Session A
Destructive Periodontal Disease in Relation to Diabetes Mellitus, Cardiovascular Diseases, Osteoporosis and Respiratory Diseases

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During the past decade the association between periodontal diseases and general diseases has attracted renewed research interest. The mouth has once again become an integral part of the rest of the human body. This review covers the possible associations between periodontal disease and diabetes, coronary heart disease, osteoporosis, pulmonary diseases and depression and focuses on more recent publications.

A majority of published studies confirms support for a relationship between periodontal disease and diabetes mellitus. Treatments of periodontal disease including the use of local or systemic antibiotics have been shown to affect the glycemic control. From a clinical point of view diabetes should be regarded as one of the factors increasing the risk for periodontal disease.

At present there is but limited evidence that periodontitis is associated with an increased risk for coronary heart disease and further research is needed to explore such a relationship in prospective studies. Studies exploring whether periodontal treatment can reduce the risk for coronary heart disease are needed.

The extent of the relationship between osteoporosis and periodontal disease still remains uncertain. Sustained oral health and better tooth retention are potentially additional benefits of hormone replacement therapy after menopause.

Aspiration of oral microorganisms may contribute to the genesis of aspiration pneumonia. Poor dental health is a factor associated to aspiration pneumonia among elderly institutionalized and hospitalized individuals.

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BACKGROUND

Periodontal disease is a multi-factorial infectious disease. It has been estimated that approximately 35% of 30 to 90-year-old adults in the United States have significant evidence of destructive periodontal disease (Albandar et al, 1999; Satcher, 2000). During the past decade the association between periodontal diseases and general diseases has attracted renewed research interest. The mouth has once again become an integral part of the rest of the human body. Is periodontal health is a prerequisite for general health? Although growing, there is significant scope for developing the evidence base for association between periodontal and general disease. This is especially true with respect to any possible cause and effect relationship.

The idea that oral infections such as destructive periodontal disease could affect systemic health was suggested more than 100 years ago. In 1891 Miller pub-

lished an article inferring that oral infections could initiate infections elsewhere in the body (Miller, 1891). As will be reported in this review, there are numerous reports claiming such associations, as well as those claiming the opposite. One reason for this apparent contradiction may be related to the different definitions of destructive periodontal disease that have been used. In the clinic, and also in research papers, the expression 'a patient with periodontitis' is often used. What precisely do we mean by this term? What signs and symptoms must be present in any specific individual in order to justify the use of the diagnosis? Should he/she have 4 pockets with bleeding upon probing or perhaps 6 such pockets? Do we require a certain number of areas with attachment loss or bone loss? Others may stress the importance of furcation involvement, or a certain level of bleeding on probing or presence of some specific microorganisms. Perhaps until the periodontal community clearly defines what is meant by 'a patient with periodontitis', there is continued scope for confusion in relation to the association of destructive periodontal disease with other diseases.

Recent reports, such as that of Renvert et al (2003) have constructed matrices of different signs that represent the features of a patient with destructive periodontal disease. Interestingly, of all the single signs, radiographic evidence of bone loss was the parameter most representative of the matrix as a whole. This relatively simple sign may prove useful in future epidemiological investigations of associations between periodontal diseases and other diseases.

The tissue destruction resulting from periodontal disease is the aftermath of a host response to microbial challenge. More than 350 different bacterial types have been encountered in diseased periodontal pockets. Destructive periodontal disease is predominantly associated with an anaerobic gram-negative microflora. Many microbiological periodontal studies have focused on the presence of the most strongly implicated gram-negative species such as *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, and *Bacteroides forsythus* (for review see Slots and Ting, 1999). *P. gingivalis* may carry specific antigenic properties that may allow this pathogen to elude host immune responses with both oral and systemic consequences. Furthermore, recent animal studies have suggested that cysteine proteinases produced by *P. gingivalis* possess virulence factors interrupting host defense mechanisms (Genco et al, 1998). *P. gingivalis* appears to be a critical pathogen in the advanced case of destructive periodontal disease and several potent antigenic factors have been identified including lipopolysaccharide (LPS) and various proteins, including heat shock proteins. Although not conclusive, there is evidence to suggest that host immune functions and differences in immune responses to periodontal pathogens are important factors in destructive periodontal disease. In some circumstances elevated IgG titres to *P. gingivalis* may provide protection against the disease (Persson et al, 1994; Chen et al, 1991; Gu et al, 1998).

This review will cover the possible associations between periodontal disease and coronary heart disease, depression, diabetes, pulmonary diseases and osteoporosis. and focuses on more recent publications.

An online computer literature search on Medline (Entrez-PubMed) was performed. The search terms; 'periodontal disease', 'periodontal diseases', 'periodontitis' and 'alveolar bone loss' were used and combined with the search terms 'diabetes', 'diabetes mellitus', 'cardiovascular diseases', 'arteriosclerosis', 'myocardial infarction', 'coronary heart disease', 'stroke', 'osteoporosis', 'osteopenia', 'pulmonary diseases', 'obstructive lung disease', 'pneumonia', 'lung disease', 'respiratory disease' 'depression', and 'stress'. The search was limited to articles published 1985 to the present in the English language. A total of 1,372 articles were retrieved. In addition to this computer search a hand search was performed. Letters, case reports and review articles were excluded. The present report is based on published studies in peer reviewed journals from which information related to the associations between periodontal disease and the above mentioned systemic diseases could be extracted focusing on papers published during the past years.

DIABETES MELLITUS AND DESTRUCTIVE PERIODONTAL DISEASE

Diabetes mellitus is a heterogeneous group of disorders with different causes but all characterized by hyperglycaemia. Type 1 diabetes mellitus (previously insulin-dependent diabetes mellitus) is due to destruction of the insulin-producing cells. Type 2 diabetes mellitus (previously non-insulin-dependent diabetes mellitus) is the result of insulin resistance coupled with relative beta-cell failure. Diabetes is a common disease affecting 3 – 4% of the general population (Bensch et al, 2003). The incidence of Type 2 diabetes mellitus is increasing possibly due to a change in lifestyle and dietary habits leading to obesity (Friedman, 2000). Type 2 diabetes mellitus has been described as a new epidemic in the context of the American pediatric population. There has been an overall 33% increase in Type 2 diabetes mellitus prevalence documented over the past decade. In 1992, Type 2 diabetes mellitus was a rare occurrence in most pediatric centers. By 1999, the incidence of new Type 2 diabetes mellitus diagnoses ranged between 8% and 45%, depending on geographic location (Kaufman, 2002).

Recent data suggest that the prevalence of diagnosed and undiagnosed diabetes in older subjects approaches 20% (Kohler et al, 1999; Meneilly and Tessier, 2001; Resnick et al, 2001). Diabetes patients have a tendency to develop long-term complications due to their disease. The major complications as a consequence of the hyperglycaemia, include retinopathy, nephropathy, neuropathy

and circulatory abnormalities. Hyperinsulinemia in elderly Type 2 diabetes mellitus subjects has also been associated with cardiovascular disease (Kuusisto et al, 2001) and odds ratios of 2:6 have been reported (Audelin and Genest, 2001). Patients with Type 2 diabetes mellitus have a two-to-four-fold risk of cardiovascular mortality compared to non-diabetic individuals (Nesto, 2001). In a recent study by Persson et al (2003a) the strongest association between diabetes and other diseases was that between diabetes and a history of heart attack and stroke. This finding is consistent with studies suggesting that a unique cluster of metabolic abnormalities, including dyslipidemia, hypertension, insulin resistance, and hyperglycaemia in subjects with diabetes may be linked to their increased risk of cardiovascular disease (Laakso, 1997; Orchard et al, 2001; Kendall and Bergenstal, 2001). Odds ratios approaching 3:1 for mortality have been reported for middle-aged patients with a combination of obesity, hypertension and diabetes (Oldridge et al, 2001).

It is generally perceived that subjects with diabetes mellitus are at greater risk of having destructive periodontal disease (Grossi et al, 1996; Taylor et al, 1998; Taylor 2001) and many studies have reported significant associations between diabetes and destructive periodontal disease (Hugoson et al, 1989; Firatli, 1997; Taylor et al, 1996; Grossi and Genco, 1998). Taylor (2001) concluded in his review of destructive periodontal disease and diabetes mellitus that there was a greater prevalence, severity, extent, or progression of at least one manifestation of periodontal diseases in the large majority of reports evaluated (supportive evidence in 44 of 48 reviewed; 37/41 cross-sectional and 7/7 cohort). The majority of these studies were carried out in populations with Type 1 diabetes. Among the relatively few studies that exist on the relationship between periodontal disease and Type 2 diabetes several are reports from an epidemiological study in the Pima Indians of the Gila River Indian Community in Arizona. Significantly poorer periodontal health was reported among Type 2 diabetics in this group of individuals. The risk of periodontal disease in subjects with diabetes was 2.6 times higher (95% CI 1.0 – 6.6), than for age and sex controls.

Although periodontal disease was common in non-diabetic Pima Indians, diabetes clearly conferred a substantially increased risk (Nelson et al, 1990). Subjects with Type 2 diabetes had an increased risk of destructive periodontitis (loss of attachment) with an odds ratio of 2.81 (95% CI 1.91 – 4.13) (Emrich et al, 1991). Taylor et al (1998) reported that poorly controlled Type 2 diabetes was positively associated with greater risk for a change in bone score as compared to subjects without Type 2 diabetes. The cumulative odds ratio of having more severe bone loss at follow-up compared to individuals without diabetes was 11.4 (95% CI = 2.5 – 53.3), and the authors concluded that poorer glycemic control leads to both an increased risk for alveolar bone loss and more severe progression over those without Type 2 diabetes.

The results found in the Pima Indian studies have been supported by others. In a study of 30 Type 2 diabetes patients and 30 controls significant differences were observed between the poorly controlled diabetic patients and the control group patients ($P < 0.01$) for probing pocket depth and periodontal attachment levels (Novaes et al, 1996). When variations in plaque and age were taken into account, a significant difference in probing attachment level was found comparing 24 patients with non-insulin-dependent diabetes mellitus compared to 24 controls matched by age and plaque levels (Morton et al, 1995). In a larger study sample including 102 randomly sampled diabetic patients and 102 age and gender matched non-diabetic subjects, sites with advanced destructive periodontal disease were found to be more frequent in the diabetic group ($P = 0.006$). However, metabolic control of the disease was not related to periodontal status (Sandberg et al, 2000). Although quite consistent data exist to verify the relationship between periodontal disease and diabetes mellitus the difference in the number of remaining teeth between subjects with or without diabetes was found to be marginal in the Surgeon General's Report of Oral Health (Satcher, 2000). In an older population of well controlled Type 2 diabetes mellitus, no differences in periodontal health in relation to controls were reported (Persson et al, 2003a). These studies were done on elderly individuals and a high general incidence of periodontal disease in this group may explain the contradictory results.

POSSIBLE MECHANISMS

During recent years several mechanisms have been suggested explaining why patients with diabetes may also be at risk for destructive periodontal disease (Oliver and Tervonen, 1993; Salvi et al, 1997; Grossi and Genco, 1998). A two-way relationship was proposed by Grossi and Genco (1998). They proposed an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from lipopolysacarids (LPS), and products of periodontopatic organisms may amplify the magnitude of the advanced glycation end product (AGE). A combination of infection and AGE-mediated cytokine upregulation may explain the increase in tissue destruction observed in diabetes patients.

The pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) produced by monocytes/macrophages and adipocytes has been reported to lower insulin sensitivity (for review see Nishimura and Murayama, 2001). An increase of TNF-α may exacerbate pre-existing periodontal disease by stimulating the synthesis of matrix degrading enzymes (Dayer et al, 1985) and stimulate osteoclasts to activate bone resorption (Kobayashi et al, 2000). After treatment with local minocycline administration in every periodontal pocket around all existing teeth once a week for a month it was demonstrated that the antimicrobial therapy signif-

icantly reduced the number of microorganisms in periodontal pockets ($P < 0.01$), and that the circulating TNF-alpha level was significantly reduced ($P < 0.015$) (Iwamoto et al, 2001). In a recent paper Nishimura et al (2003) speculated in that TNF-α may be an important candidate molecule accounting for the 2-way relationship proposed by Grossi and Genco (1998). Recently, two possible hypotheses for the association between periodontal disease and diabetes were presented by Soskolne and Klinger (2001); 1) A direct causal relationship in which the consequences of diabetes act as modifiers of periodontal disease expression; and 2) an unfortunate combination of genes resulting in a host that could develop both diabetes and periodontal disease under the influence of a variety of environmental stressors.

Chronic gram-negative infections are attributed as the etiology for destructive periodontal disease. However, periodontal pockets in subjects with diabetes mellitus do not seem to harbor more pathogens associated with destructive periodontal disease than what can be found in periodontal pockets of non-diabetic subjects (Collin et al, 1998). Thus, the similarity of pathogens associated with destructive periodontal disease in subjects with or without diabetes suggests no difference in the infectious etiology, although the prevalence of *P. gingivalis* appears to be higher in samples from subjects with diabetes mellitus (Thorstensson et al, 1995). However, diabetic subjects have been shown to react with a higher degree of inflammation to equivalent bacterial burdens (Salvi et al, 1998). Microvascular permeability is increased in both types of diabetes mellitus (Brausewetter et al, 2001). This may result in more extensive signs of gingival inflammation that may, in turn, lead to deeper probing depths in diabetic patients.

A long-term cytokine-mediated acute-phase reaction occurs in Type 2 diabetes which may contribute to high levels of inflammation (Pickup and Crook, 1998). Moreover, auto-immune factors may influence and explain the severity of destructive periodontal disease in subjects with diabetes mellitus. A linkage between periodontal inflammation and glutamic acid decarboxylase (GAD) antibody titre levels has been identified (Kono et al, 2001). For example, the levels of serum glutamic acid decarboxylase autoantibody (GAD65) in combination with elevated IgG titres to *Porphyromonas gingivalis* before periodontal treatment appears to be indicative of Type 1 diabetic patients not being responsive to non-surgical initial therapy (Sims et al, 2001; Sims et al, 2002).

THE EFFECT OF DESTRUCTIVE PERIODONTAL DISEASE AND PERIODONTAL TREATMENT ON GLYCEMIC CONTROL

Periodontal infections may increase the severity of diabetes and compromise metabolic control, similar to other infections (Grossi and Genco, 1998). Poor diabetic control seems to occur in at least 40% of adults with Type 1 diabetes mellitus and 54% in subjects with Type 2 diabetes mellitus (Schiel et al, 2001). In a study by van den Arend et al (2000) more than 60% of subjects with diabetes mellitus had poor diabetic control. Poor glycemic control in patients with advanced periodontal disease has been reported (Taylor et al, 1996; Collin et al, 1998).

In a recent paper by Tsai et al (2002) data on 4,343 persons (aged 45 – 90 years) from the NHANHES III database were used to evaluate the relationship between periodontal disease and diabetes mellitus. Severe periodontal disease was defined as ≥ 2 sites with ≥ 6 mm loss of attachment and at least one site with probing pocket depth of ≥ 5 mm. Individuals classified as having poorly controlled diabetes had glycosylated haemoglobin > 9%. It was reported that individuals with poorly controlled diabetes mellitus had a significantly higher prevalence of severe destructive periodontal disease than those without diabetes (odds ratio; 2.90; 95% CI: 1.40 – 6.03) after controlling for age, education, smoking status, and calculus. However, at least one recent study has contradicted previous perceptions that abnormal glucose tolerance is a risk indicator for periodontal disease (Noack et al, 2000) suggesting that Type 1 diabetic status in itself may not necessarily mean a higher risk for destructive periodontal disease.

Whether treatments of destructive periodontal disease in subjects with diabetes mellitus improve their blood sugar levels is still unclear both for Type 1 diabetes mellitus and Type 2 diabetes mellitus. No change in glycosylated haemoglobin after periodontal treatment has been reported by several investigators (Aldridge et al, 1995; Smith et al, 1996; Westfelt et al, 1996; Christgau et al, 1998), while others have reported such changes (Miller et al, 1992; Grossi et al, 1996; Iwamoto et al, 2001). However, those studies reporting a change in glycosylated haemoglobin after treatment either used systemic (Miller et al, 1992; Grossi et al, 1996) or local administration (Iwamoto et al, 2001) of antibiotics as an adjunct to mechanical periodontal therapy. Accordingly, the possibility that the differences in results may be related to the use of antibiotics cannot be overlooked.

CARDIOVASCULAR DISEASES AND DESTRUCTIVE PERIODONTAL DISEASE

Cardiovascular diseases (CVD) are the leading cause of death in most Western countries and may affect 50% or more of the older population. Well known cardiovascular risk factors such as elevated low-density lipoprotein (LDL), hypertension, smoking, male gender and low socio-economic factors (Keil, 2000; Wood, 2001) have failed to explain the observed variations in the prevalence and severity of CVD (Kuller et al, 2000). A link between infection in general and atherosclerotic disease

including both myocardial and cerebral infarction has been widely suggested.

Several epidemiological studies have suggested associations between coronary heart disease (CHD) and destructive periodontal disease (DeStefano et al, 1993; Mattila, 1993; Beck et al, 1996; Loesche et al, 1998; Morrison et al, 1999; Mattila et al, 2000). Other researchers have failed to find associations between CHD and destructive periodontal disease (Hujoel et al, 2000; Howell et al, 2001; Jansson et al, 2001). An association between stroke and periodontal disease has also been reported (Beck et al, 1996; Wu et al, 2000; Joshipura et al, 2003). Joshipura et al (2003) found that men who had ≤ 24 teeth at baseline were at higher risk of stroke compared to men with ≥ 25 teeth (OR 1.57: 95% CI 1.24 – 1.98), suggesting that fewer teeth (indicative of previous dental disease) may be associated to an increased risk of stroke.

It has been proposed that the reported associations between cardiovascular diseases and destructive periodontal disease may be explained by confounding factors (Hujoel et al, 2000). Smoking is considered a significant risk factor for both CHD and destructive periodontal disease. In a recent Cochrane review by Madianos (2002) it was concluded that the association between destructive periodontal disease and increased risk for coronary heart disease appears to be inconsistent at all levels of evidence. The reasons for conflicting reports may be due to the heterogeneity in design of the studies and their definitions of periodontal disease. Several cohort studies have defined destructive periodontal disease based on indices such as the Russell index (DeStefano et al, 1993; Hujoel et al, 2000, 2001), total dental index (Mattila, 1995), a questionnaire (Joshipura et al, 1996) or measurements of alveolar bone loss (Beck et al, 1996; Jansson et al, 2001). It is perhaps likely that these widely differing definitions of destructive periodontal disease have predisposed to conflicting findings. The inherent measurement error and difficulty in interpretation associated with probing measurements also contribute to difficulty in accurately defining destructive periodontal disease in individuals.

As reviews on this particular subject abound in the literature, this review is limited to those papers published from 2001 – 2003 inclusive. Data from studies on the association between CHD and destructive periodontal disease are presented in Table 1. As previously stated, the results differ considerably from no association (Jansson et al, 2001) to an odds ratio of 14.1 (Persson et al, 2003b). The reasons for these diverse findings may be due to inadequate definitions of destructive periodontal disease. There was also considerable heterogeneity in important aspects of study design such as aspects related to control subjects and confounding factors investigated. In the study by Persson et al (2003b) a significant effort was made to enroll carefully matched control subjects who received specialist examination of both cardiovascular and dental status. The individuals in the control group were matched for age, gender and smoking status. Smoking is a significant risk factor for both cardiovascular disease and destructive periodontal disease (Keil, 2000; Wood, 2001; Capewell et al, 1999; Bergström, 1989). A history of smoking has been reported as an important confounder in studies of the association between CVD and destructive periodontal disease and when accounted for the odds ratios for association between the two conditions are drastically reduced (Hujoel et al, 2001, 2002). However, even in a sub-analysis of non-smokers in the study by Persson et al (2003b) the odds of an association between acute myocardial infarction and destructive periodontal disease remained statistically significant and higher than reported for any previous study.

POSSIBLE MECHANISMS

Low-grade injury to the artery wall with a resultant inflammatory response was first postulated as the pathogenesis of atherosclerosis more than 100 years ago (Virchow, 1856). The possibility that atherosclerosis is an immune-mediated inflammatory disease has renewed interest in the potential role of infectious agents in initiating or modulating atherosclerosis (de Boer et al, 2000). Many different bacteria and viruses have been suggested as etiological factors (Valtonen, 1991; Ellis, 1997; Carlisle and Nahata, 1999; Coombes and Mahony, 1999; de Boer et al, 2000). A positive association between elevated serum titres to different pathogens and a history of acute myocardial infarction provides support for the hypothesis that there is a causal association between chronic infections and the development of coronary heart disease (Kahan et al, 2000; Shimada et al, 2000). The 'response to the injury' hypothesis includes a perception that hyperlipidemia, and especially that oxidized low-density lipoproteins, can cause endothelial cell injury. Lipopolysaccharide (LPS) from, for instance, *C. pneumoniae* can then induce macrophage foam cell formation which results in accumulation of excess cholesterol, contributing to the development of vascular atheroma (Kalayoglu and Byrne, 1998). Interestingly, periodontal disease status measured using CPITN was found to be positively associated to cholesterol and LDL-cholesterol levels in men (Katz et al, 2002).

In patients with endocardial damage, for instance, damaged heart valves following rheumatic fever or patients with artificial heart valves, bacteriemia can result in infective endocarditis, and myocardial or cerebral infarction (Debelian et al, 1994). Bacteriemia of oral origin may explain approximately 10% of all cases of infectious endocarditis (Drangsholt, 1998). Dental procedures including routine oral hygiene efforts and probing of periodontal pockets induce transient bacteriemia (Herzberg and Meyer, 1996). In a recent publication by Geerts et al

Table 1 Selected studies published after 2000 on the association between CHD and periodontitis

Authors	Number of subjects	Study design	Periodontal parameters	Outcome of CHD	Measure of association	Adjusted for
Jansson et al 2001	1393 subjects 706 females	Cohort study Up to 26 years follow up	Oral health score	Death	For individuals < 45 years OR 2.7 (p = 0.04)	Age, gender, smoking and CHD at baseline
Hujoel et al 2001	4,027 subjects 2.221 females Age 25 – 74 yrs	Cohort study Mean follow up 17 years.	The Russell Index	Fatal CHD, MI, coronary revascularization procedures	RR (95% CI): 1.02 (0.86 – 1.21)	Age, gender, race, education, poverty index, marital state, hypertension cholesterol, diabetes, BMI, physical activity, smoking, alcohol, nervous breakdown
Bazile et al 2002	80 cases 48 male 32 females Age 23 – 83 yrs (median 54) 50 cases with CAD 30 controls	Case control	PI, GI, BOP, PD, CAL, MT	Angiographic evidence of CAD. AI = acute infarction (n=20) UA = unstable angina (n=10) SA = stabile angina (n= 20)	Significant association between BOP and GI and acute infarction Significant association between CAL and unstable angina	Age, gender
Hujoel et al 2002	636 dentate cases with previous history of CHD	Cohort study	The Russell Index	New CHD events	OR (95% CI): Periodontitis 0.97 (0.72 – 1.31)	Age, gender, race, education, poverty index, marital state, hypertension cholesterol, diabetes, BMI, physical activity, smoking, alcohol, nervous breakdown
Lopez et al 2002	27 cases 34 controls Age 30-50 yrs	Case control	AL, PD: mean AL ≥ 1.5 mm	AMI, angina pectoris, unstable angina	Mean attachment level OR (95% CI) 3.17 (1.31 – 7.65) Mean PD 8.64 (1.22 – 61.2)	Systemic blood pressure, diabetes, smoking
Malthaner et al 2002	100 cases 53 CAD + 47 CAD –	Case control	BOP, PD, CAL, GR, LT, BL	CAD + = 50% stenosis in one epicardial artery	BL OR = 1.31 Mean CAL OR = 1.06 Both not significant	Age, smoking history
Persson et al 2002	77 cases 987 controls 579 females Age 60 – 75	Cross-sectional	PMX score (composite bone score measured in panoramic x-rays) Continuous variable	Questionnaire (heart attacks)	OR (SE): 1.412 (0.130) P value = 0.008	Age, gender, stroke
Persson et al 2003b	160 cases 80 with AMI 80 controls	Case control	BL	Acute myocardial infarction	OR (95% CI) 14.1 (5.5 to 28.2) p < 0.0001)ä for never smokers 5.5 (1.5 – 20.5) p < 0.01)	Age, gender, smoking

AL = attachment level, BOP = bleeding on probing, BL = radiographic bone loss, CAL = Clinical attachment level, CAD + = coronary artery disease positive, CAD - = coronary artery disease negative, GI = gingival index, GR = gingival recession, LT = loss of teeth, OR = Odds Ratio, PD = pocket depth, PI = plaque index

(2002) it was demonstrated that gentle mastication is able to induce and release bacterial endotoxins from the oral cavity origin into the bloodstream. Thus, the likelihood of recurrent bacteriemia in subjects with destructive periodontal disease is high and may explain why it is possible that oral pathogens can be found in atheroma. Periodontal pathogens, such as *A. actinomycetemcomitans*, and *P. gingivalis* have characteristic LPS cell-wall capsules (Herzberg and Meyer, 1996; Genco et al, 1998). The relationship between the presence of multiple infectious agents in human carotid specimens and patho-anatomic features of the corresponding carotid plaques has been studied, demonstrating that both *P. gingivalis* and *S. sanguis* can be found in atherosclerotic plaques (Chiu, 1999). The ability oral of pathogens, such as *P. gingivalis*, *E. corrodens*, *P. intermedia*, and *S. sanguis* to invade human coronary endothelial cells has been demonstrated (Dorn et al, 2000). Such findings suggest that the presence of these microorganisms may influence atherosclerotic plaque morphology, predisposing to plaque disruption leading to an acute coronary syndrome or ischemic stroke. Recently, Sharma et al (2000) reported that *P. gingivalis* was able to induce platelet aggregation and that vesicles (outer membrane invaginations that are shed into the environment by the bacteria) of *P. gingivalis* are potent inducers of mouse platelet aggregation *in vitro*. Their data also show that the initial adherence of the bacterium to platelet may be facilitated by *P. gingivalis* fimbriae and that *P. gingivalis* vesicles possess platelet aggregation-inducing activity. Further evidence of the role of *P. gingivalis* in the development of atherosclerosis is provided by an odds ratio of 7.0 that elevated serum IgG titres to *P. gingivalis* are associated with elevated serum cholesterol values (Cutler et al, 1999). Thus it appears that the putative infectious etiology in cardiovascular disease (CVD) and destructive periodontal disease share immunopotent factors.

The possibility that *P. gingivalis* infection may participate in the development of the atherosclerotic plaque is consistent with theories on how peripheral infection can induce a release of C reactive protein (CRP) which in turn activates endothelial cells and macrophages. This macrophage activity results in the development of foam cells, once an endothelial trauma is present, possibly induced by oxidated LPS in the blood stream (Ridker et al, 1997). The oxidated LPS may originate from organisms such as *P. gingivalis.* Thus *P. gingivalis* may be an infectious agent not only in destructive periodontal disease but may also serve as an infectious factor in cardiovascular disease.

Markers of inflammation (Il-1, Il-6) are elevated in serum of patients with atherosclerosis as well as in patients with destructive periodontal disease, suggesting that a systemic pro-inflammatory imbalance is a common denominator. Primary responses in inflammation are mediated by cytokines. For example interleukin 1 and its receptor antagonist Il-1 Ra have been of interest in exploring the role of inflammation in systemic diseases and the risk for sepsis (Stuber, 2001). A lower incidence of re-stenosis after coronary stenting has been reported in patients with the allele 2 of the Il-1 Ra gene (Kastrati et al, 2000). The observation that Il-1 β and TNF-α can induce high serum lipid level suggests a mechanism by which systemic elevation of serum lipids can be induced by cytokines in response to oral infection. Thus, such oral infection may have a significant impact on cardiovascular health. A proposed model by which such cytokines induced by the inflammatory process in destructive periodontal disease may amplify a host-response which results in a destructive-periodontal-disease-associated atherosclerosis has been suggested (Offenbacher et al, 1999). A relationship between destructive periodontal disease and carotid artery intima wall thicknesses has also been reported (Beck et al, 2001).

In a multivariate logistic regression model accounting for confounders the odds of an intima-media wall thickness $\geq$ 1 mm were higher for severe destructive periodontal disease, defined as attachment loss > 3 mm at $\geq$ 30% of sites (odds ratio of 1.31: 95% CI 1.03 – 1.66). A genetic marker has become available to determine a polymorphism genotype of patients with possibly increased susceptibility for chronic destructive periodontal disease. Thus, subjects who are genotype positive for the Interleukin-1 (IL-1) gene polymorphism appear to have more advanced destructive periodontal disease than IL-1 genotype negative patients of the same age cohort (Kornman et al, 1997). There is also evidence that Interleukin-1 (IL-1) gene polymorphism positive patients may be more susceptible to tooth loss than negative subjects (McGuire and Nunn, 1999). Prospective studies have shown that Interleukin-1 (IL-1) gene polymorphism positive non-smoking subjects over the age of 50 have significantly deeper periodontal pocket probing depths than their negative counterparts (Cullinan et al, 2001). Analysis of data from young adults has also suggested that the IL-1A(+ 4845) [1,1]/IL-1B(+ 3953) [2,2] genotype is associated with destructive periodontal disease (Thomson et al, 2001). Future research in genetic markers for patients' susceptibility to both cardiovascular diseases and destructive periodontal disease may demonstrate similar genetic trends within susceptible individuals.

In summary, there are at least three possible mechanisms by which oral infections may contribute to cardiovascular diseases namely; (1) direct effect of infectious agent in atheroma formation; (2) indirect or host-mediated responses; and (3) common genetic predisposition.

OSTEOPOROSIS

Osteoporosis is a degenerative disease that affects primarily women, but can also occur in men. Osteoporosis is characterized by a loss of bone mineral density (BMD),

and often culminates in a fracture of the hip, wrist, and/or vertebrae. The diagnosis of osteoporosis is often made using bone density measurements. The World Health Organization defines osteoporosis when BMD is 2.5 standard deviations below the average peak bone density achieved in young adults, matched by gender and race. Osteoporosis is estimated to affect approximately 20 million people in the United States and causes approximately 2 million fractures each year (National Institute of Arthritis and Skin diseases, 2000). Self-reports from subjects in a Swedish study, based on diagnostic criteria from the NHANES III in the USA, reveal that the prevalence of osteoporosis approaches 22% in women and 6.3% in men between the ages of 50 and 84 years (Kanis et al, 2000). Using panoramic evaluation of the mandibular cortex osteporosis/osteopenia was identified in 52.4% of women in a study of elderly (60 – 75 years) (Persson et al, 2002). Studies using dual X-ray absorptiometry suggest that osteoporosis can be diagnosed in 49 – 72% of women at the age of 70 (Löfman et al, 2000). Several factors have been associated with osteoporosis, including female gender, age, ethnicity, diet, and lifestyle (Eddy et al, 1998; Smeets-Goevaers et al, 1998). A diagnosis of osteoporosis, especially at the earlier stages, may be difficult. As a result, many older people may have osteoporosis without knowing it. Studies have shown that mandibular bone mass is correlated with skeletal bone mass (Kribbs et al, 1983; Kribbs and Chestnut, 1984; von Wowern et al, 1994).

OSTEOPOROSIS AND PERIODONTAL DISEASE

Spinal fractures in older women are associated with fewer remaining teeth and destructive periodontal disease, suggesting that destructive periodontal disease may be aggravated in subjects with osteoporosis (Taguchi et al, 1995; Birkenfeld et al, 1999). Subjects with a self-reported history of osteoporotic fractures also tend to have increased resorption and thinning of the mandibular lower cortex (Bollen et al, 2000).

A limited number of human studies, most of which are cross-sectional, have addressed the possible relationship between osteoporosis and periodontal disease (Table 2, 3). The studies presented in Table 2 have used tooth loss to reflect periodontal disease. Several investigators were unable to detect any association between bone mineral density (BMD) and tooth loss (Klemetti and Vainio, 1993; Klemetti at al, 1994; Hildebolt et al, 1997; Mohammad et al, 1997; Earnshaw et al, 1998), whereas others reported such an association (Krall, 1994; May et al, 1995; Watawski-Wende et al, 1996; Bando et al, 1998; Taguchi et al, 1999; Inagaki et al, 2001). However, in the study by May et al (1995) the association of tooth loss was insignificant in the females after controlling for age, BMI and smoking and in the study by Taguchi et al (1999) no association was found between BMD and loss of anterior teeth. In the above cited studies tooth loss was used as a measure of periodontal disease. Teeth may however be lost due to other reasons than destructive periodontal disease making it difficult to draw definite conclusions from such cross-sectional studies. Few longitudinal studies exist and they often include the use of either dietary supplements such as vitamin D and/or calcium or the use of hormone replacement therapy (HRT).

In other studies the possible association between systemic osteoporosis and periodontal status has been evaluated using different clinical parameters (Table 3). Several researchers report a lack of association between clinical measures of destructive periodontal disease and BMD (Elders et al, 1992; Hildebolt et al, 1997; Lundström et al, 2001) whereas others find the opposite (Von Woweren et al, 1994; Mohammad et al, 1996; Payne et al, 1999; Ronderos et al, 2000; Tezal et al, 2000). The majority of studies are cross-sectional and several possible confounders may or may not have been factored into the analyses. In a prospective study by Payne et al (1999) it is reported that osteoporotic women exhibited more loss of alveolar bone loss than controls. The patient population included in this study is limited however, and further prospective studies are needed to elucidate the possible association between osteoporosis and periodontal disease.

EFFECT OF MEDICAL TREATMENT OR PREVENTION OF OSTEOPOROSIS AND TOOTH LOSS

Osteoporosis can be treated by a variety of methods, the most common being the use of estrogens, with or without progesterone. Postmenopausal women who did not use hormone replacement therapy exhibited a negative correlation between the number of teeth retained and the time since menopause (Becker et al, 1997) and hormonal replacement therapy has been associated with better periodontal status and a decreased risk for tooth loss (Paganini-Hill, 1995).

In a prospective study of 42, 171 postmenopausal women (age 65 to 69) the risk of tooth loss was 24% lower in women who were currently using hormones. This decreased risk for current hormone users was observed regardless of the duration of use and was similar for a variety of hormone preparations, suggesting that hormone therapy may reduce tooth loss (Grodstein et al,1996). In the Farmington Heart Study the effects of hormonal replacement therapy was investigated in 488 women. Estrogen users were found to have more remaining teeth than nonusers after controlling for age, smoking status and education (Krall et al, 1997). The odds of being edentulous were found to be reduced by 6% by each year of increase in the duration of hormonal replacement therapy, suggesting that hormonal replacement therapy protects against tooth loss and reduces the risk for edentulism.

Table 2 Summary studies of the association between osteoporosis (BMD) and periodontal clinical parameters

Authors	Number of subjects	Subjects	Clinical recordings	Study design	Significant findings
Elders et al 1992	286	Peri-menopausal healthy females (21% edentulous) Age: 46 to 55 years	Clinical parameters of periodontitis and distance from cemento-enamel junction to marginal bone level on radiographs	Cross-sectional	In the dentate group, no correlation was found between BMD and clinical parameters of periodontology or alveolar bone height
Wowern et al 1994	26	12 dentate female patients with osteoporotic fractures 14 normal dentate females comparable with respect to age, menopausal age, smoking habits and social status	Clinical attachment levels at index teeth	Case-control	Significant lower forearm and mandibular BMC in osteoporotic than in control group and significant larger attachment loss in the osteoporotic group
Mohammad et al 1996	42	20 females with high and 22 with low bone density	Clinical attachment levels	Cross-sectional case control study	Individuals with low BMD had more attachment loss in the form of gingival recession
Hildebolt et al 1997	135	Postmenopausal women. Age 41 – 70 years	Probing depths	Cross-sectional	No relationship
Payne et al 1999	38	17 women with osteoporosis and 21 controls with normal BMD	Alveolar bone height loss, crestal and subcrestal bone density loss	2 year prospective study	Osteoporotic women exhibited higher frequency of alveolar bone height loss, crestal and subcrestal bone density loss
Weyant et al 1999	292	Dentate women, mean age 75.5 years	Clinical attachment levels	Cross-sectional	Insignificant association between BMD and clinical attachment level after controlling for confounders
Ronderos et al 2000	11655 NHANS III	66 men and 283 women with osteoporosis	Clinical attachment levels	Cross-sectional	The greater CAL present among women with low BMD was associated with gingival recession. Inverse relationship between oestrogen use and CAL
Tezal et al 2000	70	Postmenopausal women	Clinical attachment levels and interproximal alveolar bone loss	Cross-sectional	Skeletal BMD was related to interproximal bone loss controlling for age, age at menopause, oestrogen supplementation, BMI, smoking and supragingival plaque
Lundström et al 2001	36	15 women with osteoporosis and 21 matched controls	Gingival bleeding, probing pocket depths, marginal bone level and recession	Cross-sectional	No difference regarding clinical parameters

Table 3 Summary of studies on the association between osteoporosis (BMD loss) and tooth loss

Authors	Number of subjects	Subjects	Study design	Significant findings
Klemetti and Vainio 1993	355	Postmenopausal women.	Cross sectional	No association between tooth loss and BMD
Krall et al 1994	329	Postmenopausal women. 281 without complete dentures.	Cross sectional	A significant positive relationship between the number of teeth and BMD. Controlling for years since menopause, pack-years of smoking, education and body mass index (BMI)
Klemetti et al 1994	227	Postmenopausal women.	Cross sectional	No statistical differences
May et al 1995	1482	608 men 874 women Age 65 – 76 years	Cross sectional. Self reported tooth loss	Association between tooth loss and lower BMD in men, but less consistent in women
Krall et al 1996	189	Postmenopausal women.	7 year longitudinal study among individuals not on HRP but on different forms of vitamin D and/or Calcium supplementation	Women who lost teeth (n = 45) during the follow up period experienced less favourable BMD as compared to these not loosing teeth (n = 144). Analysis controlled for years since menopause, BMI, number of teeth at baseline, smoking, and assigned treatment
Wactawski-Wende et al 1996	70	Postmenopausal women. Age 51 – 78 years	Cross-sectional	Osteopenia was related to alveolar crest height and tooth loss. Adjusting for confounders, age, years since menopause, BMI, oestrogen use, smoking,
Hildebolt et al 1997	135	Postmenopausal women. Age 41 – 70 years.	Cross-sectional	No association between tooth loss and BMD Multivariate analysis taking age and smoking into account
Mohammad et al 1997	44	Postmenopausal women	Cross-sectional	No association between tooth loss and BMD after adjusting for age and periodontal status.
Bando et al 1998	26	Postmenopausal women. 14 periodontaly healthy (mean age 64 years) and 12 edentulous (mean age 67 years)	Cross sectional case control study	BMD was significantly lower in edentulous subjects.
Earnshaw et al 1998	1365	Early postmenopausal women. Age 45 – 59 years.	Cross-sectional. Adjusting for confounders	No relationship between tooth count and BMD.
Taguchi et al 1999	90	Post-menopausal women	Cross-sectional. Adjusting for confounders	BMD was associated with number of posterior teeth but not with the number of anterior teeth
Inagaki et al 2001	101	Post-menopausal women	Cross sectional	Among post-menopausal women, those with very low BMD had fewer teeth present than women with normal BMD

In a 3-year, double-blind, randomized, placebo-controlled study hormone/estrogen replacement therapy on postcranial bone density was accompanied by positive effects on oral bone mass. A total of 135 postmenopausal women (aged 41 – 70 years) with no evidence of moderate or severe periodontal disease were randomized to receive daily oral conjugated estrogen alone or in combination with medroxyprogesterone acetate or placebo. All subjects received calcium carbonate (1000 mg/d) and cholecalciferol (800 IU/d) supplements. Hormone/estrogen replacement therapy significantly increased alveolar bone mass compared to placebo and tended to improve alveolar crest height. Changes in alveolar bone mass correlated with bone density changes in the total femur (Civitelli et al, 2002). Other studies on older women taking hormone replacement therapy have also demonstrated better periodontal health than women not on therapy (Persson et al, 1998, 2002; Payne et al, 1999).

Other medications have also been used in order to prevent osteoporosis with possible effects on periodontal disease. Randomized, controlled trials have demonstrated that increased intake of calcium or vitamin D slows the rate of bone mineral loss at such sites as the hip and forearm, as well as the total body (Dawson-Hughes et al, 1997; Chevally et al, 1994). Tooth loss was examined in 145 healthy subjects aged 65 years and older who completed a 3-year, randomized, placebo-controlled trial of the effect of calcium and vitamin D supplementation on bone loss from the hip, as well as a 2-year follow-up study after discontinuation of these supplements. Patients on supplement therapy lost fewer teeth than the ones taking the placebo suggesting that intake of calcium and vitamin D had a beneficial effect on tooth retention (Krall et al, 2001).

POSSIBLE MECHANISMS

It has been hypothesized that osteoporosis may decrease the alveolar bone mass, making it more susceptible to resorption by the periodontal inflammatory reaction. Over the past few years a possible relationship between osteoporosis and periodontal disease has attracted research interest. However, such a relationship is difficult to assess, as confounding factors such as oral hygiene, socio-economic status, age, menopausal age, hormone intake, smoking habits, and race may affect the results (Varenna et al, 1999; von Wowern, 2001; Wactawski-Wende, 2001).

RESPIRATORY DISEASES

Respiratory diseases are major causes of significant morbidity and mortality. Lower respiratory tract diseases were recently reported to be one of the most common causes of death worldwide and chronic obstructive pulmonary disease (COPD) the sixth leading cause of mortality (Murray and Lopez, 1997). COPD is a condition characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. Emphysema is the results of an irreversible damage in which the alveoli are chronically enlarged and unable to fully discharge their contents. Cigarette smoking is considered to be the major cause of COPD.

The lower respiratory tracts are normally sterile. This condition is maintained by the tracheobronchial secretions, the mucociliary transport of inhaled microorganisms and particles, the cough reflex and the immune defense mechanisms. Respiratory infections occur when the host defense system fails to eliminate infectious agents from the lower respiratory tract. Pneumonias can broadly be divided in two types, community acquired, and hospital acquired. These two types of pneumonia differ in their causative agents. Community acquired pneumonia is typically caused by pathogens that normally reside on the oropharyngeal mucosa, such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenza, Chlamydia pneumoniae, Legionella pneumophila, Candida albicans*, and anaerobic species. In contrast hospital acquired pneumonia is often caused by bacteria that are not normally residents of the oropharynx but enter this milieu from the environment, including gram negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *Serratia* sps, *Enterobacter* sps), *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Scannapieco, 1999).

Microorganisms can reach the lower respiratory tract by aspiration of oropharyngeal contents, inhalation of infectious aerosols, spreading from contiguous sites and haematogenous spread from extra pulmonary sites of infection (Scannapieco and Mylotte, 1996). An association between periodontal diseases and respiratory diseases has been reported. Although several reviews are available the number of studies in this area is comparably few.

ASSOCIATIONS BETWEEN PERIODONTAL DISEASE AND ASPIRATION PNEUMONIA

The aspiration of oral contents is probably one of the most important links between periodontal disease and respiratory disease. In patients suffering from neurological disorders, for instance stroke victims and those suffering from Parkinson's disease, swallowing is often affected (Terpenning, 2001). The unintentional inhalation of saliva containing oral microorganisms is believed to be a significant factor for aspiration pneumonia. Common potential respiratory pathogens such as *S. pneumoniae*, *S. pyogenes*, *M. pneumoniae* and *H. influenza* can colonize the oropharynx and can be aspirated into the lower respiratory tract. Other Species, including *A. actinomycetemcomitans*, *P. gingivalis* and *Fusubacterium* species can also be aspirated and cause pneumonia (for

review see Scannapieco, 1999). It is recognized that pneumonia can be the result of an anaerobic infection and a link between the oral anaerobic microflora and aspiration pneumonia was demonstrated using transtracheal aspiration of the samples from the lung in order to avoid contamination of the samples from the oral cavity (Finegold, 1991).

Intensive care patients have poorer oral hygiene than non-hospitalized patients and have a higher prevalence of respiratory pathogen colonization on teeth and on the oral mucosa than do age and gender matched outpatients (Scannapieco et al, 1992; Scannapieco and Mylotte, 1996). Hospitalized older patients are reported to have poor oral hygiene (Mojon et al, 1995; Meurman et al, 1997; Pajukoski et al, 1999; Andersson et al, 2002a.). Frail elderly people with a high degree of dependence on others in carrying out everyday tasks are in need of assistance in carrying out adequate oral hygiene. Older frail inpatients are often unable to feed themselves and a patient may suddenly find food placed in the mouth by nursing personal at unexpected times resulting in aspiration. In a prospective study it was demonstrated that feeding by others was significantly associated with the development of aspiration pneumonia (Langmore et al,1998). Kiyak et al (1993) examined individuals at 31 nursing homes and found that 72% needed improved oral hygiene. Elderly individuals are often taking several medications that can lower the salivary flow rate thereby increasing the bacterial density in the existing saliva. A positive relationship between poor oral health status and aspiration pneumonia among elderly residents of chronic care facilities was reported by Limeback (1988). Scannapieco and Mylotte (1996) concluded that intensive care patients and nursing home residents were groups with a high risk for bacterial pneumonia. This conclusion was substantiated by Mojon et al (1997), who reported that poor oral hygiene may be a risk factor for respiratory tract infection in elderly institutionalized individuals. In a sample of 350 elderly veterans dental conditions were studied in relation to aspiration pneumonia (Losche and Lopatin, 1998). The individuals with definite aspiration pneumonia had similar numbers of missing teeth compared to individuals without pneumonia. However, the individuals with definite pneumonia had a significantly higher periodontal index score, more dental caries and higher plaque index scores. The individuals with definite aspiration pneumonia were 3.3 times more likely to have higher periodontal score (95% CI; 1.06-10.3; p=0.05) than individuals with no pneumonia. This suggests that an association may exist between poor periodontal status and aspiration pneumonia.

Terpenning et al (2001) investigated the importance of medical and dental factors in aspiration pneumonia in an older veteran population in a 10-year prospective study. Many factors increased the risk for aspiration pneumonia. Dentate individuals with eating problems had an odds ratio (OR) of 13.9 (95% CI; 3.2 – 60.8), *Streptococcus sobrinus* in saliva (OR 6.2; 95% CI; 1.4 – 27.5), and *P. gingivalis* (OR 4.2; 95% CI; 1.6 – 11.3). This study supports the significance of oral factors while controlling for medical risk factors in aspiration pneumonia.

ASSOCIATIONS BETWEEN PERIODONTAL DISEASE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Three cross-sectional studies were retrieved on the relationship between COPD and periodontal disease (Scannapieco et al, 1998; Scannapieco and Ho, 2001; Hayes et al, 1998). Scannapieco et al (1998) used cross-sectional data from NHANES-I in order to determine a possible association between COPH and periodontal disease. They demonstrated that the 41 individuals that were diagnosed as having a respiratory disease by a physician were more likely to have a significantly higher oral hygiene index score as compared to subjects without a respiratory disease. Logistic regression analysis, considering age, race, gender, smoking status and simplified oral hygiene indicated that individuals with the worst oral hygiene were 4.5 times more likely to have chronic respiratory disease compared to those with an oral hygiene score of 0. In a subsequent study by Scannapieco and Ho (2001) used cross-sectional data from NHANES-III and a multivariate logistic regression analysis in order to evaluate the relationship between COPD and periodontal disease (as defined as mean attachment loss ≥ 3 mm). Controlling for a number of covariates (age, race or ethnicity, gender, education, income, frequency of dental visits, diabetes, smoking and alcohol consumption) they found an OR of 1.45 (95% CI; 1.02 – 2.05).

In a longitudinal study of initially 1,231 adult men over a 25-year-follow-up period the likelihood that subjects would develop COPD over time was studied and related to their initial periodontal status as evidenced by alveolar bone loss. Multivariate logistic regression analysis was used to estimate the contribution of alveolar bone height at baseline. It was found that individuals with the most prominent alveolar bone loss on radiographs had a significantly higher likelihood of developing COPD over time (OR 1.77, 95% CI; 1.27 – 2.48).

In a recent review by Garcia et al (2001) the same material was further elucidated regarding the possible confounding role of smoking in the association between periodontal disease and the risk of COPD. They found that subjects in the cohort quintile with the worst periodontal health status (alveolar bone loss and probing depths) at the study baseline were at a significantly elevated risk of subsequently developing COPD (Relative Risk 1.75, 95% CI; 1.33 – 2.30 and RR 1.44, 95% CI 1.09 – 1.90 respectively). The analysis was adjusted for age, height, smoking, alcohol and education. Separate analysis using smoking as a categorical variable (current/former/

never smoker) yielded relative risk values approximately 5% smaller but still significant at the 95% level.

POSSIBLE MECHANISMS

Several mechanisms are proposed to explain the possible association of periodontal disease and respiratory diseases; 1) Teeth may serve as a reservoir for microorganisms that become washed into saliva and then aspirated into the lungs; 2) periodontal disease associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens; 3) periodontal disease associated enzymes may destroy salivary pellicles on pathogenic bacteria; and 4) cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens (for review see Scannapieco 1999). Changes in the adhesion of respiratory pathogens to respiratory epithelium that had been exposed to oral bacteria were compared to unexposed epithelial cells (Scannapieco et al, 2001). These preliminary *in vitro* studies suggest that oral bacteria may kill respiratory epithelial cells, and that pre-treatment of respiratory epithelial cells (Hep-2 cells) increased the binding of *S. aureus*.

CONCLUSIONS

A majority of published studies support a relationship between periodontal disease and diabetes mellitus. Treatments of periodontal disease including the use of local or systemic antibiotics may affect the glycemic control. Additional well-controlled prospective studies are warranted to further elucidate this possible relationship. Insufficient data are available to support a two-way relationship between destructive periodontal disease and diabetes mellitus. From a clinical point of view diabetes should be regarded as one of the factors increasing the risk for periodontal disease.

At present there is but limited evidence that destructive periodontal disease is associated with an increased risk for CHD and further research is needed to explore such a relationship in prospective studies. Studies exploring whether periodontal treatment can reduce the risk for CHD are needed.

The extent of the relationship between osteoporosis and periodontal disease still remains uncertain. It is difficult to separate the effects of osteoporosis on bone changes from alveolar bone loss as a result of a progressive periodontal disease. Additional prospective studies are needed in order to assess the role of osteopenia/osteoporosis in relation to progressive periodontal disease. Postmenopausal estrogen users may retain more teeth after menopause. Sustained oral health and better tooth retention are potentially additional benefits of hormone replacement therapy after menopause.

Aspiration of oral microorganisms may contribute to the genesis of aspiration pneumonia and several oral microbes have been isolated from pulmonary infections. Poor dental health is a factor associated to aspiration pneumonia among elderly institutionalized and hospitalized individuals.

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