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Original Research

Stress and its effect on the pathogenesis of the periodontal disease

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ABSTRACT:
Stress can best be understood as part of a complex and dynamic system of transaction between the individuals and their environment. Stress is said to influence the host defense, exerting an immunosuppressive effect, increasing one's vulnerability to disease. The evolution of periodontal diseases is influenced by many local or systemic risk factors. Psychological stress is a risk factor for periodontal disease. Stress can also increase the severity of periodontal disease and decrease the effectiveness of treatments. Stress can result in the degeneration of the immune system, mediated primarily through the hypothalamic – pituitary – adrenal and sympathetic adrenal medullary axis. The individuals with high stress levels tend to adopt habits that are harmful to periodontal health, such as negligent oral hygiene, intensification of nicotine consumption, or changes in eating habits with negative effects for the immunologic system. Current evidence indicates a relationship, presumably bidirectional, between stress and periodontitis, involving both dysregulation of the immune response and dysbiosis of the oral microbiome. Psychological stress appears to be an important modifiable risk factor for the development and progression of periodontitis and other periodontal diseases. Patient education and referral for evaluation and counselling should be considered for patients exhibiting psychological stress or depression.
Keywords: Dysbiosis, Immunologic system, Oral microbiome, Psychological stress

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INTRODUCTION

The definition of stress is "a total transaction from demand to resolution that is in response to either an environmental encounter which requires appraisal, coping and adaptation by an individual." Coping is the response of the individual to stress relationship of sound mind in maintaining healthy body, which has been recognized from most of the history recorded i.e. from the time of ancient Romans, Greeks and Chinese.[1] Seyle defined stress as a 'Response state of the organism to forces acting simultaneously on the body which if excessive, that is straining the capacity of adaptive process beyond their limits, leads to a disease of exhaustion and death'.[2]

Stressors are those forces that have the potential to challenge the adaptive capacity of the organism. The group of stressors could be mental/ psychosocial/ physical. These stressors either lead to eustress/distress, which is body's adaptive to restore homeostasis.[2]

"Periodontal disease" is an umbrella term that includes gingivitis, an inflammation of the gingiva, and "periodontitis", a set of inflammatory conditions affecting the alveolar bone in the jaw and supporting soft tissues that help anchor teeth in place.[3] The pathogenesis of periodontitis is complex but it is generally agreed that the initiating etiologic event involves infection with a group of predominantly gram-negative anaerobic bacteria that colonize the subgingival area.[4]

The preogress of disease is dependent upon a complex inter-relationship between microbial activity and the host's inflammatory response to microbial challenge, which progressively leads to connective tissue degradation and alveolar bone loss. Differences in the clinical presentation of periodontitis reflect its complex multifactorial etiology, and these varying presentations have recently led to classification of the disease as either "chronic" or "aggressive".[5] Compared to chronic periodontitis, aggressive

periodontitis is characterized by its relatively early onset, rapid progression, and familial aggregation.[6]
The etiopathogenesis of periodontal disease indicates that periodontitis is a multifactorial disease caused by periopathogens in which host and environmental factors play an important role. Bacteria play an essential role as primary etiological agents, but alone seem to be insufficient to explain the occurrence or progression of the disease. The onset and progression of the periodontal disease are influenced by many systemic diseases, environmental factors, and psychologic stress that carries the potential for alteration of the periodontal tissues and immune response, that leads to higher severity of the periodontal destruction.[7]
Although bacteria play an essential role, they seem to be insufficient to explain the occurrence or progression of the disease. Many factors like age, use of tobacco, systemic diseases, and psychological stress are the major risk factors for causing periodontitis. *De Marco*[8] gave the term "Periodontal Emotional Stress Syndrome" for those subjects having severe periodontitis and showed that the emotional stress related to the active service in Vietnam has a major role of occupational stress in the progression of periodontitis.
The present review was done to study the association of stress with progression nd severity of the periodontal disease.

MATERIALS AND METHOD

Peer-reviewed reports were collected from the publicly available database PubMed, which acquires citations from MEDLINE and other scientific data sources. Search terms for epidemiological reports included (a) "periodontal disease", OR "periodontal inflammation", OR "periodontitis"; AND (b) "stress", OR "anxiety", OR "life events", "physical stress", OR "emotional stress", OR "psychological factors". The research articles were included which studied the relation of periodontal disease with stress.

PSYCHOSOCIAL STRESSORS

Psychosocial stressors are generally classified:[9] major stressful life events and minor daily stressors or "hassles." *Holmes*[10] developed a scale to measure stress in terms of life changes, in which, the ranking of the life events is done in order, from the most stressful (death of a spouse) to the least stressful (minor violations of the law).[11]
Another set of psychosocial stressors are well-known behavioral and emotional responses to common sequela of advancing periodontal disease, which include such negative and dysphoric conditions as pain, bleeding, unpleasant tastes, and odors emanating from the mouth and unsightly appearance of the teeth and surrounding hard and soft supporting structures.[11]
Other signs and symptoms such as abscess formation with pathogenic exudates and intense pain, loosening of teeth and the perceived threat of losing one's teeth in early adulthood are also often highly worrisome, hence serving as potentially powerful negative emotional stressors. Moreover, treatment of periodontal disease is often associated with pain and discomfort as well as being time-consuming and often expensive. All these perceptions, attributions, and emotions associated with illness can themselves come to constitute and act as an important set of stressors that may induce stress system responses that are further deleterious to periodontal health.[12]

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.[13,14] However, a significant cumulative biological damage is incurred by the body as an unintended consequence of allostasis (i.e., behavioral or physiological process of achieving stability in response to stressors), which has been referred to as "allostatic load".[13,14]
Among clinical outcomes of stress, depression displays the strongest association.[15] 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.[16]
Several studies have found a positive relationship between life stressors and periodontitis.[16,17] 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.[18] In the following sections, we explore the mechanisms involved in the stress-periodontitis relationship.

ENDOCRINE CHANGES

Although interactions between stress-endocrine-periodontal changes are not yet well- understood, some hypotheses have been proposed. It has been suspected that periodontal status is related to alterations in the concentration of adrenal corticoids and by altering the response of oral tissues to bacterial toxins and other hormones involved in the general adaptation syndrome.[19]
It has been suspected that periodontal status is related to alterations in the concentration of adrenal corticoids and by altering the responses of oral tissues to bacterial toxins and other hormones involved in the general adaptation syndrome.[20] Psychosocial stressors may play in initiating a cascade of events in the corticotropin-releasing hormone/hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, and the central nervous system, the physiological consequences of which are to depress immunity, enhancing the likelihood of infection and,

specifically, periodontal disease. Recent studies had confirmed the fact that the concentrations of cytokines [interleukin (IL)-6, IL-1β, etc.,] and cortisol in the gingival crevicular fluid (GCF) are higher in persons showing depression signs.[21-25]

High cortisol levels may be especially negative on periodontal tissue because of the extremely fast turnover of some periodontal components. Elevated levels of glucocorticoids can decrease in vitro fibroblasts, collagen production and in vivo sulphated glycosaminoglycans. These alterations may be enough to cause imbalances in the synthesis and breakdown of periodontal tissues, especially if pre-existing inflammation is present.[7]

GINGIVAL CIRCULATION

The tonus of the smooth muscle of blood vessels may be altered by the emotions by way of the autonomic nervous system. Furthermore, in long or continued emotions, a constant constriction of blood vessels could alter the supply of oxygen and nutrients to the tissues.[26]

ALTERATION IN SALIVARY FLOW AND COMPONENTS

It is assumed that both increase and decrease in salivary flow, induced by emotional disturbance, may affect the periodontium adversely. Emotional distress may also produce changes in saliva pH and chemical composition like immunoglobulin (Ig)A secretion. These relationships between salivary physiology and psychological status do not necessarily demonstrate causation of periodontal disease, but they show a pathway in which periodontal health is influenced by salivary changes.[27]

LOWERED HOST RESISTANCE

Periodontal diseases are inflammatory diseases associated with local and systemic elevations of proinflammatory cytokines, such as tumor necrosis factor a, IL-6, and prostaglandins and result in tissue destruction by the contribution of matrix metalloproteinases.[28,29] Stress impairs the balance between proinflammatory and antiinflammatory responses. The relationship between stress and periodontal diseases might be mediated by alterations in GCF IL-1, IL-6 levels, and reduction in polymorphonuclear leukocyte chemotaxis and phagocytosis, and reduced proliferation of lymphocytes.[30]

Psychosocial stress stimulates the brain where its stimulation or inhibition is dependent on adaptive and maladaptive coping respectively. On stimulation, the autonomic nervous system leads to prostaglandin and protease secretion that leads to periodontal disease progression. The HPA leads to a production of glucocorticoids (cortisol) that depresses the immune system by diminishing the IgA and IgG secretions, thereby enhancing the periodontal disease progression and poor treatment response.[21]

Subsequently, this process could increase vulnerability of periodontal tissues to pathogenic microorganisms by activation of cellular responses leading to local tissue destruction.[31] Patients suffering from periodontitis, who are under stressful conditions, have increased levels of IL-622 and IL-1b23 in GCF, and similarly, patients with aggressive forms of periodontitis have elevated levels of IL-6 and IL-1b in serum.

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.[32-34]

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.[35] 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.[36]

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. 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.[37]

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.[38] P. Gingivalis alters the host immune response, thereby contributing to dysbiosis of the periodontal microbiome and magnifying its capacity to produce periodontitis.[39]

Oral microbiome signatures have been identified for chronic periodontitis, including in gene expression, relative to the oral microbiome of periodontally healthy individuals.[40,41] 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.[42] 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.[40]
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.[43] The latter scenario could certainly be the case of salivary levels of pro-inflammatory cytokines induced experimentally by stress.[44]

STRESS AND ACUTE NECROTIZING ULCERATIVE GINGIVITIS

Possibly because of its nature (acute painful onset, short lived infection, ease of diagnosis, and multiple predisposing factors), ANUG is most studied periodontal disorder in relation to psychosocial predisposing factors. A psychogenic origin has been suggested for ANUG. Psychogenic factors probably predispose to the disease by favoring bacterial overgrowth and/or weakening host resistance.[43]
Host tissue resistance may be changed by mechanisms acting through the autonomic nervous system and endocrine glands resulting in elevation of corticosteroid and catecholamine levels. This may reduce gingival microcirculation and salivary flow and enhance nutrition of Prevotella inter-media, and at the same time also depress neutrophil and lymphocyte functions, which facilitate bacterial invasion and damage. It has been reported that ANUG patients as compared to controls presented: (i) depressed polymorphonuclear leukocyte chemotaxis and phagocytosis; and (ii) reduced proliferation of lymphocytes upon stimulation by a nonspecific mitogen.[44]
Because ANUG patients were also more stressed than controls, data suggest that depression of some host defense mechanisms, under stress conditions, may be necessary in the pathogenesis of ANUG. It is not uncommon to have outbreaks of ANUG among college students during examinations and people during military service.[44]

STRESS AND WOUND HEALING

Immune function is important in the early stages of wound healing. IL-8 and pro-inflammatory cytokines, such as IL-1 and TNF, are essential in the healing process, as they help to protect against infection and prepare injured tissue for repair by enhancing the recruitment and activation of phagocytes.[45]
Furthermore, cytokines that are released by recruited cells regulate the ability of fibroblasts and epithelial cells to remodel the damaged tissue. IL-1 that is produced early after tissue injury can regulate MMP activity, which plays an important role in the destruction and remodelling of the wound. IL-1 can also regulate fibroblast chemotaxis and the production of collagen, as well as stimulate the production of other cytokines that are important for wound healing, including IL-2, IL-6 and IL-8. Therefore, deficits in these cytokines can lead to impaired or slowed wound healing.[46] Stress has been suggested to alter the production of proinflammatory cytokines that are important for wound healing, producing substantial delays in wound repair.
Patients with maladaptive coping strategies have more advanced disease and poor response to non-surgical treatment,[47] whereas positive correlation was observed in reduction of dental plaque and gingival bleeding in patients having an active coping.[48]
Furthermore, the cellular immune response plays a vital role in wound healing. Not only does it protect the wound site from infection, it also prepares the wound for healing and regulates its repair.[11]
Cytokines such as IL-1, IL-8, and TNF are extremely important in recruiting phagocytic cells to clear away the damaged tissue and to regulate the rebuilding by fibroblasts and epithelial cells. A decrease in expression in any of these cytokines could theoretically impair wound healing. Stress could suppress certain aspects of the cellular immune response such as mitogen stimulation, antibody and cytokine production, and NK cell activity. Furthermore, since stress deregulates inflammatory and immune response, stress can alter the course of oral wound healing and affect the management of other oral diseases, e.g., periodontitis.[49]

DISCUSSION

Despite numerous experimental, clinical, and epidemiological studies on the relationship between stress and periodontal disease, the exact mechanisms linking these two phenomena remain largely unknown.[50-53] As a first step, these studies have shown the indirect impact of stress on the periodontium through changes in behavior and lifestyle (food and oral hygiene, smoking, parafunctions, etc.).[8] More recently, the progress of neurology and psychoimmunoendocrinology and the growing interest in the study of stress and its medicopsychosocial consequences have made it possible to demonstrate a direct, biological impact of stress on the periodontium.[8,54]
Studies have also shown that some hormones released under stress cause a proliferation of certain bacteria such as Fusobacterium nucleate, therefore aggravating the severity of periodontal damage.[55]
Mannem and Chava showed significant association between the cortisol level and psychological stress levels recorded by demographic and subjective variables in the proforma. This could be due to deregulation of the immune system, mediated through the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary axis.[56]
The activation of this by means of stress might result in the release of an increased concentration of the corticotropin-releasing hormone from the hypothalamus, which in turn, may act on the anterior pituitary, resulting in the release of the adrenocorticotropic hormone (corticotropin). The

corticotropin may then act on the adrenal cortex enhancing the production and release of cortisol into the circulation, leading to unwanted effects throughout the body, such as suppression of the inflammatory response, modifying cytokine profiles, elevation of blood glucose levels, and alteration of certain growth factor levels.[57,58]

Breivik et al.[60] have shown stressful stimuli and extreme genetic differences in the hypothalamus-pituitary-adrenal axis structure in rats and their susceptibility to periodontal disease. These differences between individuals with high- and low-responding hypothalamus-pituitary-adrenal axis could be modulated by environmental factors.[52]

The periodontal repair process is also regulated by multiple growth factors, including the bFGF (basic fibroblast growth factor), which is the key factor in the regeneration of the periodontal ligament.[60] bFGF has multiple effects on cell proliferation, differentiation, and angiogenesis.[61] Animal studies have shown a link between stress, decreased bFGF, and the severity of periodontal disease.[62] Rats with artificially created periodontitis show a greater bone and attachment loss when subjected to stress.[63]

Individuals with an inadequate stress response also have a decreased response to nonsurgical periodontal treatments than other patients and therefore more severe periodontal diseases.[64] The 5-year clinical and microbiological follow-up of patients treated for early-stage periodontitis showed that periodontal disease evolves more rapidly in stressed patients.[50]

Lu et al.,[60] stated that this rapid evolution is because of the stimulation of the stress-induced ANS stimulation, which results in the release of neurotransmitters (catecholamine neurotransmitter, epinephrine). These neurotransmitters are capable of binding to α1- adrenergic (α1-AR) receptors present on the surface of periodontal cells, thus decreasing their biological activity and causing a massive release of inflammatory factors.[60]

So, stress via multiple mechanism has detrimental effect on the periodontal tissues leading to higher frequency and severity of the periodontal disease and stress reduction might be beneficial in prevention of periodontal disease.

CONCLUSION

Acute stress conditions are immune-enhancing, while chronic stress is immunosuppressive. Stress is associated with more severe periodontal disease as well as poorer healing responses to traditional periodontal therapy. Thus, stress should be assessed and managed properly, as it influences the periodontal tissue destruction, tissue healing, and periodontal therapy outcome.

Psychological stress is a risk factor for periodontal disease. Stress can also increase the severity of periodontal disease and decrease the effectiveness of treatments. When only the indirect action of stress on the periodontium was known (appearance of risk behaviors for periodontal-induced stress: smoking, poor food and oral hygiene), care of patients could be limited to educating patients about the consequences of these behaviors.

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