



The Potential Link Between Periodontitis and Systemic Diseases— An overview

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ABSTRACT

This article sheds light on the effects of periodontal disease on different systemic conditions such as coronary heart disease, pregnancy outcomes, diabetic complications and respiratory disease, the possible mechanisms involved and the role of periodontal therapy on systemic outcomes.

Keywords: Periodontitis, systemic disease, pregnancy, cardiovascular disease, respiratory disease, diabetes mellitus

1. Introduction

Over the past two decades a number of studies have investigated a possible role for periodontal disease as a risk factor for systemic conditions. The concept that dental diseases may influence distant structures is to some extent, a return to the theory of “focal infection” which emerged at the beginning of the twentieth century. It was based on personal clinical experience of a few dentists and physicians (O'Reilly and Claffey, 2000) and it came to an end in the early fifties. However, in the late eighties some clinicians continued to propose that certain bacteria and its products within the periodontal pocket could enter the bloodstream and thus could somehow be harmful to the whole body (Thoden and Abraham-Inpijn, 1984).

Recent advances in molecular biology, microbiology, immunology and genetics have lead researchers to resume the study of the relationship between oral and systemic diseases with a more scientifically oriented approach. An increasing number of studies suggest periodontal infection as a possible risk factor for several systemic diseases such as cardiovascular (Humphrey, et al., 2008), adverse pregnancy outcomes (Pitiphat et al., 2008), diabetes (Mealey and Oates, 2006) and respiratory (Scannapieco, et al., 2003). In addition, some emerging evidence have indicated an association with kidney disease, rheumatoid arthritis and pancreatic cancer (Henderson, 2009). In the last decade, a number of authors carried out systematic reviews to examine the link between periodontitis and systemic diseases (Cullinan, et al., 2009; Kinane and Bouchard, 2008; Seymour, et al., 2007; Scannapieco, 2005).

The purpose of this essay is to examine and discuss the evidence collected in the last fifteen years implicating periodontal infection as a risk factor for several systemic conditions, to explore the mechanisms proposed to explain this link and to summarize the effect of periodontal therapy on systemic outcomes.

2. Periodontitis and cardiovascular disease

The initial reports of an association between periodontitis and atherosclerotic complications came from Scandinavia. Matilla and co-workers in 1989 investigated the potential association between periodontal disease and myocardial infarction. They reported a highly significant association between poor oral health and acute myocardial infarction. The link with periodontitis was independent of other risk factors (Mattila et al., 1989). These findings attracted a great deal of interest among dental and medical researchers.

Since then there have been many cohort observational studies investigating a potential association between periodontal disease and cardiovascular diseases, particularly atherosclerosis (Beck et al., 2001; Engebretson et al., 2005), coronary heart disease (Loesche et al., 1998; Hung et al., 2004), and stroke (Pussinen et al., 2004; Abnet et al., 2005). The majority of these studies reported at least one significant positive association between poor oral health and the prevalence of cardiovascular disease. However, both adult periodontitis and atherosclerosis share several common risk factors including age, gender (predominantly male), smoking, obesity, hypertension, diabetes mellitus and socioeconomic status; thus the association can be attributed to the prior confounding factors (Craig, 2009). This hypothesis is not supported by the results of prospective studies that suggest that periodontitis may precede and therefore contribute to atherosclerotic complications. Recent meta-analyses have shown that periodontitis patients are at increased risk for developing cardiovascular diseases (Khader, et al., 2004; Humphrey et al., 2008). Some studies have also found that periodontal disease is an important risk factor for all forms of cerebrovascular diseases, especially non-haemorrhagic stroke (Wu et al., 2000; Joshipura, et al. 2003). Other reports, however, have failed to find any significant link (Pihlstrom et al., 2005).

At present, evidence from a large number of clinical studies supports an association between moderate to severe periodontal disease and atherosclerotic complications; however, overall the association is modest.

2.1 Possible biological mechanism

A direct causal relationship between periodontitis and atherosclerotic cardiovascular disease is not established. However, several biologically plausible mechanisms were proposed. These mechanisms include:

1. Direct effect of oral infections: infection and inflammation play an important role in the initiation and progression of atherosclerosis. A number of studies implicate a role of oral infection in this respect; some of which have identified oral bacteria in atherosclerotic

plaques (Haraszthy et al., 2000; Ford et al., 2005). However, findings have not shown whether they actually initiate atherosclerosis or invade an already damaged artery (Cullinan et al., 2009). A cross-sectional study carried out on a Finnish population, have shown that serological antibodies to periodontal pathogens were associated with increased risk of coronary heart disease (Pussinen et al., 2005).

2. Inflammation: it has been proven that moderate to severe periodontitis increases the level of systemic inflammation and has been associated with elevation of circulating cytokines and other inflammatory mediators such as C-reactive protein (CRP) and fibrinogen (D'Aiuto, et al., 2004; Dave and Van Dyke, 2008).
3. Cross-reactivity/molecular mimicry: in this theory it is proposed that the immune response to bacterial heat-shock proteins (HSPs) may result in antibodies that cross-react with self heat shock proteins expressed on damaged arterial cells. This in turn leads to progression of atherosclerosis (Tabeta et al., 2000; Wick Perschinka et al., 2001).

3. Periodontitis and adverse pregnancy outcomes

3.1 Periodontitis and preterm low birth weight

Preterm low birth weight (PLBW) is a significant cause of infant morbidity and mortality. There are a number of risk factors associated with adverse pregnancy outcomes including low socioeconomic status, the mother's age, race (with higher rates in African-Americans than in white women), multiple births, smoking, drug and alcohol abuse and systemic maternal infection, however, these risk factors are absent in about one fourth of PLBW cases, leading to continued search for other causes (Scannapieco, 2005). It has been shown that genitourinary tract infections and bacterial vaginosis, caused by aerobic and anaerobic bacteria, are associated with many adverse pregnancy outcomes including PLBW (Offenbacher et al., 1998).

It was hypothesized that periodontal infection which serves as a reservoir for anaerobic bacteria and inflammatory mediators may be a potential threat to the foetal-placental unit (Collins et al., 1994). Initial animal experiments have provided support for this hypothesis. In an important animal experiment carried out by Collins and colleagues in 1994, subcutaneous administration of low-grade *P. gingivalis*, a Gram negative bacteria commonly associated with periodontal diseases, in pregnant hamsters, resulted in an increase in some inflammatory mediators and a significant reduction of foetal weight by up to 25% (Collins et al., 1994).

The first human study to suggest an association between maternal periodontitis and PLBW was published by Offenbacher and colleague in 1996. In this study, it was found that the risk of PLBW was 7.5-fold greater if the mother had evidence of periodontal disease compared to those with no periodontal disease (Offenbacher et al., 1996). A large number of case-control and cohort observational studies were carried out to investigate the periodontal disease as a risk factor for adverse pregnancy outcomes (Offenbacher et al., 1996). Results of these studies demonstrate conflicting findings. A large number of studies have reported positive association (Dortbudak et al., 2005; Siqueira et al., 2007; Pitiphat et al., 2008). However, studies reporting no significant association (Mitchel et al., 2001; Noack, et al. 2005), constitute a small proportion

of the total available evidence collected to date. It is interesting to note that studies showing positive association involve Black and Hispanic Americans; whereas studies reporting no association are based in Europe and Asia. This could be attributed to the racial or socioeconomic differences in global population in respect to susceptibility to periodontal disease-associated prematurity (Lindhe et al., 2008).

In a recent consensus report of the Sixth European Workshop on Periodontology it has been concluded that although there is a likely association between periodontal disease and an increase risk of adverse pregnancy outcomes, there is no conclusive evidence that treating periodontal disease improves the rate of positive birth outcomes (Kinane et al., 2008).

3.2 Possible biological mechanisms

The biological mechanism proposed to explain the link between maternal periodontitis and PLBW involves translocation of inflammatory mediators or periodontal bacteria and their products from the mouth to the foetal-placental unit via the systemic circulation inducing premature labour (Irwin et al., 2008). A number of animal experiments have supported this hypothesis (Collins et al., 1994; Yeo et al., 2005). Interestingly, in 2001 Madianos and colleagues reported that high levels of foetal IgM to *Compylobacter rectus* were significantly associated with a higher risk of preterm delivery. These findings support the theory that blood-borne bacteria can reach the foetus and thus induce an immunologic response (Madianos et al., 2001).

3.3 Periodontitis and Pre-eclampsia

Pre-eclampsia is a common disorder of pregnancy that is characterized by hypertension and the presence of protein in the urine. It contributes to both maternal and foetal morbidity and mortality. Results from a cohort study indicate that after adjustment for other risk factors such as race, maternal age and smoking, maternal periodontal infection during pregnancy is associated with an increased risk for pre-eclampsia (Bogges et al., 2003). Another case-control study carried out in Colombia showed a consistent link between exposure to periodontal disease and subgingival pathogens and pre-eclampsia in pregnant women (Contreras et al., 2006).

Wimmer in 2008 performed a systematic review to examine the link between periodontal disease and adverse pregnancy outcomes (Wimmer and Pihlstrom, 2008). The author concluded that there are indications for an association between the two conditions; however, he suggested that more methodologically vigorous long-term interventional studies are needed.

4. Periodontitis as a risk for diabetic complications

Diabetes mellitus is a common multifactorial endocrine disease involving genetic, environmental and behavioural risk factors. It has been known for over sixty years that diabetes is a modifying factor for periodontal disease. This has been confirmed in many studies such that periodontal disease is now called the sixth complication of diabetes (Loe, 1993); along with retinopathy, neuropathy, nephropathy, macrovascular disease and poor wound healing. In recent

years, it has been suggested that the relationship between diabetes mellitus and periodontal disease is bidirectional; the presence of periodontal disease also being considered as a risk for diabetic complications, mainly poor glycaemic control (Taylor et al., 1996; Taylor and Borgnakke, 2008). Results from a longitudinal study that followed 628 patients with Type II diabetes for 11 years indicated that those with severe periodontitis had three times the risk of death from ischemic heart disease or diabetic nephropathy than those with no, mild or moderate periodontitis (Saremi et al., 2005).

A more recent longitudinal study that followed 500 diabetic patients (Type II diabetes) for 22 years, found that periodontitis increased the risk for end-stage renal disease by up to 3.5 times (Shultis et al., 2007). Two systematic reviews (Mealey et al., 2006; Nagasawa et al., 2010) concluded that there is a link between the two conditions and they suggested that periodontal disease may increase insulin resistance and thereby aggravate glycaemic control; however, little evidence has been reported to indicate a significant cause-effect relationship.

4.1 Possible biological mechanism

Type 2 diabetes is characterized by an increase in insulin resistance which is in turn strongly linked to the actions of pro-inflammatory cytokines such as Interleukin 6 (IL6) and Tumour necrosis factor α (TNF α). In an animal experiment, Uysal and co-workers in 1997 reported that mice lacking TNF α function were resistant to obesity-induced insulin resistance (Uysal, et al., 1997). Serum markers of inflammation are significantly higher in periodontitis patients (Loos, et al., 2000; Noack et al., 2001), and they are also strongly linked to insulin resistance (Chen et al., 2010). Therefore, it is possible that periodontal disease may serve as an initiator of insulin resistance thereby aggravating glycaemic control (Mealey et al., 2006).

5. Periodontitis as a risk for respiratory diseases

Over the last fifteen years, a number of studies have investigated the link between periodontitis and respiratory diseases. To date there have been two systematic reviews, both of which concluded that there was evidence of an association between periodontal disease and two respiratory conditions, bacterial pneumonia and chronic obstructive pulmonary disease (COPD) (Azarpazhooh and Leake, 2006).

Bacterial pneumonia is either community-acquired or hospital acquired (nosocomial). The main cause of the first type is aspiration of bacteria that reside on the oro-pharynx. Hospital-acquired pneumonia, on the other hand, is caused by bacteria within the hospital. COPD is characterized by chronic obstruction to airflow with sputum production resulting from chronic bronchitis and/or emphysema. The most important established risk factor for COPD is a history of prolonged cigarette smoking (Deo et al., 2009).

Starting in 1992, with a report by Scannapieco and colleagues, many investigators have hypothesized that periodontal infection may increase the risk for bacterial pneumonia or COPD (Scannapieco et al., 1992; Scannapieco and Ho, 2001; Deo et al., 2009). There were some reports of an association between COPD and poor oral hygiene (Scannapieco et al., 1998). However, two

systematic reviews of the studies investigating the link between periodontitis and respiratory diseases concluded that there is no sufficient evidence to say that there is an association between periodontal disease and COPD. On the other hand, there was fair evidence of an association of pneumonia with oral health (Azarpazhooh et al., 2006; Gomes-Filho et al., 2009).

From all the evidence gathered to date it is concluded that improvement of oral hygiene and professional oral health care are vital for reducing the occurrence of pneumonia among high-risk elderly adults especially those living in nursing homes (Seymour, 2009).

6. Effects of periodontal therapy on systemic diseases

Since investigators worldwide have strongly suggested a link between periodontal disease and some systemic conditions; a logical question was asked at this stage “Would treatment of periodontitis prevent the onset or reduce the severity of systemic complications?” The answer to this question is still not clear, however, there are initial interventional studies to investigate the impact of periodontal therapy on several systemic conditions and the results are promising.

6.1 Cardiovascular diseases

It has been assumed that periodontal therapy would reduce the inflammatory response and thus atherosclerotic changes (Scannapieco, et al., 2010). A number of studies have demonstrated that treatment of periodontitis has lead to a significant reduction in the cardiovascular disease biomarkers (CRP and IL-6) (D'Aiuto et al., 2004; Elter et al., 2006) and to improvement in endothelial function as assessed by measurement of the brachial artery during flow-mediated dilatation (Tonetti et al., 2007). However, in a systematic review and meta-analysis of studies investigating the effects of periodontal treatment on serum CRP levels, it was concluded that it is highly unlikely that CRP levels can be modulated by a single episode of non-surgical periodontal treatment in patients with severe periodontitis (Ioannidou, et al., 2006). A recently published systematic review of interventional clinical trials investigating the effect of periodontal therapy on atherosclerosis has indicated that periodontal treatment seems to reduce systemic inflammation and endothelial dysfunction and that there is a dose-dependent effect: better outcomes of periodontal treatment seem to be associated with more significant improvement in systemic parameters (Tonetti, 2009).

6.2 Pregnancy outcomes

A limited number of interventional studies have addressed whether the control of periodontal infection during pregnancy may result in improved pregnancy outcomes. The first randomised clinical trial carried out by Lopez and co-workers in Chile have reported a significant reduction of PLBW (Lopez, et al., 2002). Following this report a number of studies have provided evidence that periodontal treatment aimed at maternal periodontal disease may reduce the likelihood of PLBW infants by up to 50% (Jeffcoat et al., 2003; Lopez, et al., 2005; Tarannum and Faizuddin, 2007). Other studies have not found a significant effect (Michalowicz et al., 2006). The conflicting findings may be related to the variety in the ethnicity of the populations

studied or the timing and type of the periodontal intervention (Seymour, 2009). Overall, these interventional studies suggest that mechanical intervention in pregnant mothers with gingivitis or periodontitis can reduce the incidence of PLBW.

6.3 Diabetes mellitus

A number of studies were carried out to investigate the efficacy of a variety of periodontal interventions on diabetes mellitus. These studies were subjected to two meta-analyses (Janket, et al., 2008). The primary outcome measure has been changes in levels of glycosylated haemoglobin (HbA1c). Results from both meta-analyses have indicated a decrease in HbA1c level, however, the reduction was more pronounced in Type II diabetes than Type 1 (Janket et al., 2005). The evidence suggests that periodontal therapy does have an effect on blood glucose level, however, the impact is small and that Type II diabetic patients benefit more from periodontal intervention than Type 1 with respect to glycaemic control.

6.4 Respiratory disease

The evidence for the effect of periodontal therapy on bacterial pneumonia is promising. The 1996 study by DeRiso reported that the incidence of pneumonia was reduced by 60% with the use of pre and postoperative application of 0.12% chlorhexidine rinse in patients undergoing cardiac surgery (DeRiso, et al., 1996). In another important study, Yoneyama and colleagues in 2002 investigated the role of supervised tooth brushing on the incidence of pneumonia in a group of elderly people living in nursing homes in Japan. There was a 39% reduction in pneumonia over a two year period compared to the control group (Yoneyama et al., 2002). A recent review has shown that when the load of oral bacteria is reduced, the risk of pneumonia is also reduced (Azarpazhooh et al., 2006). However, these findings are limited to special care populations.

7. Conclusion

The potential link between periodontitis and systemic conditions is now the focus for a wide range of research around the world. The potential for periodontal pathogens to gain access to the systemic circulation through ulcerated pocket walls is certainly present. Both *in vitro* and animal studies have clearly demonstrated the harmful effect of these pathogens on the cardiovascular, pregnancy, diabetes and some respiratory conditions. Moreover, inflammatory mediators commonly associated with periodontitis can also affect atheroma formation, pregnancy outcomes and insulin resistance. However, in order to show causality between periodontal disease and systemic condition, better designed large-scale longitudinal studies are required. In the meantime, a good oral health would be advocated among all patients with special emphasis on the additional systemic benefits for certain conditions such as coronary heart disease, Type II diabetes, bacterial pneumonia and pregnancy.

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