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PSYCHOLOGICAL STRESS AND ORAL DISEASES – A LINK ?

Little Mahendra¹, Ravi David Austin², Jaideep Mahendra³, S.Senthil Kumar⁴

¹Dept. Of Periodontology, Rajah Muthiah Dental College and Hospital, Annamalai University, Tamil Nadu

² Raja Muthiah Dental College and Hospital, Annamalai University, Chidambaram, Tamil Nadu

³Department of Periodontology, Meenakshi Ammal Dental College, Meenakshi Academy of Higher Education and Research, Chennai

⁴Dept. of Periodontology, Raja Muthiah Dental College and Hospital Annamalai University

E-mail of Corresponding Author: littlemahendra24@gmail.com

INTRODUCTION

Epidemiologic studies and clinical observations suggest that negative life events and psychological factors may contribute to an increased susceptibility to periodontal disease. Stress a term continually being redefined in the scientific study of disease and illness, is nevertheless a confirmed and important factor in the etiology and maintenance of many inflammatory diseases, including periodontal disease. stress is an attempt to understand how the body regulates itself to maintain smooth, adaptive and homeostatic functioning when confronted with disruptive endogenous or exogenous forces. Hippocrates thought of health as a harmonious balance of the elements comprising the quality of life while disease represented disruption or disharmony among those elements.

In the seventeenth century, Sydenham suggested that pathological states represented diseases of adaptation failure of the adaptive processes to restore wellbeing. Cannon elaborated how fight or flight mechanisms represented adaptive efforts by the body to re-with psychosocial stress, distress, and depression (7, 8).

When demands imposed by events exceed a person's ability to cope, a psychological stress response composed of negative cognitive and emotional state is elicited (9). Substantial literature

establish homeostasis, a term he introduced to describe a dynamic internal physiological equilibrium which the body sought to maintain along both physical and emotional dimensions.

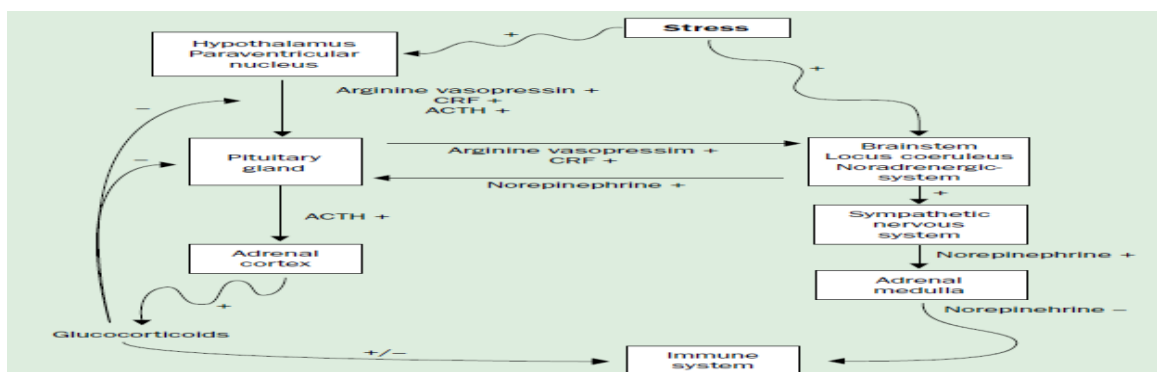
Hans Selye, the father of stress theory, describes stress as, "Everybody knows what it is, no one knows what it is. It is the nonspecific response of the body to any demand put upon it and stress is the spice of life" (1). While Stress is defined as a state induced by a stimulus that manifests itself by virtue of one's cognitive interpretation (2), the stimulus itself is considered a stressor. Accordingly, a stressor is any stimulus that evokes stress, whereas stress reactions are the observable consequences of the stressors. Several studies have demonstrated the relationship between psychological stress and diseases, from common cold (3) to cardiovascular disorders (4); from asthma (5) to rheumatoid arthritis (6). Periodontal disease being multifactorial with a complex interaction between bacterial infection and host responses, there is a reasonable amount of research indicating the association between periodontitis both in humans and animals support association between psychological stress and suppression of immune responses (10). While stress can directly influence immune function through the activation of neuro-endocrinal pathways that lead to release of hormones and neurotransmitters, such as

cortisol and catecholamines (11); it can also alter immune responses through the adoption of coping behaviors, such as smoking or drinking alcohol, which are known to compromise immunity (12).

Pathways between Stress and the Immune System:

How can stress affect the immune response? In 1936, Hans Selye defined stress physiologically as the state in which the sympatho-adreno-medullary system and the limbic-hypothalamic-pituitary-adrenal axis (HPA) are co-activated (13). A bidirectional communication pathway exists between the CNS and the immune system that modulates both the cellular and humoral immunity (14). First, stress induces the sympathetic fibers which descend from the brain into both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid tissues (15) to release a wide variety of substances that influence immune responses by binding to receptors on white blood cells (14, 15). Though all lymphocytes have adrenergic receptors, differential density and sensitivity of adrenergic receptors on lymphocytes may affect responsiveness to stress among cell subsets. For example, natural killer cells have both high-density and high affinity β_2 -adrenergic receptors, B cells have high

density but lower affinity, and T cells have the lowest density (16, 17). Second, the stress activates the hypothalamic-pituitary-adrenal axis, the sympathetic-adrenal-medullary axis or locus coeruleus-norepinephrine system, to induce secretion of adrenal hormones epinephrine, norepinephrine, and cortisol (13, 15); and also the pituitary hormones prolactin and growth hormone; and the brain peptides melatonin, β -endorphin, and enkephalin. These substances bind to specific receptors on white blood cells and have diverse regulatory effects on their distribution and function (18). Communication between the neuro-endocrine (hypothalamic-pituitary-adrenal) and immune inflammatory systems functions as a feedback loop that regulates the immune components of the inflammatory response. For example, a negative feed back loop functions such that activation of the immune system, associated with increases in levels of circulating cytokines (e.g. interleukin-1 and interleukin-6), increases activity in the corticotrophin releasing hormone/hypothalamic-pituitary-adrenal system yielding increased levels of circulating adreno-corticotrophic hormone and cortisol – major modulators of the stress system (19).



(FIGURE- 1) Pathways between Stress and the Immune System

Connection between Stress and Periodontitis:

Stress can be viewed as a process with both psychological and physiological components. Pollman and Dietrich (1979),

Moulton et al (1952) pointed out that stress may affect periodontium directly or indirectly (7). While the psychosocial stressors initiate cascade of events through the hypothalamic-pituitary-adrenal axis, the

autonomic nervous system and the central nervous system, it enhances the likelihood of infection and specifically, periodontal disease (8, 20). While cortisol has been called the hormone of stress, serum cortisol level increases during challenging or unpleasant situation (21, 22). Cortisol being an immunosuppressant influences not only the inflammatory cells, chemotaxis etc., but also the pro-inflammatory cytokines like interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1ra) (23, 24, 25). It is always being studied that stress causes activation of neuro-endocrinal pathways with release of cortisol, which in turn suppresses the immunity. And in such an environment the progression of periodontal infection by the pathogen is unhampered (7). Though this relation gives a link between stress and periodontal disease, this holds good for other inflammatory diseases as well. Though the periodontitis is initiated by the pathogens, the mediators of connective tissue breakdown are produced by host-derived enzymes called Matrix metalloproteinases (MMPs) (26). They are zinc and calcium dependent proteolytic enzymes responsible for remodeling and degradation of extracellular matrix (27). The homeostasis of extracellular matrices depends on the release of MMPs from cells such as fibroblasts and macrophages, and the presence of tissue inhibitors of matrix metalloproteinases (TIMPs), which are distributed widely in tissues and fluids (28). While the MMP gene family encodes nine or more metal-dependent endopeptidases, eight human MMPs have been cloned and sequenced, of which MMP-1 cleaves fibrillar collagen types I, II, and III (27) that constitute the gingival and periodontal connective tissue. While MMP-1 is implicated to play an important role in the

initiation of collagen degradation in periodontal disease, MMP-8 is thought to play an important role in periodontal tissue destruction (29).

Very few in-vitro studies, using exogenous steroids, have shown the effects of corticosteroids on the expression of MMPs and TIMPs in fibroblasts (30, 31). A study by Cury PR et al. (31) showed that hydrocortisone produced a dose-dependent regulation of MMP and TIMP expression, by significantly up-regulating mRNA expression of MMP-1, -2, -7, and -11 and TIMP-1 in human gingival fibroblasts. When *Pubmed* was searched for studies where endogenous cortisol, due to stress, induced expression of MMPs and TIMPs in fibroblasts, none were found.

Significant Reviews:

Several studies have demonstrated a relationship between psychological stress and inflammatory diseases such as rheumatoid arthritis, osteoarthritis etc., (20, 32, 33) and periodontitis (7, 8). *Gerard J. Linden et al.* (34) examined the association between occupational stress and the progression of periodontitis in employed adults and suggested that occupational stress may have a relationship to the progression of periodontitis. *Torbjørn Breivik et al.* (35) reviewed studies to find effects of emotional stress on immunity, gingivitis and periodontitis, and noted that emotional stressors and the nervous and neuro-endocrine responses to psychological stressors may modulate the immune response to bacteria, and thus expected stress to influence the progression and course of gingivitis and periodontitis. In a case-control study, *Moss et al.* (36) explored the association between social factors and adult periodontitis by comparing self-reported information for daily strains and

symptoms of depression. They found that an elevated Depression score may be a marker for social isolation, which could play a role in immune function during periods of social strain. *Croucher R et al.* (37) also in a case-control study investigated the role of life-events in periodontitis. The results showed that periodontitis was associated with the negative impact of life-events, the number of negative life-events, high levels of dental plaque, tobacco smoking and unemployment. *Genco RJ, Ho AW, Jeffrey Kopman et al.* (38), *Genco RJ, Ho AW, Grossi SG et al.* (8) evaluated the association of stress, distress, and coping behaviors with periodontal disease. They found that subjects with financial strain and inadequate coping had greater attachment and alveolar bone loss, in contrast to subjects with financial strain and good coping. Salivary cortisol levels were higher in a test group exhibiting severe periodontitis, as compared to a control group consisting of those with little or no periodontal disease. *Renate Deinzer et al.* (39, 40) analyzed the effects of academic stress on periodontal health of medical students and found that psychological stress was a significant risk factor for periodontal inflammation. *Elter et al.* (41) found that clinical depression may have a negative effect on periodontal treatment outcome in health maintenance organization (HMO) patients. Study by *Hugoson A, Ljungquist B, Breivik T* (42) revealed that, in addition to increased age, oral hygiene status, and smoking, the negative life events like, loss of a spouse (being a widow or widower) and the personality trait of exercising extreme external control were also associated with severe periodontal disease. *Aleksejunienė et al.* (43) tested the hypothesis that psychosocial stress and lifestyle are related

to periodontal status. Although the pathway between psychosocial stress and remaining periodontal support was not empirically supported, the researchers concluded that there was reason to believe that such link was likely. *Wimmer G et al.* (44) examined the influence of different coping behaviors on a non-surgical periodontal therapy and on the course of periodontal disease. They found patients with a defensive coping style had statistically significant poorer attachment values ($P=0.000$) after 2 years compared to patients with other coping behaviors. The number of sites with severe advanced CAL ($>5\text{mm}$) was significantly correlated with a suppressive coping style ($P=0.0001$). *Alexander Saletu et al.* (45) investigated the relationship between periodontitis and psychopathology utilizing psychometry, both observer-rating scales and self-rating scales. Partial correlation analyses between psychometric measures and dental variables revealed positive correlations of periodontal disease severity/CAL with the depression/anxiety, subjective well-being and complaints scores, and a negative correlation with quality of life. *R. Akhter et al.* (46) designed a study to identify possible relationship between stress and periodontal disease in residents of a rural Japan and found subjects who felt job stress and those who felt stress due to self health were more prone to have periodontal disease than were those who never or only rarely felt such stress. *Vettore et al.* (47) in a case-control study investigated the relationship of stress and anxiety with periodontal clinical characteristics. They found the frequency of moderate clinical attachment loss (4-6 mm) and moderate probing pocket depth (4-6 mm) significantly associated with higher trait anxiety scores, after adjusting for socioeconomic data and

cigarette consumption. J.B. Hilgert, F.N. Hugo D.R. Bandeira and M.C. Bozzetti (48) evaluated the extent and severity of chronic periodontitis and its association with the levels of salivary cortisol and the scores obtained with a stress questionnaire in a population aged 50 years. They found that the cortisol levels were positively associated with the extent and severity of Periodontitis. Fernando N. Hugo, Juliana B. Hilgert et al (49) evaluated the effects of stress, depression, and cortisol levels in dental plaque accumulation and gingivitis in a population of individuals aged ≥ 50 years. They found that stress was a significant risk indicator of elevated levels of plaque and gingivitis, whereas cortisol was a risk indicator of plaque. Amy E Rosania (50) did a cross-sectional pilot study to explore the associations between psychological factors, markers of periodontal disease, psychoneuro-immunologic variables, and behavior. She found that stress, depression, and salivary cortisol correlated with measures of periodontal disease. In addition, oral care neglect during periods of stress and depression was associated with loss of attachment and missing teeth.

CONCLUSION

Stress can be a risk factor for periodontitis, on one hand in stress the person's oral hygiene habits are altered causing accumulation of plaque and on the other it reduces the immunity of person through its endocrinal connections. Many studies have shown a positive relationship was observed between stress and periodontal disease, further representative research is needed to determine the impact of stress/psychological factors as risk factors for periodontal disease.

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