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REVIEW ARTICLE

The Relationship between Depression, Salivary Cortisol and Periodontal Diseases

Running Title: Depression and periodontal disease

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ABSTRACT

Periodontal disease is an immune-inflammatory response of tooth-supporting structures which progress will lead to loss of teeth. It is important to identify risk factors that influence the development of periodontal diseases. Different studies tried to determine the possible role of stress in the development of periodontitis. Psychological factors susceptible patients to gingivitis and periodontitis through two mechanisms. Behavioral mechanisms that relate to lifestyle and physiological factors that directly affect the host defense. In addition, activation of the hypothalamus-pituitary-adrenal (HPA) axis leads to the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus and as a result glucocorticoid from the adrenal cortex. The effects of stress on periodontal diseases can be related to the patients' approach to deal with the stress. Different strategies that patients use to cope with the stress lead to different responses of the hypothalamic-pituitary axis that control the cortisol secretion. The effect of coping mechanism on the patients' stress is one of the probable explanations for controversial results of studies about the relation of salivary cortisol level with stress. This study aims to review the relationship between depression, salivary cortisol, and periodontal diseases.

INTRODUCTION

Relation of psychological factors and periodontal diseases

Periodontal disease is an immunoinflammatory response of tooth-supporting structures which if progress will lead to loss of teeth [1]. Microorganisms and their toxins are known to be etiological factors of gingivitis and periodontitis but their presence itself is not capable of producing advanced diseases. This means that there are an individual response and an adaptation ability to have a certain amount of bacterial plaque with, a little or no progression of the disease [2]. The onset of periodontitis depends on various factors like poor oral hygiene, smoking, systemic diseases such as diabetes, cardiovascular diseases which act together to provide a suitable condition for the development of the disease [3]. It is important to identify risk factors that influence the development of periodontal diseases [4]. Figure 1 presents psychosocial stress, which influences on periodontal disease. on periodontal disease.

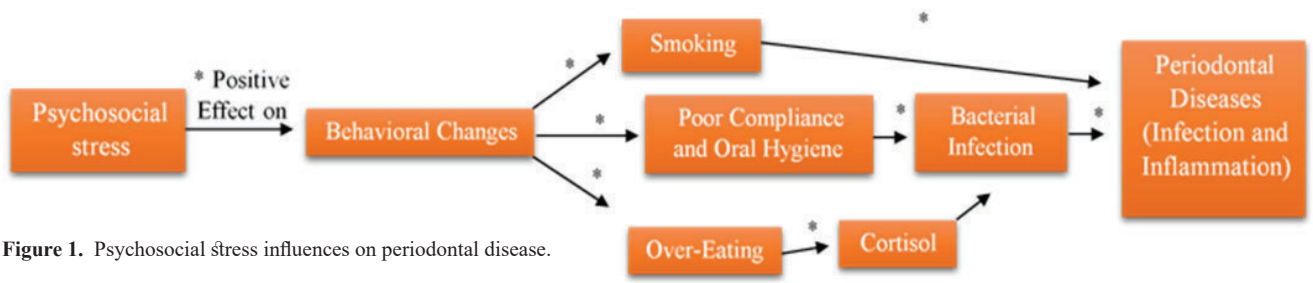

Figure 1. Psychosocial stress influences on periodontal disease.

Different studies tried to determine the possible role of stress in the development of periodontitis.

Different studies tried to determine the possible role of stress in the development of periodontitis. Stress was never considered as a certain cause of inflammatory disease [5]. Selye defined stress as a defense mechanism against threats

and forces on the body. The forces beyond the compensative mechanism of the body lead to disabling diseases. He explained that central mechanisms related to stress, activate the pituitary-adrenal axis. The appearance of symptoms related to diseases caused by chronic severe stress controlled by the autonomic nervous system. Most of these disease manifestations are the result of chronic inflammatory changes [6]. Relationship between different immune system components explained by Lersch and Dworkin. They showed the effect of stress and corticotropin-releasing hormone (CRH) on allergic reactions and inflammation by activation of glucocorticoids – catecholamines, peripheral secretion of CRH, and changes of key cytokines [7]. The relationship between neuroendocrine system, pituitary-adrenal axis, and inflammatory immune system adjusted by a feedback response [8]. Chrousos explained the interaction of stress and peripheral and central responses for maintenance of physiologic homeostasis [9]. Stress both in normal and increased level, according to specific cell receptors, have pro-inflammatory or anti-inflammatory effects on tissues. Since stress is an irreducible aspect of all human life and its role in different inflammatory diseases like rheumatoid arthritis and lupus erythematosus has been proved, so stress can probably lead to the development of periodontal diseases. Due to high pressure and physiological and social stress on the community, different studies tried to explain the relationship between stress and periodontitis. In these studies, different mechanisms are proposed for this probable relationship. These mechanisms include:

1-Endocrine and nervous changes caused by psychological stress affect the immune system.
2-Changes in oral hygiene behaviors.
3-Inappropriate habits like smoking.

These factors lead to a destructive cycle that worsens periodontal inflammation. Behavioral and emotional responses to the progressive process of periodontal disease, are another psychological and social stress [6]. Some studies supported this hypothesis that in patients with stress and anxiety, accumulation of plaque leads to a progression of periodontitis [10, 11]. Mousavi et al found a significant relationship between plaque index (PI) and the intensity of anxiety and depression [11]. Roberts et al and Moss et al designed in-vitro studies to evaluate the effect of catecholamines on subgingival microorganisms of bacterial plaque. They concluded that microorganisms from different microbial complexes show different growth responses to noradrenaline. However, the increased growth was seen in actinomyces naeslundii (%49/4), eikenella (%43/3), and campylobacter (%9/9). Changes in the components of subgingival plaque in response to stress, play an important role in the etiology and pathogenesis of periodontal diseases [12, 13]. A positive relationship was seen between PI with depression and anxiety [11]. Patients with depression and anxiety experience longer periods of gingival bleeding and are more referred to dentists [12]. Anxiety and depression cause physical disorders and lessen the quality of life that these conditions considered as a pathogenic factor for periodontitis [13]. Patients with a mean pocket depth of 3 mm and bleeding on probing of more than %25, have more anxiety and less confidence [14]. The analysis showed that anxiety has a positive relationship with pocket depth, while satisfaction of life is related to regular use of dental floss. Therefore, it concluded from the results of these studies that there is a relationship between psychological factors and periodontitis [14, 15]. Some authors show the positive relationship between depression and the number of missing teeth [16]. On the other hand, some studies could not provide strong evidence to support the hypothesis of a relationship between depression, anxiety, and disappointment with periodontitis [17, 18]. Lower sample size is one of the probable causes of non-conclusive results of these studies. Dentistry anxiety is considered a factor affecting oral health [19-21]. Eitner et al in an epidemiologic study, evaluated the prevalence of oral diseases pattern related to dentistry anxiety in young male soldiers. Due to the results of this study, anxious patients showed more caries but 'periodontal index of treatment needs' was not statistically different between the two groups [19]. Due to the direct effect of anxiety on oral health, anxiety should be considered in therapeutic protocols. Other studies evaluated the relation of self-control and self-confidence with oral hygiene behaviors in students, showed that oral and gingival health had a strong correlation with self-confidence level as a dependent variable [15]. Deinzer et al in their studies evaluated the effect of academic stressors on gingival inflammation. The results showed that gingival health in the experimental group who experienced a period of academic exams was significantly less than a control group who consists of similar students who hadn't exam in nearby past [22]. Stress causes changes in Interleukin 1 beta (IL-1β) level that lead to periodontal tissue destruction and students who had academic exams showed significantly higher levels of IL1β and gingivitis [22-24]. Also psychological and social stress leads to negligence of oral hygiene and as a result plaque accumulation [25]. Many types of research supported this hypothesis that early life experience and also other experiences during life are important determinative factors of gingivitis in teenagers [26]. and periodontitis in older patients. But there isn't strong evidence about the relation of psychological stress in children with gingivitis and periodontitis [27, 28]. Life problems, different levels of quality of life, job problems, anxiety, and depression have an effective role in periodontal diseases [26, 29-31]. Also a positive relation was found between periodontitis with age, the gender of males, smoking, and education [30]. The results of many clinical and epidemiologic studies showed that unpleasant experiences in life especially when lead to depression, are related to the progression of periodontal diseases [32, 33].

Relation of salivary cortisol and periodontal diseases

Saliva contains different biologic molecules. Steroid hormones can be found in saliva [34]. Cortisol is a glucocorticoid hormone secreted from adrenal glands and it has a diverse function in different tissues [35]. Cortisol secretion is very dependent on psychological factors like stress [36-38]. Cortisol has different effects on the surrounding tissues of the teeth and can be effective in the development and progression of periodontal diseases [39-41]. Figure 2 presents effects of stress and cortisol secretion on periodontal disease. Rosania et al showed that

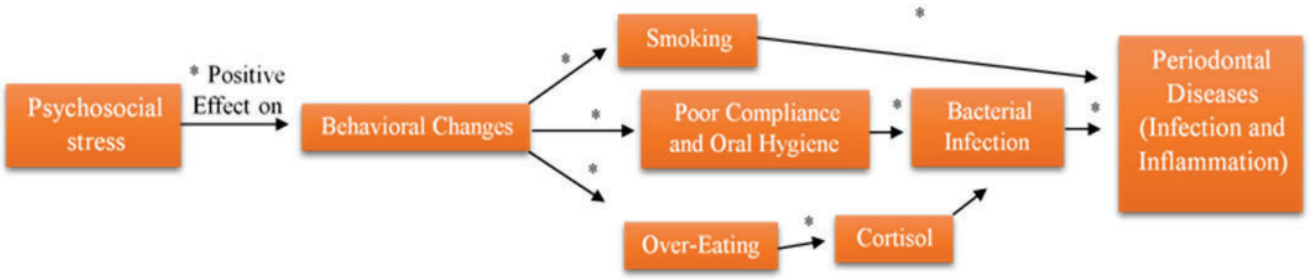

Figure 2. Effects of stress and cortisol secretion on periodontal disease. CNS=central nerveus system, ACTH=adrenocorticotropic hormone; PMN=polymorphonuclear leucocytes.

there is a direct relationship between stress and periodontitis. They concluded that this related to activation of hypothalamus-pituitary -adrenal axis that leads to the secretion of cortisol [42]. Many studies were published about the effect of physiologic, psychological, and pathologic factors on salivary cortisol and also its effects on the periodontium [43, 44]. Ishisaka et al in their study found that there is a relationship between cortisol level and clinical attachment loss (CAL) and pocket depth in a way that increased levels of this hormone led to the progression of periodontal diseases [40]. Hilgert et al achieved the same results that there is a direct relation between salivary cortisol level and severity of periodontal diseases. Nevertheless, in this study, the results of the Lipp stress questionnaire were not related to salivary cortisol level and periodontitis [42]. Ishisaka et al in another study in 2008 evaluated the relation between the severity of periodontitis based on clinical attachment loss and serum cortisol level in patients who had not a history of smoking. The results of this study showed that there is a statistically significant relation between cortisol level and periodontitis [45]. Hugo et al in a similar study achieved the same results. They introduced salivary cortisol level as an index for risk assessment of dental plaque formation [46]. However, due to Mengle's study, there was not a significant relationship between salivary cortisol level and periodontal diseases [47]. Johansen et al did not find a significant relation between salivary cortisol and periodontitis [48]. Several reasons can explain conflicting findings of these studies. In different studies, cortisol was measured from different samples including saliva and serum. In addition, patients with different forms of periodontal diseases were studied for example some studies used the patients under 30 years old that the most manifestation of periodontal diseases in this age group is gingivitis and aggressive periodontitis while in older patients' chronic periodontitis occurs. In Johanssen's study [48] all of the patients were female. Cortisol level is dependent on patients' stress [8, 49]. Stress has different effects including neglect of oral hygiene and inappropriate nutritional habits that lead to plaque accumulation [41]. Also from a pathophysiological point of view, cortisol changes the immune-inflammatory system and repair mechanisms in different tissues including periodontium that susceptible the patient to periodontal destruction [50]. Activation of the hypothalamus-pituitary-adrenal (HPA) axis leads to the secretion of CRH from the hypothalamus and as a result glucocorticoids from the adrenal cortex. Cortisol specifically affects the immune and inflammatory responses in different levels and inhibits the activation of cytokine cascades [44, 49, 51]. Cortisol restrains the immune responses related to T-cells. This inhibits the humoral immunity that leads to the growth of microorganisms activating the cellular immune responses [52]. T helper activates cytotoxic T cells and also activation of Th2 leads to the development of B-cells (precursor of plasma cells producing antibodies) [51]. Continuous activation of cellular immunity destroys periodontal tissues [53]. Salivary cortisol level has a significant relationship with CAL and bone loss in periodontal diseases [43, 46]. Also some authors showed the relation of salivary cortisol level with several missing teeth and pocket depth [40, 41].

Effects of coping mechanisms on periodontal diseases

The effects of stress on periodontal diseases can be related to the patients' approach to deal with the stress. Different strategies that patients use to cope with the stress lead to different responses of the hypothalamic-pituitary axis that control the cortisol secretion [42]. The usual psychological stress tests (Lipp and HAD) consider stress as an index that is based on the patient's understanding of the situation. The coping process is a strategy for declining the stress level. According to the coping strategy applied, the less the cortisol level was secreted from the HPA axis [49]. The effect of coping mechanism on the patients' stress is one of the probable explanations for controversial results of studies about the relation of salivary cortisol level with stress [50]. Genco et al in their study for the elimination of this confounding factor unified the study groups. 1426 patients in the age ranged between 25-40 years were studied. Salivary cortisol level, periodontal indices, and psychological factors (including life events, daily pressure, disputes, stress, and coping with problems) based on five different questionnaires were evaluated. In addition, the study groups were unified in terms of coping strategy. They found that there is a statistically significant relationship between the severity of periodontitis with salivary cortisol level and patient stress [8]. There is a reverse relation between the coping process for stress and cortisol secretion [49]. Studies about the factors affecting the epidemiology of periodontal diseases can help evaluate the role of stress, salivary cortisol, and coping mechanisms in periodontal diseases. It proposed that future studies use the psychological questionnaire that is calibrated to their society.

CONCLUSION

It was concluded from the results of these studies that psychological factors susceptible patients to gingivitis and periodontitis through two mechanisms. (A) Behavioral mechanisms that relate to lifestyle (like oral health neglection,

changes in diet, and smoking) and (B) Physiological factors that directly affect the host defense. It seems that there is a relationship between psychological condition, salivary cortisol level, and moderate to severe periodontitis. Studies strongly imply that inadequate coping and stress are leading risk indicators for periodontal disease. An adversarial impact on treatment results in patients with periodontitis has been confirmed by stress [54]. Also, stress negatively influences the immune system and sensitivity to oral infection which, experimental animal models gave further confirmation for this object, an example in in-vitro studies, social stress enhanced the production of IL-1β and TNF alpha in response to P. gingivalis lipopolysaccharide in CD11b+ spleen cells, in Bailey's study [55]. Stress and depression, including a complex interplay between coping strategies, genetic background, and environment, varying from moderate to severe state. There are important differences in the explanation of stress and depression, in evaluating relationships between different biological and clinical criteria. A need for secure standardized psychological analysis for quantifying and better defining most psychiatric disorders like depression and anxiety and the individual skill in cases to cope with adverse life events used to confusing preferences in periodontal tissue analysis and cause result misrepresentation at several stages. Although stress and periodontal disease showed a positive relationship, long-term studies are needed to determine the influence of stress and psychological factors as risk factors for periodontal disease and confirm this hypothesis.
Associations between common inflammatory periodontal diseases with various systemic diseases in the report of observational studies, make a large need on focusing on comprehensive and multicenter RCTs (randomized controlled trials) to examine the effect of periodontal treatment on the risk of systemic diseases, such as pulmonary and cardiovascular disease, unfavorable pregnancy outcomes and diabetes. Also needs for additional research in periodontology, including the advancement of biomarkers, investigation of effective community-based and population-based means of prevention, and further study to improve and examine more effective strategies for treatment that should be less invasive, more cost-effective, and have an advantage in tissue regeneration and recovery on the molecular level.

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AUTHOR CONTRIBUTIONS

All the authors contributed equally

CONFLICT OF INTERESTS

Authors of the current study present no conflict of interest in any stages of conducting this manuscript.

ETHICAL STANDARDS

These types of papers need no ethical standards

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