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STRESS AND INFLAMMATION IN PERIODONTAL DISEASE: A REVIEW OF THE BASIC BIOLOGICAL MECHANISMS

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ABSTRACT

Background Periodontitis is a multifactorial infectious disease influenced by a myriad of other conditions and factors amongst which, psychosocial stress has emerged as a potential risk indicator. In order to establish this link in a generally accepted theory, we need to better understand the physiological pathways of stress on immune response with implications in the periodontal disease.
Objective This article aims at synthesizing the current knowledge on the effect of the psychological factors on the periodontal disease and to provide an insight into the bidirectional links between stress-related disorders and periodontitis via psychoneuroimmunology studies.
Data sources A search was performed in 2 databases - PubMed and Google Scholar, supplemented by a manual search in peer-reviewed journals and cross-referenced with the articles accessed. The key terms used were: periodontal disease, periodontitis, stress, psychosocial stress, inflammation.
Study selection The inclusion criteria were all published potentially relevant articles on relationship between stress, inflammation and periodontitis on human and animal models. The exclusion criteria were articles with non-available full text and articles that were not written in English.
Data extraction Two reviewers extracted information regarding the quality and study characteristics independently. The studies were assessed for their methodology, statistical analysis, characteristics of the periodontal outcome measures, and psychological measurements.
Data synthesis Considerable evidence documents the link between psychosocial stress and periodontitis. This should redirect the attention of researchers and clinicians towards a multidisciplinary approach to periodontitis where psychosocial disturbances might be a key component into the rebus of disease progression and treatment results.

KEYWORDS

Periodontitis; Stress; Psychosocial Stress; Inflammation; Glucocorticoids.

1. INTRODUCTION

Periodontitis is a chronic inflammatory condition affecting the supporting tissues of the teeth, which results in loss of connective tissue and bone support and is a major cause of tooth loss in adults [1]. The advanced form of the disease affects a smaller part of the adult population, around 7% to 15% [2] while milder to moderate forms of the disease are found in approximately 50% of the population [3].
Its etiopathogenicity is complex with many factors interplaying, and due to this dynamic interrelated play, no isolated factor could solely explain the tissue destruction phenomenon [4]. The concepts of periodontal disease etiology have evolved towards understanding the role of the immune system and the inflammatory reaction in defining the host response. Those components do play an important role in the progression of the periodontal disease, which is further influenced by genetic and environmental risk factors [5]. Some of the genetic disorders may alter the host immune response which could predispose individuals to severe periodontal destruction. They might affect the production or function of polymor-

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phonuclears (PMN), which are known to play a pivotal role in the defense against bacteria. As a result, individuals suffering from neutropenia, agranulocytosis, Chédiak–Higashi syndrome exhibit more severe forms of periodontitis due to impaired immune response. In leukocyte adhesion deficiency (LAD) syndromes, neutrophils lack specific proteins which allow them to adhere to vessel walls and effectively migrate to the infection site. As a consequence, periodontal tissue destruction advances due to an impaired immune defense [6]. While this is clear evidence of how a deficient host response might affect periodontal disease, other conditions associated with exaggerated immune response are thought to also affect the disease.

In this light, psychosocial stress has emerged as a risk indicator with several studies documenting a positive relationship between psychosocial stress and forms of the periodontal disease [7].

As the scientific evidence is now unequivocal on the effects of psychological stress on immune systems and other systemic conditions through a network of pathways, it would be reasonable to also explore periodontitis and its relations to stress under this paradigm.

2. MATERIALS AND METHODS

A literature search was conducted for relevant studies addressing the issue of the relationship between stress, inflammation and periodontitis undertaken on human and animal models. *Data sources*: A search was performed in 2 databases-PubMed and Google Scholar, supplemented by a manual search in peer-reviewed journals and cross-referenced with the articles accessed. The key terms used were: periodontal disease, periodontitis, stress, psychosocial stress, inflammation. *Study selection: The inclusion criteria* were all published potentially relevant articles on relationship between stress, inflammation and periodontitis conducted on human and animal models. *The exclusion criteria* were articles with non-available full text and articles that were not written in English. Studies published in dental and medical journals were included together with a selection of studies from psychology literature. The studies were assessed for their methodology, statistical analysis, characteristics of the periodontal outcome measures, and psychological measurements.

The psychoneuroimmunology (PNI) studies were classified into intervention studies which evaluate the immune response after exposure to intervention (e.g. relaxation or hypnosis) and vulnerability studies which asses the functioning of the immune system in association with psychological vulnerability. These studies used inflammatory mediators or markers of inflammation to assess the immune response to stress, including mainly natural killer cell activity, cytokine production, glucorticoid levels and chatecolamine levels. The studies served to provide evidence on the association between immune response and stress components in a cellular and molecular level. The periodontology clinical studies were assessed based on the criteria used to define periodontal disease, adjustment for confounding factors, psychometric instruments, and the stress markers that were used to evaluate the stress component.

The articles included used parameters to define the periodontal disease, such as bleeding on probing, probing depth, recession level, attachment loss, alveolar bone loss and missing teeth.

The stress component was evaluated through psychometric instruments such as questionnaires or stress biomarkers such as salivary cortisol levels, crevicular interleukin levels, or urine corticosteroid levels.

3. RESULTS

The review identified the following noteworthy aspects related to stress, inflammation and periodontitis visible on human and animal models:

3.1. Stress and periodontium

Stress, can be defined as a set of emotions, triggered by an actual or perceived threat, giving rise to physiological and psychological changes [8]. As the psychological aspects get reflected in a set of behavioral reactions that redefine one's priorities, the oral hygiene habits change for the worse, new patterns of avoidance emerge together with substance abusive behaviors such as smoking and alcohol consumption [9-10]. On the other hand, physiological response that the body compiles in reaction to stressful stimuli which are perceived as threats, affects the immune system and alters the host defense as a consequence. Stress association to periodontal disease has been suggested for more than 50 years and the evidence in favor of this putative relation has been growing with different studies.

Necrotizing ulcerative gingivitis (NUG) was the first disease to be investigated in relation to stress, for its acute infectious etiology caused by bacteria that are non-pathogenic under normal oral conditions. Under these circumstances it would be reasonable to search for host defense alterations that would cause the outbreak [11].

In a study exploring the effect of stress on NUG, by measuring the corticosteroid levels in the patient's urine, the NUG cases did exhibit higher levels of the stress marker in the urine samples, yielding a positive correlation as hypothesized [12].

Earlier studies looking for a correlation between psychological stressful periods such as exam seasons in college students and the rate of NUG also showed a higher incidence of the disease in the sample [13].

The literature has provided robust evidence supporting the hypothesis of stress being a predisposing factor in NUG, through immunological mechanisms.

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3.2. Periodontium and other systemic conditions

Periodontitis as an oral inflammatory disease, can induce minor systemic inflammation through markers of inflammation like interleukin 6 (IL-6) and C-reactive protein and the spread of lipopolysaccharide (LPS) and flagellin from its causing bacteria into systemic circulation [5]. There is growing evidence that periodontitis induced inflammation can further lead to neuro-inflammation through the activation of microglia, which are brain immune cells [14].

The results of a recent clinical study conducted on over 60000 participants, support the theory of elevated systemic inflammation being associated with stress related disorders such as depression. The study revealed a significantly higher incidence rate of subsequent depression on periodontitis patients compared to the control group, suggesting that periodontitis may increase the risk of subsequent depression and can be considered an independent risk factor regardless of sex, age, and most comorbidities [15]. Furthermore, new clinical data support the evidence that increased systemic inflammation is associated with stress-disorders including depression. In a recent study, the authors measured the activity of microglia brain cells and showed that patients had increased levels of neuro-inflammation during depressive episodes when compared to a healthy control group. They concluded that there is incentive to evaluate anti-inflammatory therapies in major depressive disorder [16]. Besides this, studies conducted from a psychosocial perspective suggest that periodontitis could be contributing to stress related disorders through the psychosocial effects of halitosis, poor oral hygiene and edentulism. These could impact the patient's quality of life by inducing shame, social isolation and depression [17-18]. Alongside periodontitis putative effects on depression, there is significant longstanding evidence that it imposes a greater risk on systemic conditions such as cardiovascular disease or preterm delivery [19].

However, the link between periodontal disease and other systemic conditions seems to be bidirectional, as it is well documented that diabetes and osteoporosis increase the risk for periodontitis [20].

Analyzing these links, a common denominator has caught the attention of researchers. Considering the well-accepted fact that stress is related to cardiovascular disease, diabetes mellitus, preterm delivery, osteoporosis, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus through physiological or behavioral responses, this could point to stress as a common risk indicator for these conditions and periodontitis [9].

3.3. Pathophysiology of stress- biological mechanisms

Stress is one of the adaptive mechanisms that helps individuals navigate through challenges of all natures, making it compatible with survival forms of organisms. However, when there is a mismatch between the actual or perceived stimuli and one's stress response, neuroendocrine and biochemical changes that follow can lead to adverse effects on the proper functioning of the immune system [21-22]. In trying to understand the pathways through which stressors translate into a physiological response from the immune system, endocrine and nervous system, a growing body of evidence has been mounted through studies and experiments in the field of psychoneuroimmunology.

A synthesis of the main theories deriving from this work is presented below, aiming at elucidating the link with implications in periodontal disease.

According to a theoretical study by G. Slavich [23] "Two physiological pathways are responsible for converting social-environmental adversity into broad pro-inflammatory transcriptional programs. The first pathway involves the sympathetic nervous system (SNS), and the second pathway involves the hypothalamic–pituitary–adrenal (HPA) axis" [24].

3.4. Sympathetic nervous system

Stressful stimuli elicit a response from the autonomic nervous system, in the form of catecholamine secretion. The sympathetic branch of ANS responds by releasing norepinephrine into lymphoid organs and vasculature and perivascular tissues, altering the pro-inflammatory cytokine levels. The neurotransmitter then, reacts directly on the β-adrenergic receptors and provokes the due changes on the immune system components through signaling transcriptional messages on inflammation related genes [24-25].

In the presence of norepinephrine there is an increase in transcriptional activity on genes that are related to the production of interleukin 1 (IL1), tumor necrosis factor (TNF) and IL6 [26] with systemic pro-inflammatory effects. The role of the above mentioned cytokines in periodontitis has been studied and reviews concluded on their pro-inflammatory role and bone resorption activity in the presence of an infection [27]. Focusing on the periodontium, the catecholamine secretion in response to these stressful stimuli, as proposed on the SNS pathway, can have an influence on proteolytic enzymes with a tissue destructive potential, such as matrix metalloproteinases MMP [28].

3.5. Hypothalamic-pituitary-adrenal axis

A stressful stimuli of a less acute type is perceived by the brain and signals the hypothalamic/pituitary/adrenal (HPA) axis to release corticotropic-releasing hormone (CRH) from the hypothalamus which induces the release of adrenocorticorticotropic hormone (ACTH) from the pituitary gland and consecutively glucocorticoids from the adrenal cortex [29]. Glucocorticoids suppress the immune system functions by a number of mechanisms. They decrease the number of circulating lymphocytes, monocytes, and eosinophils; inhibit the functions of inflammatory cells through a myriad of actions such

as lowering the production of cytokines (interleukin [IL] IL-1, IL-2, IL-3, IL-6, tumor necrosis factor (TNF), interferon gamma. The cascade of the inflammation is further hindered due to an impeding of macrophage-antigen presentation and lack of lymphocyte differentiation into more specialized cells such as T-helper lymphocytes, B cells, cytotoxic lymphocytes and NK cells [30]. Glucocorticoids can further suppress the immune responses by impeding the functions of secretory IgA and IgG, and neutrophils all of which are important factors that build the host response towards infections by pathogenic bacteria. Under this altered defense response, periodontal infection can occur which may lead to tissue destruction by factors such as IL-1 and MMP and the direct effects of pathogenic periodontal microorganisms [9]. There is yet another mechanism that could be involved in elevated levels of inflammation that are related to HPA-axis response to stress.

3.6. Increased inflammation via glucocorticoid resistance - HPA-axis related

When a persistent secretion of glucocorticoids occurs, immune cells in response lower their sensitivity to it, developing what is known as glucocorticoid resistance [31]. In response to this phenomenon, HPA axis that is responsible for providing the "fight or flight" reaction to threatening stimuli of a social-environmental nature, can mount an abnormally high inflammatory response, when triggered frequently or chronically. Under conditions of prolonged actual or perceived threat, or possibly during acute stressors indicating social threat or physical danger, glucocorticoid resistance can develop, leading to excessive inflammation that increases a person's risk for several disorders [23]. A few other disorders such as anxiety, posttraumatic stress disorder, asthma, rheumatoid arthritis, cardiovascular disease, inflammatory bowel disease, autoimmune diseases, and some cancers, also show evidence of glucocorticoid resistance [32-34]. This, together with the growing body of evidence that periodontal disease is linked to the abovementioned conditions through several physiopathological processes, might suggest that glucocorticoid insensitivity happening under stressful environmental stimuli could be involved in the progression of periodontitis. Another pathway by which stress induced physiologic response modulates the immune system is the sensonic peptidergic nervous pathway, also known as "neurogenic inflammation" in which neuropeptides are released from sensory nerve fibers while stimulated by external stimuli [35 -36]. Research has provided evidence that the peripheral release of neuropeptides may promote various inflammatory processes [36].

4. DISCUSSION

Literature contains various studies conducted on humans aiming at evaluating the association between stress-driven behavioral changes and periodontal conditions, as presented below. It is now widely accepted that one of the mechanism through which stress is thought to exert its putative effect on the periodontal condition is the behavioral change in general, with stressful individuals inclined towards adopting harmful health behaviors including oral hygiene neglecting, smoking and poor compliance with dental care [9]. In a study conducted by Deinzer et al. [37] assessing the effect of academic stress on gingival inflammation, the crevicular levels of interleukin-beta were higher and the oral hygiene levels were poorer compared to the control group, indicating that academic stress was a risk factor for gingivitis. Emotional conditions that generate higher stress levels are also thought to affect the choice of a diet with an inclination towards softer foods with a high content of sugars and fat which facilitate the faster formation of plaque and enhance its adhering capacity to the teeth, affecting the periodontal health [38]. During periods of elevated stress individuals tend to increase smoking or even start it as a new habit. The harmful effects of smoking on oral health and particularly that of the periodontium, are well studied and established beyond doubts [39].

5. CONCLUSIONS

The present body of knowledge emerging from periodontology and psychoneuroimmunology interdisciplinary field has yielded strong evidence on the relation of stress and periodontitis.

The intriguing evidence of the effects of stress on the inflammatory conditions and periodontitis should guide researchers to explore its implications on the possible preventive measures, as well as treatment modalities.

Informed clinicians can then make better informed decisions and design treatment plans on patients that might include addressing psychological disturbances and referring them to specialists for an integrated care plan.

In a multifactorial disease such as periodontitis, there is a necessity for multidisciplinary attention and collaboration in considering the psychological status of the individual along other well-established etiological factors.

This approach would yield multiple benefits for the patient, with general health to be seen as a good balance between body and mind.

CONFLICT OF INTEREST

Authors declare no conflict of interest related to this manuscript.

AUTHORS CONTRIBUTION

OM: Data gathering, Data analysis, Data Interpretation, Manuscript drafting, RB: Data interpretation, Manuscript revision, BR: Data gathering, Data analysis.

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Questions

1. The advanced forms of periodontitis affect?

❑a. Over 50% of the world population;
❑b. More individuals than the milder forms of periodontitis;
❑c. Less than 15% of the world population;
❑d. Only immunocompromised patients.

2. In a study exploring the effect of stress on NUG, by measuring the corticosteroid levels in the patient's urine, NUG patients compared to the control group exhibited?

❑a. Lower levels of corticosteroids in their urine;
❑b. Higher levels of corticosteroid in their urine;
❑c. Same levels of corticosteroid in their urine;
❑d. No statistical difference between groups.

3. Glucocorticoids, suppress the immune system functions by?

❑a. Inhibiting the functions of inflammatory cells;
❑b. Increasing the production of cytokines;
❑c. Increasing the production of secretory IgA and IgG;
❑d. Increasing the number of NK cells.

4. In a study exploring the effects of academic stress on gingival inflammation, it was observed?

❑a. An increase in the crevicular levels of interleukin β;
❑b. A decrease in the crevicular levels of interleukin β
❑c. An improvement on oral hygiene;
❑d. No difference on inflammation markers between groups.