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Epidemiological assessment of the association between chronic periodontitis and psychological distress/major depressive disorder in general and renal populations

Part I: Systematic review of association between periodontitis and depression

Part II: The association of periodontitis and psychological distress among hemodialysis patients

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APPROVAL PAGE

Master of Public Health Thesis

Epidemiological assessment of the association between chronic periodontitis and psychological distress/major depressive disorder in general and renal populations

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Dedication

I dedicate this work to my family. My wife, Soo, my daugher, Elyse, and my mother, Younghee and my late father, Henry Younghong Oh, who inspired me to set higher goals in my life.

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Part I

Systematic review of the association between periodontitis and depression

Introduction

Periodontitis is an inflammatory disease of infectious etiology, caused by bacterial biofilm adhering to the tooth surfaces, resulting in the loss of supporting periodontal tissues and ultimately, tooth loss (Pihlstrom et al., 2005) . Since Löe and co-workers demonstrated the development of gingivitis by withdrawing any oral hygiene effort, bacterial infection was known as the direct causative factor to destroy the periodontium (Loe et al., 1965). An animal study also demonstrated the association between plaque accumulation and development of periodontitis (Lindhe et al., 1975). However, this animal study found two out of eight dogs failed to develop periodontitis under the same conditions. A longitudinal human study also showed the different disease progression among the cohort without proper oral hygiene. Contrary to 11% of the cohort that did not develop periodontitis with poor oral hygiene, 8% exhibited rapid progression of periodontal attachment loss (Loe et al., 1986) . Plaque accumulation alone is not enough to trigger the onset of periodontal disease. The development of periodontitis and the progression of disease varies from patient to patient due to different individual host responses and adaptation (Kornman, 2008).

Numerous studies have demonstrated that there are non-oral risk factors that strongly associate with the development of periodontitis. Such known risk factors include smoking

(Ismail et al., 1983, Bergstrom, 1989, Bergstrom and Preber, 1994), diabetes mellitus (Safkan-Seppala and Ainamo, 1992, Seppala et al., 1993, Westfelt et al., 1996), genetics (Hart and Kornman, 1997, Michalowicz et al., 1991), human immunodeficiency virus (HIV) infection (Ndiaye et al., 1997, Robinson et al., 2000, Robinson et al., 1996), obesity (Khader et al., 2009, Kongstad et al., 2009, Saito et al., 2005), osteoporosis (Payne et al., 1999, Persson et al., 2002), chronic kidney disease (Borawski et al., 2007, Ioannidou et al., 2006), alcohol dependence (Amaral Cda et al., 2008, Novacek et al., 1995) and psychosocial factors (Breivik et al., 2006, Genco et al., 1999). There are numerous psychosocial domains that are associated with periodontitis. These include psychosocial stress (such as financial insecurity and poor coping strategy) (Genco et al., 1999); passive stress-coping strategies (Wimmer et al., 2005); traumatic life events (Hugoson et al., 2002); anxiety (Vettore et al., 2003) and depressive symptoms or depression (Elter et al., 1999, Johannsen et al., 2007, Monteiro da Silva et al., 1996).

Major depressive disorder (MDD), commonly known as clinical depression, is a mental disorder characterized by manifestation of symptoms such as feelings of sadness, guilt, worthlessness, nervousness, anxiety, fatigue, and/or irritability for at least 2 weeks (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 2000). Lifetime prevalence of MDD varies widely, from 3% in Japan to 17% in the United States. In most countries the prevalence of depression is between 8% and 12% (Andrade et al., 2003, Kessler et al., 2003). By the year 2020, depression will be the second leading illness in the world as projected by the World Health Organization (WHO) (Irwin and Miller, 2007). Rates of elevated depressive symptoms that do not meet MDD diagnostic criteria are also high.

Growing evidence indicates that emotional factors such as depression are associated with a wide range of medical conditions. For example, it has been known for numerous years that emotional stress has been identified as a significant risk factor for acute necrotizing ulcerative gingivitis (Melnick et al., 1988, Shannon et al., 1969). This association has since catalyzed additional research investigating the relationship between depression and severe periodontal disease. However this relationship remains inconclusive: Some demonstrate a strong association (da Silva et al., 1995, Monteiro da Silva et al., 1996), whereas other studies have failed to find such positive correlation between both chronic diseases (Castro et al., 2006, Persson et al., 2003, Solis et al., 2004).

Few biological and psychosocial hypotheses explaining the relationship between depression and periodontal health exist. Of those proposed mechanisms that attempt to associate psychosocial factors to periodontitis is the negligence of oral health care behavior (Kurer et al., 1995) . This hypothesis is based on the assumption that depressed patients neglect oral hygiene and professional regular dental care due to reduced motivation and interest. Depression is also associated with unhealthy habits such as smoking (Breslau et al., 1993, Hall et al., 1993) and alcohol dependence (Marmorstein, 2009, Zucker, 1986) – two factors that are also known to increase one's risk for chronic periodontitis.

Another potential mechanism whereby depression may contribute to the development and progression of disease is through alterations in host immune response. Among depressed patients, there is a disturbance in the major pathways between the brain and the

hypothalamic –pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) (Elenkov et al., 2000). Specifically, the HPA axis is a major part of the neuroendocrine system that controls reactions to stress and regulates many body processes, including the immune system, mood and emotions, sexuality, and energy storage and expenditure. Elevated levels of corticosteroid releasing hormone (CRH), which is a key neuropeptide involved in immune response to stress, were shown in depressed patients (Nemeroff et al., 1984). Studies have shown that elevated CRH among depressed patients caused significant reductions in natural killer cell (NK) activity (Irwin and Gillin, 1987, Irwin et al., 1987), and also decreases cellular and humoral immune responses with sympathetic effector mechanisms (Friedman and Irwin, 2001, Strausbaugh and Irwin, 1992). Depressed patients also have elevated levels of circulating catecholamines (Irwin et al., 1991) that result in the suppression of NK cells and cellular immune response (Sanders and Straub, 2002). Stimulation of proinflammatory cytokines is also found in depressed patients. In a recent meta-analysis by Zorrilla (Zorrilla et al., 2001), increased circulating IL-6 was associated with major depression. Increases of different types of circulating pro-inflammatory markers such as CRP and IL-6 were detected in depressed patients with other chronic medical conditions such as rheumatoid arthritis (Zautra et al., 2004), cancer (Musselman et al., 2001)and cardiovascular disease (Lesperance et al., 2004).

Although there is a plausible biological hypothesis that could link MDD and depressive symptoms to development and progression of periodontal disease, results from observational studies are conflicting. Therefore, the aim of this study is to systematically review the evidence of the association between periodontal disease and depression.

Material & Methods

I. Focused question

The focused questions to be addressed include: 1) 'In an adult population, is there any association between periodontitis and MDD/elevated depressive symptoms?' 2) ' In an adult population, is there any association between MDD/ elevated depressive symptoms and patients' oral hygiene?

II. Literature search

A systematic search of the literature on the association between depression and periodontal disease limited to the English language was conducted in Ovid MEDLINE from 1966 to Jan 2010 and the Cochrane Central Register of the Controlled Trials (CCTR). We also performed a complimentary manual search by screening the reference lists of selected literatures for the systematic review. The search strategy applied was to use the medical subject heading terms (MeSH) "Periodontal disease" and "Depression". In addition, the search for subheadings was carried out by exploding both major headings ("periodontal disease", "depression").

The design of Ovid MEDLINE electronic search was:

1. exp periodontal disease/
2. periodont$.mp. [mp=title, original titile, abstract, mesh subject heading]
3. 1 or 2
4. exp depression/
5. depress$.mp. [mp=title, original titile, abstract, mesh subject heading]
6. 4 or 5
7. 3 and 6
8. limit 7 to (English language and humans]

The design of the electronic search in The Cochrane Central Register of Controlled Trials (CCTR) was performed in advanced search in the Cochrane Library website (http://mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html). The terms "periodontal disease", "periodontitis", "periodontal", "depression", "depressive symptoms" were inserted in search form by using "Search All Text" function.

III. Inclusion criteria

Studies involving human subjects were included. Full-text publications involving randomized-controlled trials (RCTs), controlled clinical trials (CCTs), cohort studies, case control and cross-sectional studies were considered. Regarding the screening of depression or depressive symptoms, we included studies that defined depression based on

either the fourth edition Diagnostic and Statistical Manual of Mental Disorder (DSM) edition IV or higher, or questionnaire screening tools (Self-reported scale, or Observer-rating scale).

IV. Exclusion criteria

Case reports, case series, editorial letters and review articles were excluded. The studies that did not address any of the focused questions were excluded.

V. Validity assessment

Two reviewers (D. O. and E. I.) independently screened the titles, summaries and abstracts of the search results for possible inclusion. Full text of all citations that were likely to meet the inclusion criteria were retrieved and evaluated by two reviewers. The discrepancy in validity assessment was resolved by discussion.

VI. Data extraction & quality assessment

Two reviewers (D. O. and E. I.) independently performed the data extraction and methodological quality assessment for the included studies. A standardized abstraction sheet was utilized to extract the following data from each study: the primary author, year

of publication, study design, subject gender and age (mean and/or range) of subjects, periodontal parameters, oral hygiene parameters, the measure of depression, and study outcome. We contacted the primary authors to clarify the data if deemed necessary. Any disagreement between the two reviewers regarding data extraction and quality assessment was resolved by discussion.

Results

I. Study characteristics

The electronic search from OVID MEDLINE identified 249 published titles. The most recent electronic search was conducted on February 7, 2010. The literature search from the Cochrane Central Register of the Controlled Trials (CCTR) failed to identify any controlled studies on the topic. Based on the screening of the title and summary, 222 publications were excluded with the following reasons:

- No information on depression or psychological factors
- No information on periodontal disease or oral health
- Case report
- Case series
- Review article

The abstracts of the 27 articles were retrieved. Upon review, 18 full text articles were obtained for further evaluation, in which13 studies were ultimately selected. The reasons for exclusion after full text article review are shown in ***Table 1***. For the manual search, 754 citations from the bibliography of 13 full text articles were screened. After screening the titles, 37 articles were considered as potentially relevant publications to review the abstracts. After review of abstracts and results, 2 additional studies were included. Thus,

a total of 15 studies were selected in the present systematic review. Fifteen studies were classified into 2 categories for the purpose of the systematic review on 2 focused questions. Two studies (Johannsen et al., 2007, Saletu et al., 2005) were included in both categories. This study selection process is summarized in a flow diagram in ***Fig. 1***.

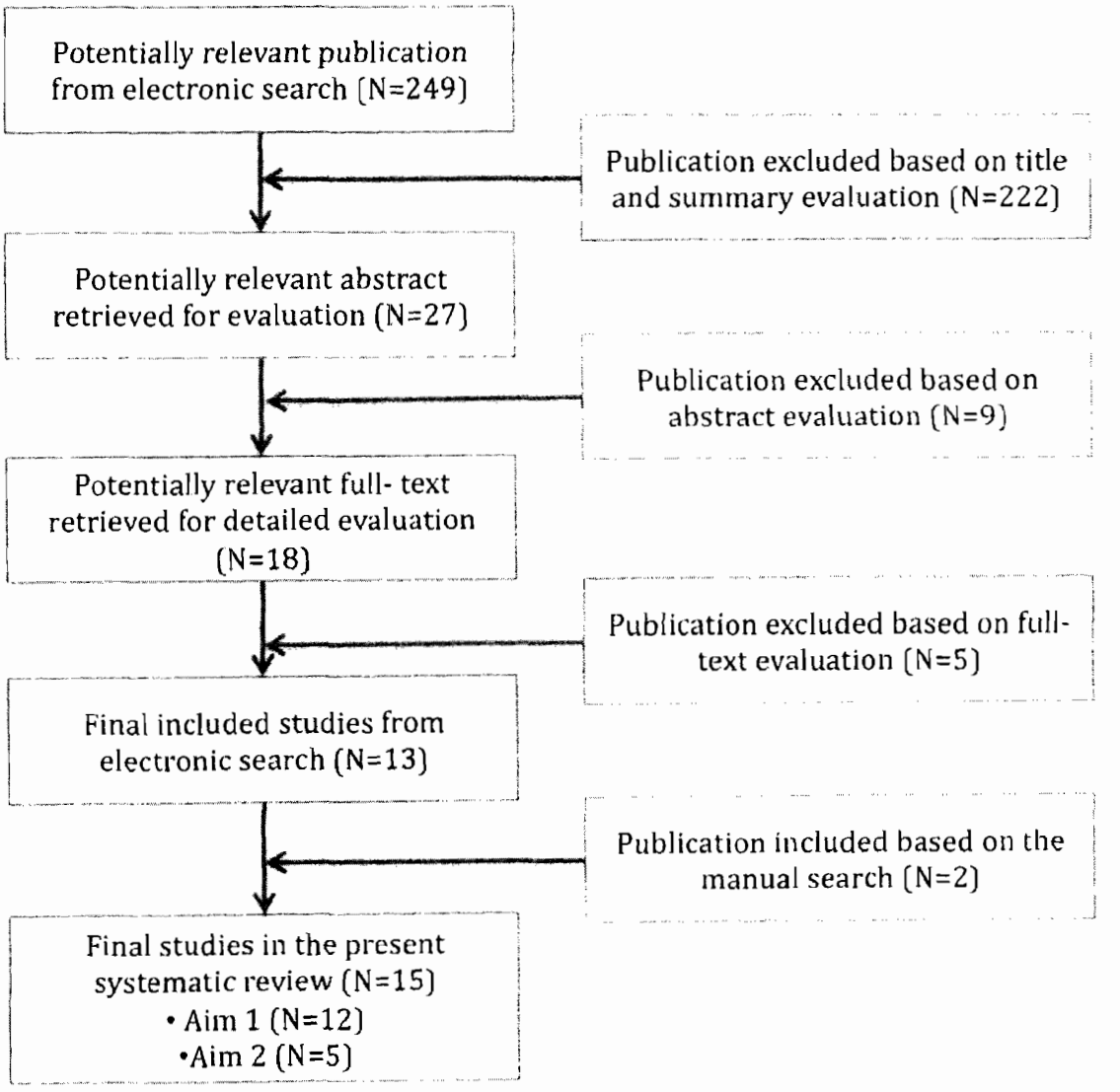

Fig. 1- Flow diagram of study selection

***Table* 1 – Reasons for exclusion after full text article review**

Ozcelik et al 2007(Ozcelik et al., 2007)	• Aimed to find the effect of periodontal treatment on quality of life • Patients with depressive symptoms were excluded from the study
Johanssen et al 2006 (Johannsen et al., 2006)	• Two studies (Johannsen et al., 2007, Johannsen et al., 2006) presented and analyzed results using same cohort
Kloostra et al 2006(Kloostra et al., 2006)	• Aimed to find the level of depressive symptoms after 2 different periodontal treatment modalities (Surgical VS Non-surgical therapy) • Missing data on prevalence of periodontitis/ oral hygiene related to depression
Merchant et al 2004(Merchant et al., 2003)	• Aimed to associate psychosocial factors and periodontitis • Missing measurement of depressive symptoms
Elter et al 2002(Elter et al., 2002)	• Aimed to associate depression and periodontal treatment outcome

Subordinate levels of studies were included such as case-control studies, cross-sectional studies, and cohort studies. No randomized-controlled studies were identified.

II. Qualitative data synthesis

Taken together, the studies included in this systematic review were heterogeneous with respect to the type of study design, population characteristic, measure of depression/depressive symptoms, and definition of periodontitis. Therefore, it was decided that a quantitative data synthesis leading to a meta-analysis was not appropriate. Instead, it was decided that the descriptive data of the selected studies should be presented in a systematic manner. The characteristics of the included studies are summarized in ***Table 2,3,4,5,6***.

III. Prevalence of periodontitis among individuals with MDD or elevated depressive symptoms

Twelve studies examined the association of periodontitis with depression and/or depressive symptoms. Specifically one study is a prospective cohort study (Elter et al., 1999), eight studies are cross-sectional studies (Anttila et al., 2001, Genco et al., 1999, Johannsen et al., 2007, Monteiro da Silva et al., 1996, Ng and Keung Leung, 2006,

Persson et al., 2003, Rosania et al., 2009, Solis et al., 2004), and three studies (Castro et al., 2006, Moss et al., 1996, Saletu et al., 2005) are case-control studies.

A positive correlation between periodontitis and MDD/elevated depressive symptoms was observed in seven out of twelve publications. Significant heterogeneities of the included studies include varying definitions of periodontitis, depression, variable assessment tools of MDD/depressive symptoms, and differing subject characteristics. Due to variation between studies, it is not possible to compare them in a formal quantitative meta-analysis. As such, each study will be discussed separately in this review.

1. The studies demonstrating a positive correlation between periodontitis and MDD/ elevated depressive symptoms

Seven out of twelve studies included in this review showed a positive correlation between periodontitis and MDD/elevated depressive symptoms.

1) Case control studies (*Table 2*)

Two case control studies demonstrated a positive association between periodontitis and depressive symptoms.

After selection of cases and controls among 1426 participants in the Erie County Risk Factor Study by the State University of New York at Buffalo, participants were followed at 1 year (cases) and 2 years (controls) (Moss et al., 1996). In their cross-sectional data, the higher score in social strain was found in the case group although the level of depressive symptoms was not significantly different after adjusting for age, sex and smoking status. Based on the data from this cross-sectional study, the longitudinal investigation was conducted to investigate factors that may predict extensive and severe periodontitis. The case group was stratified into two groups (more extensive disease activity versus less extensive disease activity as defined by the proportion of sites that developed more attachment loss (i.e. $\geq$ 8.7% of sites). In this prospective aspect of the study, they observed that individuals with elevated levels of antibody to *Bacteroides forsythus* and scored high on the depression scale showed more attachment loss.

Saletu and colleagues (Saletu et al., 2005) used both observer-rated and self-rated scales as tools to evaluate depressive symptoms in their case-control study. Using the observer-rate Hamilton Depression Scale (HAMD), significantly higher scores in periodontitis patients were observed. However, mean scores among both case and control groups were within normal limits. In self-rated scales, subjects with periodontitis demonstrated significantly higher scores compared to the control group after controlling for confounders such as age, smoking and degree of plaque accumulation. Moreover, partial correlation analysis (controlling for the effects of age, smoking and the Apporximal Plaque Index) revealed significant positive correlations between periodontal disease severity, clinical attachment loss and depressive symptoms determined by means of observer and self-rating scores.

Table 2 **– Case control studies demonstrating a positive correlation between periodontitis and MDD/ elevated depressive symptoms**

Author/ Year of publication	*Sample characteristics (Number,Gender,Age(Mean or Range))*	*Periodontal measurement*	*Definition of periodontitis*	*Measurement of depression or depressive symptoms*	*Result*
Moss et al 1996	Test: 72(F:49%) with periodontitis, Mean age 44.4 Control: 78(F:38%) with periodontally healthy, Mean age 43.8	PD,CAL,Serum Ab titer for 3 pathogen (*Bf,Pg,Aa*)	2 or more interproximal site from different teeth with CAL≥6mm and additional sites with PD≥5mm	Brief symptom Inventory (BSI) – Depression subscale (Self-report scale)	Positive association between periodontitis and *Bf* Aa, which is varied by depression score
Saletu et al 2005	Test: 40(F:40%) with periodontitis, Age(32-64) Control: 41(F:44%) without periodontitis, Age (23-70)	PD,CAL, Radiographic alveolar bone loss assessment by orthopantomogram	Periodontitis group was classified by 3 level based on radiography and mean CAL	Hamilton Depression Scale (HAMD) (Observer-rating scale), Zung Self-rating Depression Scale (SDS) (Self-rating scale)	Subjects with periodontitis showed significantly higher self-rated & observer-rated score

Aa=A.actionmycetemcomitans, Ab=Antibody, *Bf=B.forsythus,* CAL= Clinical Attachment Loss, F=Female, PD= Probing Pocket Depth, *Pg=P.gingivalis*

2) Cross-sectional studies (*Table 3*)

The following four studies are cross-sectional studies showing positive correlations between periodontitis and MDD/elevated depressive symptoms.

Genco and colleagues (Genco et al., 1999) conducted a cross-sectional study of 1426 subjects from the Erie County Risk Factor Study to investigate the effect of psychosocial factors on periodontal disease severity in a large adult population-based sample. Considering depression was evaluated on a self-reported scale, Cronbach's alpha was used to test reliability of subject's responses and internal consistency of the subscale of Brief Symptom Inventory. High Cronbach coefficients (i.e. high reliability) were recorded for all the subscales including the depression subscale in Brief Symptom Inventory. Subjects with different levels of clinical attachment level (CAL) and radiographic interproximal alveolar crestal bone level (ACH) showed similar mean depression scores. However, ordinal logistic regression analysis using CAL as a dependent variable demonstrated that an increase in attachment loss was significantly associated with depression with an odds ratio (OR) of 1.51. Other variables, such as age, heavy or moderate smoking, *Bacteroides forsythus,* and diabetes showed a higher OR than depression. However the weakness of this study is that the interpretation of the results focused on depression and failed to consider the most important risk factors. Interestingly, this study showed that periodontal status could be modified by coping behavior. More specifically, the subjects with problem-based coping behavior compared to subjects with emotion-focused coping showed less periodontal destruction even during periods of high levels of distress.

Another large-population based cross-sectional study was published with the population in Hong Kong, China (Ng and Keung Leung, 2006). The study design was similar to that of a study by Genco and colleagues (Genco et al., 1999) except that the psychological evaluation tool and method of sample recruitment differed (mainly non-regular attendees from 3 private dental clinics). Compared to the periodontally healthy samples, subjects with more advanced periodontitis as measured by attachment loss showed significantly more severe symptoms of depression with an odds ratio of 1.41(95% confidence interval (CI): 1.17-2.78). More importantly, other predictors including smoking, diabetes, and age were found to be more significant in the regression model, compared to depression. They also observed that people with problem-focused coping behavior presented less clinical attachment loss. Depression was measured with a subscale of a long questionnaire as part of psychological exam. It is important to note that subjects of this study complained of too many questionnaires, which could affect the internal consistency of the collected data although the validity of the data was assessed.

The study by Johannsen and colleagues (Johannsen et al., 2007) focused on the periodontal condition of women with a diagnosis of depression based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) compared to women without depression. After adjusting for age and smoking, a significant difference was found in probing pocket depth between women with and without depression. Nine out of 20 women in the depression group were taking a prescribed antidepressant (a selective serotonin reuptake inhibitor). Comparison of periodontal variables between depressed subjects on antidepressants and depressed patients not taking antidepressants showed no statistical significance. Another interesting

finding of this study was the observation of more pronounced gingival inflammation in the depressed group even in low bacterial plaque level. In this study, levels of IL-1β, IL-6, MMP-8, MMP-9 and cortisol found in gingival crevicular fluid (GCF) were evaluated. The level of IL-6 was significantly higher in GCF samples from depressed women. On the other hand, there was no significant difference in GCF level of IL-1β, MMP-8, and MMP-9.

Aggressive periodontitis in the adult population was more suggested to be frequently associated with psychosocial factors than chronic periodontitis (Davies et al., 1985). Monteiro da Silva (Monteiro da Silva et al., 1996) investigated the association between psychosocial factors and adult onset rapidly progressive periodontitis. This is the only included study in this systematic review that looked for the association between depression and the different classifications of periodontitis. Subjects who were under treatment for rapid progressive periodontitis and routine chronic adult periodontitis at least six month were recruited from the Periodontology clinic in a university setting. A control group consisting of periodontally healthy subjects was also evaluated. They demonstrated that subjects with a diagnosis of rapidly progressive periodontitis showed significantly higher depressive symptoms compared to those with chronic adult periodontitis and healthy periodontium.

Table 3 **– Cross sectional studies demonstrating a positive correlation between periodontitis and MDD/ elevated depressive symptoms**

Author/ Year of publication	*Sample characteristics (Number,Gender,Age(Mean or Range))*	*Periodontal measurement*	*Definition of periodontitis*	*Measurement of depression or depressive symptoms*	*Result*
Monteiro da Silva et al 1996	Test1: 50(F:66%) with rapid progressive periodontitis(RPP), Mean age 37.8 Test2: 50 (F:66%) with routine chronic ault periodontitis (RCAP), Mean age 45.2 Control: 50 (F:66%) without significant periodontal destruction, Mean age 33.8	PD,CAL, Radiographic alveolar bone loss assessment	RPP: Dx before age 35, Advanced bone loss affecting most teeth, Multiple vertical osseous defect, Gross inflammation and pus RCAP: Dx over age 35, Even or horizontal bone loss, No gross inflammation or pus Control: No radiographic bone loss, PD<4mm	Hospital Anxiety and Depression Scale (HADS) – Depression subscale	RPP group showed significantly increased depression compared to RCAP and control group
Genco et al 1999	1326 (F: 56%), Age 25-74	PD, CAL, ACH, Microbiological test	CAL, ACH were stratified into 5 ordered categories to define severity of periodontal disease	Brief symptom Inventory (BSI) – Depression subscale (Self-report scale)	An increase in CAL was significantly associated with depression. Depression and financial strain were significant predictor of CAL
Ng et al 2006	1000 (F:53%), Age 25-64	PD,GR, CAL	CAL were stratified into 5 ordered categories to define severity of periodontal disease	Symptom Check List 90-R(SCL-90R) – Depression subscale(Self-report scale) , Depression Anxiety Stress Scales -State (DASS-S) – Depression subscale (Self-report scale), Depression Anxiety Stress Scales -Trait (DASS-T) – Depression subscale(Self-report scale)	Subjects with more severe CAL had a depression score than the periodontally healthy subjects
Johanssen et al 2007	Test: 20 women with Dx of depression, Mean age 48.5 Control: 29 women, mean age 54.5	PD,CAL	N/A	DSM-IV	Depressed patients had significantly higher gingival inflammation and deeper pockets

ACH= Interproximal Alveolar Crestal Height, CAL= Clinical Attachment Loss, Dx= Diagnosis, F=Female, GR= Gingival Recession, N/A= Not applicable, PD= Probing Pocket Depth

3) Prospective cohort study (*Table 4*)

Only one published prospective cohort study has demonstrated a positive association between periodontitis and depressive symptoms, limited to specific ethnicity. Elter and colleagues (Elter et al., 1999) showed that the degree of risk for periodontal attachment loss and depressive symptoms vary by race. This study included 697 black and white subjects over the age of 65 that were followed longitudinally for over 7 years. The data were analyzed for subjects that had at least one follow-up examination. It was found that among only white subjects, depressive symptoms were positively associated with attachment loss of at least 3mm. The finding was not found among blacks; although blacks had a significantly higher incidence of attachment loss and higher depression scores using the CES-D evaluation.

***Table 4* – Prospective cohort study demonstrating a positive correlation between periodontitis and MDD/elevated depressive symptoms**

Author/ Year of publication	*Sample characteristics (Number,Gender,Age(Mean or Range))*	*Periodontal measurement*	*Definition of periodontitis*	*Measurement of MDD or depressive symptoms*	*Result*
Elter et al 1999	697 (F: 58%), Age over 65	PD,CAL – Measured from 5 sequential exam over 7 years	Change of CAL≥3mm between any examination	Center for Epidemiologic Studies Depression Scale (CES-D) (Self-report scale)	Subjects with more depressive symptom among whites had a higher rate of attachment loss

CAL= Clinical Attachment Loss, F=Female, PD= Probing Pocket Dept

2. Studies failing to show any correlation between periodontitis and MDD/ elevated depressive symptoms

The following five studies (1 case control, 4 cross-sectional study design) failed to find a link between periodontitis and depressive symptoms.

1) Case control study (*Table 5*)

Castro and colleagues (Castro et al., 2006) published a case-control study with a Brazilian population. In this study, significant predictors of periodontitis were found to be age, male gender, smoking and educational level. However depressive symptoms as assessed by 4 different scales were not associated with the disease. To assess the smoking effect on the outcome, they performed analysis of a sub-sample of a non-smoking group, which also failed to show any association between periodontitis and psychosocial variables including depressive symptoms.

Table 5 **– Case control study failing to show any association between periodontitis and MDD/elevated depressive symptoms**

Author/ Year of publication	*Sample characteristics (Number,Gender,Age(Mean or Range))*	*Periodontal measurement*	*Definition of periodontitis*	*Measurement of depression or depressive symptoms*	*Result*
Castro et al 2006	Test: 96 (F: 48%) with periodontitis, Mean age 45 Control: 69 (F:70%) without periodontitis, Mean age 41	PD,CAL	CAL≥4mm, BOP in at least 10 teeth, PD≥6mm in at least 5 teeth examination	Beck Depression Inventory (BDI) (Self-report scale)	No significant association was found between periodontitis and depression

CAL=Clinical Attachment Loss, F=Female, PD=Pocket Dept

2) <u>Cross-sectional study (*Table 6*)</u>

Four cross-sectional studies failed to find a correlation between periodontitis and depressive symptoms.

The cross-sectional study by Anttila and coworkers in Finland investigated the relationship of dental health and depressive symptoms (Anttila et al., 2001). There was no difference in periodontal status, dental caries rate and number of teeth between subjects with high versus low scores of depressive symptoms. However, subjects in the high depressive symptoms group showed less motivation for tooth maintenance. It is interesting to note that smoking was not associated with depressive symptoms and

edentulism was significantly associated with males who never smoked, but this was never found among male smokers. The authors failed to examine associations between the number of missing teeth (continuous variable) and levels of depressive symptoms (continuous variable). The use of continuous variables (e.g. number of missing teeth) versus dichotomous (edentulous versus dentate) would have increased the power and the validity of the analyses. Moreover, there was no information on the use of antidepressant medication that could affect the depression scores and the frequency of caries as they noted in their introduction.

Persson and colleagues (Persson et al., 2003) performed a cross-sectional study with a greater diverse population compared to other studies in this systematic review. The study population predominantly consisted of low-income elders, 48.0% of European descent, 35.8% of Asian descent and 10.7% of African descent. The inclusion criteria for the depressed group consisted of either a self-reported history of depression or a high score generated from the Geriatric Depression Score (GDS). It was found that a history of depression was reported among 20% of the subjects. However, clinical signs of depression as measured by the Geriatric Depression Score (GDS) were only shown in 9.8% of the population. In this study, the authors failed to show a link between depression and periodontitis among those with financial strain. Such results contradict those of the previous study from Erie County, USA (Genco et al., 1999).

A cross-sectional study by Solis and colleagues (Solis et al., 2004) used the same definition of periodontitis that was used in the study by Moss and co-workers (Moss et

al., 1996). When comparing subjects with and without periodontitis, most of the socioeconomic and demographic variables with the exception of age were not statistically different. Contrary to the study by Moss and colleagues, this study failed to demonstrate a correlation between periodontitis and depressive symptoms after controlling for other risk factors of periodontitis.

Rosania and colleagues (Rosania et al., 2009) studied the patients in a periodontal maintenance program after active periodontal treatment in a private periodontist office. The authors found a positive association between numbers of missing teeth and depressive symptoms. Periodontitis, as defined by the percentage of teeth with clinical attachment loss greater than 5mm, was not associated with depressive symptoms. However, CAL greater than 5mm, saliva cortisol levels and stress scores were found to be significant predictors, although depression scores were not included in the model. This study has thus demonstrated a positive association between periodontal destruction and emotional stress, but not depression as measured by CES-D scale.

Table 6 – **Cross-sectional study failing to show an association between periodontitis and MDD/ elevated depressive symptoms**

Author/ Year of publication	*Sample characteristics (Number, Gender, Age (Mean or Range))*	*Periodontal measurement*	*Definition of periodontitis*	*Measurement of depression or depressive symptoms*	*Result*
Antilla et al 2001	519 subjects (F: 50%), Age over 55	PD	PD≥4mm (Comparison of % of PD≥4mm)	Zung Self-rating Depression Scale(ZSDS) (Self-rating scale)	Depressive symptoms were not associated with periodontitis
Persson et al 2003	701 (F: 59%), Mean age 67	PD, Radiographic alveolar bone loss assessment with orthopantomogram	Primary: Frequencies of vertical bone defects ≥ 3mm Secondary: Proportional distribution (≥5%) of sites with PD≥ 5mm	Geriatric Depression Scale(GDS) (Self-report scale), Self-reported history of depression	Evidence of depression was not associated with risk for periodontitis in older patients
Solis et al 2004	Case: 47 (F: 60%) with periodontitis, Mean age 42.9 Control: 106 (F: 67%) without periodontitis, Mean age 34.9	PD, CAL	Two or more interproximal site from different teeth with clinical attachment level of 6mm or greater and additional site with a pocket depth of 5mm or greater	Beck Depression Inventory (BDI) (Self -report scale)	No evidence was found for an association between depression and established periodontitis
Rosania et al 2007	45 (F: 69%) with a history of non-surgical therapy & continuous maintenance	PD, CAL, REC	Number of teeth with CAL>5mm	Center for Epidemiologic Studies Depression Scale (CES-D) (Self-report scale)	Depressed subject did not show significant attachment loss

CAL=Clinical Attachment Loss, F=Female, PD=Pocket Probing Depth, REC= Gingival Recession

IV. Association between MDD/ elevated depressive symptoms and patients' oral hygiene (*Table 7*)

The following 5 studies explored the association between MDD/ elevated depressive symptoms and the degree of oral hygiene. Only one study by Kurer (Kurer et al., 1995) showed a higher plaque level among the group with depressive symptoms. Regarding gingival inflammation, only 2 studies (Johannsen et al., 2007, Klages et al., 2005) showed pronounced gingival inflammation in subjects with depressive symptoms compared to subjects without depressive symptoms. Contrary to these 2 studies, 2 other studies (Kurer et al., 1995, Saletu et al., 2005) did not observe this pronounced gingival inflammation in subjects with depressive symptoms and 1 study (Monteiro da Silva et al., 1998) did not investigate the difference of gingival inflammation.

Kurer and colleagues (Kurer et al., 1995) explored the effect of psychological mood including depressive mood on personal oral hygiene and response to oral hygiene instructions. All the subjects were regular dental attendees with a high standard of gingival health. Subjects were given both clinical and psychological exams at 5-week intervals. In their first visit, the subjects were instructed how to practice the Bass brushing technique. In spite of low plaque and gingival score in the initial exam, the subjects showed a modest reduction of the score. Depression and mean plaque score were correlated, but not to the degree of statistical significance. The authors performed a sub-sample (1/3 of group with higher depressive mood scores and 1/3 of group with lower

depressive mood scores) comparison using plaque score as an independent variable. Plaque scores among those with higher depression scores were significantly higher, but without a corresponding difference in gingival score.

Monteiro da Silva and colleagues (Monteiro da Silva et al., 1996) investigated subjects with depressed traits and with adult onset rapidly progressive periodontitis (RPP) . Based on this study, Monteiro da Silva and colleagues (Monteiro da Silva et al., 1998) speculated that depression could lead to the neglect of oral hygiene. The authors found that psychosocial factors including depression were not positively associated with plaque scores. The group with RPP was not significantly different in terms of plaque score compared to those with routine chronic adult periodontitis (RCAP). However, the study found that the RPP group smoked tobacco significantly more than the RCAP group, which may contribute to the pronounced periodontal destruction in the RPP group. The study failed to investigate the effect of smoking on the association between plaque score and depressive symptoms by stratifying the data by smoking status. Also the authors did not examine the level of gingival inflammation, an indicator reflecting the gingival tissue response.

The association between plaque level, bleeding on probing and psychosocial factors was investigated in 140 patients in a private practice (Klages et al., 2005). Proxy indicators for oral hygiene included plaque level and gingival inflammation. The level of depressive symptoms did not differ between patients representing the three grades of the plaque index. However, all the patients exhibiting sulcus bleeding had an elevated depression score compared to the group without sulcus bleeding. In addition, depression

scores and gingival inflammation were shown to be positively associated, supporting the fact that depressive symptoms may modulate the immune response.

A case-control study (Saletu et al., 2005) demonstrated that depression was not associated with oral hygiene and degree of gingival inflammation among those subjects with established periodontitis and those with a healthy periodontium.

Johannsen and colleagues (Johannsen et al., 2007) focused on middle age women with diagnosed depression. They evaluated the level of inflammatory markers in addition to plaque level and bleeding on probing. Mean dental plaque was higher among those with depression compared to those without depression, although this relationship did not reach statistical difference. However the study found that the mean level of gingival inflammation was significantly higher in the depressed group even when plaque levels were low. For the examination of inflammatory markers, the level of IL-6 in GCF was significantly higher in the depressed group, but the difference was not significant in the level of IL-1β, MMP-8, and MMP-9.

***Table 7*-Association between MDD/ elevated depressive symptoms and patients' oral hygiene habits**

Author/ Year of Publication	*Study design*	*Sample characteristics (Number, Gender, Mean or range of age)*	*Plaque and Gingival score*	*Measure of depression or depressive symptoms*	*Result*
Kurer et al 1995	Prospective Cohort study	47 subjects (Regular dental attenders) between age of 20 & 50, No data on gender	Turesky's modification of Quigley & Heines Plaque index – B&L in first incisors, premolars, molars/ Gingival index (GI) by Löe & Silness(1963) – 4 sites per tooth	Hospital Anxiety and Depression Scale (HADS)	Mean depression score was related with plaque accumulation
Monteiro Da Silva et al 1998	Case control	Test: 40(F:60%) with Rapid Progressive Periodontitis (RPP) – Mean age 33.4 Control: 40(F:60%) with Routine Chronic Adult Periodontitis (RACP) – Mean age 45.08	Plaque index (PII) by Silness & Löe(1964) – 4 sites in tooth # 3,6,12,19,23, 28	Hospital Anxiety and Depression Scale(HADS) – Depression subscale	Depression is not predictor for plaque accumulation
Klages et al 2005	Cross- sectional	140 subjects(F:66%), Mean age 40	Approximal Plaque Index(API) by Lange (1975) – Oral aspect in 1st & 3rd quad, Buccal aspect in 2nd & 4th quad/ Sulcus Bleeding Index(SBI) by Muhlemann & Sohn (1971) - Oral aspect in 1st & 3rd quad, Buccal aspect in 2nd & 4th quad	Symptom Check List 90-R(SCL-90R) – Depression subscale(Self-report scale)	Subjects with more depression showed same plaque accumulation but more gingival inflammation
Saletu et al 2005	Case control	Test: 40 (F:40%) with a diagnosis of periodontitis, age 32-64 Control: 41 periodontally healthy subjects (F:44%),age 23-70	Approximal Plaque Index(API) by Lange (1975) – 6 sites per tooth/ Papillary bleeding index(PBI) by Saxer & Muhlemann (1975) – 6 sites per tooth	Hamilton Depression Scale (HAMD) (Observer-rating scale), Zung Self-rating Depression Scale(ZSDS) (Self-rating scale)	API & PBI showed no significant correlations with psychometric variables including depression
Johanssen et al 2007	Case control	Test: 20 women with a diagnosis of depression, mean age 48.5 Control: 29 women, mean age 54.5	Plaque (Presence/Absence) - 6 sites per tooth/ Gingival index(GI) by Löe & Silness(1963)- 6 sites per tooth/ Bleeding on probing (%) – 6 sites per tooth	Diagnostic & Statistical Manual of mental disorder – 4th edition (DSM-IV)	The depressed patient had significantly higher gingival inflammation and deeper pocket

Discussion

This review was designed to focus on the association between MDD/ elevated depressive symptoms on periodontal status and oral hygiene behavioral changes. However, the results of the review were inconclusive due to heterogeneity of the included studies. This heterogeneity also precluded one to conduct a meta-analysis.

The different study methodology can explain the different results. Even though a randomized clinical trial (RCT) is considered as an optimal method to test the correlation, no RCT was identified for this review. Most of the included studies where either cross-sectional or case-control study designs. Some studies were able to demonstrate an association, but not the cause and effect relationship between these two factors. Clinical attachment level and pocket probing depth is an indicator of past periodontal destruction. Therefore, the effect of recent depression/depressive symptoms on periodontitis cannot be demonstrated with cross-sectional or case-control studies. In addition, all of the case-control studies failed to match at least one of the following demographic and socio-economic characteristics between the test and control groups; age, smoking status, gender, marital status, and education. Each study performed the statistical analysis after controlling these factors. Among cross-sectional studies, the difference in socio-demographic characteristics and sample size may explain the inconsistency of the results.

There is a lack of uniformity within the literature with respect to the definition of periodontitis and periodontal health (Tonetti and Claffey, 2005). As shown in ***Table 2***, the definitions of health and periodontitis were not in agreement among the studies presented in this review. This heterogeneity in diagnostic criteria in periodontitis has been reported as an important limitation in study result interpretation and generalizability. For this purpose, investigators challenged more than one definition in exploring associations between periodontitis and systemic conditions (Ioannidou et al., 2010, Vettore et al., 2008) and showed the effect of different definitions on the statistical analysis and data interpretation. Without any doubt, the use of arbitrary definitions of periodontitis decreased the validity of the results (Ioannidou et al., 2010)

Varying methodologies in evaluating depression/depressive symptoms is another factor that explains the discrepancies between studies. Unfortunately, none of the single biomarkers in blood and cerebrospinal fluid (CSF) identified to date such as GABA, stearate, and 3-Hydroxybutanoic acid have the desired sensitivity and specificity for the diagnosis of depression and other psychiatric disturbances(Quinones and Kaddurah-Daouk, 2009). Clinical depression is diagnosed through structured clinical interviews based on the criteria of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (Rabe-Jablonska, 1993). Depressive symptoms are different with a clinical diagnosis of depression, and are usually assessed using self-reported frequencies of feeling sad, nervous, hopeless, and worthless. Depressive symptoms can be caused by clinical depression. However, there are other possible reasons that may lead to feelings of depression, sadness or being down by non-

psychological reasons from socio-economic issues, and medical reasons from chronic diseases, cancer, and chronic pain (Mikolajczyk et al., 2008). Only one study in this review included subjects with a diagnosis of major depression based on DSM-IV (Johannsen et al., 2007). Subjects in the depressed group showed markedly higher gingival inflammation, bleeding on probing and pocket probing depth even with very low levels of plaque. It is interesting to note that subjects on antidepressant medication did not present less periodontal disease or biologic markers of inflammation compared to subjects that were not on antidepressants. It is not always possible to conduct the structured clinical interview by specialists even in medical care settings. Therefore, numerous screening tools have been specifically designed to identify depressive symptoms or possible presence of depression and self-reporting measures have been advocated as a simple, quick and inexpensive method to improve detection. Meta-analysis (Gilbody et al., 2008) by Gilbody and colleagues and the review by U.S. Preventive Service Task Force(USPSTF) (2009) showed that a self-report screening tool had a marginal impact on the detection of the depression in primary care settings when it was administered repetitively. One could argue on the validity of using only self-rated screening to define a "case". The study that used both observer-rated and self-rated questionnaires demonstrated that subjects with periodontitis showed higher depression scores in both methods (Saletu et al., 2005). In addition, no data against the use of self-reporting depression/depressive symptoms measure for epidemiologic research purpose were found in our search. The most common depression/depressive symptoms screening measures in medical settings are the Beck Depression Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CES-D), and Zung Self-Rating Depression

Scale (Sharp and Lipsky, 2002). All these instruments have different screening criteria and timing of assessment. Such differences have raised questions as to the definitions used to assess depressive symptoms. Not all the screening instruments are measuring the same symptoms or conditions. These differences limit the direct comparison of the study results included in this review (Sakakibara et al., 2009).

No consensus was found in terms of the correlation of MDD/ elevated depressive symptoms and oral hygiene in this systematic review. The discrepancy among the studies could be explained by the use of different plaque indices on different teeth and surfaces. Four different plaque-scoring systems were used in the five studies included in this review. Although the study by Klage (Klages et al., 2005) and Saletu (Saletu et al., 2005) adopted the apporximal plaque index (API) by Lange (Lange et al., 1975), Klage and colleagues (Klages et al., 2005) measured only 2 surfaces of the existing teeth. The characteristics of the study population were different in terms of dental history. Two studies (Klages et al., 2005, Kurer et al., 1995) recruited regular dental attenders in a maintenance program as a study sample, which could improve the condition of oral hygiene. Monteiro da Silva(Monteiro da Silva et al., 1998) examined the patients who may have had a professional dental prophylaxis before they were referred to university Periodontology clinic that could have also affected the interpretation of the result.

The effect of plaque accumulation on gingival inflammation was different among the studies. The differences among studies could be explained by inter-examiner variability

and a low level of reproducibility for measuring gingival inflammation. A variety of assessment methods for the measurement of gingival inflammation have been introduced. These include clinical visual-tactile indices (Loe and Holm-Pedersen, 1965), quantitative measurement of temperature (Niederman et al., 1995, Wolff et al., 1997), capillary blood flow (Matheny et al., 1993), gingival crevicular fluid flow (Lamster, 1997) and measurement of gingival erythema by diffuse reflection spectroscopy (Zakian et al., 2008). The most widely used methods for measuring gingival inflammation are the clinical indices relying on visual-tactile sensation. The indices used for the included studies in this systematic review are based on the combined assessment of tissue color, tissue form, bleeding on provocation, and spontaneous bleeding. Such measures of gingival inflammation are examiner-dependent and subjective. As such, they may contribute to the differing outcomes between studies. Specifically among indicators relying on bleeding on provocation, it is shown that probing angulation, the degree of force, and the depth of probe penetration into the sulcus are factors that influence the proportion of sites that bleed on probing (McClanahan et al., 2001). Such degree of subjectivity is demonstrated in a study by McClanahan and colleagues, in which different patterns of scoring were found while utilizing the Gingival index (Loe et al., 1965) among examiners (McClanahan et al., 2001). They found that each examiner had their own unique grade by applying arbitrary thresholds in determining the level of inflammation.

Table 8 – Description of depression/depressive symptoms scoring instruments

Measure	*Purpose*	*Construct*	*Subscales/ Items*	*Duration (Min)*	*Interpretation/ cutoff*
BDI	Screening & Symptom severity	Depressive behavior	21 items	5-10	18 or 27 has been recommended for SCI
CES-D	Screening & Symptom severity	Depressive behavior	20 items	≤ 5	16 or 19 has been recommended
ZSDS	Screening & Symptom severity	Depressive behaviour	20 items	≤ 10	39/40
BSI	Screening & Symptom severity	General Psychological Symptomatology	53 items comprising 9 subscales, including 6-item depression subscales	≤ 10	t-score>63 SCI raw score: Depression – 1.56, 2.42, 2.14
DASS-21	Screening & Symptom severity	Depression, Anxiety, Stress	21 item comprising of 3 subscales, including 7 item depression subscale	≤ 10	6, 11,15,18
HADS	Screening & Symptom severity	Depression, Anxiety	14 items comprising 7 item depression subscale	≤ 5	8
SCL-90-R	Symptom severity	Depression	30 items – 20 item depression subscale	NA	NA
GDS	Screening & Symptom severity	Depression	15 items	≤ 5	8

Conclusion

This systematic review attempted to summarize epidemiological studies that investigate the relationship between periodontal status and MMD/depressive symptoms. The reviewed studies reveal varying methodologies, and as such, reduce the possibility of drawing significant conclusions with confidence. Within the limits of the included studies and on the basis of the collected data, it can be concluded that:

I. There was not enough evidence to demonstrate a correlation between periodontitis and MDD/depressive symptoms. The consensus on the definition of periodontitis and MDD/depressive symptoms is essential in determining the correlation from different groups of people.

II. There is no clear association between clinical indicators of oral hygiene negligence and people with MDD/ elevated depressive symptoms.

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Part II

Association between periodontitis and psychological distress among hemodialysis patients

Introduction

I. Periodontitis and Psychological Distress

Despite a general understanding of the infectious etiology of periodontitis, studies have shown that environmental and host-related risk factors are strongly involved as well. Examples of such risk factors include smoking(Bergstrom, 1989, Bergstrom and Preber, 1994, Ismail et al., 1983), diabetes mellitus (Safkan-Seppala and Ainamo, 1992, Seppala et al., 1993, Westfelt et al., 1996), genetics (Hart and Kornman, 1997, Michalowicz et al., 1991), human immunodeficiency (HIV) infection (Ndiaye et al., 1997, Robinson et al., 2000, Robinson et al., 1996), obesity (Khader et al., 2009, Kongstad et al., 2009, Saito et al., 2005), osteoporosis (Payne et al., 1999, Persson et al., 2002), chronic kidney disease (Borawski et al., 2007, Ioannidou et al., 2006), alcohol dependence (Amaral Cda et al., 2008, Novacek et al., 1995), and psychosocial factors (Breivik et al., 2006, Genco et al., 1999).

The role of psychosocial factors in the etiology of periodontitis remains inconclusive. Some studies have demonstrated convincing positive relationships between psychological distress and the risk for acquiring periodontitis. One example involves a cross-sectional study with 1426 subjects in Erie County, New York. They showed that psychological distress is a significant risk indicator for more severe periodontitis among adult populations (Genco et al., 1999). However, other studies have failed to show any

significant associations between them (Anttila et al., 2001, Castro et al., 2006, Persson et al., 2003, Solis et al., 2004). Due to these inconsistencies in the literature, it is important to conduct well-designed and well-controlled epidemiological studies investigating the relationship between psychological distress and depression, and periodontitis.

II. End-Stage Renal Diseases and Psychological Distress

End-stage renal disease (ESRD) can significantly impact one's quality of life. Such patients not only experience a loss of kidney function, but may also face problems at home and work, may impact sexual function, appetite, physical strength, promote a fear of death, and dependency on treatment and medication (De-Nour, 1982, De-Nour et al., 1968, Kimmel, 2002).

Psychological distress is a discomforting emotional state experienced by an individual in response to a specific stressor. This mental state results in temporary or permanent harm to the patient (Knapp, 1988). Psychological distress is not a true medical diagnosis, but can be manifested as depression, anxiety, anger, hostility, pain, failure to verbalize ways to address problem, and/or suicide gesture (Ridner, 2004). It has been widely reported that anxiety and depression are commonly experienced by ESRD patients receiving hemodialysis (Cukor et al., 2008a, Cukor et al., 2008b, Kimmel et al., 2007, Finkelstein and Finkelstein, 2000). These psychological burdens can amplify the impact of chronic illness such as renal dysfunction and increase functional disability of the patients (Stein et al., 2006). As a consequence of the increasing concern of the psychological burden in

chronic illness patients, it is becoming more important to decrease psychological distress and subsequent aggravation of the patients' quality-of-life (Chilcot et al., 2008).

III. Assessment of Psychological Distress in Hemodialysis Patients

The Short Form 36-Item Health Survey (SF-36) is the most widely used quality-of-life assessment tool for hemodialysis patient (Rebollo and Ortega, 2002). The data on the validity and reliability of the SF-36 questionnaire for ESRD patients is reported in the literature (Gomez-Besteiro et al., 2004, Kurtin et al., 1992).

Specifically, the SF-36 consists of 36 items, and these items are used to score the eight subscales, which are:

1) Physical Function (PF) (10 items)
2) Role Physical (RP) (4 items)
3) Bodily Pain (BP) (2 items)
4) General Health (GH) (5 items)
5) Vitality (VT) (4 items)
6) Social Function (SF) (2 items)
7) Role Emotional (RE) (3 items)
8) Mental Health (MH) (5 items)

Each item comes with a five-choice response scale and gives raw scores from 5 to 25. Scores are then standardized by linear transformation to a scale ranging between 0 and 100 with high scores indicating better mental health (Ware and Gandek, 1998). The eight subscales are transformed into the Physical Component Summary (PCS) and Mental

Component Summary (MCS). The PCS is composed of Role Physical, Bodily Pain, and General Health, and the MCS is composed of Vitality, Social Function, Role Emotional, and Mental Health (Ware and New England Medical Center Hospital. Health Institute., 1994).

The Mental Health (MH) subscale and Mental Component Summary (MCS) is suitable for evaluating a patient's mental health status. Psychological domains include depression, anxiety, loss of emotional control, and psychological well-being. This tool is not diagnostic of disease, but aids in screening for depression/depressive symptoms (Berwick et al., 1991, Failde and Ramos, 2000, Strand et al., 2003, Ware and Gandek, 1998, Ware and New England Medical Center Hospital. Health Institute., 1994). Ulvik and co-workers (Ulvik et al., 2008) compared the efficacy of the SF-36 for detecting emotional distress with the Hospital Anxiety and Depression Scale (HADS) for the patients admitted to hospital for coronary angiography. They found that MH and MCS scores were strongly correlated with HADS scores and concluded that both the SF-36 and HADS questionnaires were appropriate tools to screen for psychological distress. The study involving a general population also showed high sensitivity and specificity of the MH score for the detection of depressive mood and anxiety disorder compared to the diagnoses made through structured clinical interview based on the criteria of DSM-IV (Rumpf et al., 2001).

IV. Aim of the study

Since it has been reported that hemodialysis patients suffer from more psychological distress than the general population (Cukor et al., 2007), it would be of interest to observe

the possible association of psychological distress and periodontitis in this cohort. The existing detailed SF-36 data of patients from a hemodialysis organization is a remarkable resource for this observational study. Therefore the aim of this pilot study is to investigate the association of periodontitis and psychological distress in ESRD patients undergoing hemodialysis therapy.

Material and Methods

I. Subject Recruitment

Twelve hemodialysis (HD) patients were recruited from the University of Connecticut Health Center (UCHC) Dialysis Unit following a nephrology consultation. The inclusion criteria for participation in the study were as follows: 1. Adult subjects diagnosed with ESRD, and receiving hemodialysis therapy, 2. Presence of at least 15 teeth, 3. No history of periodontal therapy within the past year, 4. No history of fistula infection or clotted access within the last month, 5. No history of antibiotic use within the past month. All current smokers were excluded from the study. This study was approved by the Institutional Review Board of UCHC. The patients attending the UCHC hemodialysis center were informed about the nature of the investigation and agreed to participate. Patients were assured that their data would be kept confidential, their clinical care would not be affected and they could withdraw from the study at any time. After the hemodialysis patients signed a written informed consent form, medical history and demographic and socioeconomic data were collected.

II. Periodontal Measurements

Two previously calibrated examiners (D.O. and E.C.) conducted a comprehensive periodontal exam. The periodontal examination involved the measurement of:

- Plaque score (PS)

- Bleeding on probing (BOP)
- Probing Pocket Depth (PPD)
- Clinical Attachment Level (CAL)

The aforementioned indicators were measured at six sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual) for all teeth excluding the third molars. Pocket depth was measured to the nearest millimeter using the North Carolina periodontal probe (Hu-Friedy, Chicago, Il, USA). Chronic periodontitis was defined by clinical attachment loss equal to or more than 5mm (CAL≥5mm) in more than 20% of measured sites.

III. Psychosocial Measurements

The most recent SF-36 data were retrieved from the patient records in the hemodialysis unit to evaluate psychological distress. The Mental Health (MH) subscale and MCS scale of SF-36 tool were used to evaluate the degree of psychological distress among the hemodialysis patients.

IV. Statistical Analysis

Data were stored in a database (Microsoft® Excel® 2008 for Mac) and analyzed using SPSS software for Windows. The mean value for PD, CAL, BOP, PS, and the percentage of sites having a CAL greater than or equal to 5mm, a CAL greater than or equal to 4mm,

and a PD greater than or equal to 4mm were calculated for each subject. The mean value for MH and MCS were compared between the groups with and without chronic periodontitis using Mann-Whitney test and Fishers exact test. Spearmen's Rho correlation calculations were performed to measure the strength of association between various psychological and periodontal domains. Finally a partial correlation test was carried out after controlling for age.

Result

Altogether, twelve hemodialysis patients were recruited from the UCHC Hemodialysis Unit. However the final sample was comprised of ten patients due to lack of SF-36 data on two patients. Five out of ten subjects were diagnosed with chronic periodontitis. The other five subjects were deemed periodontally healthy. ***Table 1*** shows the descriptive analyses on age, gender, diabetes and duration of hemodialysis. The mean age was significantly different between the groups (74.4 versus 39.4). Regarding gender, there was a higher proportion of females in the periodontally healthy group, but without a statistically significant difference. No significant differences were found with respect to the duration of hemodialysis and diabetes treatment between those with and without periodontitis. Regarding the MH and MCS scores, the groups were compared in relation to the mean scores and standard deviations of each scale (***Table 3***). Specifically, the periodontitis group showed higher mean scores than the periodontally healthy group, however these differences were not statistically significant. There is a very high correlation between MH and MCS, and this was demonstrated with a ρ value of 0.848 (p=0.002). Bivariate correlation analyses failed to reveal any significant relationships between periodontal measures and psychometric variables. However a positive correlation was found between sites exhibiting a CAL greater than or equal to 5mm and MCS (***Table 4***). This can be interpreted that patients with a higher percentage of CAL greater than or equal to 5mm have less psychosocial distress. Since there was a

statistically significant correlation between age and clinical attachment level, partial correlation analysis was carried out. After adjusting for age, there was no statistical significance was found, including the correlation between CAL greater than or equal to 5mm and MCS (***Table 5***).

Table 1 **– Sociodemographic and medical variables stratified by periodontal status**

	Periodontitis group (N=5)	Periodontally healthy group (N=5)	*p-value*
Gender (male) (%)	40%	20%	0.55
Diabetes (Presence) (%)	20%	40%	0.77
Age (mean±SD)	74.4±14.3	39.4±5.3	0.04
Hemodialysis Vintage (mean±SD)	2.5±1.3	3.75±5.5	0.69

***Table 2*- Periodontal variables stratified by periodontal status**

	Periodontitis group (N=5)	Periodontally healthy group (N=5)	*p-value*
PD (Mean ±SD)	2.74±0.25	2.64±0.40	0.23
CAL (Mean±SD)	3.80±0.47	2.70±0.37	0.29
PD≥4 (Mean%±SD)	10.6±11.1	8.7±7.0	0.13
CAL≥5(Mean%±SD)	41.4±19.0	1.6±1.8	0.01
CAL≥4(Mean%±SD)	51.7±1.6	8.7±6.3	0.01
PS (Mean%±SD)	70.2±23.0	58.3±41.9	0.04
BOP (Mean%±SD)	24.1±21.8	17.3±16.0	0.37

***Table 3*- Psychological distress domains**

	Periodontitis group (N=5)	Periodontally healthy group (N=5)	*P-value*
MH	79.2±19.7	52.8±17.8	0.57
MCS	52.9±11.1	38.2±12.1	0.93

***Table 4* – Bivariate correlation analyses between periodontal variables and sociodemographic and psychometric domains**

	MH	MCS	Age	Vintage	Gender
PD4	0.277	0.349	−0.123	−0.277	0.232
CAL5	0.631	0.659*	0.768**	−0.108	0.063
Mean PD	0.032	0.274	−0.003	−0.042	−0.092
Mean CAL	0.558	0.461	0.641*	−0.122	−0.278
BOP	0.929	0.065	−0.137	−0.212	0.105
PS	0.159	0.521	0.228	−0.828	−0.060

* Correlation is significant at the 0.01 level (2-tailed)

** Correlation is significant at the 0.05 level (2-tailed)

Table 5- **Partial correlation analyses between periodontal variables and psychometric domains after adjusting for age**

	MH	MCS
PD4	0.606 (0.08)	0.608(0.08)
CAL5	0.074(0.85)	0.272(0.48)
Mean PD	0.54 (0.14)	0.39 (0.31)
Mean CAL	0.117(0.76)	0.029(0.94)
BOP	0.227(0.56)	0.224(0.56)
PS	−0.033(0.93)	0.518(0.15)

Discussion

This pilot study has demonstrated that there are no statistically significant differences in MH and MCS scores between periodontitis and periodontally healthy subjects. This result was also confirmed with a partial correlation analysis after adjusting for age. This lack of correlation between periodontitis and psychosocial factors is supported in the literature (Castro et al., 2006, Saletu et al., 2005).

In spite of the acceptance and efficacy of the MH and MCS scores (Friedman et al., 2005, Kelly et al., 2008, Ulvik et al., 2008), it is important to point out the limitations of psychological screening instruments such as the accuracy in measuring subjective data and reliability of self-reported questionnaires. The self-questionnaire screening tool for psychological disorders is sensitive to criterion contamination especially when it is applied to chronically ill patients (Chilcot et al., 2008, Cummings, 1992, Schwab et al., 1967). Specifically, certain psychological symptoms may express themselves through somatization (Chilcot et al., 2008). With regard to ESRD, the somatic ramification of uremia, including fatigue, sleep disorders and reduced appetite overlaps with the clinical manifestation of psychological distress (Kimmel and Peterson, 2005). Differentiating between somatic and one's psychological symptoms can be challenging, particularly because physical health status in these individuals with ESRD can be variable, even on a daily basis (Watnick et al., 2005). Medical diagnoses following criteria set by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental

disorders by psychiatrists is the 'gold standard' in evaluating one's psychological state (Rabe-Jablonska, 1993).

The lack of a significant association between psychological distress and periodontitis may be explained by individual characteristics such as ways of coping with distress and social support (Genco et al., 1999). Such variables were not measured in this pilot investigation. According to Lazarus and co-workers (Lazarus et al., 1985), subjects living in the same environment do not experience stress in the same way. Hemodialysis patients have stressors in their life such as dietary restriction, time constraints, functional limitation, loss of employment, changes in self-perception, alterations in sexual function, general and perceived effects of illness, medications used to treat the illness, and fear of death (Kimmel, 2001).The response to stress varies depending on the available social support and the patient's own coping mechanisms (Folkman et al., 1986). Depression, anxiety, and loss of one's identity can occur in the absence of adaptive coping and social or familial support (Kimmel, 2001). In Genco and co-worker's study regarding the relationship of distress and periodontal diseases, the authors found that a high level of problem-based coping reduced the distress-associated risk for periodontitis, although they showed that distress manifested as a significant risk indicator for periodontitis (Genco et al., 1999).

Periodontal measurements such as clinical attachment loss and pocket probing depth are historical indicators of periodontal destruction (Griffiths et al., 1988). It is difficult to associate recent psychological distress with existing periodontal destruction (Genco et al., 1999). According to Cukor and co-workers, only 15% of hemodialysis patients consistently showed the signs of psychological distress such as depression and anxiety

during 16 months of study. The rest of the patients showed an intermittent course of distress or no distress at all (Cukor et al., 2008b). One could assume that periodontal destruction was triggered during a psychologically unstable occasion. However, the exact mechanism of psychological distress if there is any, on the onset and progression of periodontitis hasn't been investigated yet and will require further longitudinal prospective studies (Breivik et al., 2002, Hugoson et al., 2002).

Although this study shows that there is a lack of association between periodontitis and psychological distress, several limitations must be addressed. The first and most significant limitation is the small sample size as it was a subgroup analysis of a larger chronic kidney disease (CKD) population. It is well known that a small sample size gives rise to a decreased statistical power – decreasing the ability to detect a significant difference between groups.

The prevalence of periodontitis varies between different socio-demographic groups (Albandar, 2002). Although the information on gender, cigarette smoking and age distribution was collected, additional factors such as employment status, occupation, income level, educational background, and marital status could not be ascertained. These socioeconomic data may be important confounders between periodontitis and psychological status, and may be contributing factors influencing these parameters (Solis et al., 2004).

Another limitation involves the nature of the study design. Being a cross-sectional study whereby all variables were acquired at one period of time, it was not possible to evaluate

the cause and effect relationship between periodontitis and the psychological parameters. In other words, one cannot directly relate current or recent past psychological status to one's clinical presentation of periodontitis (Genco et al., 1999). Ideally, longitudinal prospective studies with larger sample sizes should be conducted in order to investigate the association of periodontitis and psychological factors. In addition the effect of psychological and pharmacological interventions on the progression of periodontitis after having had a diagnosis of psychiatric disorder made by a structured clinical interview may provide further information about the association.

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