

Oral and Medical Health Connections

Period covered July through December 2006



Quarterly Research Briefings
For Employers, Dentists,
Health Plans and Physicians

Introduction

Welcome to our second quarterly briefing report on the latest research that indicates an association between an individual's oral health and their overall health. This represents our continued exploration into the recent research that examines the potential links between oral disease and major systemic conditions, such as cardiovascular disease, diabetes and preterm births. This briefing will also discuss possible links with juvenile idiopathic arthritis and stroke. We continue to make it one of our priorities this year to accelerate the public awareness of the importance of oral health research and its connection to good overall health through this quarterly communication.

Background and Systematic Process

In March 2006, we held a National Symposium on the Oral-Medical Connection with nationally recognized researchers who presented on the most recent research in this area. If you would like a description of pre-March 2006 literature reviews, please see a summary of our National Symposium at www.deltadentalmn.org. Additionally, a new publication produced by *Scientific American* and Proctor & Gamble entitled "Oral Health and the Whole Body" has recently been made available that provides an excellent overview of the knowledge base concerning the links between oral and systemic health.

Moving forward beyond March 2006, our Office of Strategy Management conducted a systematic review of peer reviewed articles related to the oral-medical connection that yielded more information on periodontal disease and its association to: 1) preterm, low-birth-weight babies; 2) diabetes; 3) cardiovascular disease and; 4) other systemic disorders.

For purposes of our literature review, articles were identified through EBSCO Host, PubMed, Ovid and Medline databases and selected for review only if published by highly regarded peer reviewed journals in July through December 2006.

Is There an Oral-Medical Connection? What is the Evidence To-Date?

Emerging scientific evidence continues to support the positive effect that treatment and prevention of periodontal disease may have on improving a person's overall systemic health and well being. These effects could impact some of the United States' most prevalent, debilitating, and costly conditions, such as preterm and low-birth-weight babies, diabetes, heart disease and stroke. Although the evidence is not yet definitive, studies are continually being published that show an association between periodontal disease and systemic conditions. Periodontal disease is a common bacterial disease of the gums for which efficacious treatments exist. Ultimately, the ability to effectively treat and manage prevalent chronic conditions is an efficient way to enhance the quality and reduce the cost of care for employers, payors and providers while improving the health of our nation.

Periodontal Disease Linked with Pregnancy, Diabetes and Cardiovascular Disease

(Articles published by peer reviewed journals in recent months)

I. Periodontal Disease and Adverse Pregnancy Outcomes

The literature review for this topic includes eight scholarly works (3 reviews, 4 case-control studies and 1 randomized interventional control study).

Reviews:

Shub et al. **Periodontal disease and adverse pregnancy outcomes.** *The Journal of Maternal-Fetal and Neonatal Medicine* (September 2006)

The authors highlight the findings of previous studies that found an association between periodontal disease and pregnancy related complications, most notably preterm low-birth-weight (PLBW). The majority of the studies to-date show some association with periodontal disease and PLBW, but there is little standardization between the studies concerning the definition of periodontal disease and there is some disparity between

the definitions of PLBW, but most generally follow the World Health Organization (WHO) parameters. The lack of continuity between the various studies make direct comparisons very difficult and given the specific characteristics of the groups evaluated, it is nearly impossible to make conclusions that are applicable to the general population. The author indicates the need for large randomized trials of treatment to prove causation, of which three are underway at the time of publication of this article.¹

Bobetsis et al. **Exploring the relationship between periodontal disease and pregnancy complications.** *Journal of the American Dental Association* (October 2006)

This paper represents another review of the current knowledge concerning the association between periodontal disease and pregnancy related complications. Additionally, the authors indicate that evidence is coming to light that the fetal inflammatory response to bacterial challenge across the placenta may have profound long-term post-natal effects. The authors' conclusions are as follows:

“Although there are some conflicting findings and some potential problems regarding uncontrolled underlying risk factors, most clinical studies point to positive correlation between periodontal disease and preterm birth. This association is supported by microbiological and immunological findings, most notably the notion of fetal/placental exposure to periodontal pathogens leading to a fetal inflammatory response resulting in preterm birth. Some animal studies indicate that this prenatal infection may have profound developmental effects on infant after birth.”

The authors further indicate that, at this time, there is insufficient evidence to recommend periodontal therapy as a prevention for pregnancy related complications.²

Bogges et al. **Oral health in women during preconception and pregnancy: implications for birth outcomes and infant oral health.** *Maternal and Child Health Journal* (July 2006)

This article, directed towards physicians, provides a solid background in the concepts of dental caries and periodontal disease. The links of PLBW and periodontal disease are discussed and once again, the authors

indicate only association, not causation. Similar findings come out of the discussion of preeclampsia (pregnancy related hypertension) and periodontal disease. The authors go on to discuss the transmission of caries related bacteria from mother to child, indicating that the establishment of good oral hygiene practices by the mother can potentially lead to a decrease in the vertical transmission of *S.mutans* to the infant. While the conclusions concerning association between periodontal disease and PLBW are similar to other reviews, the authors make an important statement concerning oral health and systemic health in pregnant women:

“Regardless of the potential for improved oral health to improve pregnancy outcomes, public policies that support comprehensive dental services for vulnerable women of childbearing age should be expanded, so not only their own oral and general health is safeguarded but also that their children’s risk of caries is reduced. The power of prevention needs to be brought to bear, as both periodontal disease and caries are overwhelmingly preventable through well recognized strategies including regular and effective home care for periodontal disease and the use of fluoride and sealants for caries.”³

Implications: The mutual recognition by both physicians and dentists of the value of good oral health as part of overall health can lead to the establishment of good home care practices in pregnant mothers and those healthcare values can be passed on to their children, leading to a decrease in dental morbidity. The establishment of new dental attitudes by the public would additionally make it easier to manage the relationship between periodontal disease and systemic diseases if future research does indeed prove causation.

Case-Control Studies:

Khader et al. **Lack of association between periodontal parameters and preeclampsia.** *Journal of Periodontology* (October 2006)

This case-control study sought to determine whether there is an association between periodontal parameters and preeclampsia among women in the north of Jordan. The conclusions were as follows:

- The only parameter that maintained a significant association with preeclampsia was decayed

surfaces (adjusted OR of 1.13; 95% CI's 1.02 and 1.25).

- There were no periodontal parameters (PPD, CAL, plaque or BOP) that had a significant association with preeclampsia.

Implications: The results of this study indicate that periodontal therapy for the management of preeclampsia is not indicated. There may be limited value in incorporating a caries control regimen in pregnant women who are prone to preeclampsia.⁴

Bosnjak et al. **Pre-term delivery and periodontal disease: a case-control study from Croatia.** *Journal of Clinical Periodontology* (October 2006)

The second case-control study comes from Croatia. The aim of this report was to assess the strength and influence of periodontitis as a possible risk factor for pre-term birth (PTB) in a cohort of 81 primiparous Croatian mothers aged 18-39 years based on periodontal measures taken two days after delivery.

- Multivariate analysis reveals that the presence of CAL ≥ 4 mm in $\geq 60\%$ of analyzed sites was a significant factor for PTB. OR 7.2 (3.0-34.1).
- This finding occurred despite 17 women having PTB and 64 women having normal births.

Implications: Periodontal disease, as specifically defined in this study, is a significant factor for PTB. There are strong indicators that periodontal therapy should form a part of preventative prenatal care for women of Croatia. Croatia is subject to approximately 2,000 PTBs/year out of 40,000 live births. The authors postulate that the elimination or control of periodontal disease could prevent nearly 500 PTBs/year.⁵

Radnai et al. **Possible association between mother's periodontal status and preterm delivery.** *Journal of Clinical Periodontology* (December 2006)

This was a case-control study undertaken to detect whether initial chronic localized periodontitis could be a risk factor for preterm birth (PB) and fetal growth restriction. One hundred sixty-one Hungarian women (77 cases, 84 controls) received a periodontal examination within three days of delivery. Initial chronic localized periodontal disease was defined as BOP at $\geq 50\%$ of teeth and had PD of ≥ 4 mm in at least one site, while preterm birth was defined when a patient had a

threatening premature event during pregnancy, pre-term rupture of membranes or spontaneous pre-term delivery before the 37th week of pregnancy and/or weight of the newborn was < 2500 g. (WHO guidelines). Additionally, the investigators sought to determine the most important factor among demographic, socio-economic and periodontal factors that influenced pregnancy outcomes. They also examined whether initial chronic localized periodontitis of the mother during pregnancy influenced the birth weight of the newborn. The following results were found:

- The presence of periodontal disease as defined by this study has an OR of 3.32 (1.64, 6.69) for PLBW, while smoking alone has an OR of 4.55 (1.20, 17.19). Mothers with periodontal disease had lower average birth weights when compared with controls.
- PB occurred more frequently when both mother and father had low levels of education.
- Having ≥ 4 mm PD at least at one site and BOP at $\geq 50\%$ of all teeth was significantly related to PB. Fifty-seven patients (39 cases, 18 controls) had periodontitis according to the definition provided by the authors.
- Periodontitis and smoking were significantly related to PB.
- Patients with periodontitis had significantly lower average birth weights than periodontally healthy counterparts.

Implications: Initial chronic localized periodontitis was associated with preterm delivery and lower average birth weight, making it the second most important factor behind smoking. There may be benefit to providing dental hygiene to pregnant patients to help reduce these adverse pregnancy outcomes, but this needs to be determined through large clinical trials where patients receive treatment.⁶

Bassani et al. **Periodontal disease and perinatal outcomes: a case-control study.** *Journal of Clinical Periodontology* (December 2006)

This case-control study with 304 cases and 611 controls, examined women of varying ethnicities from Brazil. The study sought to measure the association of maternal periodontitis with low birth weight (LBW), pre-term LBW and intra-uterine growth restriction. Periodontal disease was defined as having three different sites in

three different teeth with ≥ 3 mm of clinical attachment level (CAL). Further divisions were based upon severity of CAL. LBW was defined as < 2500 g at > 27 weeks gestation. The following key results were found:

- 59% of the cases and 55% of the controls were born to mothers with some degree of periodontitis.
- Controlling for other factors, periodontitis had an OR of 0.93 (0.63, 1.41) when combining all severities for LBW and 0.92 (0.54, 1.57) for preterm LBW.
- The association of the presence of periodontal destruction (measured through attachment loss) and LBW was not significant and the association with intra-uterine growth restriction was crude at best.

Implications: In contrast to other case-control studies, this study indicates that there is no association of periodontal disease and the three measured parameters of adverse birth events analyzed. The data must be carefully interpreted, as this population had a higher incidence of other noted adverse pregnancy outcome confounders, such as low SES, lack of prenatal care, nutritional problems and smoking/alcohol consumption.⁷

Randomized Clinical Intervention Trial:

Michalowicz et al. **Treatment of periodontal disease and the risk of preterm birth.** *The New England Journal of Medicine* (November 2006)

This study subjected women of 13 to 17 weeks gestation to scaling and root planing (SRP) either before 21 weeks gestation or after delivery. Patients in the treatment group were also given monthly tooth polishing and oral hygiene instruction. The following results were found:

- 12.8% of the controls experienced PTB compared to 12% of the treated subjects (not significant). All clinical parameters significantly improved in the treatment group. No significant difference in birth weight parameters (averages and number of low birth weights/group).
- These rates of PTB are in concordance with statistics put forth by the Centers for Disease Control and Prevention.⁸
- No data on smoking for either group were made available.

Implications: Much of the debate concerning the link between periodontal disease and PTB has hinged upon the fact that most studies show association and there is a lack of studies that evaluate cause/effect of periodontal treatment on PTB. This study with a large, diverse population has failed to show any alteration in the rate of PTB with SRP and supportive periodontal therapy. This study is at variance with other studies where periodontal treatments have successfully reduced the frequency of PTB and LBW babies. As other studies of similar magnitude report their results, the medical and dental communities will have to come to a consensus concerning the value of periodontal therapy as part of a PTB prevention program.⁹

II. Periodontal Disease and Adverse Diabetic Outcomes

(Articles published by peer reviewed journals in recent months)

The recent literature concerning the association between diabetes and periodontal disease consisted of three reviews, two cross sectional studies, one case-control study, and one randomized clinical trial. It is generally agreed that diabetes is a risk factor for the development of periodontitis; the dispute arises as to whether control of periodontitis can have an effect on glycemic control.

Reviews:

Herring et al. **Periodontal Disease and Control of Diabetes Mellitus.** *Journal of the American Osteopathic Association* (July 2006)¹⁰

Mealey, B. **Periodontal disease and diabetes: a Two-way street.** *Journal of the American Dental Association* (October 2006)¹¹

Kim et al. **Periodontal disease and systemic conditions: a bidirectional relationship.** *Odontology* (September 2006)¹²

Implications: These reviews conclude that the effect of periodontal therapy on diabetes needs more focused research to determine the exact mechanisms by which glycemic control and periodontal disease are related, so our treatment can provide maximum effect for our patients. In the meantime, proper management of periodontal disease should be encouraged for overall health and patients suffering from diabetes should be

encouraged to seek dental care due to the high likelihood of having periodontal complications.

Cross Sectional Study:

Al-Emadi et al. **Systemic diseases among patients with and without alveolar bone loss.** *Quintessence International* (Nov/Dec 2006)

This was a cross sectional study of 420 patients 18 years of age and older who had at least 20 teeth at time of examination. Two hundred ten patients had moderate to severe chronic periodontitis and two hundred ten had either mild or no periodontal disease. Disease was defined by measurement of radiographic alveolar bone loss (mod/advanced: $\geq 2.5\text{mm}$, no/mild: $<2.5\text{mm}$). The radiographs were not standardized. Presence of systemic disease (HTN, diabetes, respiratory disease, allergies and arthritis) was self-reported. The following conclusion was reached:

- Patients with moderate to advanced chronic periodontitis had higher prevalence of both HTN and diabetes than those with mild or no periodontal disease when controlling for age, gender, smoking, marital status and number of teeth.¹³

Implications: Like other studies of this kind, the findings indicate that there is a higher incidence of systemic disease in individuals with periodontal disease. This study, however, has a few design problems that make it less powerful than other studies of the same type. The definition of periodontal disease was made using measurements on non-standardized radiographs without the aid of a digitizing program to compensate for the differences in radiograph angulation. Additionally, the inclusion of mild periodontal disease with no periodontal disease further complicates the final analysis, as these findings seem to indicate that only moderate to severe disease has a systemic relationship, but mild disease does not. A better division of disease severity would have divided it into severe, moderate, mild and a separate category of no disease acting as a control.

Engbretson et al. **Plasma levels of tumor necrosis factor α in patients with chronic periodontitis and type 2 diabetes.** *Journal of Clinical Periodontology* (December 2006)

Tumor necrosis factor α (TNF- α) has been implicated in the pathogenesis of Type 2 Diabetes.¹⁴ Most TNF- α is thought to be derived from adipocytes, but there may be significant contribution from inflammation and infection, most notably chronic periodontal disease. Plasma TNF- α was assayed in 46 individuals with periodontal disease and Type 2 Diabetes and the following results were found:

- Subjects with severe periodontitis (mean whole mouth attachment loss $>4\text{mm}$) had significantly higher plasma concentrations than those with mean whole mouth attachment loss $<3\text{mm}$.
- With adjustments for BMI, the association between attachment loss and TNF- α increased to an OR of 24.3 (2.0-300). Similar findings occurred when adjusting for sex and age.
- The presence of greater than median levels of plasma endotoxin conferred an OR of 4.3 (1.1-17.7) of having elevated plasma TNF- α level.¹⁵

Implications: Increased levels of periodontal disease (i.e., increased attachment loss) appear to be significantly associated with increased plasma TNF- α level. This increase in TNF- α may be a significant contributor to type 2 diabetes and associated insulin resistance. Future studies should focus on the effect of periodontal therapies on reducing plasma TNF- α level and its subsequent effect on the parameters of Type 2 Diabetes.

Case-Control Study:

Davila-Perez et al. **Distribution of genotypes of porphyromonas gingivalis in type 2 diabetic patients with periodontitis in Mexico.** *Journal of Clinical Periodontology* (December 2006)

Porphyromonas gingivalis is a known putative periodontal pathogen, but the response of the host to the pathogen is equally, if not more important in the progression of periodontal disease. This case-control study was conducted to determine and compare the distribution of *P. gingivalis* *fimA* genotypes in type 2 diabetes mellitus patients affected by periodontitis using non-diabetic subjects with and without periodontitis as controls. Subgingival plaque was harvested from 75 subjects in Mexico and revealed the following:

- Group 1 (non-diabetic, no periodontal disease) showed a predominance of type 1 *P. gingivalis*.

- Group 2 (non-diabetic, chronic periodontitis) showed a predominance of type 1b *P. gingivalis*.
- Group 3 (type-diabetic, chronic periodontitis) showed a mix of both type 1 and type 3 *P. gingivalis*.¹⁶

Implications: Type 1 and type 3 *P. gingivalis* are typically regarded as less virulent than types 1b and 2 which occur frequently in chronic periodontitis in patients without type 2 diabetes. The findings of this study indicate that type 2 diabetes may have a profound effect on host response to less virulent forms of *P. gingivalis* leading to periodontal destruction more commonly seen with more virulent forms. This study reinforces the notion that diabetics are more susceptible to periodontal breakdown than counterparts with normal glycemic control.

Randomized Clinical Intervention Trial:

Jones et al. **Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study.** *Journal of Clinical Periodontology* (December 2006)

This randomized clinical trial studied 165 veterans with poor glycemic control over a four month period to determine the effect of periodontal therapy (SRP, systemic doxycycline and daily chlorhexidine use) vs. no treatment (usual care) on reducing HbA1c scores. The following results were found:

- Simple and multiple variable linear regressions showed no differences between groups or HbA1c change for either unadjusted or adjusted analyses.
- After adjustment the OR for improving HbA1c 0.5% and 1.0% was found to be 1.67 (0.84, 3.34) and (0.81 3.44), respectively.
- Subjects receiving periodontal therapy were more likely to have improvements of 0.5% to 1.0% in HbA1c, but this failed to reach statistical significance.¹⁷

Implications: This study failed to find any value in performing periodontal therapy for the reduction of HbA1c over a 4 month interval. There were some design problems, most notably difficulty in randomizing the two arms of the study. Additionally, the duration of the study may have been too short to fully realize any differences between the groups. Twelve month data

from this group will be published at a later date, which may indicate a difference between the two treatment groups.

III. Periodontal Disease and Adverse Cardiovascular Disease Outcomes

(Articles published by peer reviewed journals in recent months)

The literature review concerning cardiovascular disease and periodontal disease included five papers (1 review, 2 cross sectional studies, 3 case-control studies, and 1 laboratory animal study).

Review:

Demmer et al. **Periodontal infections and cardiovascular disease.** *Journal of the American Dental Association* (October 2006)

This article reviewed the studies evaluating the association between periodontal infections and cardiovascular disease. Several key points were brought forth by the authors:

- Recent studies have enhanced the specificity of infectious exposure definitions by measuring systemic antibodies to selected periodontal pathogens or by directly measuring and quantifying oral microbiota from subgingival dental plaque.
- To answer whether the possible risk of CVD from periodontal disease is best managed by treatment of existing disease or through prevention before a threshold of irreversible subclinical CVD is reached, large-scale randomized intervention trials specifically designed to answer these questions are necessary.

With these findings in mind, the conclusion reached in this paper indicated that “recommending periodontal treatment solely for the purpose of atherosclerotic CVD prevention is not warranted based on current scientific evidence”.¹⁸

Cross Sectional Studies:

Beckstrom et al. **Correlation between carotid area calcifications and periodontitis: a retrospective study of digital panoramic radiographic findings in**

pretreatment cancer patients. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* (December 2006)

This was a retrospective study of the digital panoramic radiographs on 201 patients who were in the pretreatment phase for head and neck cancer. The patients were Finnish with 138 men, 63 women, with an average age of 52.1 years (11-87 years). The presence or absence of either unilateral or bilateral carotid calcifications were verified by a board certified Oral and Maxillofacial Radiologist. These findings were then correlated with the percentage of alveolar bone loss as determined using digital radiographic software. Findings included:

- There was a highly significant correlation between carotid artery-area calcifications visible on panoramic radiographs and percent alveolar bone loss. Radiographs showing unilateral and bilateral calcifications had a mean percent bone loss of 24.2% +/- 13.0% and 25.7% +/- 13.0%, respectively compared with those with no calcification at 10.4% +/- 9.9%.
- There was no statistical difference between having unilateral or bilateral calcifications and percentage of alveolar bone loss.¹⁹

Implications: Published studies indicate that prevalence of carotid artery calcifications on panoramic radiographs is around 2-5% for the general population.^{20, 21} This study seems to indicate that patients with periodontal disease may present more frequently with carotid calcifications in panoramic films. This by no means indicates that panoramic radiographs should be taken specifically for the detection of carotid calcifications, but that any time a panoramic radiograph is used for diagnosis, analysis of the carotid bifurcation should be included. Larger studies are necessary to confirm the increased prevalence of carotid calcifications in patients with alveolar bone loss.

Caplan et al. **Lesions of Endodontic Origin and Risk of Coronary Heart Disease.** *Journal of Dental Research* (November 2006)

Lesions of endodontic origin (LEO) have similar characteristics to periodontal lesions. They are primarily caused by Gram-negative, anaerobic bacteria and they can also induce an increase in systemic cytokine levels.

This longitudinal radiographic analysis of 708 men found that:

- the development of CHD (MI, chronic ischemic heart disease or angina) was closely associated with the incident finding of a LEO during radiographic evaluation.
- this finding held true in men under 40 years of age, but its significance decreased after the age of 40.²²

Implications: While this study shows a potential association between LEO and the development of CHD, the association isn't nearly as strong as those seen with periodontal disease and systemic disorders. There is difficulty in providing a standardized definition of LEO and often times, the lesion has been present for an extended period of time before it appears radiographically making an exact time reference between the beginning of a lesion and the onset of any subsequent CHD difficult. Further refinement of experimental design involving the endodontic lesion is necessary before any solid conclusions can be made.

Case-Control Studies:

Geismar et al. **Periodontal disease and coronary heart disease.** *Journal of Periodontology* (September 2006)

This is a case-control study aimed to test the hypothesis that a high prevalence of periodontal disease among CHD patients could be explained, at least in part, by mutual risk factors (such as smoking and diabetes). The subjects studied were Danish, 110 of which were verified to have coronary heart disease (CHD). Periodontal parameters measured included PD (mm), CAL(mm), BOP(%), and alveolar bone level (ABL). The significant findings were:

- CHD group had significantly poorer outcomes with respect to all periodontal variables.
- CHD group had significantly greater self reporting of diabetes, lowered physical activity, fewer years of education, and incidence of smoking.
- Greater ABL was associated with increased number of pack years.
- Significantly higher odds ratio (OR=6.6) for individuals <60 years old of being CHD patients

when having a mean ABL >4mm based upon measurement of radiographs.

- The association between CAL and CHD for all age groups remained significant after adjustment and was even greater under the age of 60.²³

Implications: In patients under the age of 60 who have advanced bone loss (in conjunction with smoking and diabetes), there may be increased likelihood of having CHD. Further research is needed to evaluate the value of providing periodontal therapy to lessen the occurrence of CHD in this patient population.

Furuholm et al. **Salivary matrix metalloproteinase-8 in patients with and without coronary heart disease may indicate an increased susceptibility to periodontal disease.** *Journal of Periodontal Research* (October 2006)

The focus of this large Finnish study (n=556) was to study whether salivary MMP-8 levels were different among patients with or without CHD. The following observations were presented:

- Salivary MMP-8 levels were found to be significantly higher in patients with CHD.
- Additionally, MMP-8/albumin and MMP-8/total protein levels were found to be higher in patients with CHD.²⁴

Implications: Salivary MMP-8 is considered an important marker reflecting the severity of periodontal inflammation. The findings of this study indicate that measuring MMP-8 levels may be useful in future studies of the association between CHD and periodontal disease; however, the present investigation failed to show any difference in periodontal disease levels between the groups despite the salivary MMP-8 levels.

Söder et al. **Levels of matrix metalloproteinases-8 and -9 with simultaneous presence of periodontal pathogens in gingival crevicular fluid as well as matrix metalloproteinase-9 and cholesterol in blood.** *Journal of Periodontal Research* (October 2006)

This is a Swedish study of 33 subjects who had been diagnosed with chronic periodontitis for at least 16 years. The following observations were made:

- Oral health parameters were generally poorer in patients than in controls.

- HTN and associated therapy had no bearing on MMP-9 levels in the plasma.
- The most pathogenic bacterial species were detected in both groups but more abundantly in the periodontal patients.
- For MMP-9 in plasma, smoking, *P. gingivalis*, and dental plaque were the main independent predictors of increased MMP-9 (OR 6.45, 6.21, 5.39 respectively).
- In GCF, both MMP-8 and -9 were significantly higher than controls.
- *P. gingivalis* and *T. forsythia* were both found to be among the independent factors contributing to the increase in MMP-8 and -9 in both plasma and GCF.²⁵

Implications: It is speculated that the increased MMP-9 levels in the GCF could lead to an increase in MMP-9 in the plasma. Increased MMP-9 levels are shown to be present in patients who are at risk for CVD, with a history of CVD and peripheral artery disease, thus making MMP-9 an early marker for general inflammation and even as an indicator of future cardiovascular disease.

Animal Study:

Hashimoto M. et al. **Selective Proteolysis of Apolipoprotein B-100 by Arg-Gingipain Mediates Atherosclerosis Progression Accelerated by Bacterial Exposure.** *Journal of Biochemistry* (October 2006)

Implications: While not immediately clinically applicable, research on the actual mechanism of atherosclerotic plaque formation and the association with periodontal bacteria will lead to more precise research measures, thereby improving our understanding of the association of periodontal disease and cardiovascular disease and eventually leading to proof of causation.²⁶

IV. Periodontal Disease and Other Systemic Disorders

(Articles published by peer reviewed journals in recent months)

While the vast majority of research is dedicated to finding links between pregnancy, cardiovascular disease, diabetes and periodontal disease, there are other systemic disorders that are thought to have an

association with periodontal disease. This literature review has three such articles that address juvenile idiopathic arthritis, stroke (which is a subset of cardiovascular diseases), and kidney disease.

Case-Control Studies:

Miranda et al. **Changes in periodontal and rheumatological conditions after 2 years in patients with juvenile idiopathic arthritis.** *Journal of Periodontology* (October 2006)

This study of Brazilian subjects sought to assess the influence of rheumatic disease activity and anti-rheumatic medication on clinical and immunological parameters of periodontal inflammation in these individuals.²⁷

Implications: Due to the lack of periodontal treatment and ambiguous clinical parameters, there are no current clinical recommendations based on these findings.

Borawski et al. **The periodontal status of pre-dialysis chronic kidney disease and maintenance dialysis patients.** *Nephrology Dialysis Transplantation* (December 2006)

This was a case-control study that compared the periodontal status of three groups of chronic kidney disease patients: 1) those undergoing hemodialysis, 2) those treated with chronic ambulatory peritoneal dialysis and 3) pre-dialysis chronic kidney disease patients with controls consisting of patients having advanced periodontal disease without chronic kidney disease and normal patients from the general population. The following was observed:

- The GI and PI for hemodialysis patients were higher than that for all the other groups except the periodontal controls. The absolute value of CAL was in the hemodialysis group was equivalent to the periodontal disease control group, and higher than the other groups. The deepest periodontal pockets (CPI 4) were found as frequently in hemodialysis patients as periodontal disease controls.²⁸

Implications: Patients with severe chronic kidney disease requiring hemodialysis may present more frequently with severe manifestations of chronic periodontal diseases. Although larger clinical trials are necessary to prove the hypothesis, there may be some

benefit in providing prophylaxis and early periodontal disease detection in this patient population improving both oral and systemic health.

Retrospective Analysis:

Lee et al. **The association between cumulative periodontal disease and stroke history in older adults.** *Journal of Periodontology* (October 2006)

This study was a retrospective analysis of the Third National Health and Nutrition Examination Survey (NHANES III). There were 5,123 subjects who were edentulous, partially edentulous and dentate. The following was observed:

- Fully and partially edentulous subjects had significantly higher self-report of stroke than fully dentate individuals.²⁹

Implications: This study provides some evidence of an association between periodontal disease and stroke in older adults, but based upon the findings, it is unclear whether periodontal disease is an independent risk factor or if it simply acts as a risk marker reflecting detrimental effects common to both periodontal disease and stroke.

V. Periodontal Disease and Its Effect on Treatment Costs for Individuals with Systemic Diseases.

(Articles published by peer reviewed journals in recent months)

Albert et al. **An examination of periodontal treatment and per member per month (PMPM) medical costs in an insured population.** *BioMed Central Health Services Research* (August 2006)

- This study examined if periodontal treatment can contribute to changes in overall risk and medical expenditures for three chronic diseases [Diabetes Mellitus (DM), Coronary Artery Disease (CAD) and Cerebrovascular Disease (CVD)] for patients receiving the following dental services: 1) periodontal treatment (periodontitis and gingivitis); 2) regular dental maintenance services (DMS); 3) other dental services; or 4) no dental services. The study included 116,306 individuals with both Aetna medical and dental insurance coverage between

January 1, 2001, and December 31, 2002, and who had one or more of the following conditions: DM, CAD or CVD. The results of their analysis were as follows:

Patients treated for periodontal disease had higher per member per month medical expenditures (PMPM) than those who were treated in the other dental categories. The periodontitis treatment group had a lower retrospective risk for their chronic condition (DM, CAD, and CVD) than patients who did not have periodontitis treatment and received treatment within the three other dental categories.³⁰

Implications: There will likely be an increase in PMPM for the treatment of periodontitis by third party insurance providers; however this treatment may lead to a decreased risk of exacerbation of the underlying chronic disease. Further studies that control for other factors common to periodontal disease, diabetes and cardiovascular disorders (such as smoking and SES) are necessary to fully elucidate this relationship. In the interim, it would be reasonable to recommend an examination of the oral cavity be included in guidelines for care of patients with DM, CAD, and CVD and that public health programs and insurers work together to raise awareness of the need for periodic dental visits for those members of the population who have diabetes and cardiovascular disease.

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