How Does Stress Influence Periodontitis?

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Abstract

Stress has long been considered to be a major contributor to the clinical manifestation of many diseases. In this review the role that stress might play in chronic periodontitis is considered. Sufficient evidence is available to support the notion that stress could be a contributing factor in periodontal destruction in the presence of periodontal pathogens in a susceptible individual.

Key words: stress, periodontitis, infection, wound healing, treatment response

Introduction

An association between a sound mind and a healthy body has been assumed for centuries; however, it wasn't until Selye's classic work in the 1930s and 1940s that a relationship was established (Boyapati and Wang, 2007). Seyle proposed that the hypothalamus-pituitary-adrenal cortex (HPA) axis response to stress was beneficial in the short term; however, prolonged stress was detrimental to the body by diminishing its ability to respond to a perceived challenge (Selye, 1998; originally 1936, Selye, 1956). This was defined as the general adaptation syndrome (GAS; Selye, 1956). More recent studies have concluded that prolonged stress can be harmful to the body, often resulting in depression (Breivik *et al.*, 1996; Croucher *et al.*, 1997; Ballieux, 1991; Genco *et al.*, 1999), thus substantiating Seyle's earlier work. In addition, it has been shown that individual variations in the way a person copes with a stressful event may be more important to health than the stressor itself (Breivik *et al.*, 1996; Genco *et al.*, 1999; Haffajee *et al.*, 1991).

Physiological definitions and effects of stress

Stress can be defined as the psychophysiological response of an organism to a perceived threat or challenge (Breivik *et al.*, 1996). Physiologically, the HPA is stimulated in response to stress. The anterior hypothalamus secretes corticotropin-releasing factor and arginine vasopressin, which act on the anterior pituitary gland. The pituitary gland then releases adrenocorticotrophic hormone, which acts on the adrenal cortex and increases production of glucocorticoid hormones (predominantly cortisol) and releases them into the bloodstream. Glucocorticoids have a wide range of effects within the body, including modifying the inflammatory response, altering cytokine profiles, increasing blood glucose levels (because of the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells), and altering levels of certain growth factors (Miller and O'Callaghan, 2002). Meanwhile, corticotropin-releasing factor, adrenocorticotrophic hormone and other neuroendocrine hormones contribute to mediation of the immune system.

The autonomic nervous system is also activated to release adrenaline from the adrenal medulla, and various neuropeptides (such as substance P) from sensory nerve fibers (Bartold *et al.*, 1994; Gyorfi *et al.*, 1994). The adrenal medulla acts like a modified sympathetic ganglion releasing noradrenaline and adrenaline directly into the bloodstream in response to stress. This response increases the ability of the body to perform vigorous muscle activity by increasing blood flow to active muscles while decreasing flow to organs that are not needed for rapid motor activity. Furthermore, this response also increases the rate of cellular metabolism throughout the body, increases blood glucose concentration (increases glycolysis in the liver and muscle), and increases the rate of blood coagulation. In addition, the sympathetic nervous system has a role in regulating immune cell activities (Glaser and Kiecolt-Glaser, 2005).

Under ideal circumstances these factors (the HPA and the sympathetic-adrenal-medullary [SAM] axis) function in harmony to enable the organism to ward off the stressful event and maintain homeostasis. In contrast, increased levels of cortisol and adrenaline that occur when stressful stimuli are prolonged can result in the deregulation of the immune system, leading to increased susceptibility to disease. Examples include chronic anxiety states and depression (Ballieux, 1991; Genco *et al.*, 1999; Glaser and Kiecolt-Glaser, 2005).

Modulation of the immune response by the central nervous system is mainly mediated by the pathways mentioned previously (the HPA axis and the autonomic

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nervous system), thereby provoking the release of pituitary and adrenal hormones. The majority of immune cells have receptors for one or more of the hormones that are associated with the HPA and SAM axes. Stress hormones may modulate the immune response through one of two pathways: directly, through binding of the hormone to its receptor at the surface of a cell; or indirectly – for example, by inducing dysregulation of the production of cytokines, such as interferon-γ (IFN-γ), interleukin-1 (IL-1), IL-2, IL-6 and tumour-necrosis factor (TNF) (Glaser and Kiecolt-Glaser, 2005). In addition, the communication between the central nervous system (CNS) and the immune system is bidirectional, such that the immune cell production of cytokines such as IL-1 can provide feedback and influence the production of corticotropin-releasing hormone (CRH) by the hypothalamus. Lymphocytes can also produce hormones such as adrenocorticotrophic hormone (ACTH), prolactin and growth hormone, while studies have shown that nerve fibers in the spleen and thymus deliver direct connections between the sympathetic nervous system and lymphoid organs (Bellinger *et al.*, 2001). Therefore, there are many pathways through which stress might influence immune function (Glaser and Kiecolt-Glaser, 2005).

Stress and depression have been shown to sensitize the inflammatory response, thereby producing heightened responsiveness to subsequent stressful events, as well as to antigen challenge (Glaser *et al.*, 2003; Maes *et al.*, 2001; Johnson *et al.*, 2002). For example, mild depressive symptoms have been associated with amplified and prolonged inflammatory responses. Following influenza vaccination of older adults, an increase in IL-6 (an important inducer of C-reactive protein in the liver) was observed in subjects who reported depressive symptoms prior to vaccination (Glaser *et al.*, 2003). These stress-related changes have broad implications for health, with increased levels of pro-inflammatory cytokines being linked to various age-related diseases and conditions (including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, frailty and functional decline) and to certain cancers, such as chronic lymphocytic leukaemia (Glaser and Kiecolt-Glaser, 2005).

In addition to the direct influence of one's psychological state on immune function, individuals under stress are more likely to have habits that are known to increase risk to their health, including poor sleep patterns, poor nutrition, less exercise and a greater tendency for substance abuse (Alati *et al.*, 2005; Hall *et al.*, 1993). Furthermore, an individual's stress levels may directly lead to negligence in performing oral hygiene practices, failure to seek dental care, altered food intake, and bruxism (Deinzer *et al.*, 2001; Moss *et al.*, 1996). These indirect effects would involve immune and endocrine consequences. For example, Sakki *et al.* (1995) evaluated 780 individuals from a Finnish community and reported that lifestyle characteristics were associated with periodontal health status. Individuals who smoked, had inadequate dietary habits, used alcohol or were physically inactive tended to be more irregular tooth brushers (Sakki *et al.*, 1995).

Depression has consistently been associated with smoking. In addition, a combination of both smoking and depression has been used in studies as an indicator of the level of stress that a subject may be under (Paperwalla *et al.*, 2004). As smoking is a well-established risk factor for periodontitis (Tomar and Asma, 2000), and depression has also been described as a risk factor for periodontal disease, then it could be expected that depression-related smoking could have a compounding adverse effect on periodontal disease. In addition, smoking has been shown to impair collagen synthesis and to increase matrix metalloproteinase-8 (MMP-8) levels in blister wounds, compared to non-smoker controls (Knuutinen *et al.*, 2002). Furthermore, cytokine production may also be influenced by smoking and stress, leading to an imbalance that disturbs the host-parasite relationship. Kamma *et al.* (2004) found that gingival crevicular fluid (GCF) IL-8 was increased in 65 patients with aggressive periodontitis with stress who smoked, presenting a statistically significant interaction with smoking status and aggressive periodontitis (Kamma *et al.*, 2004). The same group also found in another study that in periodontally diseased patients (20 with aggressive periodontitis, 20 with chronic periodontitis) GCF levels of IL-1β, IL-6 and IL-8 were significantly elevated, correlating to smoking and stress levels (Knuutinen *et al.*, 2002). Therefore, the authors concluded that the production of inflammatory cytokines in the presence of smoking and stress could have substantial clinical consequences.

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. 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 (Glaser and Kiecolt-Glaser, 2005). Stress has been suggested to alter the production of

proinflammatory cytokines that are important for wound healing, producing substantial delays in wound repair.

A well-referenced human study evaluating wound healing in chronically stressed individuals studied women experiencing long-term stress due to caring for a relative with Alzheimer's disease (Kiecolt-Glaser *et al.*, 1995). These women took 24% longer than socio-demographically matched controls to heal a small standardised dermal wound, while peripheral blood leukocytes (PBLs) IL-1β mRNA levels were down-regulated in response to lipopolysaccharide (LPS) stimulation compared with that of controls (Kiecolt-Glaser *et al.*, 1995). In another study evaluating students, wounds produced in the hard palate three days before important examinations healed an average of 40% more slowly than identical wounds made during summer holidays, while stimulated IL-1β production was also shown to be reduced (Marucha *et al.*, 1998). Broadbent and colleagues (2003) investigated the relationship between psychological stress and wound repair in patients following routine surgery. Forty-seven adults who were undergoing incision repair of inguinal herniae were given standardised questionnaires to assess levels of perceived stress before and after surgery. Wound healing was measured using levels of IL-1, IL-6 and MMP-9. As predicted, higher reported levels of stress prior to surgery were associated with reduced IL-1 and MMP-9 at the wound site (Broadbent *et al.*, 2003).

These findings have been confirmed in mouse models investigating the effect of stress on wound healing. Mice, subjected to restraint stress and to a standardized 3.5-mm full-thickness cutaneous punch-biopsy wound, healed on average 27% more slowly than control mice, and exhibited diminished leukocyte infiltration (Padgett *et al.*, 1998). Furthermore, the reduction of early cytokine production (IL-1α, IL-1β and TNF) at wound sites pre-treated with glucocorticoids has also been observed in mouse studies (Hubner *et al.*, 1996). Human studies have also validated these findings, showing a transient suppression of IL-1β, TNF and platelet-derived growth factor (PDGF) production with stress-induced glucocorticoid increase (DeRijk *et al.*, 1997). Altogether, these studies suggest that individuals under greater stress could be more prone to poorer wound healing following periodontal therapy.

Stress and infectious disease risk

The herpes simplex virus (HSV) pathogen is characterized by its ability to cause an acute infection at a peripheral site and to form a latent infection in the local sensory ganglia, with stress exacerbating HSV lytic infection. The effect of stress on the pathophysiology of HSV latent and lytic infections has been studied extensively in mouse models over the last 15 years, with studies showing convincing evidence that stress can enhance the development and severity of HSV infection, as well as suppress cytotoxic T lymphocyte (CTL) responses to HSV infection (Glaser and Kiecolt-Glaser, 2005). Human studies have confirmed that psychological stressors have been linked to more frequent recurrences of lesions in individuals who are latently infected with HSV-1 or HSV-2 (Luborsky *et al.*, 1976).

With the finding of abundant herpesvirus in periodontitis lesions and a world-wide prevalence of HSV-1 of 78% with aggressive periodontitis and 26% with chronic periodontitis, as well as a significant prevalence of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in patients with periodontitis, this suggests a potential viral contribution to the disease in some susceptible individuals (Slots, 2010b). Slots (2010) proposed a model for the development of periodontitis. This model suggests a sequential infectious process that proceeds from bacteria-herpesvirus-bacteria. Initially, bacteria in the dental biofilm induce gingivitis, which permits latent herpesviruses-infected macrophages, T lymphocytes and B lymphocytes to infiltrate the periodontium. Re-activation of the latent herpesviruses may occur spontaneously or during periods of decreased host defenses, such as drug-induced immunosuppression, concurrent infection, unusual and prolonged emotional stress, hormonal changes, or physical trauma. The reactivated herpesvirus infection results in a major release of pro-inflammatory cytokines including MMPs and impairment of antibody-mediated host defenses against exogenous bacterial species, causing overgrowth of pathogenic bacteria (Slots, 2010a). This provides a model to link stress and the reactivation of HSV with periodontitis.

With respect to periodontal pathogens, studies have shown that these organisms differ in growth responses to adrenaline and noradrenaline (Roberts *et al.*, 2002; Roberts *et al.*, 2005). Forty-three microbial organisms, normally found within the subgingival environment, were grown *in vitro* with iron, noradrenaline or *Escherichia coli* autoinducer-supplemented media. The results demonstrated large, significant increases in growth in cultures supplemented with iron, *E. coli* autoinducer and noradrenaline, compared with non-supplemented controls (Roberts *et al.*, 2005). The data suggested that catecholamines have an autoinducer mechanism that affects oral microorganisms, thus providing a further link between stress and periodontal disease. In addition, Nylander *et al.* (2008), in an *in vitro* model of platelet suspensions, demonstrated that *P. gingivalis* sensitises platelets to adrenaline, resulting in platelet aggregation. The authors of this study suggested that *P. gingivalis*-derived arg-specific gingipains activate a small number of protease-activating receptors (PARs) on the surface of the platelets. This leads to an unexpected calcium

mobilization and a marked aggregation response when adrenaline subsequently binds to α-adrenergic receptor. These results are consistent with the potential connection between periodontitis and stress as well as periodontitis and atherothrombosis (Beck *et al.*, 1998). Furthermore, this study describes a novel mechanism whereby periodontitis and stress may contribute to pathological platelet activation (Nylander *et al.*, 2008).

Evidence of the role of stress in periodontal disease
Animal studies

Animal studies have demonstrated a strong link between a depressed immune response and prolonged stress stimuli such as noise, isolation, increased population density, male–female proximity, handling by animal keepers, exposure to cold temperatures and deliberate physical trauma (Boyapati and Wang, 2007). Furthermore, Riley (1981) demonstrated that a single mildly stressful stimulus could cause significantly increased plasma cortisol levels, thereby adversely affecting the animal's immune response. Results from animal studies suggest that prolonged stress has adverse effects on periodontal tissues such as reduced alveolar crest bone height, increased probing depths, reduced clinical attachment levels, and delayed wound healing. These animal studies, therefore, provide evidence of a potential link between stress and a compromised immune response to poorer periodontal clinical outcomes (Boyapati and Wang, 2007).

Takada *et al.* (2004) presented a valuable murine model to study the effects of stress on periodontal healing. Ligature-induced periodontitis was created around the maxillary second molars in 100 male Wistar strain rats, which were randomly assigned to either stress or control groups. The rats in the stress group were restrained in flexible wire mesh for periods of 12 hours at a time. The animals were not allowed food or water in either experimental group. Stress was measured by monitoring blood glucose levels, corticosteroids and adrenaline. Atrophy of the thymus and spleen were also measured by histologic examination. Periodontal status was assessed by measuring alveolar bone changes utilizing digital subtraction radiography. The study concluded that animals in the restraint stress group demonstrated increased levels of periodontal bone loss. In a similar study, Benatti and co-workers examined the effects of immobilisation stress combined with nicotine administration on periodontal breakdown in 20 Wistar rats with ligature-induced periodontitis created around their mandibular molars. Compared with the study by Takada (2004), the results interestingly demonstrated that stress alone did not affect periodontitis; however, stress significantly enhanced the effect of nicotine on periodontal tissues (Benatti *et al.*, 2003).

In another study using ligature-induced periodontitis in Wistar rats, Huang *et al.* (2011) investigated the potential role of stress on the severity of periodontitis and the effect on hypoxia-inducible factor-1α in periodontal tissues. Sixty-six age-matched male Wistar rats were stressed by means of restraint, cold-water immersion, and cat shock, which were all applied randomly. The rats were sacrificed at weeks 1, 4, 6, and 8 of the experiment. The results demonstrated that attachment loss in the experimental periodontitis plus stress stimulation group was significantly higher than that of the experimental periodontitis (control) group at weeks 4, 6, and 8 ($p < 0.01$), and this group was associated with increased hypoxia-inducible factor-1α expression scores. The study concluded from these data that there is a correlation of periodontitis severity with psychological stress and periodontal tissue hypoxia.

It has been well established that periodontal disease is the result of an inappropriate host response to periodontal pathogens. Furthermore, it has been hypothesized that a dominant T helper 2 cell response increases susceptibility to infectious diseases and potentially a T helper 1 cell response may be protective against periodontitis. A T helper 2 cell response may facilitate a B-cell immune response and subsequently increase periodontal breakdown (Seymour *et al.,* 1996). In order to test this hypothesis, a study utilised genetically variable cortisol-responding rat strains, demonstrating that the high cortisone-responding rats generated a stronger T helper 2 cell response to infectious agents (*Trichinella spiralis*) with high IgE titers compared with rats with a relative hyporeactive HPA axis (Kavelaars *et al.*, 1997).

In 2000, Breivik *et al.*, in an experimental model of periodontitis, compared two different strains of Wistar rats: one that had a high corticosterone response to stress with another strain that was low corticosterone responding. The strain that produced high levels of corticosteroids had greater fiber and bone loss (histologically and radiographically) with ligature-induced periodontitis, suggesting that genetic factors may determine periodontal disease susceptibility (Breivik *et al.*, 2000).

Collating the data from the above studies, it has been suggested that chronic stress could cause a shift to a T helper 2 cell immune response, thereby leading to an exacerbation in periodontal disease. These findings are only preliminary and have yet to be confirmed in human studies.

Human studies

Necrotising ulcerative gingivitis and periodontitis (NUG and NUP) are the most frequently associated and well documented periodontal conditions associated with psychological stress (Monteiro da Silva *et al.*, 1998). Several authors have reported significantly elevated cortisol levels in individuals with NUG that returned to normal after recovery (Cohen-Cole *et al.*, 1983). This suggests involvement of the

neuroendocrine system, which can lead to lymphocytopenia and alterations in polymorphonuclear leukocyte function, as well as macrophage dysfunction (Cogen *et al.*, 1983). These immune complex changes have also been associated with blood dyscrasias, malnutrition, immunodeficiency conditions, and malignancy that together with other diseases have been associated with an increased incidence of NUG. Furthermore, smoking is very well established in this patient population (Murayama *et al.*, 1994), which is highly associated with periodontal disease and immunomodulation (Sopori and Kozak, 1998). Successful treatment of NUG is dependent on the removal of the bacterial microflora, even if the stressful events and/or smoking continue (Cohen-Cole *et al.*, 1983).

Human studies have also proposed a correlation between stressful life events and altered behavioural modifications with an increased incidence and severity of chronic periodontitis (Stanford and Rees, 2003). Denzier and colleagues conducted a series of studies investigating the oral effects of academic stress. They reported that bacterial plaque accumulation and gingival inflammation were significantly increased in medical students undergoing academic examinations when compared to control students who were not being tested. They also identified increased levels of IL-1β in crevicular fluid of stressed individuals and reduced salivary immunoglobulin A. In a split mouth design, students voluntarily neglected oral hygiene of two quadrants for 21 days, while maintaining good oral health in the remaining quadrants. Examination students showed significantly higher levels of IL-1β at both the experimental sites and sites of good oral hygiene, indicating that stress may affect periodontal health through suppressed immune system activity. In addition, the study found that this relationship was more pronounced when oral hygiene was not maintained (Deinzer *et al.*, 1998). These studies suggest that psychosocial stress induces significant behavioural changes in conjunction with alterations in host resistance and immunity.

In a case-control study of psychosocial factors and adult periodontitis, Moss *et al.* (1996) collected self-reported information about depression and level of daily strain from factors such as job, financial, family, and role-related issues, while identifying individuals with active periodontal disease according to specified criteria (Machtei *et al.*, 1992). The immune system response was evaluated by examining the levels of serum immunoglobulin G (IgG) antibody to three periodontal pathogens: *Bacteroides forsythus, Porphyromonas gingivalis* and *Actinobacillus (Aggregatibacter) actinomycetemcomitans*. The results of this study indicated that IgG to *B. forsythus* was significantly associated with elevated odds for being a periodontal disease case, but only among individuals who had higher scores for depression (Moss *et al.*, 1996). Furthermore, the odds for progression of disease at the one-year follow-up were significantly raised for those who were smokers at baseline. Interestingly, individuals who scored high on the self-reported information about depression at baseline also had increased odds for detecting IgG to *B. forsythus*. Furthermore, in a study to evaluate the general immune response in individuals with ongoing chronic stress (caring for a spouse with progressive dementia) compared to former caregivers or controls, lower antibody titres (IgG) were found in caregivers six months post-bacterial (pneumococcal pneumonia) vaccination (Glaser *et al.*, 2000). This study once again showed an altered host immune response to bacteria or bacterial vaccine in patients with ongoing stress or depression.

There is some debate in the literature as to whether a major life event can affect the health of the periodontium, and how this compares with effects of chronic stress (Genco *et al.*, 1999, Croucher *et al.*, 1997). Croucher *et al.* (1997) enrolled 100 clinical cases with at least one periodontal site with pocket depth exceeding 5 mm, and controls who had no periodontal pockets greater than 3 mm. This study found a significant relationship between major life events, as measured by the Holmes-Rahe Social Readjustment Rating Scale, and physical indicators of periodontal disease, such as plaque levels. The association remained significant after controlling for variables such as level of education and number of missing teeth, but not after controlling for smoking (Croucher *et al.*, 1997).

Monteiro da Silva *et al.* (1996) reported that depression and loneliness were more prevalent in patients with aggressive periodontitis than in those with either chronic periodontitis or good periodontal health. Becker *et al.* (1988) studied personality traits of periodontal patients who did or did not adhere to a periodontal maintenance program following therapy. They reported that the maintained group displayed a more positive image of themselves and had a lower incidence of stressful life events than those who did not adhere to the maintenance protocol (Becker *et al.*, 1988). Vettore and colleagues examined 79 patients for trait anxiety, and found that scores of trait anxiety were statistically associated with moderate clinical attachment loss and moderate probing depths, after adjusting for socioeconomic status (Vettore *et al.*, 2003). Axtelius *et al.* (1998) investigated stress levels in relation to periodontal therapy response. In a small study, individuals with more psychosocial stress and more passive-dependent personalities reported less of a response to periodontal therapy as compared with rest of the study participants (Axtelius *et al.*, 1998). However, this study examined a very small sample, and most large studies examining personality characteristics and periodontal disease have not shown any clear patterns to favour certain personality traits (LeResche and Dworkin, 2002). More recent studies have attempted to evaluate the roles of coping styles, cognitive factors and emotional characteristics rather

than specific personality traits in periodontal disease.

As mentioned earlier, other studies have evaluated the effects of poor coping skills and risk for periodontal disease. In a cross-sectional study, Hugoson *et al.* (2002) evaluated 298 dentate people between the ages of 50 and 80, finding that traumatic life events were correlated with increased risk for periodontal disease, especially in individuals with poorer coping mechanisms (external locus of control) versus individuals who had an internal locus of control, where they believed that that they could influence the progression of their disease (Hugoson *et al.*, 2002). Moreover, in a large cross-sectional study of 1,426 subjects, regression analysis revealed that financial strain was associated with greater attachment and alveolar bone loss among individuals (adjusting for age, gender and smoking) who were deemed to have inadequate coping behaviours (high emotion-focused coping) as compared to subjects with financial strain and better coping strategies (problem-based coping). Interestingly, the subjects under financial strain who had good coping skills had no more periodontal disease than those without financial strain (Genco *et al.*, 1999). In a more recent study, 80 patients with chronic periodontitis were treated non-surgically and maintained for two years. This study found that the healing responses of patients with defensive coping styles were significantly impaired, as indicated by poorer clinical attachment levels (Wimmer *et al.*, 2005). These studies support the concept that the effect of an individual's ability to cope with stress is more important for periodontal health and improved outcomes for periodontal therapy than the stressor itself.

Limitations on human studies evaluating periodontitis and psychosocial stress

There are inherent difficulties in assessing the relationship between physical disease status and the quality and quantity of psychosocial stress. A number of studies evaluating the relationship between periodontitis and psychosocial stress can be identified as "preliminary examinations" with limited sample size. In addition, there is high variability associated with self-reported measures of psychological stress as there is an overall lack of standardised methods to define and quantify stress. There is also a large degree of variability in the way periodontitis has been clinically defined. In addition, the type of studies that predominate in this area of investigation are case series and cross-sectional studies, precluding any cause-and-effect relationship. With these limitations it is difficult to make comparisons among studies and limits the ability to make conclusions about potential associations (LeResche and Dworkin, 2002).

Peruzzo *et al.* (2007) attempted to collate studies on the influence of stress and psychological factors on periodontal disease in a systematic review of the literature. Fourteen articles complied with specific selection criteria set out by the authors of the systematic review (seven case-control studies, six cross-sectional studies, and one prospective clinical trial) and were included in the analysis, from an original 48 articles. Eight of the fourteen studies showed a positive relationship between psychological factors and stress with periodontal disease (Peruzzo *et al.*, 2007). However, the authors did recognise the difficulties in combining or aligning data where different criteria were used to determine periodontal disease or health, psychological health and the assessment of levels of stress.

Conclusion

There is sufficient evidence to consider that stress could be a contributing factor in the process of periodontal destruction in the presence of periodontal pathogens in susceptible individuals. Current animal and human studies suggest that stress increases the severity of periodontal disease, as well as impairing the healing response to therapy. Stress is thought to result in poorer periodontal outcomes due to its immunosuppressive effects and potential for behaviour modification (for example, smoking). This suggests that assessing a patient's stress level during periodontal treatment may be valuable in providing another potential prognostic tool. Further studies using prospective clinical trials should be considered to elucidate further the role of stress in periodontitis.

References

Alati, R., Lawlor, D.A., Najman, J.M., Williams, G.M., Bor, W. and O'Callaghan, M. Is there really a 'J-shaped' curve in the association between alcohol consumption and symptoms of depression and anxiety? Findings from the Mater-University Study of Pregnancy and its outcomes. *Addiction* 2005; **100**:643-651.

Axtelius, B., Soderfeldt, B., Nilsson, A., Edwardsson, S. and Attstrom, R. Therapy-resistant periodontitis. Psychosocial characteristics. *Journal of Clinical Periodontology* 1998; **25**:482-491.

Ballieux, R.E. Impact of mental stress on the immune response. *Journal of Clinical Periodontology* 1991; **18**:427-430.

Bartold, P.M., Kylstra, A. and Lawson, R. Substance P: an immunohistochemical and biochemical study in human gingival tissues. A role for neurogenic inflammation? *Journal of Periodontology* 1994; **65**:1113-1121.

Beck, J.D., Offenbacher, S., Williams, R., Gibbs, P. and Garcia, R. Periodontitis: a risk factor for coronary heart disease? *Annals of Periodontology* 1998; **3**:127-141.

Becker, B.E., Karp, C.L., Becker, W. and Berg, L. Personality differences and stressful life events. Differences between treated periodontal patients with and without maintenance. *Journal of Clinical Periodontology* 1988; **15**:49-52.

Bellinger, D.L., Felten, D.L., Lorton, D. and Brouxhon, S. Effects of interleukin-2 on the expression of corticotropin-releasing hormone in nerves and lymphoid cells in secondary lymphoid organs from the Fischer 344 rat. *Journal of Neuroimmunology* 2001; **119**:37-50.

Benatti, B.B., Nogueira-Filho, G.R., Diniz, M.C., *et al.* Stress may enhance nicotine effects on periodontal tissues. An *in vivo*

study in rats. *Journal of Periodontal Research* 2003; **38**:351-353.

Boyapati, L. and Wang, H.L. The role of stress in periodontal disease and wound healing. *Periodontology 2000* 2007; **44**:195-210.

Breivik, T., Sluyter, F., Hof, M. and Cools, A. Differential susceptibility to periodontitis in genetically selected Wistar rat lines that differ in their behavioral and endocrinological response to stressors. *Behavior Genetics* 2000; **30**:123-130.

Breivik, T., Thrane, P.S., Murison, R. and Gjermo, P. Emotional stress effects on immunity, gingivitis and periodontitis. *European Journal of Oral Sciences* 1996; **104**:327-334.

Broadbent, E., Petrie, K.J., Alley, P.G. and Booth, R.J. Psychological stress impairs early wound repair following surgery. *Psychosomatic Medicine* 2003; **65**:865-869.

Cogen, R.B., Stevens, A.W., Jr., Cohen-Cole, S., Kirk, K. and Freeman, A. Leukocyte function in the etiology of acute necrotizing ulcerative gingivitis. *Journal of Periodontology* 1983; **54**:402-407.

Cohen-Cole, S.A., Cogen, R.B., Stevens, A.W., Jr., *et al.* Psychiatric, psychosocial, and endocrine correlates of acute necrotizing ulcerative gingivitis (trench mouth): a preliminary report. *Psychiatric Medicine* 1983; **1**:215-225.

Croucher, R., Marcenes, W.S., Torres, M.C., Hughes, F. and Sheiham, A. The relationship between life-events and periodontitis. A case-control study. *Journal of Clinical Periodontology* 1997; **24**:39-43.

Deinzer, R., Hilpert, D., Bach, K., Schawacht, M. and Herforth, A. Effects of academic stress on oral hygiene--a potential link between stress and plaque-associated disease? *Journal of Clinical Periodontology* 2001; **28**:459-464.

Deinzer, R., Ruttermann, S., Mobes, O. and Herforth, A. Increase in gingival inflammation under academic stress. *Journal of Clinical Periodontology* 1998; **25**:431-433.

DeRijk, R., Michelson, D., Karp, B., *et al.* Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha (TNF alpha) production in humans: high sensitivity of TNF alpha and resistance of IL-6. *Journal of Clinical Endocrinology and Metabolism* 1997; **82**:2182-2191.

Genco, R.J., Ho, A.W., Grossi, S.G., Dunford, R.G. and Tedesco, L.A. Relationship of stress, distress and inadequate coping behaviors to periodontal disease. *Journal of Periodontology* 1999; **70**:711-723.

Glaser, R. and Kiecolt-Glaser, J.K. Stress-induced immune dysfunction: implications for health. *Nature Reviews: Immunology* 2005; **5**:243-251.

Glaser, R., Robles, T.F., Sheridan, J., Malarkey, W.B. and Kiecolt-Glaser, J.K. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. *Archives General Psychiatry* 2003; **60**:1009-1014.

Glaser, R., Sheridan, J., Malarkey, W.B., MacCallum, R.C. and Kiecolt-Glaser, J.K. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosomatic Medicine* 2000; **62**:804-807.

Gyorfi, A., Fazekas, A., Suba, Z., Ender, F. and Rosivall, L. Neurogenic component in ligature-induced periodontitis in the rat. *Journal of Clinical Periodontology* 1994; **21**:601-605.

Haffajee, A.D., Socransky, S.S., Lindhe, J., *et al.* Clinical risk indicators for periodontal attachment loss. *Journal of Clinical Periodontology* 1991; **18**:117-125.

Hall, S.M., Munoz, R.F., Reus, V.I. and Sees, K.L. Nicotine, negative affect, and depression. *Journal of Consulting and Clinical Psychology* 1993; **61**:761-767.

Huang, S., Lu, F., Zhang, Z., Yang, X. and Chen, Y. The role of psychologic stress-induced hypoxia-inducible factor-1alpha in rat experimental periodontitis. *Journal of Periodontology* 2011; **82**:934-941.

Hubner, G., Brauchle, M., Smola, H., *et al.* Differential regulation of pro-inflammatory cytokines during wound healing in normal and glucocorticoid-treated mice. *Cytokine* 1996; **8**:548-556.

Hugoson, A., Ljungquist, B. and Breivik, T. The relationship of some negative events and psychological factors to periodontal disease in an adult Swedish population 50 to 80 years of age. *Journal of Clinical Periodontology* 2002; **29**:247-253.

Johnson, J.D., O'Connor, K.A., Deak, T., *et al.* Prior stressor exposure sensitizes LPS-induced cytokine production. *Brain, Behavior, and Immunity* 2002; **16**:461-476.

Kamma, J.J., Giannopoulou, C., Vasdekis, V.G. and Mombelli, A. Cytokine profile in gingival crevicular fluid of aggressive periodontitis: influence of smoking and stress. *Journal of Clinical Periodontology* 2004; **31**:894-902.

Kavelaars, A., Heijnen, C.J., Ellenbroek, B., van Loveren, H. and Cools, A. Apomorphine-susceptible and apomorphine-unsusceptible Wistar rats differ in their susceptibility to inflammatory and infectious diseases: a study on rats with group-specific differences in structure and reactivity of hypothalamic-pituitary-adrenal axis. *Journal of Neuroscience* 1997; **17**:2580-2584.

Kiecolt-Glaser, J.K., Marucha, P.T., Malarkey, W.B., Mercado, A.M. and Glaser, R. Slowing of wound healing by psychological stress. *Lancet* 1995; **346**:1194-1196.

Knuutinen, A., Kokkonen, N., Risteli, J., *et al.* Smoking affects collagen synthesis and extracellular matrix turnover in human skin. *British Journal of Dermatology* 2002; **146**:588-594.

LeResche, L. and Dworkin, S.F. The role of stress in inflammatory disease, including periodontal disease: review of concepts and current findings. *Periodontology 2000* 2002; **30**:91-103.

Luborsky, L., Mintz, J., Brightman, V.J. and Katcher, A.H. *Herpes simplex* virus and moods: a longitudinal study. *Journal of Psychosomatic Research* 1976; **20**:543-548.

Machtei, E.E., Christersson, L.A., Grossi, S.G., *et al.* Clinical criteria for the definition of "established periodontitis." *Journal of Periodontology* 1992; **63**:206-214.

Maes, M., Ombelet, W., De Jongh, R., Kenis, G. and Bosmans, E. The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system. *Journal of Affective Disorders* 2001; **63**:85-92.

Marucha, P.T., Kiecolt-Glaser, J.K. and Favagehi, M. Mucosal wound healing is impaired by examination stress. *Psychosomatic Medicine* 1998; **60**:362-365.

Miller, D.B. and O'Callaghan, J.P. Neuroendocrine aspects of the response to stress. *Metabolism* 2002; **51**:5-10.

Monteiro da Silva, A.M., Newman, H.N., Oakley, D.A. and O'Leary, R. Psychosocial factors, dental plaque levels and smoking in periodontitis patients. *Journal of Clinical Periodontology* 1998; **25**:517-523.

Monteiro da Silva, A.M., Oakley, D.A., Newman, H.N., Nohl, F.S. and Lloyd, H.M. Psychosocial factors and adult onset rapidly progressive periodontitis. *Journal of Clinical Periodontology* 1996; **23**:789-794.

Moss, M.E., Beck, J.D., Kaplan, B.H., *et al.* Exploratory case-control analysis of psychosocial factors and adult periodontitis. *Journal of Periodontology* 1996; **67**:1060-1069.

Murayama, Y., Kurihara, H., Nagai, A., Dompkowski, D. and Van Dyke, T.E. Acute necrotizing ulcerative gingivitis: risk factors involving host defense mechanisms. *Periodontology 2000* 1994; **6**:116-124.

Nylander, M., Lindahl, T.L., Bengtsson, T. and Grenegard, M. The periodontal pathogen *Porphyromonas gingivalis* sensitises human blood platelets to epinephrine. *Platelets* 2008; **19**:352-358.

Padgett, D.A., Marucha, P.T. and Sheridan, J.F. Restraint stress slows cutaneous wound healing in mice. *Brain, Behavior, and Immunity* 1998; **12**:64-73.

Paperwalla, K.N., Levin, T.T., Weiner, J. and Saravay, S.M. Smoking and depression. *Medical Clinics of North America* 2004; **88**:1483-1494, x-xi.

Peruzzo, D.C., Benatti, B.B., Ambrosano, G.M., *et al.* A systematic review of stress and psychological factors as possible risk

factors for periodontal disease. *Journal of Periodontology* 2007; **78**:1491-1504.

Riley, V. Psychoneuroendocrine influences on immunocompetence and neoplasia. *Science* 1981; **212**:1100-1109.

Roberts, A., Matthews, J.B., Socransky, S.S., *et al.* Stress and the periodontal diseases: effects of catecholamines on the growth of periodontal bacteria *in vitro*. *Oral Microbiology and Immunology* 2002; **17**:296-303.

Roberts, A., Matthews, J.B., Socransky, S.S., *et al.* Stress and the periodontal diseases: growth responses of periodontal bacteria to *Escherichia coli* stress-associated autoinducer and exogenous Fe. *Oral Microbiology and Immunology* 2005; **20**:147-153.

Sakki, T.K., Knuuttila, M.L., Vimpari, S.S. and Hartikainen, M.S. Association of lifestyle with periodontal health. *Community Dentistry and Oral Epidemiology* 1995; **23**:155-158.

Selye, H. What is stress? *Metabolism* 1956; **5**:525-530.

Selye, H. A syndrome produced by diverse nocuous agents. 1936. *Journal of Neuropsychiatry and Clinical Neurosciences* 1998; **10**:230-231.

Seymour, G.J., Gemmell, E., Kjeldsen, M., *et al.* Cellular immunity and hypersensitivity as components of periodontal destruction. *Oral Diseases* 1996; **2**:96-101.

Slots, J. Herpesviral-bacterial interactions in periodontal diseases. *Periodontology 2000* 2010a; **52**:117-140.

Slots, J. Human viruses in periodontitis. *Periodontology 2000* 2010b; **53**:89-110.

Sopori, M.L. and Kozak, W. Immunomodulatory effects of cigarette smoke. *Journal of Neuroimmunology* 1998; **83**:148-156.

Stanford, T.W. and Rees, T.D. Acquired immune suppression and other risk factors/indicators for periodontal disease progression. *Periodontology 2000* 2003; **32**:118-135.

Takada, T., Yoshinari, N., Sugiishi, S., *et al.* Effect of restraint stress on the progression of experimental periodontitis in rats. *Journal of Periodontology* 2004; **75**:306-315.

Tomar, S.L. and Asma, S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. J *Periodontology 2000*; **71**:743-751.

Vettore, M.V., Leao, A.T., Monteiro Da Silva, A.M., Quintanilha, R.S. and Lamarca, G.A. The relationship of stress and anxiety with chronic periodontitis. *Journal of Clinical Periodontology* 2003; **30**:394-402.

Wimmer, G., Kohldorfer, G., Mischak, I., Lorenzoni, M. and Kallus, K.W. Coping with stress: its influence on periodontal therapy. *Journal of Periodontology* 2005; **76**:90-98.