

**PSYCHOSOCIAL STRESS AS A RISK FACTOR FOR PERIODONTAL DISEASE**

**An Evidence-Based Report**

**Jaclyn Chin  
Rebecca Cohen  
Abid Hidayat  
Rachel Mills  
John Yun  
Sepehr Zahedi**

**Abstract**

Several risk factors that include oral hygiene, smoking, advancing age and some systemic diseases are involved in periodontal disease. This evidence-based investigation of the literature examined the relationship between another potential risk factor, psychosocial stress, and periodontal disease and set out to determine the extent of this association. This review was based on information gathered via electronic databases, references from the obtained articles and consultation with a graduate student at the University of Toronto's Department of Periodontology. From these sources, 18 articles were determined to be relevant and were critically appraised using a checklist for assessing causation. Of these 18 articles, 6 met the criteria of scoring above 7/13 and were included in this review. From these 6 relevant studies, there was one randomized controlled split-mouth trial and five case-control studies. The studies used either questionnaires or quantification of biological markers to evaluate stress and clinical examinations to evaluate the periodontal conditions. Overall, the findings were deemed to be inconclusive due to conflicting results drawn from the various studies. Future research with more stringent study designs is needed to make a decision about a definitive causal relationship between psychosocial stress and periodontal disease.

## Introduction

Periodontal disease is defined as an inflammatory process of the gingival tissues and/or periodontal membrane of the teeth, resulting in deep gingival sulci, and possibly producing periodontal pockets and supporting alveolar bone loss.<sup>1</sup> The prevalence of gingivitis among school children in the United States has ranged from 40%-60% in national surveys.<sup>2,3</sup> Likewise, although 15% of any population has been estimated to suffer from severe generalized periodontitis, moderate cases affect most adults.<sup>4,5</sup> With annual case management costs and treatment time required to manage all affected patients in the U.S. ranging up to 6 billion dollars and 35 million hours, respectively, periodontal disease remains a significant economic issue.<sup>6</sup> Physiologically, if left untreated it will undermine the supporting structures of the dentition, such as cementum, the periodontal ligament, and alveolar bone, ultimately causing tooth loss. In view of such concerns, it is important to identify risk factors that influence the development and progression of the disease.

It is widely recognized that several risk factors that include, but are not limited to, oral hygiene, smoking, advancing age and systemic diseases such as diabetes mellitus are involved.<sup>7</sup> The relationship between psychosocial stress and periodontal disease has also been analyzed. Selye, who was largely responsible for giving the term *stress* its current saliency in relation to the contest between health and disease, classified it as a “response state of the organism to forces acting simultaneously on the body, which if extensive lead to disease”.<sup>8</sup> Specifically, *psychosocial stress* is classified as particularly tense behavioural and emotional life events.<sup>7,9</sup> They have been found to influence host defenses exerting an immunosuppressive effect and affecting one’s vulnerability to

periodontal disease.<sup>7</sup> It is, therefore, necessary and worthwhile to understand these mechanisms in pursuit of analyzing the relationship between psychosocial stress and periodontal disease.

Several excellent reviews have sought to synthesize current concepts underlying interactions of behaviour (psychosocial stress), central nervous system (CNS), and cells of the immune system. Figure 1 summarizes a complex immuno-neuro-endocrine system that constitutes the hypothalamic-pituitary axis (HPA), primarily cortisol and cytokines such as interleukins (IL) as being responsible for mediating these interactions.<sup>8</sup> Inadequate coping when faced with psychosocial stress results in activation of CNS. It is proposed that acute cases use the prostaglandin pathway to initiate periodontal disease. As the infectious process becomes more chronic, inflammation occurs producing increased levels of cortisol, cytokines, and other modulators of stress, manifesting themselves as clinically evident periodontal disease.<sup>8</sup> Cortisol, the most important glucocorticoid, is a marker of stress and produced in the adrenal cortex.<sup>7</sup> Amongst its other roles, it has major immunosuppressive and anti-inflammatory effects, by inhibiting the production of lymphocytes and antibodies, and proliferation of fibroblasts in the inflammatory granulation tissue. Additionally, experimental studies have shown a pronounced inhibitory effect on the production of IL-12 in monocytes in the human blood. Since IL-12 regulates the differentiation of T-helper cells to Th-1 cells, stress has been found to induce a selective suppression of Th1 cells.<sup>10</sup> On the other hand, the role of IL-1 $\beta$  is extremely diverse including induction of collagenases and calcium resorption in the bone.<sup>11</sup> *In vitro* studies have found increased levels of IL-1 $\beta$  in the gingival crevicular fluid, gingival connective tissue, and blood serum of patients with periodontal

disease. Other studies have found that elevated levels of IL-1 $\beta$  indicate an incipient attachment loss and appropriate means of identifying active pockets.<sup>12</sup>

While dysregulation of the stress system is involved in periodontal disease, it is difficult to distinguish between cause and effect since the system is, to a large extent, non-specific and responds in similar ways to a wide variety of stressors. Therefore, based on current research, this report validates that while etiological mechanisms have not been fully experimentally recognized, psychosocial stress does modulate neuroendocrine and immune system activity linked to periodontal disease. The report will assess the strength of existing evidence in pursuit of studying the extent of relationship between psychosocial stress and periodontal disease.

## **Methods**

A systemic method was used to search, identify, and critically evaluate the pertinent studies.

### ***Search strategy***

Initial search and review of data bases led to the conclusion that the initial search terms – *stress* and *dental disease* – were too broad, contained many embedded questions, and lacked research concentration on the topic. Based on these results, however, it was evident that psychosocial stress and its relationship with periodontal disease had received significant attention in recent years. A systematic method was then established to search for these articles using the search terms *psychosocial stress* and *periodontal disease*.

First, the search involved the use of PubMed, Medline, as well as a Graduate Periodontology Consultation. They yielded 154, 48 (47 repeated), and 25 (24 repeated)

articles respectively for a total of 156 articles. Second, the reference lists of these articles were examined to identify and search for additional relevant studies and yielded 5 extra articles. All articles retrieved had to adhere to the following inclusion criteria:

- articles published between January 1969 and 2007
- articles published in English
- articles limited to studies on human subjects
- articles involving primary studies
- articles available through the University of Toronto Libraries in hardcopy or e-journal format

### ***Determination of relevance***

A total of 161 articles were reviewed for relevance to the topic. A four step rejection criteria was used. Articles were rejected at: title, abstract page, full copy, and then at critical appraisal. At the title stage, the relevance of study was determined. For instance, articles that dealt with specific population subtypes, such as only pregnant women, were not used. At this point, 72 out of 161 articles remained. At the abstract stage, all review articles and those that did not measure causality were excluded. The full copy of the 36 articles left after the abstract stage were then read to exclude any articles that were not based on randomized control trials (RCT), cohort, and case-control designs.

### ***Validity instrument***

Each of the 18 articles deemed relevant to the topic were independently critically appraised by two authors using the “checklist for assessing causation” developed by Leake (Table 1).<sup>13</sup> The highest possible score was 13. Any articles that scored less than 7 were excluded, leaving 6 final articles.

**Table 1 Checklist for assessing causation for each relevant article**<sup>13</sup>**General questions**

1. Was the study ethical?
2. Was a strong design used to assess causation or risk?
3. Were cases defined validly and reliably measured?
4. Were the risks validly and reliably measured?
5. For diseases with multi-factorial risks, were the risks assessed controlling for other factors and was the model's prediction power strong
6. Do the findings meet the tests for causation? (use questions below)

**Questions about causation related to noninfectious agents**

1. Did the "cause" precede the effect?
2. Was the estimate of risk beyond chance, and large?
3. Was there a dose-response relationship?
4. Was reversibility demonstrated?
5. Is the "cause" consistently observed in different times, places?
6. Is the "cause" biologically plausible?
7. Is the "cause" specific to that disease?
8. Is the "cause" analogous to another established disease/exposure?

**Results**

Of the six relevant studies, no one study scored higher than 9 out of 13 on the Checklist for Assessing Causation (Table 1).<sup>13</sup> This indicates that none of these studies were considered to present a strong level of evidence. The strongest evidence came from a randomized controlled trial and the five remaining studies were weaker designs and thus lower levels of evidence (Table 2).

The randomized controlled split-mouth trial by Deinzer *et al.* involved inducing experimental gingivitis and measuring levels of interleukin-1 $\beta$  in a group of students undergoing academic stress as compared to a non-stressed control group.<sup>14</sup> The experimental group was found to have significantly higher levels of the immunological mediator at the sites of experimental gingivitis than the control group and also higher levels at sites of experimental gingivitis as compared to sites of perfect oral hygiene. This not only showed a relationship between psychosocial stress and periodontal conditions, but suggested a synergistic relationship for the increase of interleukin-1 $\beta$  via

stress and presence of plaque. This study was well controlled and can be considered strong evidence (Table 2). Of the five remaining studies, one was also conducted as a randomized trial but for the question being considered here it is more appropriately classified as a case-control design. Trombelli *et al.* conducted a similar randomized split-mouth to that of Deinzer *et al.* which induced experimental gingivitis in subjects but measured stress differently.<sup>14,15</sup> The findings were not able to establish a relationship between stress and the periodontal effects. In this study questionnaires were used to gather information on personality traits, current level of stress, social support and life events over the previous year and these were then correlated to the periodontal conditions over a 21 day period (Table 2).

In an effort to resolve the discrepancy presented by using different measurements of stress, a study by Mengel *et al.* was examined in which levels of immunological mediators and glucocorticoids were related to subjective measures of stress in a case-control study to determine if a relationship existed.<sup>7</sup> Overall it was determined that not only did the stress levels not differ significantly between the cases and controls, but also that the immunological mediator and glucocorticoid levels did not positively correlate with the registered stress values as determined by questionnaire (Table 2).

Three additional case-control studies used a variety of questionnaires and clinical measures in an attempt to link psychosocial stress and periodontal disease, with inconsistent results. Two of the three studies, by Croucher *et al.* and Vettore *et al.*, found that the periodontally diseased cases were more likely to have increased stress as compared to the controls, while the third study by Locker & Leake failed to find a significant relationship.<sup>16,17,18</sup> The studies were analysed by similar methods, using

bivariate and multivariate analyses to examine relationships between a variety of factors and periodontal disease, however the study by Locker & Leake was the most thorough and will thus be considered stronger than the other two studies which were not as well controlled.<sup>17</sup> The study by Croucher *et al.* matched the cases and controls according to both age and sex and was considered to be stronger than the remaining study by Vettore *et al* (Table 2).<sup>16,18</sup>

**Table 2 Studies presenting evidence on the relationship between psychosocial stress and periodontal disease**

Authors (and study design)	Population	Definition of and measure of disease	Measure of stress	Control of confounding variables	Outcome and statistical significance	Critical appraisal	Conclusions and strength of evidence classification
Deinzer <i>et al.</i> <sup>14</sup> (randomized control trial)	26 participants (8 female, 18 male), aged 21-26 years old. All were medical students from the University of Dusseldorf.  Exclusion criteria included diseases of the immune system, HIV infection, diabetes, psychiatric diseases, drug abuse, nicotine consumption > 5 cigarettes per day, pregnancy, current orthodontic or dental treatments, untreated caries, defect fillings, inadequate dental restoration, probing depths > 3mm, major periodontal recessions, BOP at any site at beginning of study, use of Ca <sup>2+</sup> -blockers, anti-convulsants, immuno-stimulants, immuno-suppressives, antibiotics.	Split mouth trial where participants were randomly assigned to refrain from oral hygiene in 2 opposing quadrants to mimic gingivitis and to maintain perfect oral hygiene at all other sites.  Two trained examiners with good inter-rater reliabilities assessed plaque accumulation and gingivitis by PI and papillary bleeding index.	Half of the students experienced a stressful exam period, and the other half did not take part in the exam period.  ELISA technique used to measure IL-1 $\beta$ concentration in GCF collected using a periopaper inserted 1 mm into gingival crevice.	Controlled for oral hygiene by instructions on brushing and flossing and weekly assessments of plaque levels and BOP.  All subjects used standardized oral hygiene aids: medium-soft toothbrush, NaF toothpaste, and dental floss.  Student t-test used for independent measures, exclusion of outlying variables and Kolmogorov-Smirnov goodness of fit for each variable.	Stress induces an increase in IL-1 $\beta$ in gingival crevice with both perfect oral hygiene and with plaque accumulation, but the levels increase twice as much in the test group  Plaque induces an increase in IL-1 $\beta$  There is a synergistic effect on release of IL-1 $\beta$ from stress and plaque accumulation.	<ul style="list-style-type: none"> <li>• Small sample size for the study</li> <li>• Only researched one mediator involved in the stress response</li> <li>• Participants differ in stressor appraisal and ability to cope, and therefore likely differ in immunological stress response.</li> <li>• Papillary bleeding index too rough a measure to demonstrate stress-induced differences between groups.</li> </ul>	Stress and plaque accumulation increase IL-1 $\beta$ levels, appear to act synergistically and are therefore related to periodontal disease.  Two potential pathways for stress-periodontitis relationship: 1. Stress induced increase in IL-1 $\beta$ 2. Stress induced plaque accumulation that results in increased IL-1 $\beta$ .  Level I evidence Grade A Classification
Trombelli <i>et al.</i> <sup>15</sup> (case-control)	96 participants (50 females, 46 males), with mean age of 23.6 years.  Inclusion criteria included non-smokers and no conditions known to modify the inflammatory response.	Clinical measurements include GI, PI, GCF volume, angulated bleeding score and cumulative plaque exposure.  Two trained and calibrated examiners with good to excellent intra- and inter-examiner agreement carried out all measurements.	Self-administered questionnaires prior to trial including Hardiness scale and Courtauld Emotional Control Scale (personality traits), Visual Analogue Scale – Total Distress (subjective stress), Multidimensional Scale of Perceived Social Support (social support) and Life Experience Survey (life events).	Bivariate analysis and multiple regression analysis of relationship between clinical parameters and psychological measures.  Pearson's correlation test for parametric variables and Spearman's rank correlation test for the non-parametric variables.	Cumulative plaque exposure had a statistically significant positive relationship with GCF levels, even after controlling for psychosocial variables ( $p < 0.001$ ).  No other statistically significant relationships between clinical and psychological measures.	<ul style="list-style-type: none"> <li>• Randomized split mouth trial</li> <li>• Different individual perception and effect of stress taken into account by measuring personality traits and social support</li> <li>• Number of cases investigated not large enough for adequate conclusions to be drawn</li> <li>• Due to the nature of a controlled trial, the plaque deposits observed in the study may not be representative of actual oral hygiene.</li> </ul>	Differences in the current level of stress and psychosocial variables, indicative of stress susceptibility, do not account for variability in plaque accumulation and gingival inflammation.  Level II-2 Evidence Group D Classification

Authors (and study design)	Population	Definition of and measure of disease	Measure of stress	Control of confounding variables	Outcome and statistical significance	Critical appraisal	Conclusions and strength of evidence classification
Mengel <i>et al.</i> <sup>7</sup> (case-control)	80 participants (40 cases, 40 controls). Cases were treated and untreated AGP, untreated ALP and CGP. The treated AGP patients came from the Department of Periodontology recall program at Philipps-University, which is also where the CGP and ALP patients were referred and where the controls were recruited.  There was specific inclusion criteria for each case group and exclusion criteria that included systemic diseases, pregnancy, orthodontic treatment, myoarthropathies, extensive carious lesions, medication in the 6 months prior to the study, psychiatric disorders.	Clinical measurements included PI, GI, PPD, gingival recession, CAL and radiographs.  Calibrated examiner was used for all measurements.	Questionnaire given to patients including questions about psychosocial stress on the job and in the family, attitude towards life, smoking and classification into harmonious/content, neutral, tense/discontent.  Samples of peripheral blood taken to measure levels of IL-1 $\beta$ , IL-6, and cortisol using ELISA.	Control group and case group were age-sex matched.  Standard distribution checked with the Kolmogorov-Smirnov test, Mann-Whitney U-Wilcoxon test used to compare blood serum values and clinical parameters, Kruskal-Wallis test used to compare patient groups. All data were correlated using Spearman's rank correlation coefficient and significance levels determined with $\chi^2$ test.	Correlation between IL-1 $\beta$ and IL-6 in all AGP patients.  IL-6 was detected in all patients and controls with no significant differences except of increased levels in those with untreated AGP ( $p < 0.05$ ), and this was correlated with increased CAL.  No significant differences in cortisol levels between case and control groups.  Untreated AGP patients were found to be more pessimistic	<ul style="list-style-type: none"> <li>Questionnaire was not standardized to a representative sample</li> <li>Quality criteria such as objectivity, validity and reliability were not defined</li> <li>Number of patients investigated was too small for adequate conclusions to be drawn</li> <li>Use of sensitive ELISA</li> <li>Rigid exclusion criteria</li> <li>Combination of questionnaires with immunological mediators and glucocorticoids to assess correlation.</li> </ul>	No correlation between IL-1 $\beta$ , IL-6, cortisol and psychosocial stress with respect to pathogenesis of periodontal disease, although increased levels of IL-6 were detected in peripheral blood of patients with untreated AGP and correlated with CAL.  Level II-2 Evidence Group D Classification
Locker & Leake <sup>17</sup> (case-control)	624 participants, aged 50 years and over, living independently in 4 communities in Ontario, Canada (inner city, urban, rural, and northern).  Participants identified by telephone interview survey based on random digit dialing.	Arbitrary division into 2 groups, above and below upper 20 <sup>th</sup> percentile of distribution of mean attachment loss. Severe periodontitis was thus defined as mean attachment loss $\geq 3.83$ mm.  3 examiners trained and calibrated to a standard examiner.	Detailed personal interview.	Associations between mean attachment loss, proportion of sites with loss of 2 mm or more and a variety of socio-demographic, general health, behavioural, psychosocial and oral health variables were examined in bivariate analyses by use of t-tests, one-way analysis of variance, linear and logistic regression analyses.	Clinical attachment loss was greater in those that were: <ul style="list-style-type: none"> <li>- over 75 years old</li> <li>- lower education</li> <li>- lower income</li> <li>- living in Northern populations</li> <li>- were smokers</li> <li>- did not floss frequently</li> <li>- had fewer teeth</li> <li>- had untreated coronal and root decay</li> <li>- had emotional distress and diabetes (although this was not significant).</li> </ul>	<ul style="list-style-type: none"> <li>Life stress hard to measure and this study only used crude indicators</li> <li>Life stress only concerned last 6 months but periodontal disease reflected a life course</li> <li>Disease indicators used provide a historical record of periodontal breakdown and may bear little relationship to current disease status or future activity.</li> </ul>	Social and behavioural factors are associated with periodontal disease but there is no relationship between life stress and periodontal status.  Socio-demographic, general health, behavioural, and psychosocial variables are risk indicators for periodontal disease.  Level II-2 evidence Grade D Classification

Authors (and study design)	Population	Definition of and measure of disease	Measure of stress	Control of confounding variables	Outcome and statistical significance	Critical appraisal	Conclusions and strength of evidence classification
Croucher <i>et al.</i> <sup>16</sup> (case-control)	100 participants (68 female, 32 male), aged 30-59 years (case mean 42.3 years, control mean 42.4 years). Cases were attending the Periodontal Consultant Clinic and the controls were attending the Community Dental Care Unit, both at The Royal London Hospital Dental Institute.  Exclusion criteria included anyone that was pregnant, had systemic diseases or was taking medication for hypertension.	Test group: Presence of at least one site with PPD $\geq$ 5.5 mm.  Control group: No PPD $<$ 3 mm.  Clinical measurements included dental plaque, presence of pockets, and number of missing teeth.	1. Social Readjustment Rating Scale (SRRS) to measure number of life events in the last 12 months 2. Impact scale to measure meaning and desirability of each event, ranging from very positive (+2) to very negative (-2).	Collected behavioural and socio-demographic data and performed multiple conditional logistic regression analyses.  Behavioural data included toothbrushing, dental attendance frequency, history of smoking.  Socio-demographic data included age, marital status, ethnic origin, employment status, level of education, social class.	Conditional simple logistic regression analysis showed that periodontitis was correlated with negative impact of life events ( $p < 0.01$ ), number of negative life-events ( $p < 0.05$ ), high levels of dental plaque ( $p < 0.01$ ), tobacco smoking ( $p < 0.01$ ), being unemployed ( $p < 0.05$ ).  These relations remained statistically significant after adjusting for oral health behaviour and socio-demographic variables, but not tobacco smoking ( $p > 0.05$ ). Marital status became statistically significant ( $p < 0.05$ ) after adjusting for the other variables.	<ul style="list-style-type: none"> <li>• High response rate (89.2% for the test group, 84.8% for the control group) which minimizes selection bias</li> <li>• Cases and controls matched for age and sex</li> <li>• Findings do not establish a causal link, but it is more likely that life-events cause periodontitis than not</li> <li>• Although the association between tobacco smoking and periodontitis did not remain statistically significant after adjusting for other variables, it was still associated with other variables and overadjustment may have occurred</li> <li>• Standardized questionnaires used to measure stress</li> <li>• Only single measure of periodontitis used.</li> </ul>	Psychosocial factors; (impact of life events, employment and marital status, and dental plaque levels, and tobacco smoking) are associated with periodontitis.  Level II-2 evidence Grade B Classification

Authors (and study design)	Population	Definition of and measure of disease	Measure of stress	Control of confounding variables	Outcome and statistical significance	Critical appraisal	Conclusions and strength of evidence classification
Vettore <i>et al.</i> <sup>18</sup> (case-control)	<p>79 participants, aged 35-67 years (mean 46.9 years) attending the Clinical Dentistry Department of the Dental School of the Federal University of Rio de Janeiro.</p> <p>Inclusion criteria stated that all subjects should be &gt;35 years old, should have at least 50% of dental surfaces with PI<math>\geq</math>2.</p> <p>Exclusion criteria included any patients with ANUG, ANUP, systemic conditions associated with periodontal disease, taking medication related to periodontal alterations or psychotropic drugs, pregnancy, or periodontal therapy within the last 6 months.</p>	<p>Subjects were assigned to 3 groups in accordance with their PPD:</p> <p>1. Control group: less than 4 sites with PPD = 4.0mm</p> <p>2. Test group 1: at least 4 sites with PPD <math>\geq</math>4mm and <math>\leq</math>6mm</p> <p>3. Test group 2: at least 4 sites with PPD &gt;6mm.</p> <p>Clinical measurements which included PI, GI, CAL and PPD were measured at six sites per tooth.</p>	<p>1. Stress Symptoms Inventory (SSI) to detect whether a patient presents a clinical stress syndrome</p> <p>2. Social Readjustment Rating Scale (SRRS) used to measure stressful life events and their impacts in the last 12 months</p> <p>3. Spielberger State-Trait Anxiety Inventory to assess anxiety.</p>	<p>Socioeconomic data including age, gender, employment and marital status, education level, family income, smoking and alcohol consumption history were collected.</p> <p>The three groups were compared with respect to age by a Kruskal-Wallis test and <math>X^2</math> tests were performed for the remaining socioeconomic data.</p>	<p>GI, PPD and CAL had <math>p &lt; 0.01</math> for all 3 groups.</p> <p>No significant difference between the 3 groups with respect to percentage of clinical stress (SSI), SRRS scores and trait &amp; state anxiety scores.</p> <p>No significant differences between the 3 groups with respect to socioeconomic status parameters.</p> <p>Moderate CAL (4-6mm) and moderate PPD (4-6mm) were significantly associated with high anxiety trait scores after adjusting for socioeconomic data (<math>p &lt; 0.05</math>).</p>	<ul style="list-style-type: none"> <li>Used a variety of psychometric instruments that explain discrepant results found in other studies</li> <li>Lack of control for confounding variables for periodontal disease makes it hard to conclude on the effects of psychosocial factor over periodontitis.</li> <li>Periodontal disease is a chronic event and patients stress responses may reflect a recent event</li> <li>Criteria used to classify periodontal disease in different studies is usually not the same</li> <li>Variety of study methods applied in these investigations, the absence of a control group and lack of control for confounding variables for periodontal disease makes it hard to conclude on the effects of psychosocial factors over periodontitis</li> <li>Difficult to draw conclusions regarding plaque scores due to inclusion criteria of PI <math>\geq</math>2 on at least 50% of tooth surfaces.</li> </ul>	<p>Study demonstrated that individuals with high levels of trait anxiety were more prone to periodontal disease.</p> <p>Level II-2 Evidence Group B Classification</p>

PI = Plaque Index, GI = Gingival Index, PPD = Periodontal Probing Depth, CAL = Clinical Attachment Loss, GCF = Gingival Crevicular Fluid, ANUG = Acute Necrotizing Ulcerative Gingivitis, ANUP = Acute Necrotizing Ulcerative Periodontitis, CGP = Chronic Generalized Periodontitis, ALP = Acute Localized Periodontitis, IL = interleukin, ELISA = Enzyme-Linked ImmunoSorbent Assay.

## Discussion

Based on the literature review it can be seen that the evidence to support psychosocial stress as a risk factor for periodontal disease is relatively weak and inconclusive. There are a variety of reasons for this, which stem particularly from the fact that this question is one with variables that are difficult to define. First of all, there is no generally accepted method of measuring stress. Subjective measures are inherently unreliable and a well accepted biological measure has not yet been determined. There will always be significant variability between the way individuals perceive and cope with stress, and also in the way that it affects them.<sup>14</sup> The studies reviewed here have used biological markers like interleukin-1 $\beta$ , interleukin-6 and cortisol,<sup>14,7</sup> standardized questionnaires such as the Social Readjustment Rating Scale (SRRS), the Stress Symptom Inventory (SSI), the State-Trait Anxiety Inventory (STAI) and impact scales,<sup>16,18</sup> and non-standardized questionnaires<sup>17,7</sup> to measure stress. Secondly, it is difficult to define cases and controls since there is no widely accepted definition of severe periodontal disease.<sup>17</sup> The definition of periodontal disease varied between all studies examined ranging from having at least one site of probing depth > 5.5 mm, to being ranked in the upper 20<sup>th</sup> percentile for mean attachment loss.<sup>16,17</sup> It must also be recognized that while the measures of stress employed in all of the studies only considered a recent time period, up to 12 months prior to the beginning of the study, the measures of periodontal disease in actuality reflect the conditions over a lifetime and were not matched to the same time period.<sup>16,17,18</sup> Because so many differences exist in the way studies in the area of stress and periodontal disease are conducted it becomes difficult to effectively compare their results. Standardization of the definitions and

methods of measuring and quantifying both psychosocial stress and periodontal disease could help to resolve this complexity.

Strength of study design also plays a role. The highest levels of evidence are achieved with systematic reviews and randomized controlled trials, however for questions related to causation it is often more practical, appropriate and ethical to resort to weaker study designs, such as case-control and cohort studies.<sup>19</sup> The majority of studies examined here were case-control by design, of which an important disadvantage is that they are subject to recall bias.<sup>19</sup> Another significant variable is the difficulty in demonstrating a definitive causal relationship.<sup>14</sup> A properly designed clinical trial would be ideal, and it is defined as a design that will not find a statistically significant relationship when one does not exist and at the same time will not fail to show a statistically significant relationship when one does exist.<sup>20</sup> Particular implications for periodontal diseases that must be kept in mind are the need to define the disease, the determination of the number of measurements needed to be considered representative of the whole mouth, problems in measurement error, inter- and intra-observer variability and length of observation period.<sup>21</sup> A problem with experimental designs is simply due to the nature of the question being addressed here. Chronic conditions such as periodontal disease are often difficult to work with. In addition, the periodontal measures used are considering the outcome of disease and do not necessarily relate to current status of disease or the ability to predict future disease activity.<sup>17</sup>

The inconsistent results between studies can also be attributed to the fact that, except for the study by Locker and Leake, all groups worked with small sample sizes for which the results likely could not be generalized for the population at large.<sup>17</sup> The

Deinzer *et al.* study in particular only had 26 participants and the second largest study by Croucher *et al.* was only 100 participants.<sup>14,16</sup> With these small sample sizes the results become more unreliable and thus the evidence is weaker.

In the future some of these limitations could be avoided by implementing the following changes:

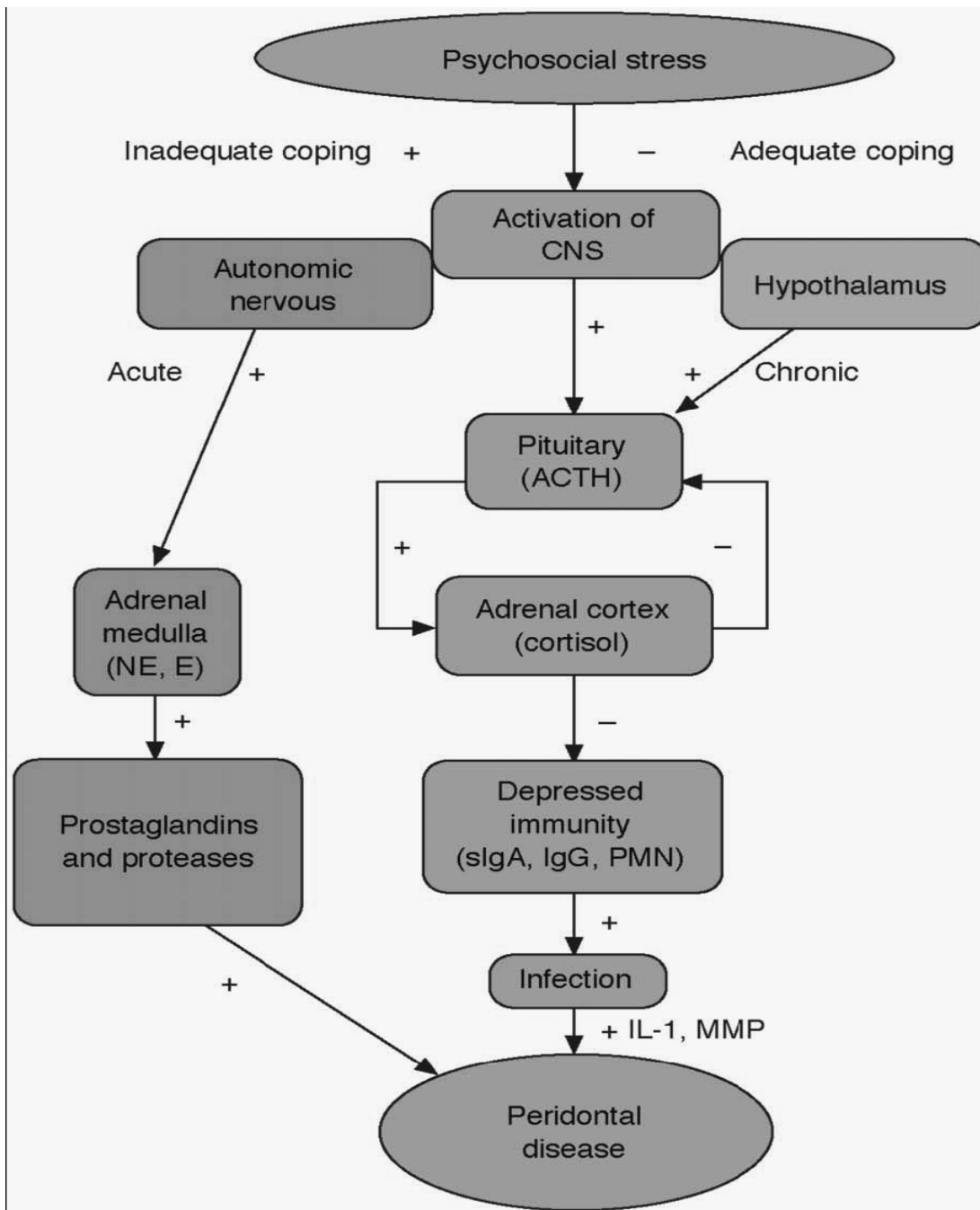
- Making use of stronger study designs, such as prospective longitudinal studies in which stress and periodontal status can be monitored concurrently.<sup>17</sup>
- Determination of a biological marker that correlates well with levels of stress and serves as an appropriate experimental measure of stress.
- As in the case of interleukin-1 $\beta$ , investigating whether there are compensating mechanisms within the tightly regulated bone formation-resorption system to accommodate for stress-induced increases in concentration.<sup>14</sup>
- Using larger sample sizes.
- Using longer periods of time over which to conduct the studies.

In conclusion, the evidence that is currently available is inconclusive and therefore does not establish a causal relationship between psychosocial stress and periodontal disease. Thus it cannot be considered a risk factor. For the present it is suggested that psychosocial stress may be a risk indicator for periodontal disease, but further research using stronger study designs is necessary to gain more conclusive causal evidence.

### **Acknowledgements**

The authors would like to thank Dr. John Mayhall for his assistance with this report.

## Tables and Figures



**Figure 1.** A physiological model for the effects of stress on periodontal diseases. CNS = central nervous system, CRH = corticotropic releasing hormone, ACTH = adrenocorticotrophic hormone, NE = norepinephrine, MMP = matrix metalloproteinase.<sup>8</sup>

## References

1. American Dental Association.  
[http://www.ada.org/public/topics/periodontal\\_diseases.asp](http://www.ada.org/public/topics/periodontal_diseases.asp). Accessed January 25, 2007.
2. Bhat M. Periodontal health of 14 to 17 year old US schoolchildren. *J Public Health Dent* 1991; 51:5-11.
3. U.S. Public Health Service, National Center for Health Statistics. Periodontal disease and oral hygiene among children, United States. Washington, DC: Government Printing Office; 1972. DHEW publication number (HSM) 72-1060, Series 11 No. 117.
4. Third National Health and Nutrition Examination Survey, 1988-94. Hyattsville, MD: Centers for Disease Control; 1997. Public use data file no. 7-0627.
5. Hugoson A, Laurell L, Lundgren D. Frequency distribution of individuals aged 20-70 years according to severity of periodontal disease experience in 1973 and 1983. *J Clin Periodontol* 1992; 19: 227-232.
6. Canadian Task Force for Preventive Health Care. [www.ctfphc.org/](http://www.ctfphc.org/) Accessed January 18, 2007.
7. Mengel R, Bacher M, Flores-de-Jacoby L. Interactions between stress, interleukin-1 $\beta$ , interleukin-6 and cortisol in periodontally diseased patients. *J Clin Periodontol* 2002; 29:1012-1022.
8. LeResche L and Dworkin SF. The role of stress in inflammatory disease, including periodontal disease: review of concepts and current findings. *J Clin Periodontol* 2001; 30:91-103.

9. Locker D. Stress in dental practice. Introduction to behavioural science and dentistry. New York: Routledge; 1989: 178-185.
10. Marshall, GD. Agarwal, SK., Ilyod, C, Cohen, L, Henninger, EM & Morris, GJ. Cytokine dysregulation associated with exam stress in healthy medical students. *Brain Behavioural Immunity*. 1998; 12: 297-307.
11. Dinarello, C. A. Biology of interleukin 1. *FASEB Journal*. 1988; 2:108-115.
12. Gemmell, E. and Seymour, G. J. Cytokines and prostaglandins in immune homeostasis and tissue destruction in periodontal disease. *Periodontology* 2000; 14: 112-143.
13. Leake JL. Community Dentistry Department of Biological and Diagnostic Sciences, Faculty of Dentistry, University of Toronto. Unpublished document. Course notes DEN 300Y 2006. The checklist was adapted from Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology - the essentials. 3<sup>rd</sup> ed. Baltimore: Williams and Wilkins, 1996; and Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach. EBM. 2<sup>nd</sup> ed. New York: Churchill Livingstone, 1997.
14. Deinzer R, Forster P, Fuck L, Herforth A, Stiller-Winkler R, Idel H. Increase of crevicular interleukin 1 $\beta$  under academic stress at experimental gingivitis sites and at sites of perfect oral hygiene. *J Clin Periodontol* 1999; 26:1-8.
15. Trombelli L, Scapoli C, Tatakis DN, Grassi L. Modulation of clinical expression of plaque-induced gingivitis: effects of personality traits, social support and stress. *J Clin Periodontol* 2005; 32:1143-1150.

16. Croucher R, Marcenes WS, Torres MCMB, Hughes WS, Sheiham A. The relationship between life-events and periodontitis: A case-control study. *J Clin Periodontol* 1997; 24:39-43.
17. Locker D, Leake JL. Risk indicators and risk markers for periodontal disease experience in older adults living independently in Ontario, Canada. *J Dent Res* 1993; 72(1):9-17.
18. Vettore MV, Leao ATT, Monteiro da Silva AM, Quintanilha RS, Lamarca GA. The relationship of stress and anxiety with chronic periodontitis. *J Clin Periodontol* 2003; 30: 94-402.
19. Sutherland S. Evidence-based dentistry: Part IV. Research designs and levels of evidence. *J Can Dent Assoc* 2001; 67:375-8.
20. Chilton NW, Fleiss JL. Design and analysis of plaque and gingivitis clinical trials. *J Clin Periodontol* 1986; 13:400-406.
21. Goldberg JD, Weiss AI, Koury KJ. Design of clinical trials for chronic diseases: implications for periodontal disease. *J Clin Periodontol* 1986; 13: 411-414.