factor-alpha, interleukin-6 and interleukin-1beta change in response to therapy with commercially available antidepressants in patients with major depressive disorder. Studies were included only if serum markers were obtained before and after treatment. The results revealed that treatment with specific serotonin re-uptake inhibitors reduced the symptoms of depression as well as the serum levels of interleukin-1beta and interleukin-6. A similar trend was found for levels of tumor necrosis factor-alpha in response to specific serotonin re-uptake inhibitors. Other antidepressants, including serotonin and norepinephrine re-uptake inhibitor and tricyclic antidepressants, reduced depressive

symptoms but exerted minimal, if any, effects on serum markers of inflammation. The authors interpreted these findings to suggest that inflammatory cytokines can contribute to depressive symptoms and that antidepressants have the potenital to impede the effects of inflammatory cytokines on the brain (56). Collectively, these findings suggest that comorbidities, such as obesity and periodontitis, which are associated with elevations in systemic markers of inflammation, have the potential to modify the severity of depression.

Influence of psychosocial factors in periodontitis

Chronic inflammatory diseases, such as periodontitis, have a complex pathogenesis and a multifactorial etiology, involving complex host–parasite interactions (75). (Fig. 2) Genetic variations in genes encoding the molecular components of the host immune defense (74, 139), coupled with specific bacterial species in the subgingival plaque, set the stage for individual differences in risk for periodontitis. Compared with women, men appear at greater risk for periodontitis (41, 121). Basic and clinical studies document the potential for comorbidities (e.g. diabetes) and co-infections (e.g. herpesviruses) to modify the initiation and/or progression of periodontitis (76, 124, 126). Cigarette smoking, poor nutrition, alcohol consumption and low socio-economic status also have been shown to be associated with a higher risk of periodontitis (132).

A substantial body of evidence indicates that psychological stress (107) and ineffective coping (44) can influence the onset and progression of many chronic diseases, including periodontitis (95). Early studies provided both anectoctal and clinical evidence of an association between psychosocial stress and acute necrotizing periodontal diseases, especially necrotizing ulcerative gingivitis (28, 118), as well as periodontitis (43, 53, 83). The nature of the association, however, was based largely on a temporal concordance between the 'stressful' event, gingival infection, and physiological measure of stress, such as urinary hydroxycorticosteriod. Similarly, associations have been made between stress and depression and aggressive ('rapidly progressive') periodontitis based on psychosocial and clinical data obtained at the same time (34, 99).

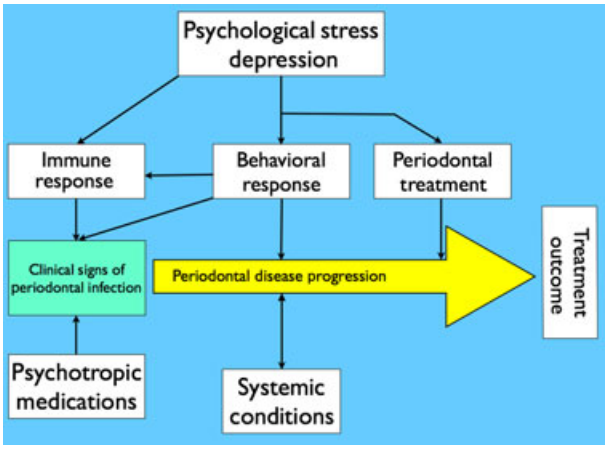

Fig. 2. Model of the effects of chronic psychological stress and depression on periodontal disease. Adpated from Elter et al. (42).

Therefore, chronic stress and depression have been hypothesized to reduce immune responsiveness, resulting in more pathogenic infection and concomitant periodontal tissue destruction. Evidence also indicates that chronic stress and depression can mediate risk and progression of periodontitis through changes in health-related behaviors, such as oral hygiene, smoking and diet (3, 45). Although stress can adversely impact multiple health-related behaviors, including oral hygiene (32, 58), there is strong evidence that stress plays a contributory role in the pathophysiology of periodontitis. Peruzzo et al. (103) conducted a systematic review of the evidence on the influence of stress and psychological factors on periodontal disease. Of the 14 studies (seven case–control, six cross-sectional and one prospective clinical trial) meeting inclusion criteria for the review, the majority (57%) reported a positive relationship between stress/psychological factors and periodontal disease. Another 28.5% of the studies observed a positive relationship between some characteristics of stress and periodontal disease, demonstrating that the majority of the work published to date examining this relationship have indeed found significant associations (103). In a recent study not included in the systematic review, stress scores and salivary stress markers (chromogranin A, cortisol, alpha-amylase and beta-endorphin) were shown to be significantly correlated with clinical parameters of periodontal disease in 100 adult patients with periodontitis (105). Salivary cortisol and beta-endorphin were significantly associated with tooth loss and periodontal clinical parameters, after adjusting for stress variables. Moreover, the greatest tooth loss was observed in those patients who neglected to brush their teeth during stressful periods (105). The results of these studies are consistent with the hypothesis that stress can modify the host defense and progression of

periodontal infections in patients susceptible to periodontitis (37).

Depression has also been linked to periodontitis in clinical studies in adolescents/young adults (35, 79) and adults (1, 44, 65, 66, 89, 90, 110, 115). In a case–control study, Moss et al. (90) found that smoking and elevated antibody titers to *Tannerella forsythia* at baseline were associated with more severe periodontal breakdown in patients scoring high on a depression inventory. In a cross-sectional investigation, patients with rapidly progressive periondontitis showed significantly higher scores on measures of depression and loneliness compared with adults with either chronic periodontitis or without significant clinical attachment loss (89). Genco et al. (44) found that stress and distress manifested as depression was a significant risk indicator for more severe periodontitis in a cross-sectional study of 1,426 subjects between 25 and 74 years of age. Johannsen et al. (65) found that women on long-term sick leave for depression had more severe periodontitis and higher concentrations of interleukin-6 in gingival crevicular fluid compared with healthy controls. These clinical results are consistent with findings in an established animal model of depression. Breivik et al. (16) tested whether depression induced by olfactory bulbectomy in rats and treatment with the antidepressant serotonin re-uptake enhancer, tianeptine, could influence susceptibility to ligature-induced periodontitis. When compared with sham-operated controls, olfactory bulbectomy rats were shown to develop significantly more periodontal bone loss. Tianeptine treatment significantly inhibited alveolar bone loss. However, a clomipramine-induced model of depression in Lewis rats did not alter the pathogenesis of ligature-induced periodontitis (127).

Susceptibility to periodontal breakdown in response to stressful life events appears to depend, in part, on the effectiveness of a person's coping behavior (61, 135). In a cross-sectional investigation, Genco et al. (44) examined the relationship of periodontal disease and stress, distress and coping behaviors in a large population-based adult sample (44). This study revealed that psychosocial measures of stress (financial strain) and distress, manifest as depression, were significant risk indicators of periodontal disease severity in adults, after adjusting for gender (male), smoking, diabetes mellitus, *T. forsythia* and *Porphyromonas gingivalis* (44).

Several clinical studies have failed to demonstrate an association between measures of depression and periodontal disease in community-based samples (5, 21, 102, 128). Persson et al. (102), for example, did not find an association between depression and radiographic bone loss or periodontal probing depths (5 mm or greater) in a sample of 701 older adults. However, depression (self-reported or based on a psychometric score) was associated with a history of greater tooth loss, which may reflect greater susceptibility to periodontal destruction during periods of depression. Anttila et al. (5) reported a positive correlation between depression and edentulousness in a sample of 780 Finnish residents. It is noteworthy that depression often manifests with multiple comorbidities, including obesity and diabetes, many of which are independently associated with elevations in systemic markers of inflammation (102). In general, studies exploring the association between depressive symptoms and periodontitis have been based on nonpsychiatric populations without consideration of comorbidities, limiting the potential of these studies to identify an association between depression and periodontal disease.

Studies of serum and salivary stress-related steriods provide further evidence of an association between stress, depression, and periodontal disease. In a cross-sectional study, Rosania et al. (111) asked patients with periodontitis to complete psychometric tests and questionaires as well as to undergo clinical examinations and measurement of salivary cortisol levels (111). Stress, depression and salivary cortisol scores were found to correlate signficantly with severity of periodontitis and the number of missing teeth, when controlling for age, family history and brushing frequency. Moreover, patients who reported neglecting their oral care during stressful or depressed periods exhibited the greatest clinical attachment loss and highest number of missing teeth. In a similar study of 111 dentate patients, ≥40 years of age, Mannem & Chava (82) reported that stress scores and salivary cortisol levels significantly discriminated between patients with and without periodontitis. Similar associations have also been reported between serum levels of the stress-related steroids, such as cortisol and dehydroepiandrosterone-sulfate, and measures of periodontal disease (52, 63). Patients with periodontitis often have higher systemic levels of C-reactive protein, interleukin-6, interleukin-1 and tumor necrosis factor-alpha (104). The mechanisms underlying the relationship of psychlogical stress and depression with periodontitis probably involve a combination of factors related to alterations in behavior and neuroimmunologic function.

Experimental animal models provide additional evidence that stress adversely affects immune defense and susceptibility to oral infection. Bailey et al. (8)

found that social stress enhances the production of interleukin-1beta and tumor necrosis factor-alpha in $CD11b^+$ spleen cells in response to *P. gingivalis* lipopolysaccharide (8). The latter finding suggests that stress can enhance the responsiveness and production of inflammatory cytokines by macrophages in response to an oral pathogen. Macrophages from the spleens of mice exposed to this same stressor were shown to express significantly higher levels of both toll-like receptor-2 and toll-like receptor-4 (7). Breivik et al. (16) also found that injection of lipopolysaccharide provoked a significant increase in the circulating levels of corticosterone and alterations in cytokine levels, consistent with dysregulation of the immune system, in an animal model of depression. Psychological stress has been also shown to exacerbate oral infection with the opportunistic pathogen, *Candida albicans*, in rodents (97, 98).

Finally, stress and depression have been shown to exert a negative effect on treatment outcomes in patients with periodontitis. Elter et al. (42) examined whether depression was predictive of the proportion of residual probing periodontal sites (5 mm or greater) and tooth loss between the initial and 1-year post-treatment examinations in 697 patients enrolled in a health-maintenance organization. A diagnosis of depression was documented from medical records in 12.2% of the patients. Depression was significantly associated with both poorer periodontal treatment outcome and tooth loss during the 1-year follow-up period. Kamma & Baehni (67) found that scores on a stress inventory predicted future clinical attachment loss in patients with aggressive periodontitis in supportive periodontal care over a period of 5 years (67). Linden et al. (77) found that a measure of occupational stress was a significant predictor of clinical attachment loss in 23 patients with periodontitis in regular periodontal maintenance over a period of nearly 6 years. These findings parallel other reports (112) indicating that psychosocial factors play a significant role in recovery from surgery and are predictive of surgical outcome.

Summary

An extensive body of experimental and clinical evidence documents the negative impact of chronic psychological stress and depression on the immune system and health. Brief stressors appear to suppress cellular immunity whilst preserving measures of humoral immunity; in contrast, chronic stressors generally result in dysregulation of the immune system, involving both cellular and humoral pathways (117). Therefore, chronic stress and depression have been hypothesized to reduce immune responsiveness, resulting in a higher rate of infection with pathogenic organisms and a greater degree of periodontal tissue destruction. In general, the evidence is consistent with the hypothesis that stress can modify the host immune defense and permit the progression of periodontal infections in patients susceptible to periodontitis (37). However, substantial evidence also indicates that these conditions can mediate risk for disease, including periodontitis, through changes in health-related behaviors, such as oral hygiene, smoking and diet (3, 45). Stress and depression are commonly associated with comorbidities, such as diabetes (96), that can modify the onset and progression of periodontal disease; however, these conditions have generally not been addressed in available studies. In addition, stress and depression appear to fall into a spectrum, ranging from mild to severe, involving a complex interaction of genetic background, coping strategies and environment. Differences in the conceptualization of stress and depression are probably important in assessing associations with other biologic and clinical measures. Elevations in serum markers of inflammation, for example, have been found to be greater in patients diagnosed with depressive disorders than in subjects with depressive symptoms based on standardized inventories (59). Future studies are necessary to clarify the complex interactions of chronic stress and depression in periodontal diseases.

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